



# Circadian Factors in Stroke: A Clinician's Perspective

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Received: December 14, 2022 / Accepted: March 27, 2023 / Published online: May 16, 2023  
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## ABSTRACT

Stroke remains one of the leading causes of mortality and long-term and permanent disability worldwide despite technological innovations and developments in pharmacotherapy. In the last few decades, the growing data have evidenced the role of the circadian system in brain vulnerability to damage, the development and evolution of stroke, and short-term and long-term recovery. On the other hand, the stroke itself can affect the circadian system via direct injury of specific brain structures involved in circadian regulation (i.e., hypothalamus, retinohypothalamic tracts, etc.) and impairment of endogenous regulatory mechanisms, metabolic derangement, and a neurogenic inflammatory response in acute stroke.

Moreover, the disruption of circadian rhythms can occur or exacerbate as a result of exogenous factors related to hospitalization itself, the conditions in the intensive care unit and the ward (light, noise, etc.), medication (sedatives and hypnotics), and loss of external factors entraining the circadian rhythms. In the acute phase of stroke, patients demonstrate abnormal circadian variations in circadian biomarkers (melatonin, cortisol), core body temperature, and rest-activity patterns. The approaches aimed at the restoration of disrupted circadian patterns include pharmacological (melatonin supplementation) and non-medication (bright light therapy, shifting feeding schedules, etc.) interventions; however, their effects on short- and long-term recovery after stroke are not well understood.

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**Keywords:** Stroke; Brain lesion; Sleep; Circadian rhythms; Melatonin; Clock genes; Sleep disorders; Cardiovascular health; Neuroplasticity; Bright light therapy

### Key Summary Points

Increasing evidence shows that the circadian system is implicated in the regulation of processes mediating vulnerability to stroke, as well as stroke evolution and post-stroke recovery.

The interaction between the circadian system and brain damage is bidirectional, and post-stroke circadian rhythm disruption is commonly found via assessment of the circadian variation in the main circadian biomarkers and parameters. The impact of these changes on post-stroke recovery and long-term prognosis is not well established and needs further investigation.

The approaches to manage circadian disruption include medication (melatonin) and non-medication (bright light therapy and resetting molecular clocks by other external signals, such as shifting feeding schedule and physical activity). The evidence on their applicability and efficiency in patients with stroke is limited.

## INTRODUCTION

In 2022, the American Heart Association (AHA) updated and enhanced the approach to assessing cardiovascular health “Life’s Essential 8” [1]. An important update is the inclusion of sleep health as a new crucial component in optimizing and preserving cardiovascular health, because sleep metrics provide an independent additional predictive value for cardiovascular events above the original seven metrics of cardiovascular health (diet, physical activity, nicotine exposure, body mass index, blood lipids, blood glucose, and blood pressure). The AHA, mainly focusing on sleep duration, emphasizes the need for the investigation of other sleep metrics in relation to cardiovascular

health. Sleep health extends far beyond the recommended duration of sleep [2, 3], as it is a multidimensional construct with multiple interacting components (duration, timing, regularity, efficiency, satisfaction, and impact on daytime alertness) [4] and it should also be considered as a part of the circadian sleep–wake cycle. Increasing evidence highlights the important role of the circadian system in cardiovascular functioning. Based on the 2016 report of the Global Burden of Disease 2016 Lifetime Risk of Stroke Collaborators, the global lifetime risk of stroke for both men and women aged 25 years or older has been increasing in the last 3 decades and is estimated at 25% [5].

This review will focus on the role of circadian factors in stroke, which remains one of the leading causes of mortality and long-term disability worldwide [6, 7]. It is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

## CIRCADIAN PATTERN OF STROKE OCCURRENCE

### Circadian Timing in Different Stroke Types

Like other major cardiovascular events, the incidence of stroke demonstrates an uneven circadian pattern with two peaks, a major one in the morning, between 06:00 and 12:00 [8–11], and a lower one in the evening [12]. A meta-analysis of 31 publications assessing the circadian timing of 11,816 patients showed such a double-peak distribution in both ischemic and hemorrhagic strokes, although it is more clear in ischemic stroke, and it is independent of age, gender, vascular risk factors (such as hypertension, diabetes mellitus, hyperlipidemia, smoking habits), prior cerebrovascular or cardiovascular events, and previous treatment with antiplatelet or anticoagulant drugs. In ischemic stroke, the morning peak is typical for all TOAST stroke subtypes, but is most pronounced in the large artery atherosclerosis subtype [10]. However, the National Institute of Neurological Disorders and Stroke (NINDS) rt-

PA Stroke Trial did not find clear circadian variation in the onset of ischemic stroke which might be due to the selection bias as patients admitted to the hospital later than 3 h after symptoms onset were not included in this study [13].

### Stroke Occurrence Timing and Prognosis

Although experimental studies confirm the association of both occurrence and brain lesion volume with the time of stroke onset [14], the clinical data on the association between the stroke occurrence time and the prognosis is limited. A retrospective analysis of 3689 patients demonstrated that night-onset stroke survivors had a worse 30-day prognosis, compared to the patients with day-onset strokes. This association was present only in ischemic strokes, and among those, only in the cardioembolic subtype. The difference in the prognosis was explained by the limited therapeutic window for thrombolytic therapy [15]. Similar conclusions were made on the basis of the results of the prospective NINDS rt-PA Stroke Trial [13]: patients with the stroke onset between 00:00 and 06:00 were less likely to get treatment within 90 min. In a recently published large Korean study ( $n = 17,461$ ), night-onset strokes were more severe and were associated with higher rates of early neurological deterioration and a lower likelihood of a favorable functional outcome compared to day-onset strokes independent of other covariates and revascularization therapy. The association of night-onset (versus day-onset) strokes with early neurological deterioration was significant and most pronounced in the large artery atherosclerosis subtype compared to other stroke subtypes [16]. On the basis of the data from the Japanese Takashima Stroke Registry, morning-onset strokes were associated with a significantly higher risk of a 28-day lethal outcome compared to afternoon-onset strokes independently of age, gender, and stroke severity [17].

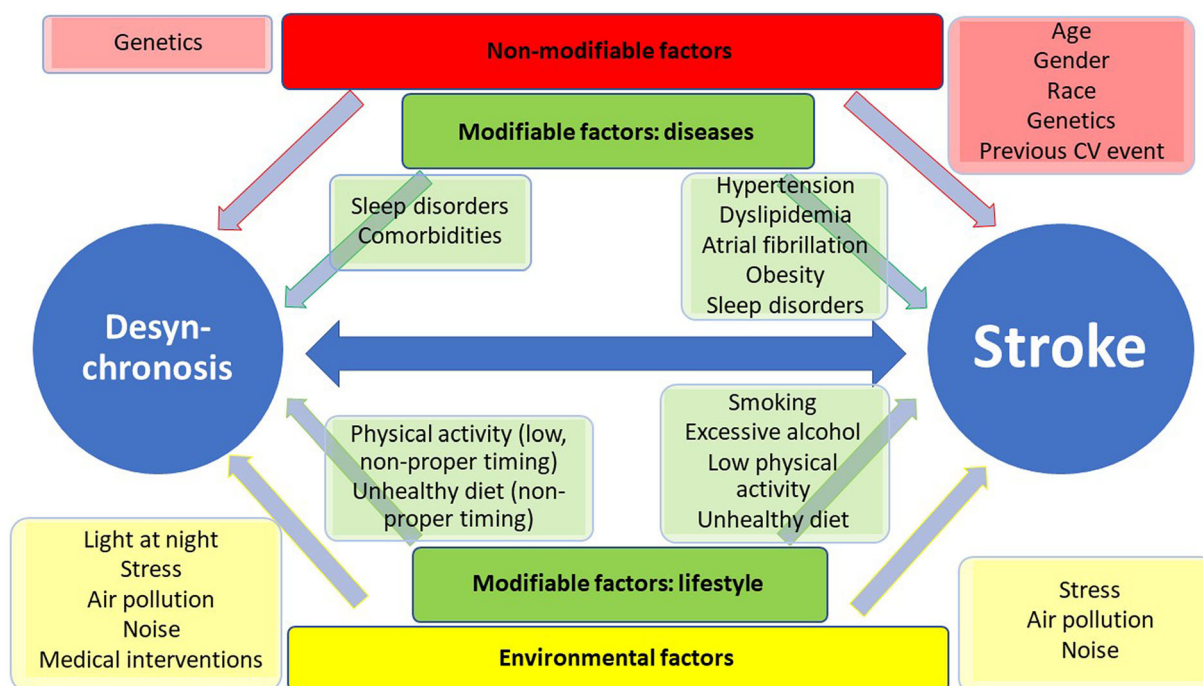
The explanations for the diurnal pattern of stroke occurrence include circadian and/or postural changes in some pathophysiological

factors observed at awakening and resumption of physical and mental activities such as increased platelet aggregation, decreased thrombolysis, proinflammatory factors, surges of blood pressure (BP) and heart rate (HR), and higher catecholamine levels, reflecting a peak in circadian sympathetic activity along with the increased activity of the renin–angiotensin–aldosterone system [18, 19].

### Circadian Misalignment in Stroke: Cause or Consequence?

Both experimental and clinical studies provide evidence of the impact of circadian misalignment on stroke development (Fig. 1), including an increase in the brain lesion volume, demonstrated worse functional dysfunction, and higher mortality which is likely due to the imbalance in the expression of pro- and anti-inflammatory cytokine genes in the brain [20–22]. However, some authors suggest that single light-induced circadian disruption is not potent enough to cause increased cerebral vulnerability to ischemia, and other concomitant factors or diseases are required [23]. Cantone et al. demonstrated that exogenous air pollution could lead to the reprogramming of the molecular circadian system (clock genes), which is associated with the severity of subsequent stroke (assessed by the National Institutes of Health Stroke Scale (NIHSS) score) and 3-month disability (evaluated by the modified Rankin Scale, mRS) [24].

The circadian misalignment appears to be a potential risk factor for cardiovascular events including stroke. Even short-term (12-h) circadian misalignment simulating a shift-work inversion of the behavioral cycle results in the increase in 24-h BP, reduced BP dipping, enhanced inflammatory markers (such as C-reactive protein, tumor necrosis factor alpha, resistin, and interleukin-6), and caused autonomic imbalance with diminished parasympathetic tone [25]. In a large Japanese cohort ( $n = 78,115$ ), a self-reported irregular daily routine was significantly associated with an increased risk of incident cardiovascular diseases including stroke in women but not in men



**Fig. 1** Association between stroke and circadian misalignment (desynchronization)

[26]. A meta-analysis of five studies by Li et al. did not find an increased risk for the development of ischemic stroke (non-significant combined RR, 1.03; 95% CI 0.99–1.07) [27]. However, the association between shift work and incident stroke might be modified by the genetic variants, i.e., melatonin receptor type 1B (*MTNR1B*) rs10830963 polymorphism (G-allele displaying a protective role while C-allele being unfavorable) or other factors [28].

Abnormal patterns in the circadian variation of BP (non-dipping or extreme dipping [18, 19]) and HR [29] observed in diseases (and sometimes considered a sign of circadian misalignment) represent predictive factors for stroke, independently of awake and sleep systolic BP [30, 31]. On the other hand, the available evidence indicates that the abnormal circadian BP patterns in acute stroke can develop secondary to stroke resulting from the stroke-related autonomic imbalance. Thus, patients in the acute phase of stroke demonstrate diminished BP variability throughout 24 h and decreased day–night BP difference. These abnormalities correlate with the changes in the circadian variability in other neurohumoral factors, in

particular, the levels of endothelin-1 and brain natriuretic peptide (BNP) [32–34]. Patients with acute stroke also demonstrate increased catecholamine levels. The loss of the circadian BP profile and non-dipping patterns are also common (up to 90% of patients with stroke) [35–38]. Some authors report the association between the abnormal circadian BP pattern and the specific location of the brain lesion [33, 36] and other characteristics (e.g., the presence of cortical microbleeds [39], asymptomatic lacunar infarcts [40], and other signs of small vessel disease [41], brain atrophy [42]), although the data are controversial. Some results suggest that post-stroke survivors with abnormal circadian BP profiles (non-dippers, reverse dippers) are more likely to have a poor outcome [38], although some reports are conflicting [43]. Makikallio et al. found elevated levels of cortisol and natriuretic peptides in half of patients with stroke who died during the follow-up versus stroke survivors. Cortisol levels were associated with atrial natriuretic peptide (N-ANP) and N-BNP levels, catecholamine levels ( $r = 0.55–0.94$ ,  $p < 0.01$  for all), and measures of neurologic deficit ( $r = 0.36–0.44$ ,  $p < 0.05$ ) on

the 2nd and 7th days. High acute-phase cortisol levels assessed either in the morning (RR = 5.4,  $p < 0.05$ ) or in the evening (RR = 5.8,  $p < 0.05$ ) predicted long-term mortality after stroke analysis [44].

An imbalance in prothrombotic (plasminogen activator inhibitor 1, PAI-1) [45] and antithrombotic (tissue factor pathway inhibitor) [46] factors, which show clear antiphase 24-h rhythms independent of the sleep–wake cycle, may play a contributing role to circadian variation in stroke occurrence [47].

The potential impact of sleep-related factors and disorders should be also considered. The autonomic instability and abrupt surges of sympathetic activity are typical in REM sleep periods that are the longest in the early morning hours before awakening [48, 49]. Sleep disorders per se can be a contributing factor, and among them, sleep apnea is the most significant. Untreated severe OSA doubles the risk of stroke. According to expert consensus, the role of insomnia, periodic limb movements, and circadian misalignment is disputable and lacks solid evidence [50].

On the other hand, the stroke itself can result in the disruption of circadian rhythms. Direct cerebral injury, compression of hypothalamic structures, and impairment of endogenous regulatory mechanisms, as well as changes in cerebral blood flow, metabolic derangement, and a neurogenic inflammatory response are the main factors underlying circadian disruption in acute stroke. In addition, the disruption of the diurnal sleep/wake pattern due to exogenous factors, such as hospitalization itself, the conditions in the intensive care unit, light conditions, loss of external zeitgebers of circadian rhythm, and the use of sedative or hypnotic drugs can affect circadian patterns [51, 52].

## CIRCADIAN SYSTEM AND STROKE

### Circadian System Structure and Regulation

In mammals, the circadian system comprises a master pacemaker located in the

suprachiasmatic nucleus (SCN), which coordinates and synchronizes cellular clocks in various tissues and organs.

The circadian system is self-regulated and at the cellular level functions via interaction between circadian genes (the core genes include *CLOCK*, *BMAL1*, two cryptochrome genes *CRY1* and *CRY2*, three period genes *PER1*, *PER2*, *PER3*) and their protein products. The oscillation cycle of the transcription–translation feedback loop is about 24 h entrained by the light–dark cycle. The positive arm of the feedback loop involves the protein products of circadian genes *CLOCK* (or *NPAS2* in brain tissue) and *BMAL1*. They form a heterodimer in the cytoplasm which is translocated to the cell nucleus where it binds to the E-box promotion region of the circadian genes *Period* (*PER*) and *Cryptochrome* (*CRY*) driving their translation. In the negative arm of the loop, the *Per* and *Cry* proteins form a heterodimer in the cytoplasm translocating to the nucleus, where it binds to the complex *Clock*–*Bmal1* and thereby suppresses the transcription–translation cascade [53, 54]. Another pair of a regulatory loop includes circadian genes encoding nuclear receptors *Rev-erb $\alpha$*  and *RAR*-related orphan receptors (*ROR $\alpha$* ) binding the promoter of the *BMAL1* gene.

Routinely, the external signals reset molecular clocks, and the main synchronizer is light (photic signals); however, the circadian clocks (in particular, peripheral ones) can be also entrained by neural, humoral, and metabolic (food-induced) signals [55].

### Circadian Genes in Stroke

Circadian genes can play a role in stroke incidence, evolution, and recovery via direct modulation of neuronal damage and recovery and their impact on various cardiometabolic factors and processes [47, 56–58]. Clock genes modulate microglia activation [59] and neuroinflammation [60, 61], thus regulating the vulnerability and tolerability to brain injury, demonstrating neuroprotective effects [62–65].

The G-allele of the *CLOCK* gene was shown to be protective against stroke in the PREDIMED (PREvencion con DIeta MEditerranea) trial



cohort; however, it is noteworthy that the association between the *CLOCK* gene rs4580704 single nucleotide polymorphism (SNP) and stroke risk was found only in the subcohort of patients with type 2 diabetes mellitus [66], but not in subjects without diabetes. Other genetic variants of the *CLOCK* gene were shown to be involved in the metabolic traits pathways [67], suggesting the potential impact of the *CLOCK* gene on cardiovascular risk.

Circadian genes are involved in vascular function, tone regulation [68, 69], coagulation factors, and thrombogenicity [70, 71] as shown by experimental and clinical studies. It is noteworthy that different circadian genes have a discrete impact on the circadian variation of these factors. Thus, some authors suggest that *Bmal1* and *CLOCK* are essential for circadian blood pressure oscillations while *NPAS2* is important for the precise timing of the rhythmic variability in the presence of *CLOCK* and can substitute the latter one in the case of *CLOCK* gene mutation/deficiency [68, 69]. *CLOCK* and *BMAL1* are essential for maintaining a diurnal variation in thrombogenesis, PAI-1 expression, and display opposite effects on time to vessel occlusion [70, 71].

*PER2* mutation is associated with impaired endothelial function independent of cardiometabolic risk factors, as well as the alteration in a diurnal change in endothelial-mediated vascular response. On the other hand, the deficiency of *PER2* plays a cardioprotective role due to a lower apoptosis rate and lower macrophage infiltration [56, 72, 73]. This can be partly explained by the hypoxia-independent but hypoxia-inducible factor 1-alpha (HIF-1 $\alpha$ )-mediated upregulation of vascular growth factors and angiogenesis [74]. One can hypothesize that in various tissues, deficiency or impairment of circadian genes might have different effects playing either protective or deleterious roles depending on the synchronization/desynchronization state between the SCN and peripheral clocks, as well as other factors.

Alternatively, clock genes are tuned via DNA methylation, one of the mechanisms of gene expression regulation [75] that is sensitive to environmental pollution, e.g., particulate matter. In 55 patients with acute stroke, Cantone

et al. evaluated the effects of exposure to particulate matter experienced before stroke on clock gene methylation levels, in order to investigate their possible role in modulating patients' prognosis after the event. They found that clock gene methylation was modified by short-term particulate matter exposure. Moreover, DNA methylation of the studied clock genes (i.e., *CRY1*, *PER1*) was associated with the neurological disability assessed by mRS [24]. An increased level of low-grade inflammation and prothrombotic state is suggested as the biological link between exposure to pollutants and deteriorating cardiovascular health and can be mediated by DNA methylation at clock genes.

### Assessment of Circadian Rhythm Parameters in Stroke

#### *Challenges in Circadian Rhythm Evaluation in Patients with Stroke*

The evaluation of the circadian profile includes various approaches, i.e., subjective (questionnaires, e.g., Horne–Östberg Morningness Eveningness Questionnaire (MEQ) and the Munich Chronotype Questionnaire (MCTQ); sleep logs) and objective ones (laboratory biomarkers such as melatonin, cortisol diurnal patterns; rest-activity periods by actigraphy; core body temperature pattern, etc.). However, in patients with stroke, implementation of these methods can be limited because of neurological deficits (altered consciousness, cognitive decline, amnesia, aphasia, etc.) and other post-stroke changes. Thus, paresis, low activity, as well as micro-movements of the limbs can impede the actigraphy results [76], although recent developments suggest various solutions to overcome these problems (i.e., armband devices [76] or ankle fixation of the device [77, 78], the calculation of specific indices, such as the Asymmetry Rate Index [79] for detecting the asymmetry of spontaneous movements between the paretic and non-paretic arm; or the Proportional Integrating Measure [80] which is the ratio between the mean motor activities of both arms [67]). Post-stroke xerostomia prevalent in up to 50–60% of stroke survivors [81] might limit saliva sampling, while post-stroke

hyperthermia (a common feature in diencephalic strokes) can affect the circadian profile of core body temperature [82, 83]. Melatonin is a reliable circadian marker not affected generally by the sleep–wake cycle, mood changes, stress factors, etc. Cortisol displays a clear circadian variation, although the influence of some environmental factors can be significant. Moreover, the results may vary depending on stroke characteristics, such as stroke severity, location, the phase after stroke onset (acute, subacute), etc. [84].

### **Cortisol**

The diurnal pattern of cortisol is commonly disturbed and the cortisol levels are elevated in acute stroke compared to reference levels, while they tend to normalize 1 month post-stroke [85, 86]. The elevated cortisol is associated with a worse prognosis, more severe motor dysfunction [87], and post-stroke complications, including post-stroke depression [88]. Murros et al. found that evening cortisol (19:00 at baseline and 1 week after admission to the hospital) better predicted the prognosis and severity of neural deficit than morning cortisol (07:00) [87]. Also, patients with a more severe stroke demonstrate a loss of the circadian pattern [85, 89] or a more disturbed diurnal variation of cortisol, compared to mild strokes [90, 91]. The majority of studies evaluated cortisol once or twice daily [85–88], with only a minority performing multiple measurements [90, 91] during the day. The latter confirms that in a non-severe stroke, the circadian variations of cortisol are preserved although they demonstrate an advanced circadian rhythm with elevated values at each time point compared to controls [64].

### **Melatonin**

Similarly, the majority of studies vary by time of the collection of samples, the type of biosamples (serum, saliva, urine), the method of melatonin assessment, etc., which limits the direct comparisons of the results. The majority of studies report abnormal melatonin levels and/or patterns in patients with stroke [92–94]. Thus, in a cohort of 127 patients with anterior

strokes, the urinary excretion of both melatonin and its metabolite 6-sulfatoxymelatonin was significantly reduced compared to healthy individuals [93]. Fiorina et al. showed decreased levels of nocturnal melatonin urinary excretion independent of the size of the cortical lesion which remained low by the 14th day post-stroke [94]. The lesions in the brainstem, lateral and third ventricles, basal ganglion, frontal, frontoparietal, and parietotemporal lobes are associated with the abolished circadian rhythm of melatonin [89]. On the other hand, Beloosesky et al. found a similar total 24-h amount of melatonin in patients with stroke and controls, with the preserved although 4-h delayed melatonin secretion in the first post-stroke days and restoration of the normal pattern by the 10th day after stroke onset [95]. It should be noted that this study included patients with extensive cortical and deep strokes of both hemorrhagic and ischemic types. The authors explain the delayed rhythm of melatonin by potential impairment in light perception at the SCN and consider it as a factor contributing to post-stroke hypothalamic-glandular axis dysregulation. In moderate stroke, not involving directly the regions regulating melatonin pineal production, the circadian rhythm of serum melatonin is sustained [90, 91], demonstrating a clear although flattened periodic pattern [64]. Adamczak-Ratajczak et al. hypothesize that the lower levels of melatonin are due to its increased rapid utilization for the reduction of oxidative damage within the acute phase of cerebral ischemia [91]. Some authors demonstrated that lower levels of melatonin were associated with a worse prognosis (higher 30-day mortality) [96].

The disruption of the circadian pattern of melatonin in patients with stroke can be related to direct damage to SCN or brain areas participating in the regulation of SCN (paraventricular nucleus of the hypothalamus (PVN), and intermediolateral nucleus of the spinal cord (IML), the thalamic intergeniculate leaflet (IGL), raphe nuclei, parietal cortex) [97, 98] and pineal activity or indirect influences [95], or disorder in autonomic regulation [99].

### **Core Body Temperature**

Acute brain damage is associated with the increase in body temperature and a disruption or inversion in the core and brain temperature rhythm [82, 100–103] (in particular, in lesions involving the frontotemporal area, hypothalamus, and brainstem [104]). In patients with stroke, the rise in body temperature starts 4–6 h after stroke onset and is related to initial stroke severity, usually observed in major strokes and not evident in patients with mild-to-moderate strokes, although some controversial data are reported depending on the time of temperature measurement, stroke severity, etc. [105, 106]. Hyperthermia within the first 24–72 h after stroke onset (but more than 6–8 h after stroke onset) has an unfavorable prognostic impact being a negative predictor of the 3-month outcome [105, 107, 108]. At the same, time low body temperature at admission less than 6 h after stroke onset is associated with more severe stroke (which some authors explain by the possible detrimental effect of lower temperature on clot formation and lysis) and a negative prognosis at discharge [109] and at a long-term follow-up [108, 110]. In a retrospective study [111], the peak body temperature positively correlated with the NIHSS score, female gender, rectal (vs. tympanic) temperature, dysphagia assessed by swallowing test, intubation, high C-reactive protein or signs of infection at admission, and antipyretic treatment within 48 h.

However, only a few studies evaluated circadian variation in body temperature in patients with stroke. Some clinical observations indicate a severe disruption of temperature circadian rhythms [112]. It seems that the circadian rhythm disruption is more prevalent and profound in more severe strokes, in particular those causing the development of disorders of consciousness when both basal temperature and brain temperature rhythms are severely disrupted (or completely absent) [82, 102, 113]. This observation is confirmed by Takekawa et al. in a mixed group of patients with ischemic cardioembolic stroke ( $n = 11$ ) and cerebral hemorrhage ( $n = 22$ ). The circadian rhythm was preserved in conscious patients while infradian rhythms of body temperature with a periodicity

of approximately 2.5 days (28.6–125.6 h; median 59.7 h) were present in those with disturbed consciousness (39% of patients). They did not find any association between the circadian vs. infradian rhythm and lesion location, but there was a correlation with the mRS. In a larger cohort of patients with stroke mainly with preserved consciousness ( $n = 50$ ), the same group found a strong correlation between the mRS at a 3-month follow-up and the disruption of the circadian rhythm assessed by both rectal temperature and wrist motor activity (by an accelerometer) independent of the mRS at admission. No association was found between the diurnal rhythm and the brain lesion location.

### **Rest–Activity Patterns**

The majority of studies of actimetry data in patients with stroke are focused on the assessment of physical activity patterns [114–116] or sleep parameters [117–120], and only a limited number of papers consider actigraphy-evaluated diurnal rhythmicity metrics in post-stroke survivors, such as interdaily stability (IS, characterizing the day-to-day stability of activity patterns); intradaily variability (IV, evaluating the fragmentation of activity rhythms); and the amplitude of rest–activity rhythms [121]. Gonçalves et al. showed that patients with cerebrovascular events had more fragmented rhythms and reduced activity, compared to controls [122]. An autopsy study by Sommer et al. demonstrated that more disrupted 24-h rest–activity rhythms were associated with a higher burden of arteriosclerosis and subcortical infarcts at death in subjects with verified small vessel disease [123]. In the Rotterdam study, Zuurbier et al. demonstrated an association between small vessel disease and 24-h rhythm fragmentation independent of sleep parameters, although lacunar infarcts were not associated with any of the diurnal rhythmicity measures [124]. The association between 24-h rhythm fragmentation and stroke characteristics and prognosis remains unclear.

The fragmentation of the 24-h rhythm is in accord with sleep–wake disturbances often found in stroke survivors. Bakken et al. investigated sleep–wake patterns and found a large



variation in sleep during night-time within the first 2 weeks after stroke occurrence with sleep disturbances registered more often in men than in women [118]. Stroke survivors in the chronic post-stroke phase spend more time in bed with the intention of sleeping and actually asleep and significantly more time awake overnight than healthy controls; however, these measures were unrelated to the severity of motor impairment [120]. It was shown that the derivative indices calculated as ratios between 24-h motor activity registered from both affected and unaffected arm better predicted the prognosis in post-stroke survivors [80, 125]. Thus, the Asymmetry Rate Index correlates with the NIHSS [79] and 3-month mRS [125], while the Proportional Integrating Measure predicted the mRS at 3 months [80].

### **Circadian Gene Expression**

Critically ill patients with hemorrhagic stroke demonstrate complete loss of rhythmicity in circadian gene (*CRY1*, *CRY2*, *PER1*, *PER2*, *PER3*, *RORA*, *NR1D1*, *BMAL1*, *CLOCK*, and *TIMELESS*) expression in peripheral tissues and no correlation with either rest–activity rhythmicity or melatonin rhythm [83]. The severity of encephalopathy and exposure to adrenergic agonist medications appear to be the main factors contributing to these changes [126, 127].

On the other hand, patients with mild-to-moderate stroke seem to have preserved diurnal variation in peripheral clock genes (*NR1D1*, *PER1*, *PER3*, *BMAL1*), although they demonstrate specific circadian desynchrony in both positive and negative loops of the circadian system, correlating with the diurnal changes in melatonin and cortisol levels [90]. The association of these changes with prognosis and treatment effects is unknown.

## **CIRCADIAN SYSTEM AND POST-STROKE RECOVERY**

The circadian system is involved in the regulation of tissue repair and regeneration after the injury. Glial cell populations play a crucial role in neuronal recovery after brain injury and display both beneficial and detrimental effects

on the ischemic lesion zone [128, 129]. *Bmal1* regulates the activation of microglia [130] and astrocytes [131]. Clock genes modulate glutamate uptake by regulating the expression and activity of its transporters, thus being involved in excitotoxicity [132] and neuronal cell death regulation [133]. No less important is the involvement of the circadian gene in the regulation of inflammatory response, including the immune function, i.e., trafficking of immune cells, phagocytosis, secretion of cytokines, chemokines, and other factors [61, 72, 74, 132, 134, 135].

Angiogenesis is an important factor for post-stroke recovery, and it is tightly related to the activation and functioning of glial cells [136]. Clock genes (in particular, *Cry1/2*) are involved in the regulation of different stages of the angiogenesis process [137, 138]. Multiple angiogenic factors are implicated in the post-stroke angiogenesis, and vascular endothelial growth factor (VEGF) is a protein that is a well-known factor regulating and inducing angiogenesis in various pathological conditions and is associated with elevated transdifferentiation of reactive astrocytes into neuroprogenitors and new neurons [139]. Low-level light at night can lead to a reduction in the hippocampal expression of VEGFA and brain-derived neurotrophic factor (BDNF) and increased VEGFR1 [140].

Clock genes *Rev-erb $\alpha$*  and *ROR $\alpha$*  modulate the expression of antioxidant enzymes and reactive oxygen species production [141] and can play a protective role in the inflammatory response of microglia [142, 143].

The neurotrophic factors involved in the regulation of post-stroke recovery demonstrate clear 24-h rhythmicity, although influenced by other endogenous factors (i.e., levels of sex hormones) [144]. One of these factors, BDNF, can modulate circadian system functioning via the regulation of SCN plasticity [145, 146]. BDNF could act via GABA ( $\gamma$ -aminobutyric acid), NMDA (*N*-methyl-*D*-aspartate), or AMPA ( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) transmitter systems and regulate the light-induced circadian resetting of the SCN pacemaker. Local paracrine interactions between BDNF and TrkB receptors could provide an endogenous signaling pathway for the

intercellular regulation of cellular and metabolic activity within the SCN and thus for pacemaker cell synchronization [145, 147].

## CIRCADIAN SYSTEM AND TREATMENT DEVELOPMENTS IN STROKE

### Pharmacotherapy Development

#### *Chronotherapy Approaches*

Several therapeutical interventions are being discussed in relation to circadian system functioning in stroke. First, chronotherapy approaches [148], in particular for antihypertensive medications, are promoted by some groups of authors, although recent evidence does not provide any benefit of evening vs. morning administration of antihypertensive drugs regarding long-term cardiovascular outcomes [149, 150].

Other treatments (antiplatelet [151], anticoagulants [152], thrombolytic drugs [153, 154], etc.) might have a greater capacity within the chronotherapy approach, although further investigation is needed [47]. Thus, as mentioned above, there is strong evidence confirming circadian variation in the activity of fibrinolytic and prothrombotic factors, in particular, the balance between the tissue plasminogen activator (tPA) and its inhibitor, the tissue plasminogen inhibitor-1 (PAI-1). The latter shows peak concentrations in the morning, which can contribute to a higher risk of atherothrombotic events, as well as to the lower efficiency of fibrinolytic treatment. In a retrospective analysis, diurnal (from 09:00 to 21:00;  $n = 92$ ) tPA treatment (intravenously administered alteplase 0.9 mg/kg, 10% in bolus, 1 h infusion) was associated with higher rates of middle cerebral artery (MCA) complete recanalization assessed by transcranial duplex compared to the group which was treated during the night period (from 21:00 to 9:00;  $n = 43$ ): 45.6% vs. 23.2% ( $p = 0.01$ ). Moreover, those treated during the day demonstrated better 3-month clinical outcomes evaluated by the mRS [153]. However, the NINDS rt-PA

Stroke Trial ( $n = 624$ ) did not find any association between the stroke onset time (and rt-PA treatment given within 3 h of stroke onset) and 3-month outcomes, although there was an association with the occurrence of a symptomatic intracranial hemorrhage within 36 h: patients with stroke onset between 04:01 and 08:00 who received rt-PA had a lower risk of having a symptomatic intracranial hemorrhage [13]. Some authors explain such an effect by the endogenous circadian rhythm in blood–brain barrier permeability, which shows reduced trafficking during the active phase compared to other periods during the day [154].

The data regarding the protective effects of antiplatelet drugs (in particular, low-dose aspirin) [155] administered depending on the time of the day are rather conflicting [151, 156].

#### *Melatonin Supplementation*

Second, the modulation of the circadian rhythm by *melatonin supplementation* has been widely discussed in the last decade. Acting via MT2 receptors, melatonin provides a number of neuroprotective effects including antioxidant, anti-inflammatory, antiexcitotoxic, antiapoptotic, and other properties [157–159]. In animal models, exogenous melatonin reduces the brain lesion size and neural loss [160, 161] and improves functional outcomes [162, 163], which can be related to the decrease in ischemia–reperfusion injury via modulation of the circadian gene expression leading to the phase-delayed expression of *PER1*, *PER2*, and *Cry1*, as well as expression of genes involved in hypoxia-mediated signaling pathways [164, 165]. Moreover, melatonin alleviates circadian disturbances and improves sleep, increasing delta power and decreasing sleep fragmentation in rats after an induced stroke [166]. In clinical settings, melatonin supplementation was associated with a lower risk of post-stroke delirium (a single dose of 2 mg/day at 20:00 within the first 24 h of ischemic stroke onset) compared to the control group [167] and with the shorter duration of mechanical ventilation and length of stay in the intensive care unit in a cohort of patients with hemorrhagic stroke (30 mg melatonin every night during a stay at the intensive care unit) [168]. In early

and late rehabilitation periods, melatonin administration (3 mg daily for 3 months) led to an increase in the BDNF level that correlated with improved sleep, emotional status, and quality of life [169, 170]. Regarding effects on functional outcomes, a pilot randomized study showed that 5-day treatment with melatonin in the acute phase of stroke led to a greater reduction in median NIHSS score, but not in mRS at a 3-month follow-up [171]. Ongoing trials aim to investigate both short- and long-term effects of melatonin in patients with stroke: Role of Melatonin in the Acute Phase of Stroke as Measured by Interleukin 6 Biomarker, NCT03843008; The Role of Circadian Factors in Regulation of Neuroplasticity in Ischemic Stroke (Interventional), NCT05247125.

### Non-Medication Developments

A number of *non-medication interventions*, which can reset molecular clocks and modulate circadian rhythms, draw attention as potential neuroprotective strategies, in particular, bright light therapy, physical exercise, and shift in food intake.

#### **Bright Light Therapy**

*Bright light therapy* exhibits various effects including mood improvement (even included as a complementary or alternative treatment for depressive disorders, in particular, for seasonal depression, by various professional associations [172, 173]), increasing alertness, and reduction in fatigue and sleepiness in different cohorts [174]. However, only a few studies evaluated the effects of light in post-stroke survivors, and the evidence on long-term effects is lacking. In a placebo-controlled randomized study, light therapy (10,000 lx, 30 min in the morning) was shown to decrease insomnia symptoms, daytime sleepiness, and fatigue, and improve the emotional state in post-stroke survivors [175]. In post-stroke rehabilitation, naturalistic light in the ward was associated with reduced fatigue, increased levels of melatonin, and present diurnal rhythmicity by discharge, while patients staying at standard indoor light at rehabilitation did not exhibit melatonin diurnal

rhythmicity at discharge [176]. However, the study was uncontrolled and no long-term follow-up after discharge was performed. In a study involving patients with past brain injury, including post-stroke subjects in a chronic phase of stroke, bright light therapy was associated with a reduction in subjective sleep quality (sleep disturbance and insomnia symptoms) and improved psychomotor vigilance [177]. More data is expected from the ongoing trials assessing bright light therapy effects in patients with stroke: Role of Melatonin in the Acute Phase of Stroke as Measured by Interleukin 6 Biomarker, NCT03843008; The Role of Circadian Factors in Regulation of Neuroplasticity in Ischemic Stroke (Interventional), NCT05247125; Effects of Colored Light Exposure on Sleep Disturbance, Fatigue, and Functional Outcomes Following Acute Brain Injury, NCT03125967.

#### **Gene Therapy**

Last but not least, *gene therapy* presents a promising neuroprotective approach being investigated in animal models [178–180], and clock genes are a candidate potent target.

## CONCLUSION

Despite the increasing evidence of the bidirectional influence of the circadian system and brain damage in stroke, there are a number of gaps in understanding the precise underlying mechanisms. Moreover, the data on the 24-h variation of the main circadian biomarkers and parameters in patients with stroke in acute, subacute, and chronic phases are rather scarce, and their clinical implications and association with the prognosis are not fully understood. The implementation of various approaches and techniques for circadian rhythm entrainment in patients with stroke appears to be a promising complementary treatment for improving post-stroke recovery. However, the criteria to select the subgroups of patients who will benefit most from these interventions are to be established.

## ACKNOWLEDGEMENTS

**Funding.** No funding or sponsorship was received for this study or publication of this article.

**Author Contributions.** Lyudmila Korostovtseva: concept, draft preparation, revision; Sergey Kolomeichuk: revision, final approval of the text.

**Disclosures.** Lyudmila S Korostovtseva and Sergey N Kolomeichuk have nothing to disclose.

**Compliance with Ethics Guidelines.** This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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