Nocturnal Deterioration after Ischemic Stroke and Autonomic Dysfunction: Hypothesis and Implications

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Key Words

Ischemic stroke · Early deterioration · Sleep · Autonomic function

Abstract

Background: A significant number of patients admitted to hospital after acute ischemic stroke deteriorate clinically. Deterioration is generally noted within the first 48 h after stroke onset. The mechanisms leading to this deterioration are not fully understood. **Summary:** One potential cause of this deterioration may be altered or impaired autonomic function. We expect the hemodynamic changes regulated by the autonomic nervous system that are dysregulated after stroke to be exaggerated during sleep, resulting in arrhythmia and blood pressure fluctuations in these patients. Such physiological changes could result in worsening the overall outcome of the ischemic stroke patient or in sudden death. Therefore, it is necessary to summarize yet unrelated observations and hypothesize on their individual effects and interactions as they relate to poststroke deterioration. **Key Messages:** If the hypothesis is correct that dysautonomia occurs to the degree that it affects clinical outcomes negatively, this would have important implications for the prevention of neurological deterioration and sudden death after ischemic stroke.

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Introduction

Clinical deterioration after acute ischemic stroke occurs mostly within the first 48 h after stroke onset and overnight [1]. Stroke is one of the leading causes of all death globally [1, 2], with stroke victims often recovering from the initial ischemia only to decline suddenly and unexpectedly [3]. Potential cerebral mechanisms of early poststroke deterioration are failure of collateralization, clot progression, raised intracranial pressure, seizures, recurrent stroke and hemorrhagic transformation [4, 5]. Sykora et al. [6] (2009) hypothesized that stroke-related autonomic imbalance may promote secondary brain injury due to local inflammation, hyperglycemia or altered cerebral perfusion due to increased blood pressure (BP) variability and impaired cerebral autoregulation. Hilz et al. [7] (2011) showed that increasing stroke severity is associated with progressive decline of parasympathetic activity, baroreflex sensitivity (BRS), total autonomic cardiac modulation and increased sympathetic drive. Obstructive sleep apnea (OSA) has been independently associated with the first-ever stroke and all-cause mortality [8], and impaired sleep architecture in stroke has been associated with poor clinical outcome [9, 10].

The reasons for early deterioration remain unclear, but may be linked to cardiac complications such as ar-

rhythmia and/or BP fluctuations after stroke [7, 11]. Cardiovascular reflexes are strongly influenced by specific sleep phases [12, 13], but sleep architecture is altered in stroke [9, 10] and the association between sleep structure and cardiovascular events in stroke is not well established.

The pivotal pathophysiological mechanisms of OSA are debated, but some events are linked to cardiovascular modulation: apneic events are associated with reduced BRS during night sleep (whereas it is increased in healthy subjects) [14], and arousals are associated with increased sympathovagal balance [15] and changes of BP [16]. Ding et al. [17] (2004) found that an arousal index was inversely associated with the change in volume in white matter disease; hence, they proposed that arousal response could reflect a protective mechanism against sudden death. We expect the autonomic fluctuations that occur after stroke to be exaggerated during sleep, resulting in arrhythmias and BP fluctuations in these patients. Such mechanisms could result in worsening of clinical outcomes or in sudden death.

Sleep and Acute Stroke

Sleep Evaluation

Sleep-related complaints and disorders are common in the general population and significantly affect quality of life [14, 16]. The specific syndromes that are frequent companions of stroke and relate to risk for stroke and mortality are OSA (50–70%) and excessive daytime sleepiness (EDS, 20–40%) [17–19]. As a cerebral bioelectrical phenomenon, sleep is represented by two cycling states that are distinguished by the presence or absence of rapid eye movements (REM) [20]. Non-REM (NREM) sleep is a synchronous brain activity with four stages and is characterized by micro-arousals in cyclic alternating patterns that are transient periods of lightening of sleep depth [21]. The first stage of NREM (drowsy) is represented by mixed frequency activity; the second stage takes about half of total sleep time in adults and is distinguished by sleep spindles (12–14 Hz); the third and fourth stages are represented by slow-wave activity of 0.5–2 Hz. REM sleep is desynchronized brain activity (usually dreaming) with one stage and is characterized by atonic muscles and sawtooth waves (2–6 Hz) preceding a burst of REM. A sleep cycle (from the beginning of NREM sleep to the end of REM sleep) usually takes about 1.5 h [20]. The amount and timing of sleep and sleep stages are determined by several factors. Important

among these factors are the environment, circadian rhythms and time awake. In the assessment of daytime sleepiness and sleep efficiency, the Multiple Sleep Latency test is helpful, where sleep latency is the time from lights off until onset of each stage of sleep [22]. EEG recording of sleep can be transformed from the time domain into the frequency domain in power spectral analysis, where the EEG quantification demonstrates the distribution of power over frequency in time frame. As sleep is not only a global brain phenomenon but a local one as well, detailed sleep analysis includes examination of cerebral functional connectivity with the help of the coherence technique that measures correlation in the frequency domain [23]. Considering that sleep phases are associated with cardiac modulation by the autonomic nervous system (ANS) [12, 24] and that symptomatic presentation of sleep disorders (e.g. EDS) can be combined with pathophysiological (e.g. circadian rhythms) or systemic (e.g. breathing disturbances) manifestations, it is important to evaluate sleep in the context of intersystemic relationships (polysomnography) [25].

Association of Sleep Architecture and Stroke Outcome

In acute stroke, nocturnal brain activity is typically fragmented, and impaired sleep architecture is associated with worse short- and long-term outcome [6, 7, 10, 12]. Hachinski et al. [26–28] proposed that the presence of stage 2 of NREM sleep has a prognostic value in stroke outcome. Giubilei et al. [29] (1992) found a link between slow-wave sleep and the amount of stroke volume (positive association). In the 2002 study, Müller et al. [30] showed that slow-wave activity low-ratio NREM/wakefulness negatively correlates with stroke severity. Bassetti and Aldrich [9] (2001) noted that patients with poor short-term outcome had less NREM stage 2 and a significant reduction in well-developed sawtooth waves compared with patients with good short-term outcome. Gottselig et al. [31] (2002) found an association between the power and coherence of sleep spindle frequency activity and long-term stroke outcome. Urakami [32] (2009) showed that reduced spindles were associated with an absence of activation in the ipsilateral hemisphere.

Autonomic Dysfunction and Acute Stroke

The ANS has been extensively implicated in the triggering of sudden death [33]. The reason for sudden death remains unclear, but may be linked to cardiac complications such as arrhythmias and BP changes in stroke [7, 11]. Davies et al. [34] (1994) found that OSA patients have nondipping BP; thus, they suggested that a sleep-

related rise in BP may contribute to the excess cardiovascular morbidity and mortality experienced by patients with OSA. Selic et al. [35] (2005) showed that OSA contributes to the overall poststroke increase of systolic and diastolic BP during the first 3 days after stroke onset. The authors confirmed that nondipping BP independently results in greater stroke severity and poor outcome. In acute stroke, systolic BP has increased variability; elevated at stroke onset, it suddenly declines (the higher the initial BP the greater the decline) within a 3- to 10-day period [36, 37].

Sympathetic overactivity plays a key role in the development of essential hypertension [38]. Normotensive OSA patients have higher heart rate and norepinephrine plasma levels at rest during wakefulness and a higher response of arterial BP to head-up tilt compared to controls [39]. Cortelli and Provini [40] (2012) hypothesize that, in OSA, episodic recurrence of sympathetic surges during the night may result in adaptation of the autonomic network (chronic hypertensive state). The causes of sympathetic overactivity are multiple, but all of them have a common pathway through the neural integration of baroreceptor activity [38]. The baroreflex maintains a stable BP by adjusting the heart rate (vagal component) and total peripheral resistance (sympathetic adrenergic component) [40, 41]. BRS is reduced in acute stroke patients [37]; importantly, low BRS independently contributes to cardiac mortality [33].

Autonomic dysfunction can emerge from impaired peripheral branch (baroreceptors and sympatho/vagal activity) or from central structures (cerebral cortical and subcortical network that includes the bilateral insular cortex, anterior cingulate gyrus, amygdala and hypothalamus) [40]. Oppenheimer et al. [42] (1992) demonstrated that cardiovascular changes can be provoked by insular stimulation. Abboud et al. [43] (2006) compared insular and noninsular stroke and found that right insular stroke was associated with an increased 2-year mortality (vascular and all-cause).

Evaluation of Autonomic Function

Greater stroke severity is associated with progressive decline of parasympathetic activity, BRS and total autonomic cardiac modulation, while sympathetic dominance shows an increased drive [7]. The large prospective Autonomic Tone and Reflexes after Myocardial Infarction (ATRAMI) study [33] showed that the prognostic markers of autonomic function that are independent of other vascular risk factors are heart rate variability (standard deviation of normal-to-normal intervals) and BRS.

BRS is a quantitative description of baroreflex gain as a response of arterial BP and heart rate to a sudden increase in BP [33, 37]. Besides global assessment of BRS, it is reasonable to assess its vagal and adrenergic components separately, as baroreflex is a result of increased vagal activity and decreased sympathetic activity [44, 45]. The 'gold standard' for the evaluation of adrenergic BRS is a modified Oxford technique [46]; however, this method has limitations as it involves injections of nitroprusside and phenylephrine, and it may alter BRS via inhibition of the central nuclei [47]. The best evaluation of the adrenergic component results from direct recordings of muscle sympathetic nerve activity, but this test is not applicable for routine clinical practice; adrenergic BRS during Valsalva maneuver (VM) is expected to be a more practical measurement [41]. As altered breathing efforts (OSA) are linked to the most reduced BRS during night sleep [14, 45], and independently associated with first-ever stroke and all-cause mortality [8], we consider to evaluate nocturnal spontaneous VM in stroke as a potential prognostic marker (e.g. the more significant the pressure the greater the hemodynamic changes). Certainly, spontaneous VM in poststroke OSA could be lower than one in classical OSA due to less severe apnea-hypopnea index (AHI). In addition, AHI severity may depend upon ANS dysfunction; thus, we suggest evaluating the complex of spontaneous VM and AHI after acute stroke is reasonable.

Given the following factors: (1) BRS is a prognostic and independent autonomic marker of cardiovascular risk [33]; (2) estimation of spontaneous BRS partially includes the gain of the baroreceptors in a closed-loop system; (3) disrupted nocturnal baroreflex gain is potentially linked to the clinical deterioration after acute ischemic stroke [24, 37, 38]; (4) nondipping BP independently results in greater stroke severity and poor outcome [35], and (5) nocturnal cardiac modulation within the first 48 h after acute ischemic stroke may be responsible for the sudden clinical deterioration [1], nocturnal spontaneous BRS is a prospective early marker of stroke deterioration.

Potential Role of Autonomic Dysfunction in Nocturnal Deterioration

The physiological, neurochemical and anatomical aspects of sleep processes are a solid core for cooperation with autonomic regulation in a dynamic and synchronic way (e.g. phasic fluctuations of sympathetic and parasympathetic activity during REM sleep compared with relatively stable parasympathetic predominance in NREM) [40]. There are interesting physiological patterns of car-

Fig. 1. Normal autonomic repatterning in cardiac modulation regarding sleep phases.

Table 1. Sleep-dependent autonomic modulation

	NREM sleep	REM sleep
Normal sleep	Cardiac parasympathetic predominance [24, 27]; a slight increase in systolic BP in deep sleep (NREM 3-4) [12, 24, 64, 65]	Peripheral sympathetic activation [24], increased BP, heart rate variability and BRS [12, 44, 64, 66-68]; baroreflex control is more effective in buffering the increased sympathetic activation at the end of the night sleep [69]
OSA	Disrupted nocturnal baroreflex gain and thus increased chance of arrhythmic-ischemic events [24]	Alteration of BRS repatterning [14]

diac modulation, and one could divide them into the three groups of sleep phases: circadian (day-time wakefulness vs. night-time sleep), intraphasic (difference within NREM sleep stages) and phasic (difference between REM and NREM phases; table 1; fig. 1).

The autonomic network normally gives respiration a sleep-dependent repatterning (remarkably regular breathing in NREM sleep, but erratic in REM sleep [40]). Apneic events during REM sleep are associated with alteration of BRS phasic repatterning [14]. Disrupted nocturnal baroreflex gain during cyclic alternating patterns (micro-arousals) in NREM sleep may increase the chance of arrhythmic-ischemic events [24]. Nocturnal BRS is normally at its highest during deep sleep, but in OSA combined with EDS, it is found to be decreased [14].

Lombardi et al. [14] (2008) concluded that aggravated reduction of overnight BRS and increased sympatho-vagal balance in NREM sleep were positively associated with EDS.

As described above, sleep structure is normally associated with central autonomic regulation, with the specific behavior of cardiovascular reflexes modulating arterial BP (slight reduction or increase, changes of total variability) according to the sleep phase [12]. Within the first 3 days after onset of acute stroke, sleep structure is not only impaired but appears in a certain manner [30]. Thus, linked to the sleep structure, autonomic repatterning is also supposed to be impaired in stroke. As sleep fragmentation is linked to stroke severity [30], and NREM is the most prognostic sleep stage in stroke out-

Fig. 2. Summarized autonomic findings in sleep, which probably play a major role in stroke development.

come [9, 10], impaired autonomic repatterning may relate to poststroke cardiovascular dysfunction. Moreover, better-illuminated pathogenesis of OSA may be important for understanding the mechanisms of stroke deterioration in sleep. The insula may be implicated in generating cardiac instability, resulting in more frequent arrhythmias in stroke patients [3]; as yet, no study has been undertaken to investigate systematically acute stroke development (fig. 2).

Discussion

Occurrence of poststroke early deterioration was estimated to be from 13 to 38% in different studies [48]. Recent statistics are lesser by half compared to those of the past decade and possibly due to the impact of modern treatments and stroke unit care [49]. It is hard to rely on even modern studies due to different definitions used for worsening detection. The majority of studies have several limitations compromising the accuracy of ANS findings in acute stroke due to lack of strict randomization (population, comorbid status, ongoing treatment, imprecise stroke locations/volume, etc.). Different techniques/parameters of ANS evaluation in stroke have been used, though in the normal population the reliability of nocturnal autonomic changes and sleep patterns are not established as well. Unfortunately, there has been no evalua-

tion of the relationship between sleep architecture and ANS impairment in the first 72 h after stroke.

While our hypothesis is focused on ANS dysfunction during night sleep, it is sensitive to stroke localization. At the same time, poststroke sympathetic overactivity may reflect a general failure of regulation of cardiovascular functions (arrhythmia and BP variability) due to declining BRS or secondary brain injury worsening the infarction outcome [7]. In addition, stroke volume by itself positively correlates with NIHSS regardless of localization. We would suggest that dysfunction of both the ANS and central nervous system structures mediating arousal will correlate with more severe NIHSS, particularly the prominent sleep-regulating structures such as ‘noradrenergic’ pons (locus coeruleus) and ‘cholinergic’ thalamus (projections from pedunculopontine and laterodorsal tegmental nuclei [50]). Lesions of corticocortical afferents of the arousal system (‘melanin-, orexin-, hypocretinergic’ hypothalamus and ‘acetylcholine-, GABAergic’ basal forebrain) [50] may result in increased stroke severity due to circadian rhythm impairment. Insula, as a cerebral site of multifunctional integration, may also be a key point of sleep architecture, leading to BRS impairment, arrhythmias and deterioration in acute stroke.

Sleep-related hemodynamic changes were studied as a potential cause of nocturnal poststroke deterioration as well, but rather controversial data were obtained: the de-

cline in MCA blood flow was associated only with the duration of obstructive hypopneas but not with OSA, and correlated with the magnitude of fall in arterial oxygen saturation from baseline [51]; changes of cerebral oxygenation saturation were more profound in the unaffected hemisphere, except for oxygenated hemoglobin, than in the affected hemisphere [52]. Impaired cerebral autoregulation during wakefulness was correlated with OSA severity [53], while severe disturbances of cerebrovascular reactivity and increase of arterial stiffness in MCA are more profound during consecutive respiratory events [51].

Even though early complex sleep and autonomic evaluation may be difficult, determining pathological sleep patterns and autonomic changes during the early stages of acute stroke could alert the physician to the potential for clinical deterioration. By being aware when deterioration occurs, it may be possible to intervene either with nonpharmacological or pharmacological means by treatment of acute autonomic dysfunction (i.e. altered BP mediated by autonomic dysfunction). Unfortunately, up to now there are no evidence-based therapeutic options available highlighting the necessity for further investigation.

Hypothetically, management of sleep-modulated autonomic imbalance may correspond to brain structures involved including pontine, thalamic or cortical/insular involvement. Pontine involvement with significant REM suppression [29, 54] is accompanied by suppression of the noradrenaline system leading to sudden death [55]. It was theorized that arousals in pontine lesions may be a protective physiological mechanism against sudden death [17], assuming that noradrenergic pontine structures (including the locus coeruleus) are most active in awake states after stroke [56]. This might be a potential reason to avoid CPAP in acute pontine stroke as OSA in this case is a secondary preventive mechanism. Moreover, it might explain why CPAP does not appear to improve calculated vascular risk [57].

In contrast, thalamic lesions in stroke are characterized by 'suspending' in the drowsy state (extended NREM 1), decreased arousal index and no major REM sleep alterations [58], supposedly accompanied by exaggerated sympathetic activation with preserved parasympathetic drive to the cardiovascular system [59]. The possible approach here could be controlling nondipping BP at bedtime (chronotherapy [60, 61]) with angiotensin receptor blockers [62, 63].

Due to cerebral multifunctional association, insular lesions could be similar to cortical lesions (decreased

NREM 2–4 and REM but increased arousal index [9, 10, 29–31]), but with more severe failure of NREM-associated nocturnal BRS gain and arrhythmias. Thus, CPAP would be an appropriate strategy to reduce arrhythmic-ischemic events.

Conclusion

Polysomnographic studies in acute stroke show sleep EEG changes associated with autonomic regulation of the cardiovascular system. Altered sleep architecture in stroke correlates with stroke severity and outcome. Nondipping arterial BP, impaired nocturnal heart rate variability and BRS in OSA are linked to stroke outcome. Understanding of heart-brain interactions in sleep may have important implications for preventing stroke worsening and sudden death. We hypothesize that modification of sleep stages may improve outcome in patients with acute ischemic stroke. This may be necessary within 3 days after stroke onset, when EEG abnormalities show progressive poststroke deterioration that is linked to acute cardiovascular events including sudden death. Thus, early complex sleep and autonomic evaluation is a potential new strategy in stroke to improve clinical outcomes.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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Erratum

In the article by Kaste et al., entitled ‘Safety, tolerability and pharmacokinetics of MCI-186 in patients with acute ischemic stroke: new formulation and dosing regimen’ [*Cerebrovasc Dis* 2013;36:196–204, DOI: 10.1159/000353680], the following information was erroneously omitted:

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