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CLINICAL REVIEW

Wake-up stroke: From pathophysiology to management

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SUMMARY

Wake-up strokes (WUS) are strokes with unknown exact time of onset as they are noted on awakening by the patients. They represent 20% of all ischemic strokes. The chronobiological pattern of ischemic stroke onset, with higher frequency in the first morning hours, is likely to be associated with circadian fluctuations in blood pressure, heart rate, hemostatic processes, and the occurrence of atrial fibrillation episodes. The modulation of stroke onset time also involves the sleep-wake cycle as there is an increased risk associated with rapid-eye-movement sleep. Furthermore, sleep may have an impact on the expression and perception of stroke symptoms by patients, but also on brain tissue ischemia processes via a neuroprotective effect. Obstructive sleep apnea syndrome is particularly prevalent in WUS patients. Until recently, WUS was considered as a contra-indication to reperfusion therapy because of the unknown onset time and the potential cerebral bleeding risk associated with thrombolytic treatment. A renewed interest in WUS has been observed over the past few years related to an improved radiological evaluation of WUS patients and the recent demonstration of the clinical efficacy of reperfusion in selected patients when the presence of salvageable brain tissue on advanced cerebral imaging is demonstrated.

Introduction

Wake-up stroke (WUS) is an important issue as it represents around 20% (14%–24%) of all acute ischemic strokes [1–3]. WUS patients are those who went to sleep healthy and woke up with stroke symptoms; therefore, the exact moment of stroke onset is unknown while the only approved pharmacological treatment (intravenous thrombolysis with alteplase) for acute ischemic stroke (AIS) is still limited to patients whose stroke began within 4.5 h before the infusion [4]. Moreover, it has been shown that the efficacy of reperfusion therapy is time dependent resulting in a limited proportion of patients with a favorable clinical outcome when treatment is initiated later [5–8]. Until recently, the short time window of reperfusion therapy for stroke was based on experimental evidence showing that longer cerebral artery occlusions produced increasingly larger infarcts in rodents [9]. However, the progression of cerebral infarction over time in humans is heterogeneous and some stroke patients admitted late still exhibit large area of salvageable brain tissue on cerebral imaging. Recent therapeutic trials have demonstrated that we should move toward brain tissue viability-based selection for reperfusion therapy in stroke rather than basing therapeutic decision on time window alone. Management of WUS has recently dramatically changed with the publication of randomized trials that have demonstrated the clinical benefit of intravenous thrombolysis (IVT) and mechanical thrombectomy (MT) in selected WUS patients with imaging evidence of salvageable brain tissue [10–13]. The reported data suggest that a substantial proportion of WUS patients have ischemic but not yet infarcted brain tissue because of good cerebral arterial collaterals and/or occurrence of stroke in the second part of the night, resulting from the interaction between circadian fluctuation and sleep-wake cycle associated modulation of vegetative tone and thrombosis phenomena [14]. This paper aims to provide a comprehensive review of the pathophysiological substrate, clinical and imaging characteristics, and therapeutic issues regarding WUS.

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Abbreviations and acronyms

AF	atrial fibrillation
AIS	acute ischemic stroke
BP	blood pressure
CBF	cerebral blood flow
CMRO2	cerebral metabolic rate of oxygen
CT	computed tomography
DWI	diffusion-weighted imaging
FLAIR	fluid attenuated inversion recovery
HR	heart rate
IVT	intravenous thrombolysis
MRI	magnetic resonance imaging
m-RS	modified Rankin scale
MT	mechanical thrombectomy
NIHSS	National Institute of Health stroke scale
OSA	Obstructive sleep apnea syndrome
PWI	perfusion-weighted imaging
REM	Rapid eye movement sleep
WUS	Wake-up stroke

Circadian variation in onset of ischemic stroke

Epidemiological data: a higher risk of stroke in the morning hours

Epidemiological studies have shown a circadian rhythm of ischemic stroke; a higher frequency is found in the morning and a lower frequency is found during sleep [14–17]. In a large population of AIS patients, Casetta et al. observed that symptom onset was more frequent in the morning (between 6:00 am and noon; major peak around 8:30 am), with a second, minor, peak in the evening and minimum occurrence during the night [17]. This higher risk of ischemic stroke in the morning appeared to be independent of clinical stroke subtypes (atherothrombosis, cardioembolism, small vessel disease, undetermined cause, and other determined cause) and of the presence of risk factors; hypertension, diabetes, hyperlipemia, smoking habits, previous vascular events, and treatment with antiplatelet agents or anticoagulant drugs did not modify the circadian pattern of ischemic stroke onset. In a meta-analysis of 31 publications reporting the circadian timing of 11 816 strokes, all subtypes of stroke displayed a significant circadian variation in time of onset; the risk was higher in the morning hours (49% increased risk between 6:00 am and noon) and lower during the nighttime period (midnight to 6:00 am) [15]. This chronobiological pattern is similar to that of acute myocardial infarction and sudden death, suggesting that some underlying mechanisms may be common [18,19].

Pathophysiological hypotheses: circadian and vigilance state-associated regulation of vegetative tone and coagulability

Circadian factor

Several risk factors for ischemic stroke exhibit a circadian variation leading to an increased risk of stroke in the early morning hours. The circadian rhythmicity in cardiovascular function is regulated by the central biological clock located in the suprachiasmatic nuclei of the hypothalamus [20]. In particular, it has been suggested that the circadian variability of blood pressure (BP), resembling the temporal biphasic pattern of ischemic stroke, and a concurrent morning hypercoagulability may be determinant in this increased risk of AIS in the morning [21,22]. The circadian pattern of BP is characterized by a mid-morning peak, a progressive decline to the lowest level during the nighttime hours of sleep (in "normal-dippers", the sleep-time BP mean is reduced by 10–20% relative to the daytime mean), and a rise again just before morning awakening [23]. This immediate morning systolic BP rise amounts to about 20–25 mm Hg, but may reach 40–60 mm Hg in the elderly who have less compliant and elastic arteries [20]. The circadian heart rate variation is close to that of BP in healthy individuals, with a relative nocturnal bradycardia. In pathological conditions, such as hypertension but also obstructive sleep apnea syndrome (OSA), these physiological fluctuations may be impaired, nocturnal BP dipping in particular [20].

A recent prospective study has found an independent association between newly diagnosed atrial fibrillation (AF) and WUS; the odds of detecting a newly diagnosed AF were 3-fold higher among wake-up cerebrovascular events than among non-wake-up events [24]. In this prospective study including 356 patients (274 stroke and 82 transient ischemic attack, median age 72 y interquartile range, IQR [62–78]), AF was detected with immediate and continuous electrocardiographic monitoring for at least 72 h after admission: 41 (11.5%) events occurred during night sleep. Among WUS patients, 17.1% were newly diagnosed with AF (vs. 6.3% of non-WUS patients, $p = 0.015$), and the association remained significant after adjusting for age, sex, hypertension, severity of neurological deficit on admission, left ventricular fraction, atrial area, and diabetes mellitus [24]. The association between AF and WUS may be related to the circadian variation of AF that is reported to most frequently occur in the morning hours. For instance, in a large cohort of 3343 patients with new-onset AF, the distribution of paroxysmal AF onset showed a double peak, with a significant increase in the number of episodes in the morning and (to a lesser degree) a second rise in the evening [25]. In addition, severe sleep-disordered breathing has been associated with nocturnal AF (odds ratio, OR: 4.02, 95% confidence interval, CI [1.03; 15.74]) and nocturnal hypoxia due to OSA has been shown to be an independent predictor of AF in patients with subacute ischemic stroke [26,27].

Another point to note is that the hemostatic system exhibits a circadian rhythm that is characterized by morning increase in platelet aggregation, coagulation factors, fibrinolytic activity, plasma viscosity and hematocrit, and morning endothelial dysfunction has also been reported [28–30].

Sleep-wake cycle

The morning peak in the frequency of vascular events may not only be related to circadian variations but also to rapid eye movement (REM) sleep morning preeminence. Indeed, the last sleep cycles of the night contain more REM sleep, a state of autonomic instability dominated by remarkable fluctuations between parasympathetic and sympathetic influences, whereas non-REM sleep is associated with an increase in vagal drive and a decrease in cardiac sympathetic activity [31–33]. More specifically, phasic REM sleep periods are characterized by a transient increase in muscular tone, rapid eye movements, and pontine cholinergic discharges associated with bursts of sympathetic activity responsible for sudden increase in BP and changes in heart rate (HR) [34,35]. REM sleep thus constitutes a period of vascular vulnerability as compared to non-REM sleep; this has been highlighted in the setting of myocardial infarction in patients with coronary artery disease [36]. Finally, late night sleep is punctuated by more arousals (either spontaneous or stimuli-induced) which have been shown to be associated with transient increase in BP and HR caused by activation of the autonomic system [37,38]. Thus, the early morning, before awakening, appears to be a period at increased risk for vascular events as compared to the first part of the night.

Taken together, circadian and vigilance state-associated factors suggest that there is an increased risk of WUS just prior to awakening [39].

Wake-up stroke and the sleeping brain

Stroke as a trigger of awakening

The benefit of reperfusion therapy in WUS may be related to the persistence of salvageable brain tissue associated with good collateral circulation but may also suggest that a significant proportion of WUS occur shortly before awakening, either because of their onset time or because the stroke itself may have woken up the patient.

The latter hypothesis supposes that the sleeping brain has perceived the occurrence of a neurological deficit. Indeed, while it is generally accepted that the loss of consciousness during sleep period is associated with a drastic reduction of stimulus input, some information processing persists according to the intensity and the relevance of the stimulations [40,41]. Cortical responses to auditory, visual, somatosensory, and painful stimulations have been reported during sleep, suggesting that not only detection but also discrimination of the intrinsic significance of the stimulus persists, at least during non-REM Stage 1–2 and REM sleep [42,43]. Such preservation, even if partial, of some sensory integration capacity of the brain during sleep may allow the recognition of relevant stimuli (in case of stroke: decreased mobility, sensory symptoms …) and may lead to the awakening of the sleeper [44].

Another explanation for the potential stroke arousing effect could be related to the ischemic lesion itself, which may directly affect brain areas involved in vigilance states regulation or indirectly have a wake-promoting effect through the liberation of neuromodulators and cytokines [45–47].

Sleep-associated neuroprotection against ischemia

In almost 50% of WUS, brain MRI demonstrates the presence of not yet infarcted brain tissue [48]. This observation suggests either that stroke has occurred recently, that the stroke is not very recent but that the patient's collateral cerebral circulation is effective, or that the brain tissue has been resistant to ischemic injury. The latter hypothesis may suppose a relative preservation of ischemic brain tissue during sleep in comparison to wakefulness state. This vigilance state-associated modulation of brain vulnerability may involve the variations of neuronal activity according to the sleep-wake cycle, with fluctuations in cerebral blood flow (CBF) and metabolism [49]. A decrease of up to 25% in CBF and cerebral metabolic rate of oxygen (CMRO2) has been reported during NREM sleep in comparison with the awake state, whereas CBF and CMRO2 were found to be practically the same during REM sleep and during the awake state [50]. It is, however, important to note that modifications of CBF during sleep have local specificities related to the underlying neuronal activity [51].

Recently, several authors have reported the neuroprotective effect of sleep deprivation pre-ischemia in experimental paradigms; such procedures aim at inducing an adaptive response (i.e., sleep rebound) following a noxious stimulus (i.e., sleep deprivation) [52,53]. In this way, it has been observed that sleep deprivation pre-ischemia led to an acute increase in the total amount of sleep and significantly reduced infarct volume in animal models of stroke [54,55]. More specifically, this sleep-associated neuroprotective effect could involve increase in the amount of REM sleep and gene expression in the melanin-concentrating hormone and orexin systems [52]. The beneficial effect of slow-wave sleep has also been reported in pharmacological studies using baclofen and gamma hydroxybutyrate, but is more likely to be related to increased brain neuroplasticity (with enhanced functional recovery) than to a reduction in the size of brain injury [56,57]. In addition, other neurotransmitters involved in sleep regulation and neuroprotection, such as adenosine, could also be involved [58].

Sleep disorders and wake-up stroke: obstructive sleep apnea

Various sleep-wake disturbances (insomnia, restless leg syndrome with periodic leg movements during sleep …) have been associated with an increased risk of stroke but only OSA has been specifically implicated in the occurrence of WUS [59–61]. The Fig. 1 summarizes the potential pathophysiological mechanisms of OSA-associated WUS.

OSA is a risk factor of stroke

OSA is an independent risk factor for stroke and is associated with a three-fold increased incidence of stroke in men [62,63]. Nocturnal oxygen desaturation secondary to OSA may trigger cerebral ischemia or may increase the risk of stroke mediated by hypertension [60,61] as hypoxia and carbon dioxide retention induced by OSA may disturb autonomic nervous activity, which affects heart rate and cardiac function and leads to increased BP [64]. OSA is also associated with nocturnal arrhythmia, in particular AF [27]. Recurrent nocturnal oxygen desaturation may also be associated with a hypercoagulable state related to an increased blood viscosity, increased platelet aggregation, or a decreased fibrinolytic activity [64–66]. More specifically, studies have shown increased blood fibrinogen and platelet aggregation activity in OSA patients during the morning hours [67,68]. OSA may also impact cerebral hemodynamics; decreased middle cerebral artery blood flow and decreased cerebral vasoreactivity have been observed in severe OSA syndrome [69,70]. It has been shown that impaired vascular regulation in patients with OSA may be improved by continuous positive airway pressure [71].

Severe OSA is associated with WUS stroke

Prevalence of OSA in WUS patients depends on the definition of OSA severity used as assessed by apnea-hypopnea index (AHI) and on diagnosis procedure. In a recent case-control study including 107 patients (among which 40 WUS), OSA prevalence estimated using the Berlin questionnaire was 72.5% in WUS vs. 45% in non-WUS patients (OR: 3.25, 95%CI [1.397; 8.38]; $p = 0.0053$) [72]. In a prospective study, Hsieh et al. reported severe OSA (AHI $\geq$30/h) as assessed by polygraphy in 38.5% WUS patients vs. 8.9% of non-WUS patients ($p = 0.003$) [60]. In the same study patients with WUS had higher oxygen desaturation index and lower mean blood oxygen saturation than those with non-WUS while no significant difference was observed in terms of demographic data and stroke risk factors. Multivariate logistic regression, that included obesity and diabetes, showed that severe sleep-disordered breathing (defined as AHI$\geq$30) was the only independent variable significantly associated with WUS. These results are in line with those reported by Siarnik et al. in 88 patients (16 WUS) explored in the acute phase of stroke with full night polysomnography: while the frequency of OSA, defined as AHI > 5, in WUS patients (81.3%) did not significantly differ from the frequency in non-WUS patients (59.7%; $p = 0.105$), moderate-to-severe SAS (AHI >15) and severe SAS (AHI >30) were significantly more frequent in WUS patients than in non-WUS patients (respectively 68.8% vs. 29.2%, $p = 0.003$ and 43.8 vs 15.3%, $p = 0.011$), and higher values of desaturation index were also found in WUS patients [73]. The cross-sectional analysis of data from the Sleep Apnea in Transient Ischemic Attack and Stroke

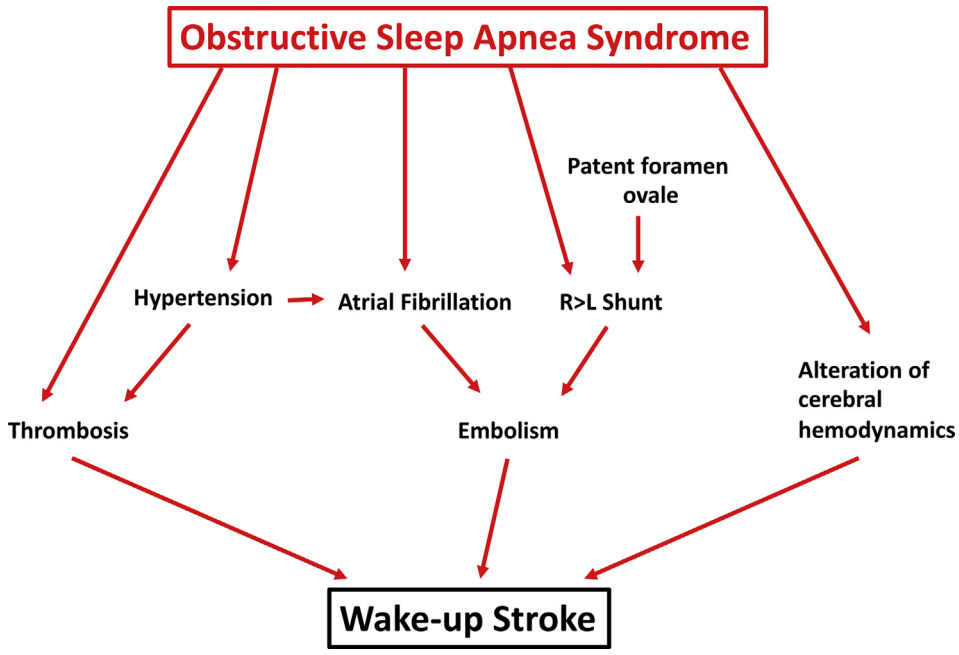

Fig. 1. Pathophysiological mechanisms of OSA-associated WUS. The figure represents direct influence of OSA on risk factors (hypertension, atrial fibrillation, cardiac R > L (right to left) shunt) and on mechanisms (thrombosis, embolism, alteration of cerebral hemodynamics) involved in the occurrence of stroke.

(SLEEP TIGHT) study has also shown in 81 stroke patients who underwent polysomnography in the subacute phase (median interval from stroke: 48 d) that patients with WUS had significantly higher rates of severe OSA but this difference was only significant for men (AHI>30: 45.0% vs. 17.6%; $p = 0.03$) [74]. Such a difference in sex was recently confirmed by Brown et al. in 259 women with acute ischemic stroke who benefited from apnea screening using the ApneaLink Plus device (AL; Resmed, Poway, CA, USA) a median 11 d post-stroke: WUS was not associated with the presence or severity of OSA in unadjusted or adjusted analysis (prevalence of respiratory event index $\geq$10/h: 55.4% in WUS vs 52.4% in non-WUS women) [75].

Mechanisms underpinning the association between OSA and WUS

Taken together, these data suggest that severe OSA is more frequent in WUS than in non-WUS patients, at least in men, and that nocturnal oxygen desaturation may be a determining factor. In an recent study of 298 AIS patients (26.5% with WUS), the proportion of nocturnal oxygen desaturation (defined as an oxygen desaturation index > 5 per hour during the first night in the stroke unit) assessed by pulse oximetry was significantly greater in patients admitted with WUS as compared to patients admitted without WUS (29.1% vs. 12.3%, $p = 0.001$) [66]. Patients with nocturnal oxygen desaturation were significantly older and more obese than patients without nocturnal oxygen desaturation. The mean heart rate (HR) was higher in the nocturnal oxygen desaturation group and HR was significantly increased during desaturation events. Using multivariate logistic regression analysis, it was found that nocturnal oxygen desaturation was associated with a higher risk of WUS (OR: 3.25, 95% CI [1.63; 6.46]; $p = 0.001$) after adjusting for relevant confounding variables. The results of this study suggest that nocturnal oxygen desaturation represents a possible modifiable risk factor for the occurrence of WUS. Finally, it has been suggested that OSA may lead to transient right-sided chamber pressure elevation and to right-to-left shunting with subsequent paradoxical embolism in patients with WUS and patent foramen ovale [76]. This may be more specifically the case in patients with long apneas: in a prospective study Ciccone et al. found that WUS was more frequent among patients with right to left shunting and long obstructive sleep apneas (lasting $\geq$20 s) than in patients without this association [77].

The high prevalence of OSA in WUS patients should encourage systematic polygraphic or polysomnographic screening in WUS patients given the demonstrated benefit of OSA treatment on clinical symptoms, functional status, and quality of life [78,79]. The long-term effect on cardiovascular outcomes remains, however, uncertain but may depend on treatment (mainly continuous pression air pressure) adherence [80,81].

Clinical and imaging characteristics

Clinical data

Some clinical and imaging studies indicate that WUS may occur close to the time of awakening or at least that salvageable brain tissue is present in a significant proportion of WUS patients [82,83]. For instance, in a prospective registry of ischemic stroke patients, clinical features of patients with WUS (27% of 364 patients) did not differ significantly from those with known onset time; there was also no significant difference in age, sex, severity of neurological deficit [1]. Another large population-based study has shown that WUS cannot be distinguished from other strokes by clinical features or outcome; no significant difference was found between WUS and all other ischemic strokes with regard to baseline demographics, risk factor profile, or clinical outcome, and, furthermore, there were no significant differences in the discharge functional outcome or 90-day mortality after adjusting for age, sex, race, pre-stroke functional status, severity of neurological deficit, and prior atrial fibrillation between the wake-up and non-wake-up groups [3]. In addition, some authors have reported a smaller initial clinical severity for WUS as compared to stroke while awake with secondary deterioration to comparable morbidity and mortality, highlighting the potential responsiveness of WUS for reperfusion therapy [84].

Imaging data

Mismatch concept in stroke

The concept of imaging mismatch - the difference between the amount of "core" tissue that is likely to infarct despite reperfusion and the "penumbra" of ischemic brain at risk for infarction without reperfusion - is of increasing interest for reperfusion therapy triage in acute stroke, especially in the setting of WUS or stroke with unknown onset time. The size of the core can be evaluated with MR diffusion-weighted imaging (DWI). Penumbra can be visualized with MR or CT perfusion imaging. Patients with significant imaging mismatch (small core, large penumbra) are considered to be good candidates for reperfusion therapy, often even beyond accepted temporal treatment windows [85]. Apart from the perfusion mismatch, another current imaging approach that may help in the selection of WUS patients likely to benefit from reperfusion is based on the DWI-FLAIR mismatch concept. This DWI-FLAIR mismatch pattern has been shown to identify patients presenting within 4.5 h of actual symptom onset. The DWI-FLAIR mismatch indirectly estimates time of stroke onset with a high positive predictive value (83–87%) [86].

Imaging data in WUS and non-WUS

Regarding imaging data, comparable rates of early cerebral ischemic signs on brain computed tomography (CT) have been reported in WUS patients as compared to AIS patients imaged within the first 3 or 6 h of symptom onset [87,88]. A prospective cohort study has also shown that the frequencies of CT perfusion mismatch (approximation of salvageable tissue) and of large-vessel intracranial occlusions were similar among the groups of WUS and AIS with known onset time [82]. WUS patients and patients with known onset time of stroke show similar DWI MRI and perfusion-weighted imaging (PWI) MRI lesion volumes when imaged within 3 h of stroke detection; in this study, DWI-PWI mismatch was present in 73% of WUS patients [1]. In a large prospective cohort of 1005 ischemic stroke patients with unknown time of symptom onset (including 867 WUS patients) otherwise considered potential candidates for thrombolysis, almost half of the patients had a DWI-FLAIR MRI mismatch, rendering them likely to be within a time window for effective thrombolytic therapy [48].

These data highlight that, while WUS are potentially detected later (with a theoretical onset time within the last 7–8 h depending on sleep duration), the imaging mismatch does not differ from stroke diagnosed while awake (and thus potentially diagnosed earlier). As discussed above, this may reflect the circadian pattern of stroke occurrence, with a peak early in the morning, and/or good collateral circulation in these patients, and/or a protection against cerebral ischemia during (and by) sleep. Independently of the pathophysiological mechanisms, the data strongly suggest that patients with WUS should undergo multimodal imaging in order to evaluate the presence of salvageable brain tissue and treatment eligibility.

Treatment

A mismatch-based treatment approach

The current management of WUS has recently dramatically changed with the publication of randomized trials investigating reperfusion therapy in patients with favorable risk-benefit profiles based on advanced multimodal imaging (Table 1). Until recently, when the time of stroke onset was not known, the last moment the patient was known to be well was used to determine eligibility for reperfusion therapy. This conservative approach was based on the increasing risk of treatment-related cerebral bleeding and the declining clinical benefit over time. However, as detailed above, advanced imaging using perfusion CT or MRI can determine whether there is a mismatch between the volume of salvageable ischemic brain tissue and a smaller volume of already infarcted tissue, leaving opportunities for safe and effective treatment of selected WUS patients [89,90].

Some pioneer non-randomized studies had suggested that reperfusion of cerebral vessels was beneficial in patients who have a mismatch between the volume of salvageable brain tissue and that of infarcted tissue, even when the reperfusion is obtained late [91–100]. This was confirmed by more recent randomized studies that demonstrated that reperfusion therapy based on the presence of an imaging mismatch pattern rather than on the time after the onset of stroke symptoms is beneficial in acute ischemic stroke patients [10–12].

Intravenous thrombolysis in WUS

The results of the WAKE-UP trial have recently been published [12]. This randomized, double-blind, placebo-controlled, multicenter study evaluated the benefit of IVT with alteplase in patients with unknown stroke onset time and a DWI-FLAIR mismatch (presence of a cerebral ischemic lesion on DWI but no clearly visible signal change in the corresponding region on FLAIR) indicative of lesion age less than 4.5 h. The study was terminated early due to cessation of funding from the sponsor after screening 1362 patients and randomizing 503 (63%) of an anticipated 800 patients. Nearly half of excluded patients were so due to lack of DWI-FLAIR mismatch. The most frequent reason for an unknown time of stroke onset was that the patient had awakened from nighttime sleep with symptoms (89% in the total study population). The rate of favorable outcome (modified Rankin scale score 0 or 1 at 90 d) was significantly higher in the alteplase group than in the placebo group (53.3% vs. 41.8%; $p = 0.02$). However, the alteplase group had numerically more deaths (4.1% vs. 1.2%, $p = 0.07$) and symptomatic intracranial hemorrhage (2.0% vs. 0.4%; $p = 0.15$) than the placebo group. The interpretation of the safety results is limited by the early discontinuation of the trial; the observed trend towards a higher rate of deaths may have become significant with a larger sample size. Moreover, as patients in whom MT was planned were excluded from the trial, the potential benefit of IVT before MT in WUS patients remains unknown and should be evaluated in future randomized trials.

The results of another trial (EXTEND) evaluating IVT guided by perfusion imaging between 4.5 and 9.0 h after the onset of stroke or on awakening with stroke (if within 9 h from the midpoint of sleep) have been published a few months ago [13]. In this multicenter trial, patients with stroke who had hypoperfused but salvageable regions of brain detected on automated perfusion imaging were randomly assigned to receive intravenous alteplase or placebo. A total of 225 patients were enrolled in the trial; 65% of the patients awoke with stroke symptoms with an unknown time of onset. The likelihood of a good outcome at 90 d was 44% higher in the alteplase group than in the placebo group (adjusted risk ratio, 1.44; 95% CI [1.01; 2.06]; $p = 0.04$) but there were more cases of symptomatic cerebral hemorrhage in the alteplase group than in the placebo group.

Mechanical thrombectomy in WUS

In the DAWN (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing

Table 1
Comparison of randomized clinical trials of reperfusion therapy including wake-up stroke patients.

RCT	Reperfusion therapy	Time window	Number of WUS patients/total number of patients	Median NIHSS score	TICI score 2b/3, %	90-day m-RS 0–2, %	s-ICH, %	90-day mortality, %
DAWN Nogueira et al., 2018 [10]	Mechanical thrombectomy	6–24 h from last known to be well	110/206	17	84	I: 49, C: 13	I: 6, C: 3	I: 19; C: 18
DEFUSE 3 Albers et al., 2018 [11]	Mechanical thrombectomy	6–16 h from last known to be well	91/182	16	76	I: 45, C: 17	I: 7, C: 4	I: 14, C: 26
WAKE-UP Thomalla et al., 2018 [12]	Intravenous thrombolysis with Alteplase	>4.5 h from last known to be well	472/503	6	NR	I: 74, C: 65	I: 2, C: 0.4	I: 4, C: 1
EXTEND Ma et al., 2019 [13]	Intravenous thrombolysis with Alteplase	Between 4.5 and 9.0 h or on awakening with stroke (if within 9 h from the midpoint of sleep)	146/225	12	NR	I: 49, C: 43	I: 6, C: 1	I: 12, C: 9

RCT: randomized clinical trial; I: intervention group; C: control group; DAWN: DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo; DEFUSE 3: Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke; EXTEND: Extending the Time for Thrombolysis in Emergency Neurological Deficits; WAKE-UP: Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke; WUS: wake-up stroke; NIHSS: National Institute of Health Stroke Scale; TICI: Thrombolysis in Cerebral Infarction; m-RS: modified Rankin Scale; s-ICH: symptomatic intracranial hemorrhage.

Neurointervention with Trevo) trial, MT plus standard medical care was compared to standard medical care alone for the treatment of patients with stroke who had last been known to be well 6–24 h earlier and who had a mismatch between the severity of the clinical deficit and the infarct volume, with mismatch criteria defined according to age [10]. This multicenter study using a prospective randomized open blinded end-point (PROBE) design randomized patients with a proven large artery occlusion (intracranial internal carotid artery, proximal middle cerebral artery (MCA), or both). Most patients randomized in the DAWN trial were WUS, and the mean time since last seen well was 13 h. Patients randomized to the MT group were 2-fold more likely to have an improvement in their neurological status and more likely to achieve independence at 90 d. The rates of safety end points and serious adverse events did not differ significantly between the treatment groups. Moreover, the safety profile for MT performed 6–24 h after the onset of stroke in patients who have a mismatch between the severity of the clinical deficit and the infarct volume appears similar to the previously observed safety profile for MT performed within 6 h after the onset of stroke [93].

Another recent trial (DEFUSE 3) enrolled WUS patients if they could undergo initiation of MT between 6 and 16 h after the time they had last been known to be well and had evidence of a potentially salvageable region of brain tissue on perfusion imaging [1]. In this study, patients with stroke related to an occlusion of the cervical or intracranial internal carotid artery or the proximal MCA on CT angiography or magnetic resonance angiography were eligible if they had an initial infarct volume (ischemic core) of less than 70 ml, a ratio of volume of ischemic tissue to initial infarct volume of 1.8 or more, and an absolute volume of potentially reversible ischemia (penumbra) of 15 ml or more. These selected patients are likely to present favorable collateral circulation and slower infarct growth. The rate of WUS was 53% in the MT group and 47% in the medical care group. The trial was terminated early for efficacy after 182 patients had undergone randomization; MT resulted in better 90-day functional outcomes and lower 90-day mortality than standard medical care.

Taken together, even if the optimal therapeutic modalities (IVT or MT with/without IVT when proximal arterial occlusion is present) remain to be specified, these studies have demonstrated that a significant proportion of WUS may benefit from reperfusion therapy and need appropriate advanced imaging in order to be effectively treated if ischemic but not yet infarcted brain tissue exists.

Conclusion

WUS result from the close interaction between pathological processes and vigilance states, which results in specificities regarding diagnosis, treatment, and prevention. They represent a significant proportion of all strokes and partly reflect the early morning increase in vascular risk, associated with circadian and sleep-related factors. Understanding WUS pathophysiology has direct consequences for primary and secondary stroke prevention; in WUS patients, emphasis should be placed on the diagnosis of AF, OSA, and patent foramen ovale with right to left shunting in patients with OSA. Regarding primary prevention, circadian adaptation of hypertension treatment may influence not only prevalence of non-dipping but also cardiovascular events [101]. Bedtime rather than awakening intake of antiplatelet should also be considered to reduce the high risk of cardiovascular events associated with morning hours [102]. The specific influence of sleep on ischemia processes may be involved in relative preservation of brain tissue in stroke occurring during nighttime while the presence of a favorable collateral cerebral circulation is the major factor influencing a slow progression of the brain ischemic lesion in WUS patients. WUS are associated with important imaging and therapeutic issues as it has recently been demonstrated that selected WUS patients are amenable to urgent reperfusion therapy based on multimodal advanced brain imaging.

Practice points

1. Wake-up stroke represent 20% of all ischemic strokes
2. Wake-up stroke incidence pattern results from the interaction between physiological (circadian and sleep state-associated modulation) and pathological (OSA, atrial fibrillation) factors
3. Sleep may modulate expression of stroke symptoms and may exert a neuro-protective effect on ischemic cerebral lesions
4. Advanced multimodal imaging allows to select wake-up stroke patients with salvageable brain tissue
5. Reperfusion therapy including intravenous thrombolysis or endovascular thrombectomy is effective in selected WUS patients

Research agenda

1. The influence of sleep disorders on the occurrence of wake-up stroke should be better elucidated and the benefit of systematic polygraphic or polysomnographic screening in WUS patients should be evaluated.
2. Consideration of circadian fluctuation in blood pressure, heart rate, and hemostasis in preventive treatments should be evaluated in order to minimize the morning-associated increased risk of vascular events
3. The optimal modalities of brain and vascular imaging in the setting of WUS should be defined in order to improve the selection of patients for safe and effective reperfusion therapy.
4. The optimal therapeutic approach should also be better defined regarding the indication of endovascular thrombectomy.

Conflicts of interest

Dr Laurent Derex received honoraria for speaking from Boehringer Ingelheim.

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