Check for updates

Circulation Research

CIRCADIAN MECHANISMS IN CARDIOVASCULAR AND CEREBROVASCULAR DISEASE COMPENDIUM

Circadian and Diurnal Regulation of Cerebral Blood Flow

Alastair J.S. Webb, Elizabeth B. Klerman, Emiri T. Mandeville

ABSTRACT: Circadian and diurnal variation in cerebral blood flow directly contributes to the diurnal variation in the risk of stroke, either through factors that trigger stroke or due to impaired compensatory mechanisms. Cerebral blood flow results from the integration of systemic hemodynamics, including heart rate, cardiac output, and blood pressure, with cerebrovascular regulatory mechanisms, including cerebrovascular reactivity, autoregulation, and neurovascular coupling. We review the evidence for the circadian and diurnal variation in each of these mechanisms and their integration, from the detailed evidence for mechanisms underlying the nocturnal nadir and morning surge in blood pressure to identifying limited available evidence for circadian and diurnal variation in cerebrovascular compensatory mechanisms. We, thus, identify key systemic hemodynamic factors related to the diurnal variation in the risk of stroke but particularly identify the need for further research focused on cerebrovascular regulatory mechanisms.

Key Words: blood pressure ■ cardiovascular diseases ■ cerebrovascular circulation ■ heart disease risk factors ■ risk factors

Downloaded from http://ahajournals.org by on April 3, 2025

Cardiovascular events occur more frequently in the morning between 6 am and 12 noon,[1] are more common in patients with a mismatch between endogenous circadian rhythm and the environment,[2] are increased in patients with abnormal diurnal blood pressure changes,[3] and recovery from stroke may be worse if a stroke occurs at night.[4] This reflects behavior, environmental rhythms, and endogenous circadian variation in physiological mechanisms from blood clotting[5] to cardiac arrhythmias.[6] However, although there has been extensive study of diurnal variation (ie, the nonlinear combination of endogenous circadian and evoked changes from sleep/wake state, activity levels, posture, eating, and other factors) in systemic hemodynamics,[7,8] there has been limited focus on diurnal variation in cerebral blood flow (CBF) and its dependence on both systemic physiology and cerebrovascular regulatory mechanisms.

Endogenous circadian variation increases survival probability by adapting physiological needs to anticipate the influence of the earth's 24-hour cycle, with diurnal variation in systemic blood pressure as the archetypal cardiovascular example. The associated cardiovascular risk may, therefore, result either from normal hemodynamic diurnal variation, exacerbated in later life by both the increased absolute cardiovascular risk and impaired compensatory mechanisms; from pathologically abnormal circadian rhythms; and from asynchrony between endogenous circadian rhythms and the environment as we become less dependent on the natural environment. Outcomes associated with diurnal rhythms may potentially be altered by changing or minimizing some of the factors (eg, timing of activity, posture changes, or eating) that determined both these diurnal cycles and how they interact with the underlying endogenous circadian rhythms.

CEREBROVASCULAR RISKS ASSOCIATED WITH CIRCADIAN AND DIURNAL RHYTHMS

Although early studies identified an evening peak in cerebrovascular events,[9] the majority of studies have demonstrated

Correspondence to: Alastair J.S. Webb, DPhil, Department of Clinical Neurosciences, Wolfson Centre for Prevention of Stroke and Dementia, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom. Email alastair.webb@ndcn.ox.ac.uk

For Sources of Funding and Disclosures, see page 705.

© 2024 The Authors. *Circulation Research* is published on behalf of the American Heart Association, Inc., by Wolters Kluwer Health, Inc. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution, and reproduction in any medium, provided that the original work is properly cited.

Circulation Research is available at www.ahajournals.org/journal/res

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
CBF	cerebral blood flow
CVR	cerebrovascular reactivity
NO	nitric oxide
PDE	phosphodiesterase
SCN	suprachiasmatic nucleus
VSMC	vascular smooth muscle cell

a strong morning peak between 6 am and 12 noon,[10–12] with an overall increased risk of ischemic stroke of 49% compared with other times of day[1] and an even stronger association with hemorrhagic stroke.[1] The high incidence of cerebrovascular events is specifically associated with a surge in blood pressure soon after waking,[13] with a time-of-day bimodal peak in incidence in some cohorts[4,14] consistent with the bimodal variation in blood pressure. However, studies of diurnal variation in the etiological subtype of ischemic stroke have been less consistent. There is a consistent increase in morning cardioembolic and large artery strokes but a greater than expected incidence of patients waking up with lacunar strokes,[15] potentially due to an increased nocturnal risk when blood pressure is low.[15–17] The correlation between blood pressure and risk implies that diurnal variation in CBF and its regulation is critical to both the triggering of stroke and the brain's resilience to variation in blood flow. This correlation, thus, provides a pathological marker of diurnal hemodynamic rhythms and a marker of the pathophysiological distinction between cardioembolic stroke,[18] large vessel disease,[19] and small vessel occlusion.[20] However, 50% of strokes of unknown, mixed, or rarer etiology (dissection, prothrombotic states, vasculitis, etc) may have differing diurnal rhythms.[21]

In addition to stroke incidence, cross-sectional analysis of large acute stroke imaging databases has identified a reduced ratio of stroke penumbra to core in strokes that occur in the night,[22] with a worse outcome after endovascular treatment[23] and an increased risk of early neurological deterioration,[24] indicative of an interaction with resilience to vessel occlusion, while the probability of death or a poor outcome is greater for strokes occurring during the night.[4]

Although acute stroke is the clearest manifestation of cerebrovascular disease, resulting in both physical disability and cognitive impairment,[25] chronic cerebrovascular disease may also be exacerbated by circadian and diurnal influences on CBF. Cerebral small vessel disease, manifested as chronic white matter hyperintensities, microbleeds, dilated perivascular spaces, and lacunar infarcts,[26] is associated with an increased risk of acute events,[27] causing 30% of ischemic stroke, 80% of hemorrhagic stroke, and a 40% risk of all-cause dementia, late-onset refractory depression,[28] and a markedly increased risk of functional dependence, late-life multimorbidity, and frailty.[29] This is particularly associated with hypertension and strongly influenced by differences in diurnal rhythms between individuals with increased severity of disease in patients with excessive nocturnal blood pressure.[30]

MECHANISMS OF CIRCADIAN AND DIURNAL CONTROL OF PHYSIOLOGY

Diurnal variation in CBF results from the integration of cerebrovascular mechanisms with circadian variation in systemic blood pressure due to the external environment, our behavioral responses, and endogenous circadian rhythms. The cellular circadian clock and its synchronization with the external world via environmental zeitgebers such as light have been dissected in great detail and extensively reviewed elsewhere.[31] Briefly, the central cellular clock is driven by heterodimerization of the circadian locomotor output cycles kaput (CLOCK) and BMAL1 (basic helix-loop-helix ARNT-like protein 1) proteins that promote gene transcription affecting up to 10% of cellular proteins[32] through ebox targets. This includes transcription of 5 core clock genes that provide negative transcriptional/translational feedback loops, with binding of 3 PERIOD (period circadian regulator) proteins (PER1-3) and 2 cryptochromes (CRY1/2), together with casein kinase (CK) to form a complex that is phosphorylated, resulting in translation to the nucleus. Similar negative feedback loops work in parallel through proteins such as Rev-erb (nuclear receptor subfamily 1 group D). Together, these prevent CLOCK/BMAL1-dependent transcription and heterodimerization and BMAL1 transcription.[31] This reverberating cellular cycle produces a spontaneous rhythm of gene transcription with a period of slightly longer than 24 hours in humans and other day-active mammals and slightly shorter in rodents.

These cellular circadian rhythms do not have the same cycle length within[33] and across tissues and may lose phase synchrony,[34] requiring synchronization to each other and to the external environment. The principal zeitgeber is light, detected by photosensitive retinal ganglion cells,[35,36] and transmitted via the retinohypothalamic tract[37] to the suprachiasmatic nucleus (SCN) in the hypothalamus, the master clock in mammals.[38] The SCN then synchronizes intrinsic cellular circadian rhythms throughout the brain and the body, first locally via both chemical signals[39] and neuronal connections,[40] and then throughout the body via mechanisms that are not fully resolved but include hormonal release from the pituitary gland,[41] the pineal gland, and modulation of the descending autonomic nervous system.

Integrated Control of Systemic Hemodynamics and Cerebral Perfusion

Maintenance of cerebral perfusion is one of the central purposes of the cardiovascular system, receiving up to

Downloaded from http://ahajournals.org by on April 3, 2025

20% of cardiac output despite weighing only 2% of body weight.[42] In common with the kidneys, the brain has a low-resistance vascular bed optimized to receive high blood flow continuously throughout the cardiac cycle to meet the constant demand of energy-hungry, high-metabolic activity tissue, resulting in a close following response of CBF on systemic blood pressure. However, the cerebral circulation is not a passive recipient but actively modifies vascular resistance to integrate this perfusing pressure with the needs of the brain,[43] predominantly due to a distal change in tone[44] both to adapt CBF to changes in blood pressure (autoregulation),[45] to regional neuronal demand (neurovascular coupling),[46] and to global stimuli such as the P_{CO_2}, pH, and oxygen (cerebrovascular reactivity [CVR]).[47] Nonetheless, the low resistance of the cerebral circulation and its close proximity to the heart means that the brain is still particularly exposed to variations in blood pressure, a cost of the need to maintain continuous perfusion while minimizing pulsatility in the microcirculation.[48]

CBF is, therefore, strongly affected by both cardiac output and total peripheral resistance, the 2 key determinants of systemic perfusing pressure. An acute fall in cardiac output directly results in a fall in CBF,[49,50] even in the context of limited changes in arterial blood pressure, which results in a greater increase in peripheral vascular resistance than cerebrovascular resistance[51] to maintain blood pressure and cerebral perfusion. A chronic reduction in cardiac output, such as due to heart failure, is also associated with chronically decreased CBF and improved by treatment with ACE inhibitors[52] or heart transplantation.[53] Similarly, an increase in peripheral vascular resistance, particularly due to neurohumoral stimuli such as adrenaline or sympathetic innervation as occurs in the early morning, increases mean blood pressure and, thus, cerebral perfusing pressure although this is partially counteracted by concomitant increases in cerebrovascular resistance.[50] In addition to increases in the mean blood pressure, the pulsatile arterial waveform is also dampened at points of impedance (eg, the carotid bifurcation) and regions of vessel tortuosity such as the carotid siphon in humans[48] and the rete mirabile in other mammals,[54] with further dampening of the waveform as the total area of the vascular system increases and resistance decreases with the transition to arterioles and capillaries. Finally, the pulsatility of the arterial waveform also depends on the length of the cardiac cycle, with increasing pulsatility at lower heart rates exacerbating transmission through stiff vessels to the brain[55] and potentially increasing the risk of chronic cerebrovascular disease in older patients.[56,57]

Autoregulation aims to maintain stable CBF across a broad range of blood pressures although the classical formulation of cerebral autoregulation as constant blood flow across a wide range of blood pressure was defined in anesthetized animals[58–60] and may not accurately reflect the awake state in humans although it is a readily comprehensible formulation to understand cerebrovascular injury during hypotension[61] or hypertension.[62] However, most blood pressure fluctuations are rapid or rhythmic,[63] and the autoregulatory response is not instantaneous.[64] Therefore, a modern formulation of cerebral autoregulation is defined by the speed and efficiency by which CBF returns to normal in the face of a change in blood pressure.[65–68] The mechanisms of autoregulation have been reviewed in detail[43]; there are 3 key mechanisms: a myogenic mechanism, whereby smooth muscle vascular tone rapidly changes in direct response to intravascular pressure; metabolic mechanisms controlled by chemical influences mediated by the endothelium (such as nitric oxide [NO]) or acting on vascular smooth muscle cells (VSMCs; such as CO_2-dependent pH changes), which adjusts both basal vasomotor tone and the gain of the vasomotor response to other stimuli;[69] and autonomic innervation of the vessels. The latter 2 processes show both intrinsic diurnal variation and are dependent on endothelial function, particularly NO release from the endothelium which then induces VSMC relaxation.[70]

Cerebral perfusing pressure is also modified by CVR, the vasomotor response to global stimuli such as P_{CO_2}. Cerebral vasodilatation in response to increased carbon dioxide is likely mediated by a decrease in extravascular pH and its influence on VSMCs[71] and measurable by the blood flow response to inhaled carbon dioxide or respiratory maneuvers with transcranial ultrasound or magnetic resonance imaging,[72] with similar but smaller responses to a low P_{O_2} or tissue acidosis. This mechanism interacts with multiple vasodilatory and vasoconstrictor stimuli, including the autoregulatory response to blood pressure changes, with reduced autoregulatory gain as carbon dioxide increases.[73] These vasodilatory tests, thus, provide an index of both VSMC function and underlying activity of the endogenous vasodilatory mechanisms, depending on the endothelial release of NO and subsequent relaxation of VSMCs, as demonstrated by their modification by drugs that donate NO,[74] increase intracellular cGMP,[72] or increase the response to carbon dioxide.[75]

Finally, local neuronal demand induces a potent vasodilatory stimulus to increase supply to meet the extra metabolic demand. Although the exact mechanisms of neurovascular coupling remain disputed, they are likely mediated by rapidly acting vasoactive molecules (such as NO) from neurons and astrocyte endfeet, hyperpolarization of local endothelial cells in nearby capillaries, and rapid backpropagation of signals up the capillary tree to tonically activate pericytes and VSMCs in local arterioles and first- and second-order capillaries.[76] Circadian and diurnal influences on neurovascular coupling may, therefore, interact with circadian and diurnal effects on CVR and autoregulation, which depends on the same vasodilator effectors[77] and partially on endothelial function.

Downloaded from http://ahajournals.org by on April 3, 2025

Circadian and Diurnal Rhythms in Systemic Determinants of CBF

Blood Pressure: The Archetypal Diurnal Rhythm

Systemic blood pressure is perhaps the most well-investigated physiological diurnal rhythm in humans[78] and one of the most studied diurnal risk factors for disease.[79] Blood pressure is normally higher during the day to meet the demands of an active, mobile organism and declines at night by 10% to 20% (dipping). In addition to the strong correlation between the diurnal peak in cerebrovascular risk with the diurnal peak in blood pressure,[1] both a lack of or a reversal of this normal dipping behavior[30] and extreme dipping below 20% of daytime levels[3] are associated with an increased risk of all cardiovascular events.[80] Indeed, nocturnal blood pressure is the strongest hemodynamic predictor of future cerebrovascular events,[81] exceeding the predictive value of daytime blood pressure; it is, therefore, an additional treatment target in both European[82] and international blood pressure guidelines.[83] In contrast, the association between extreme dipping profiles and cardiovascular risk is not consistent but may interact with age with a relationship only in older patients.[3] In this group, there is aortic stiffening, reduced vessel elasticity, and diastolic pressure fall. Given the greater resulting transmission of pulsatile pressure to the brain, this may explain some of the greater risk of lacunar strokes occurring on wake-up compared with other stroke etiologies, reflecting hypoperfusion events in those patients with low nocturnal pressures and stiff vessels (Table).[84]

The normal nocturnal fall in blood pressure is particularly associated with a fall in heart rate resulting in a fall in cardiac output.[85] This is dependent on both the endogenous cardiac myocyte circadian clock,[86] which has a potent influence on heart rate, combined with circadian variation in the autonomic nervous system, with a strong parasympathetic vagal drive at night, under the influence of the SCN.[87,88] As awakening approaches, there is a surge in sympathetic drive, associated with a release of pituitary-dependent sympathomimetic hormones, including cortisol.[89] This is followed by arousal and awakening and the transition to the upright posture. These trigger the morning surge in blood pressure, the magnitude of which is reflective of sympathetic activity, is associated with an increased risk of cardiovascular events,[90] and is associated with a lower CBF in older adults.[91] Subsequently, blood pressure falls in the mid-morning, particularly in patients on antihypertensive medication, often with a bimodal pattern during the day driven by a postprandial early afternoon fall in blood pressure.[92] This diurnal variation in blood pressure determines the input pressure to the brain, providing greater flow in active periods, but with an increased risk of hypoperfusion during the night.

Key evidence for the role of the autonomic innervation of the heart in normal dipping, under the influence of both the SCN and peripheral autonomic reflexes, arises from patients with high cervical spinal cord injuries versus thoracic spinal cord injuries,[93] diurnal variation in microneurography of sympathetic nerves,[88] and loss of dipping in patients with dysautonomia.[94] First, sympathomimetic neurohumoral modulation of diurnal blood variation is seen with morning adrenergic surges[89,95] and normalization of a nondipping profile with nighttime administration of melatonin.[96] Second, in circadian misalignment in a model of jet lag, the heart rate determinant of cardiac output shows a mismatch between the PR interval (indicative of the endogenous cardiac myocyte clock) and the heart rate (as driven by autonomic drive).[6] Third, the nocturnal dip in blood pressure itself varies by the timing of sleep[97,98] and by periodic nighttime arousals. In pathological circumstances, and in rapid eye movement sleep (ie, one of the stages of sleep) when blood pressure rises, there is increased sympathetic nerve activity and prohypertensive hormone release.[99] Consistent with this parasympathetic/sympathetic imbalance, renal sympathetic denervation has a specific effect in reducing nocturnal BP. Heart rate changes, however, are also due to reflex changes to changes in venous return. The normal decrease in the body's oxygen consumption at night is expected to reduce venous return from skeletal muscle and the gastrointestinal tract and reduce afferent activity of atrial stretch receptors that sense cardiac filling, thereby reducing the contribution of this reflex to promote tachycardia and permitting a predominance of parasympathetic influence on heart rate and any endogenous effects of a cardiac myocyte circadian clock.

However, chronotherapy that aims to modify blood pressure by drug dosing at different times of day has produced mixed results. The Hygia Chronotherapy Trial[100] was associated with a marked reduction in cardiovascular events, but this has not been confirmed. This was a long-term outcome trial within a single regional service but lacked many of the features expected of a modern clinical trial (eg, independent oversight, transparent randomization procedures) and was associated with an unrealistic clinical benefit, including a marked reduction in noncardiovascular mortality. In contrast, the rigorously performed TIME (Treatment in Morning versus Evening) trial[101] found no difference in clinical outcomes with morning versus nighttime dosing. This is consistent with limited effects on measured ambulatory blood pressure at different times of day in the HARMONY (Hellenic-Anglo Research into Morning or Night Antihypertensive Drug Delivery) trial.[102]

Circadian and Diurnal Cardiac Rhythms

The intrinsic circadian rhythm of myocytes has been extensively studied, with both cell models and ex vivo whole heart physiological models. Ex vivo myocyte cultures demonstrate circadian rhythms in the core clock genes (CLOCK, BMAL1, PER1, etc), driving

Downloaded from http://ahajournals.org by on April 3, 2025

Table. Physiological Studies in Humans Assessing Diurnal Variation in Control of Cerebral Blood Flow

Study	Population	n	Metric	Method	Findings
Cerebral blood flow					
Droste et al[140]	Healthy	10	MFV	TCD over 24 h	MFV is greater during the day than at night.
Diamant et al[148]	Healthy, aged 50–66 y	3M, 4F	MFV	TCD over 24 h	MFV is lower in the morning in the supine position and increases by seated posture.
Conroy et al[141]	Healthy, aged 19–38 y	10M, 2F	MFV	TCD over 24 h	MFV falls from midnight peak through the night to nadir at about noon.
Strohm et al[145]	Healthy, aged 22–36 y	6M, 4F	MFV	TCD, daytime	Stable MFV across the daytime.
Shariffi et al[146]	Healthy, aged 22–31 y	6M, 6F	MFV	TCD, daytime	Stable MFV in the morning, afternoon, and evening.
Cummings et al[149]	Healthy, mean age 25 y	20M	MFV	TCD, daytime	MFV is greater in the afternoon than morning,
Lewis et al[150]	Healthy, mean age 26 y			TCD, tilt test	MFV is 12% lower in the morning, at baseline, and during tilt. No TCD diurnal variation in orthostasis.
Labrecque et al[147]	Healthy, mean age 25 y	10M, 8F	MFV	TCD, daytime	Stable baseline MFV through the day, with a greater proportional increase in the afternoon to BP change.
Cerebrovascular reactivity					
Ainslie and Duffin[71]	Healthy, mean age 25 y	20M	MFV/$etCO_2$	TCD, 5% CO_2	Increased CVR to CO_2 in the afternoon compared with early morning, parallel to FMD.
Cummings et al[149]	Healthy, mean age 25 y	20M	MFV/$etCO_2$	TCD, 5% CO_2	Increased CVR to CO_2 in the afternoon compared with early morning.
Hajjar et al[155]	No stroke, mean age 53.6 y, elderly	46M, 56F	MFV/$etCO_2$	TCD, 5% CO_2	Reduced CVR in nondippers.
Strohm et al[145]	Healthy, aged 22–36 y	6M, 4F	MFV/$etCO_2$	TCD, respiract	Increased CVR to $etCO_2$ in the evening.
Ameriso et al[154]	…	20	MFV/$etCO_2$		Increased CVR to CO_2 in the afternoon/evening compared with early morning.
Shariffi et al[146]	Healthy, aged 22–31 y	6M, 6F	MFV	TCD, CO_2 inhalation	Increased cerebrovascular reactivity in the evening compared with morning.
Cerebral autoregulation					
Ainslie and Duffin[71]	Healthy, mean age 25 y	20M	MFV/MBP	TCD, ARI	Increased ARI in the afternoon compared with early morning, implying better pm autoregulation.
Burma et al[156]	Healthy, mean age 25 y	8M, 8F	MFV/MBP	TCD, dCA by TF	No significant diurnal variation in gain, coherence, or phase.
Abadjiev et al[158]	Patients with stroke, aged 26–83 y	21M, 7F	MFV/MBP	TCD, MMPF phase	Increased phase shift in afternoon vs morning at <0.05 Hz but not at higher frequencies. Possible better autoregulation.
Neurovascular coupling					
Hodkinson et al[165]	Healthy, aged 23–38 y	13M	CBF+fMRI	MRI-ASL+BOLD	Decreased functional connectivity with reduced CBF in default mode network regions in pm vs am.
Blautzik et al[166]	Healthy, mean age 23 y	6M, 9F	fMRI	BOLD	Diurnal rhythmicity in default mode network present.
Schroeter et al[167]	Healthy, aged 20–27 y	11M	Hb, dHB	fNIRS	Reported as no diurnal variation, but data imply greater Hb increase to visual stimulation in pm.

ARI indicates autoregulatory index; BOLD, blood oxygen level dependent; CBF, cerebral blood flow; CVR, cerebrovascular reactivity; dCA, dynamic cerebral autoregulation; dHB, deoxyhemoglobin; $etCO_2$, end-tidal CO_2; F, female; FMD, flow-mediated dilatation; fMRI, functional magnetic resonance imaging; Hb, oxyhemoglobin; M, male; MBP, mean blood pressure; MFV, mean flow velocity; MMPF, multimodal pressure flow; MRI-ASL, magnetic resonance imaging–autoregulatory index; TCD, transcranial ultrasound; and TF, transfer function.

Downloaded from http://ahajournals.org by on April 3, 2025

circadian oscillation in 10% of the cardiac myocyte transcriptome.[32] This circadian variation switches the cell between a predominantly catabolic state of high ATPase activity, protein synthesis, and fatty acid oxidation in periods of activity to periods of fatty acid storage and tissue repair and regeneration at times of rest. This includes rhythmic transcription of e4bp4,[103] key ion channels responsible for the key transmembrane currents, particularly Kv1.5 and Kv4.2 potassium channels,[104] and the sodium HCN4 channel responsible for the funny current that is key to determining the endogenous sinoatrial nodal rate.[105,106] Diurnal oscillations are evident in the classical components of the ECG at night with lengthening of the PR interval, as wells as the RR interval and the QT interval. The cardiomyocyte clock is not directly driven by light in humans, but evidence for an autonomic mechanism for synchronization with the SCN is demonstrated by ex vivo resetting of the clock by noradrenaline[107] or angiotensin II,[108] addition to culture media.

Clinically, the nocturnal resting heart falls in humans to a similar degree to the decline in blood pressure (by ≈15%–20%; Figure 1).[109] This is limited by autonomic denervation, evident in transplanted hearts, cardiomyocyte monolayers,[107] or explanted hearts[110] but is not abolished.[111] Similarly, SCN ablation and pharmacological

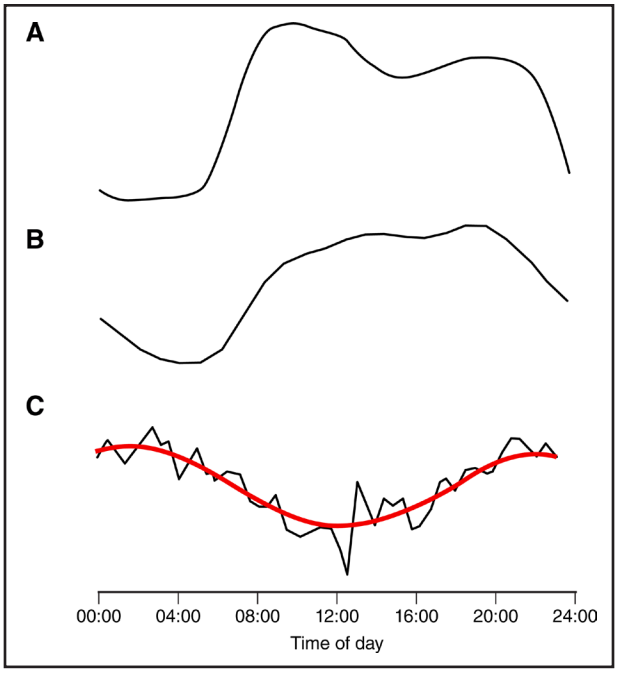


Figure 1. Haemodynamic diurnal variation.
Diurnal variation at rest in (**A**) mean arterial pressure (blood pressure), (**B**) heart rate, and (**C**) middle cerebral artery velocity. (**C**) is adapted from Conroy et al[139] with permission. Figure credit: Ben Smith.

autonomic system blockade also reduce diurnal variation in heart rate,[112] correlated with the diurnal variation in sympathomimetic hormone levels[89] and sympathetic nerve activity.[87,88] Asynchrony between the endogenous cardiomyocyte rhythm and the autonomic nervous system is demonstrated by a model of human jet lag in which a rapid phase shift in light results in rapid synchronization of heart rate under the influence of the synchronized SCN and (diurnal) behaviors that affect heart rate but a more gradual resynchronization of the PR interval, reflective of the intrinsic cardiomyocyte clock.[6] This variation in heart rate may result in a differential effect on systolic and diastolic flow as the heart rate affects cerebral pulsatility,[55] with a reduced diastolic perfusing pressure at the end of the cardiac cycle. This may also have effects on glymphatic drainage of the brain, which is driven by arterial pulsatility, which demonstrates an important diurnal variation and relationship with sleep,[113] dealt with in another article within this compendium. We could identify no published studies of diurnal variation in cerebral pulsatility at this time. Abnormal dipping of heart rate is also associated with increased cardiovascular risk, comparable to abnormal dipping behavior of blood pressure.[114]

There is less direct evidence for circadian or diurnal variation in contractility and stroke volume, beyond the circadian oscillation in metabolic activity[86] and transcription of contractile proteins,[110] although this may be partially inferred from neurohumoral levels that have a morning peak in concentration and have a direct positive inotropic effect on the heart.

Circadian and diurnal cardiac rhythms may also predispose to arrhythmia. Sinus bradycardia and sinus pauses are particularly common at night due to the vagal drive. This can predispose to nocturnal heart block[115] and to an increased probability of atrial fibrillation (AF),[116] with a greater probability of reversion to sinus rhythm in the morning. This phenomenon could be partially responsible for larger relative ischemic cores in the early hours,[22] as AF-related occlusion may affect larger vessels and multiple vascular territories (when AF-related, more severe large vessel occlusion could predominate). However, a greater burden of AF at night may also exacerbate intermittent hypoperfusion of the brain synergistically with lower mean blood pressure, as suggestive by greater imaging and cognitive decline in AF, independent of embolic events.[108]

Blood Viscosity

Blood viscosity, a key determinant of CBF and blood flow velocity,[117] also displays diurnal variation. More than 5 decades ago, Seaman et al[118] reported that hematocrit, total protein, hexosamine, protein-bound carbohydrate, and blood viscosity were high early in the morning. During diurnal cycles of human inactivity and bed rest, blood plasma volume is reduced by dehydration as gravitational forces shift plasma constituents to interstitial spaces and increase water excretion.[119]

Elevated blood viscosity increases blood flow resistance, induces platelet aggregation, and presents a risk factor for cerebrovascular stroke. Blood viscosity minimally impacted CBF in healthy young subjects whose autoregulation was not disrupted,[120] consistent with a preclinical result in healthy animals showing a nonsignificant trend for decreased CBF at elevated viscosity. However, under high CBF states such as hypercapnia and chronic hypoxia, blood viscosity affects CBF,[121] presumably due to an attenuated capacity for compensatory vasodilation. Therefore, blood viscosity may contribute to the diurnal variation in stroke risk in patients with comorbid states and disrupted autoregulation.

Several studies have also demonstrated that blood viscosity, especially in the diastolic cardiac phase, is associated with small vessel strokes such as lacunar stroke and silent ischemic lesions more than other stroke subtypes.[122,123] Moreover, blood viscosity was correlated with early neurological deterioration in patients with lacunar infarct.[124] The association of small vessel stroke with viscosity might result from the dependence of blood viscosity on vessel size—smaller vessels have a lower shear rate and, therefore, higher viscosity than large arteries and a greater tendency to aggregate red blood cells,[124] thus contributing to the potential association between an increased risk of lacunar infarction at night in patients with reduced perfusing pressures.[15]

Downloaded from http://ahajournals.org by on April 3, 2025

Vasomotor Tone

Flow-mediated dilatation studies of the systemic circulation in humans demonstrate increased basal vasomotor tone in the morning with impaired flow-mediated dilatation, concurrent with the morning surge in blood pressure and the increased incidence of stroke,[125] predominantly reflecting alpha-adrenergic sympathetic nerve activity,[88,126] with parallel effects causing impaired dilatation of cutaneous skin responses.[95] In animal studies, there is ex vivo circadian variation in aortic tone, indicative of an endogenous circadian rhythm in rats with dopamine beta-hydroxylase deficiency in whom this is not dependent on adrenergic stimulation.[127] This is consistent with circadian variation in both core clock genes[128] and their transcriptional targets in mouse aorta,[129] with integration between intrinsic circadian rhythms in vascular tissue and synchronization via the central clock.

The vasomotor tone is dependent on the release of vasodilatory molecules from the endothelium, inducing relaxation of VSMCs,[130] and vasoconstrictors released by either the endothelium (endothelin-1 or angiotensin 2),[131] circulating in the blood (adrenaline) or released by autonomic nerves innervating the vessels. These act on the VSMCs to decrease or increase vasomotor tone in the vessels and control peripheral vascular resistance. Mutation of the clock gene Per2 results in impaired systemic endothelial function with a reduced aortic endothelial response to acetylcholine in mice, particularly at the transition between the inactive sleep phase and the active phase, and reduced release of NO,[132,133] while loss of Bmal1 results in loss of circadian rhythms in response to induced vasoconstriction, likely via ROCK2 (Rho associated coiled-coil containing protein kinase 2),[134] as well as independent circadian variation in NO synthase activity.[130] Reduced NO is associated with reduced circadian variation in vascular function,[135] while obesity suppresses both NO activity, circadian gene expression, and endothelial function.[136] Furthermore, there is circadian variation in vasoconstrictor hormones, such as endothelin-1.[137] Overall, although there are endogenous clocks in both endothelial cells and VSMCs, circadian variation in systemic vasoconstrictor hormones and autonomic innervation is the predominant determinant of circadian variation in vasomotor tone.

Circadian and Diurnal Rhythms in Cerebrovascular Function

Cerebral Blood Flow

CBF in the rat is increased in the active nocturnal phase of the cycle[138,139] and significantly lower in the rest phase in awake animals although its dependence on activity versus endogenous rhythms is less clear. In humans, limited studies demonstrate a similar pattern of reduced blood flow and blood flow velocity during the night (Figure 1),[140,141] with a ≈20% reduction at its nadir from its peak, similar to changes in blood pressure. CBF is more reduced in patients with obstructive sleep apnea[142] and rises during rapid eye movement sleep,[143,144] indicative of the importance of diurnal arousal versus endogenous circadian rhythms. However, studies are inconsistent, with some studies demonstrating a relatively stable middle cerebral artery velocity throughout the day,[145–147] except when stimulated by activity,[148] but the majority demonstrating a lower middle cerebral artery velocity in the morning compared with the evening at rest.[141,149,150] This is in contrast to systemic perfusing pressure. Instead, the increase in CBF velocity appears to reach its peak at approximately midday, with an elevated evening CBF velocity compared with the morning and a ≈6-hour phase delay with the diurnal oscillation of blood pressure and core body temperature (Figure 1).[141] This persists even in people who remain awake throughout the 24-hour cycle.[141] However, these results are strongly dependent on activity, with an increased middle cerebral artery velocity induced by activity, dominating this underlying rhythm, although the increased propensity for morning syncope,[151] reduced orthostatic tolerance in the morning,[64,150] and the diurnal variation in stroke incidence[4] indicate a role for underlying physiological mechanisms in adapting to diurnal behaviors.

Cerebrovascular Function

In contrast to the relatively extensive evidence for circadian variation in systemic vasomotor tone, there are limited data on circadian variation in cerebrovascular tone. In animals, there is rhythmicity in myogenic tone in the context of experimental subarachnoid hemorrhage,[152] but measures of nocturnal cerebrovascular endothelial function in humans are challenging. The most direct index is reactivity to inhaled carbon dioxide during measurement of CBF by transcranial ultrasound or blood flow sensitive brain imaging (blood oxygen level dependent or arterial spin labeling–magnetic resonance imaging, perfusion CT, etc), but this is impractical in sleeping subjects. Furthermore, despite functional similarities between cerebral and systemic vascular endothelium during the day, this cannot be assumed at night. In a cohort of healthy volunteers, both CVR and flow-mediated dilatation in the forearm were more impaired in the morning than the afternoon,[153] confirmed by studies demonstrating lower CVR in the morning to carbon dioxide compared with the afternoon,[149,153,154] and reduced cerebrovascular resistance through a greater mean flow velocity increase per blood pressure increase in the afternoon[147] although some studies have not demonstrated this.[145] Furthermore, absent or reversed dipping of blood pressure is associated with impaired CVR (Figure 2).[155]

Cerebral autoregulation shares similar effector mechanisms to CVR, being dependent on vasomotor tone controlled by VSMCs. In 20 healthy volunteers,

Downloaded from http://ahajournals.org by on April 3, 2025

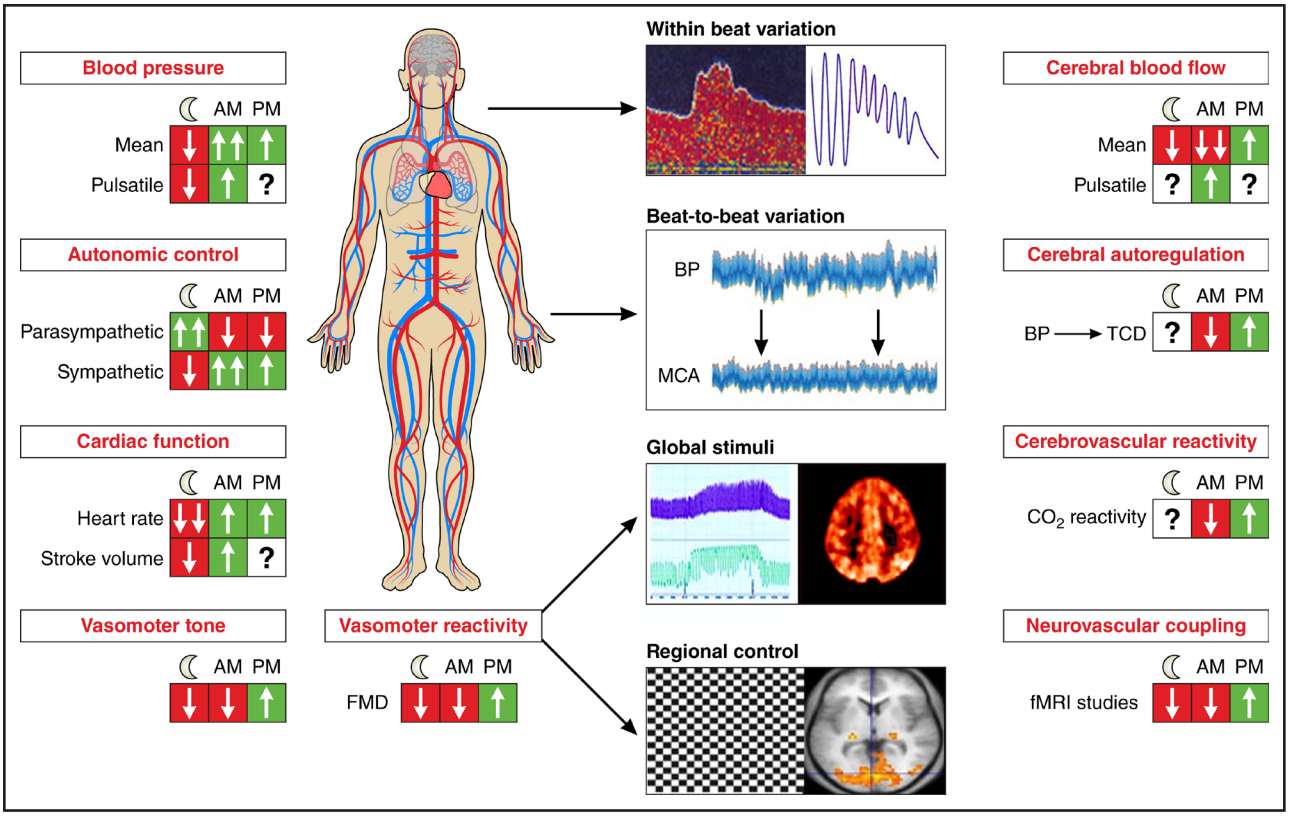


Figure 2. Diurnal variation in systemic and cerebral mechanisms determining cerebral perfusion.
The direction of change in each index is shown for night, morning, and afternoon, with the magnitude of change indicated by the number of arrows. Figure credit: Ben Smith. BP indicates blood pressure; FMD, flow-mediated dilatation; fMRI, functional magnetic resonance imaging; MCA, middle cerebral artery; and TCD, transcranial ultrasound.

Downloaded from http://ahajournals.org by on April 3, 2025

autoregulation was reduced in the morning between 6 and 12 noon, measured as the autoregulatory index from spontaneous fluctuations in blood pressure and middle cerebral artery blood flow velocity on transcranial ultrasound.[153] There was a concurrent reduction in CVR in cerebral vessels and in flow-mediated dilatation peripherally. However, a smaller study in 16 patients did not find any diurnal variation in autoregulation but measured autoregulation as phase shift and gain from a transfer function analysis during rhythmic squat-stand maneuvers,[156] a test designed to have improved reproducibility.[67,157] In contrast, in an older group of patients in the 48 hours after recovery from stroke, there was an improved phase relationship at <0.05 Hz between blood pressure and CBF using transfer function analysis at rest. This was present for both the stroke and nonstroke sides of the brain and was interpreted by the authors as better autoregulation in the afternoon,[158] but there was no significant diurnal variation in any autoregulation index in the frequency range indicative of autoregulation,[45] but only in the frequency range more dependent on changes in carbon dioxide, indicating a difference in vasoreactivity rather than autoregulation.

Overall, empirical evidence for diurnal variation in cerebral autoregulation is limited and remains inconsistent. The autonomic component of autoregulation is associated with interindividual variation in measures of autonomic function elsewhere in the body.[45] These do show a significant influence on circadian rhythms[159] under the control of the SCN. Therefore, it may be hypothesized that cerebral autoregulation would also be reduced in the morning, consistent with the limited studies of systemic autonomic function such as heart rate variability.[153]

Neurovascular coupling orchestrates regional control of CBF. There are endogenous circadian rhythms in the key cell types of the neurovascular unit (VSMCs,[106,160] endothelial cells,[161,162] pericytes,[163] and astrocytes), circadian variation in endothelial functions including blood-brain barrier permeability[161] and glymphatic function,[113] and evidence for intercellular circadian synchronicity of the components of the neurovascular unit.[163] However, there is limited direct evidence for a circadian variation in neurovascular coupling in humans although central cellular elements in neurovascular coupling demonstrate circadian periodicity.[164] This is a potential issue for functional magnetic resonance imaging studies that use blood flow as a proxy for neuronal function and depend on stable neurovascular coupling. However, although there is also diurnal variation in spontaneous neuronal, vascular networks in the brain[165,166] circadian influences

on neurovascular coupling have previously been felt to have minimal effects on functional magnetic resonance imaging.[167]

Overall, regulatory mechanisms for control of CBF demonstrate diurnal variation. There is reduced absolute blood flow during the night and morning, with increased morning vasomotor tone and reduced endothelial responsiveness. However, there remain limited data particularly, about neurovascular coupling and cerebral autoregulation. This is true in waking hours, where the relevance of autoregulation to the increased morning risk of cerebral ischemic and hemorrhage may be critical to understand the underlying pathophysiology and to identify treatments. However, there is virtually no data on these cerebrovascular functions during the night as opposed to the day.

Clinical Implications of Integrated Circadian (and Diurnal) Cardiovascular Physiology

The diurnal variation in cerebrovascular events[1] and stroke outcomes[4] occurs in the context of prominent circadian and diurnal rhythms in nearly all aspects of systemic and cerebral cardiovascular hemodynamics. Diurnal variation in other mechanisms involved in stroke pathogenesis also contributes to this increased cerebrovascular risk,[5] such as diurnal variation in thrombotic factors or inflammation.[168] However, the powerful changes in hemodynamic function that correlate so closely with variation in cerebrovascular risk ensure that this is a key target to reduce a modifiable proportion of strokes.

Systemic blood pressure provides a reference to understand the interaction between circadian and diurnal variation in these mechanisms. The nadir in blood pressure at night results principally from a fall in cardiac output due to bradycardia, under the influence of endogenous circadian rhythms and descending vagal activity. This nocturnal nadir in blood pressure is largely independent of vasomotor tone but may contribute to the decline in CBF during the inactive period. This hypotensive nadir, with bradycardia and increased vagal activity, may theoretically drive an increased predisposition to stroke associated with hypotension and is a potential explanation for the apparent increased risk of lacunar stroke in patients with wake-up stroke.[15] This may be particularly relevant in extreme dippers with a nocturnal blood pressure drop >20% who have increasingly stiff vessels[3] and hypoperfusion in the white matter of the brain with existent small vessel disease.[169] It is also potentially a driver of the larger core:penumbra ratio in large vessel occlusion at night.[22,23] Nocturnal bradycardia may also increase the probability of AF, resulting in a greater proportion of embolic strokes due to cardioembolic disease than large artery disease (despite a lower overall incidence than in the morning), which may further contribute to the size of vessel occlusion and diurnal variation in core:penumbra ratios. This is likely to be exacerbated by the lower CBF at night, limiting the brain's reserve to tolerate ischemia, but there is inadequate data about endothelial responsiveness overnight.

Before waking, the SCN-dependent release of hormones such as growth hormone and prolactin and the arousal and postural shift–driven increase in sympathomimetic hormones, such as adrenaline and noradrenaline, increase the sympathetic drive to blood vessels. This results in a sharp increase in vasomotor tone, coincident with an increase in heart rate and cardiac output, resulting in a surge in blood pressure and elevated blood pressure through the morning until lunchtime. Despite this elevation in blood pressure, CBF in humans appears not to increase until lunchtime,[170] and this likely reflects concurrent increases in cerebrovascular tone that increases cerebrovascular resistance and reduces CBF. It is unclear whether this is part of the systemic drive to increase blood pressure to meet the demands of daytime mobility or a myogenic vasoconstrictive response secondary to the systemic rise in blood pressure.

Following the morning surge in blood pressure, there is usually a postprandial lunchtime dip in blood pressure, at a time when CBF increases, endothelial function improves, and there may be an improvement in autoregulatory capacity,[92] after which there is on average a rise in blood pressure in the evening, which may explain the evening peak in stroke risk in some studies, before the nocturnal decline in heart rate, cardiac output, and blood pressure. However, direct measures of CBF and cerebrovascular function at this time of day are limited.

This model of the relationship between hemodynamic changes and diurnal variation in risk and recovery supposes an increased risk of hypoperfusion at night and an increased risk of hyperperfusion in the morning, explaining the morning excess risk of embolic and hemorrhagic stroke. Such a relationship between blood pressure and cerebral perfusion at specific times of day raises the possibility of chronotherapy. This provides a hypothesis that can be tested to understand the mechanism of these strokes and their outcome, subdivided by etiology. However, most studies have had inadequate phenotyping at the individual patient level of both the etiological subtype of stroke and the blood pressure phenotype (nondipping versus reverse dipping versus extreme dipping), including chronotherapy trials that did not account for relationships between individual blood pressure behavior and chronotherapy. Furthermore, some antihypertensive treatments may be better than others at normalizing maladaptive blood pressure phenotypes such as nondipping.[171,172] Finally, in the acute setting of large vessel occlusion at times of increased risk of a poor outcome, maintenance of cerebral perfusion by limiting nocturnal blood pressure decline could be beneficial although the magnitude of any effect is likely to be far less than the benefit of reperfusion.

Downloaded from http://ahajournals.org by on April 3, 2025

Diurnal variation in heart rate presents another possible chronotherapeutic target. If nocturnal bradycardia is a driver of nocturnal hypoperfusion in at-risk individuals, then prevention of excessive sinus bradycardia could be beneficial either through cessation of rate-limiting drugs such as β-blockers or changing settings in patients with a rate-responsive pacemaker. This may have the added benefit of preventing precipitation of AF at night. Although historically preventing episodes of AF was thought to have little impact on embolic risk, the recent Early Treatment of Atrial Fibrillation for Stroke Prevention Trial AF Network 4 trial suggests that a rhythm control strategy may reduce the risk of cardiovascular events.[173]

No studies have targeted diurnal variation in cerebrovascular function to improve resilience to ischemia, beyond trials of time of day of antihypertensive administration.[101] Drugs that improve endothelial function and reduce vasomotor tone may be of particular benefit, particularly in people with an exaggerated morning surge in blood pressure, adverse nocturnal dipping behavior, or vulnerable aging cerebral circulations. Drugs targeting CVR and endothelial function may be particularly beneficial in this latter group with cerebral small vessel disease. The LACI-2 (Lacunar Intervention Trial 2)[174] demonstrated reduced progression of cognitive dysfunction in patients with previous lacunar stroke with the vasodilating, NO donor isosorbide mononitrate, and possible improvement in functional impairment with the PDE (phosphodiesterase) 3 inhibitor cilostazol. Both drugs improve CVR,[75] with reduced recurrent stroke rates with the addition of cilostazol to other antiplatelets,[175] or in comparison with other antiplatelet drugs.[176,177] Interestingly, cilostazol also increases the heart rate and reduces cerebral pulsatility, indicative of improved systemic hemodynamic function,[178] which could, therefore, ameliorate harms associated with nocturnal bradycardia. Further trials are currently testing drugs that target the endothelium, and their interaction with diurnal variation in cerebrovascular function may improve their utility[72,179,180] and improve outcomes for large vessel occlusions at adverse times of the day.[181]

In addition to targeting normal circadian variation in hemodynamic function and cerebral perfusion, reducing cardiovascular events is feasible through targeting abnormal circadian rhythms, whether by normalizing dysfunctional circadian rhythms such as nondipping/reverse dipping of blood pressure or minimizing the dyssynchrony between exogenous diurnal rhythms and intrinsic circadian rhythms that occur in jet lag[6] or shift work.[31] Although chronotherapy targeting blood pressure nonspecifically has not been shown to be beneficial, prevention of reverse dipping of blood pressure overnight and inducement of normal dipping may be beneficial. This may be achievable through treatment of obstructive sleep apnea,[182] weight loss, or salt-depleting antihypertensives, or potentially through circadian neurohormonal interventions such as melatonin.[170]

Recommendations for Future Research

Physiologically, the most consistent finding from this review is the relative lack of research in humans on circadian (rather than diurnal) variation in cerebrovascular function and particularly the lack of research on cerebrovascular function overnight. This research should appropriately separate circadian from diurnal influences because countermeasures for the 2 influences differ. First, there is still limited data to confirm that CVR, and associated endothelial function, has a circadian oscillation, and there are few studies specific to patients at risk of different types of stroke or with different blood pressure phenotypes. There are also no studies that have measured CVR overnight. However, this methodological challenge may be met by modern methods of continuous blood pressure and CBF measurement that could allow measurement of spontaneous fluctuations in blood pressure, CBF, and carbon dioxide that reflect endothelial function and reactivity, even during sleep.[43,183] Opportunistic assessment of the cross-sectional diurnal variation in existing studies is feasible but will be limited to daytime changes, and the majority of studies that have measured CVR are limited in size. Finally, new studies that measure both systemic reactivity and CVR at different times of day are needed to assess whether they share underlying circadian mechanisms.

Circadian variation in cerebral autoregulation is even less well understood but may be more amenable to investigation. Although the response to a blood pressure intervention remains the optimal method of assessment of autoregulation, modern methods also use the relationship between spontaneous changes in blood pressure and CBF at rest, and so autoregulation could be more easily assessed by continuous monitoring throughout the 24-hour period. This approach has been applied in neurointensive care units in patients with head injury,[184,185] but this population does not have normal circadian and diurnal rhythms. Furthermore, the balance of autonomic and autoregulatory mechanisms at specific frequencies measured during continuous blood pressure and CBF monitoring can provide additional information as to carbon dioxide sensitivity and the potential sympathetic versus parasympathetic balance controlling autoregulation, as well as providing specific targets for interventions to dissect underlying mechanisms.[43,67]

Systemically, there are still outstanding questions about the role of heart rate versus vasomotor tone in inducing the day-night difference in blood pressure; the balance of endogenous cellular circadian rhythms compared with external modulation; and how these mechanisms are disordered in circadian disorders and asynchrony between circadian rhythms and the environment. These questions are amenable to systematic

Downloaded from http://ahajournals.org by on April 3, 2025

testing in animal models, where selective neurohumoral blockade can be applied in animals exposed to continuous darkness (a free-running clock), in natural lighting conditions, or in imposed alterations in the external light signal (eg, in models of jet lag). However, these models need validating in humans, whether by selective blockade by adrenergic antagonists or opportunistic studies in patients given drugs for different reasons. The effect of heart rate can also be tested in patients with pacemakers who are routinely paced with a stable base rate without any circadian variation.

CONCLUSIONS

Circadian and diurnal variation in CBF and its control is key to understanding diurnal variation in cerebrovascular risk, with an increased risk in the morning for most stroke subtypes but a possible further increase in lacunar infarction overnight, as well as worse physiological and clinical outcomes for nocturnal onset events. Understanding circadian and diurnal variation in CBF, however, requires an understanding not only of blood pressure but the integration of all mechanisms that determine cerebral perfusion from the heart to systemic vasomotor tone to cerebrovascular endothelial compensatory mechanisms. Extensive evidence demonstrates circadian and diurnal variation in systemic functions and blood pressure, in particular, resulting in associations between normal circadian variation, abnormal circadian function, and increased cerebrovascular risk. However, there are limited data for circadian variation in CBF and its dynamic control, which restricts understanding of the mechanisms underlying circadian variation in risk.

ARTICLE INFORMATION

Affiliations

Department of Clinical Neurosciences, Wolfson Centre for Prevention of Stroke and Dementia, University of Oxford, United Kingdom (A.J.S.W.). Department of Neurology, Massachusetts General Hospital, Boston (E.B.K.). Division of Sleep and Circadian Disorders, Department of Medicine, Brigham and Women's Hospital, Boston, MA (E.B.K.). Division of Sleep Medicine, Harvard Medical School, Boston, MA (E.B.K.). Departments of Radiology and Neurology, Neuroprotection Research Laboratories, Massachusetts General Hospital, Harvard Medical School, Boston (E.T.M.).

Sources of Funding

This work was supported by the Leducq Foundation for Cardiovascular and Neurovascular Research.

Disclosures

A.J.S. Webb received funding from the Wellcome Trust, Medical Research Council, Alzheimer's Society, and the British Heart Foundation and received consulting fees from Woolsey Pharmaceuticals. E.B. Klerman reports consulting for the American Academy of Sleep Medicine Foundation, Circadian Therapeutics, the National Sleep Foundation, the Sleep Research Society Foundation, and the Yale University Press; travel support from the European Biological Rhythms Society, École polytechnique fédérale de Lausanne, Pavilion, the Sleep Research Society, and the World Sleep Society; and the Scientific Advisory Board (unpaid) for Chronsulting. E.B. Klerman's partner is the founder, the director, and the chief scientific officer of Chronsulting. E.T. Mandeville reports no conflicts.

REFERENCES

1. Elliott WJ. Circadian variation in the timing of stroke onset: a meta-analysis. *Stroke*. 1998;29:992–996. doi: 10.1161/01.str.29.5.992
2. Chellappa SL, Vujovic N, Williams JS, Scheer F. Impact of circadian disruption on cardiovascular function and disease. *Trends Endocrinol Metab*. 2019;30:767–779. doi: 10.1016/j.tem.2019.07.008
3. Palatini P, Verdecchia P, Beilin LJ, Eguchi K, Imai Y, Kario K, Ohkubo T, Pierdomenico SD, Saladini F, Schwartz JE, et al. Association of extreme nocturnal dipping with cardiovascular events strongly depends on age. *Hypertension*. 2020;75:324–330. doi: 10.1161/HYPERTENSIONAHA.119.14085
4. Ripamonti L, Riva R, Maioli F, Zenesini C, Procaccianti G. Daily variation in the occurrence of different subtypes of stroke. *Stroke Res Treat*. 2017;2017:9091250. doi: 10.1155/2017/9091250
5. Scheer FA, Shea SA. Human circadian system causes a morning peak in prothrombotic plasminogen activator inhibitor-1 (PAI-1) independent of the sleep/wake cycle. *Blood*. 2014;123:590–593. doi: 10.1182/blood-2013-07-517060
6. Hayter EA, Wehrens SMT, Van Dongen HPA, Stangherlin A, Gaddameedhi S, Crooks E, Barron NJ, Venetucci LA, O'Neill JS, Brown TM, et al. Distinct circadian mechanisms govern cardiac rhythms and susceptibility to arrhythmia. *Nat Commun*. 2021;12:2472. doi: 10.1038/s41467-021-22788-8
7. Paschos GK, FitzGerald GA. Circadian clocks and vascular function. *Circ Res*. 2010;106:833–841. doi: 10.1161/CIRCRESAHA.109.211706
8. El Jamal N, Lordan R, Teegarden SL, Grosser T, FitzGerald G. The circadian biology of heart failure. *Circ Res*. 2023;132:223–237. doi: 10.1161/CIRCRESAHA.122.321369
9. Marshall J. Diurnal variation in occurrence of strokes. *Stroke*. 1977;8:230–231. doi: 10.1161/01.str.8.2.230
10. Wroe SJ, Sandercock P, Bamford J, Dennis M, Slattery J, Warlow C. Diurnal variation in incidence of stroke: Oxfordshire community stroke project. *BMJ*. 1992;304:155–157. doi: 10.1136/bmj.304.6820.155
11. Lago A, Geffner D, Tembl J, Landete L, Valero C, Baquero M. Circadian variation in acute ischemic stroke: a hospital-based study. *Stroke*. 1998;29:1873–1875. doi: 10.1161/01.str.29.9.1873
12. Ricci S, Celani MG, Vitali R, La Rosa F, Righetti E, Duca E. Diurnal and seasonal variations in the occurrence of stroke: a community-based study. *Neuroepidemiology*. 1992;11:59–64. doi: 10.1159/000110913
13. Butt MU, Zakaria M, Hussain HM. Circadian pattern of onset of ischaemic and haemorrhagic strokes, and their relation to sleep/wake cycle. *J Pak Med Assoc*. 2009;59:129–132. PMID: 19288934
14. Turin TC, Kita Y, Rumana N, Takashima N, Ichikawa M, Sugihara H, Morita Y, Hirose K, Murakami Y, Miura K, et al. Morning surge in circadian periodicity of ischaemic stroke is independent of conventional risk factor status: findings from the Takashima Stroke Registry 1990-2003. *Eur J Neurol*. 2009;16:843–851. doi: 10.1111/j.1468-1331.2009.02605.x
15. Chaturvedi S, Adams HP Jr, Woolson RF. Circadian variation in ischemic stroke subtypes. *Stroke*. 1999;30:1792–1795. doi: 10.1161/01.str.30.9.1792
16. Huart J, Persu A, Lengele JP, Krzesinski JM, Jouret F, Stergiou GS. Pathophysiology of the nondipping blood pressure pattern. *Hypertension*. 2023;80:719–729. doi: 10.1161/HYPERTENSIONAHA.122.19996
17. Kario K, Pickering TG, Matsuo T, Hoshide S, Schwartz JE, Shimada K. Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. *Hypertension*. 2001;38:852–857. doi: 10.1161/hy1001.092640
18. Yiin GS, Howard DP, Paul NL, Li L, Mehta Z, Rothwell PM; Oxford Vascular Study. Recent time trends in incidence, outcome and premorbid treatment of atrial fibrillation-related stroke and other embolic vascular events: a population-based study. *J Neurol Neurosurg Psychiatry*. 2017;88:12–18. doi: 10.1136/jnnp-2015-311947
19. Rerkasem K, Rothwell PM. Temporal trends in the risks of stroke and death due to endarterectomy for symptomatic carotid stenosis: an updated systematic review. *Eur J Vasc Endovasc Surg*. 2009;37:504–511. doi: 10.1016/j.ejvs.2009.01.011
20. Tuttolomondo A, Casuccio A, Della Corte V, Maida C, Pecoraro R, Di Raimondo D, Vassallo V, Simonetta I, Arnao V, Pinto A. Endothelial function and arterial stiffness indexes in subjects with acute ischemic stroke: relationship with TOAST subtype. *Atherosclerosis*. 2017;256:94–99. doi: 10.1016/j.atherosclerosis.2016.10.044
21. Schulz UG, Rothwell PM. Differences in vascular risk factors between etiological subtypes of ischemic stroke: importance

Downloaded from http://ahajournals.org by on April 3, 2025

of population-based studies. *Stroke*. 2003;34:2050–2059. doi: 10.1161/01.STR.0000079818.08343.8C
22. Reidler P, Brehm A, Sporns PB, Burbano VG, Stueckelschweiger L, Broocks G, Liebig T, Psychogios MN, Ricke J, Dimitriadis K, et al. Circadian rhythm of ischaemic core progression in human stroke. *J Neurol Neurosurg Psychiatry*. 2023;94:70–73. doi: 10.1136/jnnp-2021-326072
23. Burbano VG, Wolfer TA, Vlegels N, Quandt F, Zimmermann H, Wischmann J, Kellert L, Liebig T, Dimitriadis K, Saver JL, et al; GSR investigators. Association of the time of day of EVT with clinical outcomes and benefit from successful recanalization after stroke. *Ann Clin Transl Neurol*. 2023;10:1917–1923. doi: 10.1002/acn3.51877
24. Ryu WS, Hong KS, Jeong SW, Park JE, Kim BJ, Kim JT, Lee KB, Park TH, Park SS, Park JM, et al. Association of ischemic stroke onset time with presenting severity, acute progression, and long-term outcome: a cohort study. *PLoS Med*. 2022;19:e1003910. doi: 10.1371/journal.pmed.1003910
25. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. *Lancet Neurol*. 2009;8:1006–1018. doi: 10.1016/S1474-4422(09)70236-4
26. Duering M, Biessels GJ, Brodtmann A, Chen C, Cordonnier C, de Leeuw FE, Debette S, Frayne R, Jouvent E, Rost NS, et al. Neuroimaging standards for research into small vessel disease-advances since 2013. *Lancet Neurol*. 2023;22:602–618. doi: 10.1016/S1474-4422(23)00131-X
27. Lau KK, Li L, Schulz U, Simoni M, Chan KH, Ho SL, Cheung RTF, Küker W, Mak HKF, Rothwell PM. Total small vessel disease score and risk of recurrent stroke: validation in 2 large cohorts. *Neurology*. 2017;88:2260–2267. doi: 10.1212/WNL.0000000000004042
28. Teodorczuk A, Firbank MJ, Pantoni L, Poggesi A, Erkinjuntti T, Wallin A, Wahlund LO, Scheltens P, Waldemar G, Schrotter G, et al; LADIS Group. Relationship between baseline white-matter changes and development of late-life depressive symptoms: 3-year results from the LADIS study. *Psychol Med*. 2010;40:603–610. doi: 10.1017/S0033291709990857
29. Inzitari D, Pracucci G, Poggesi A, Carlucci G, Barkhof F, Chabriat H, Erkinjuntti T, Fazekas F, Ferro JM, Hennerici M, et al; LADIS Study Group. Changes in white matter as determinant of global functional decline in older independent outpatients: three year follow-up of LADIS (leukoaraiosis and disability) study cohort. *BMJ*. 2009;339:b2477. doi: 10.1136/bmj.b2477
30. Zweiker R, Eber B, Schumacher M, Toplak H, Klein W. "Non-dipping" related to cardiovascular events in essential hypertensive patients. *Acta Med Austriaca*. 1994;21:86–89. PMID: 7701925
31. Foster RG. Sleep, circadian rhythms and health. *Interface Focus*. 2020;10:20190098. doi: 10.1098/rsfs.2019.0098
32. Martino T, Arab S, Straume M, Belsham DD, Tata N, Cai F, Liu P, Trivieri M, Ralph M, Sole MJ. Day/night rhythms in gene expression of the normal murine heart. *J Mol Med (Berl)*. 2004;82:256–264. doi: 10.1007/s00109-003-0520-1
33. Welsh DK, Logothetis DE, Meister M, Reppert SM. Individual neurons dissociated from rat suprachiasmatic nucleus express independently phased circadian firing rhythms. *Neuron*. 1995;14:697–706. doi: 10.1016/0896-6273(95)90214-7
34. Albrecht U. Timing to perfection: the biology of central and peripheral circadian clocks. *Neuron*. 2012;74:246–260. doi: 10.1016/j.neuron.2012.04.006
35. Lucas RJ, Freedman MS, Munoz M, Garcia-Fernandez JM, Foster RG. Regulation of the mammalian pineal by non-rod, non-cone, ocular photoreceptors. *Science*. 1999;284:505–507. doi: 10.1126/science.284.5413.505
36. Freedman MS, Lucas RJ, Soni B, von Schantz M, Muñoz M, David-Gray Z, Foster R. Regulation of mammalian circadian behavior by non-rod, non-cone, ocular photoreceptors. *Science*. 1999;284:502–504. doi: 10.1126/science.284.5413.502
37. Moore RY, Lenn NJ. A retinohypothalamic projection in the rat. *J Comp Neurol*. 1972;146:1–14. doi: 10.1002/cne.901460102
38. Stephan FK, Zucker I. Circadian rhythms in drinking behavior and locomotor activity of rats are eliminated by hypothalamic lesions. *Proc Natl Acad Sci USA*. 1972;69:1583–1586. doi: 10.1073/pnas.69.6.1583
39. Kalsbeek A, Fliers E, Hofman MA, Swaab DF, Buijs RM. Vasopressin and the output of the hypothalamic biological clock. *J Neuroendocrinol*. 2010;22:362–372. doi: 10.1111/j.1365-2826.2010.01956.x
40. Kalsbeek A, Palm IF, La Fleur SE, Scheer FAJL, Perreau-Lenz S, Ruiter M, Kreier F, Cailotto C, Buijs RM. SCN outputs and the hypothalamic balance of life. *J Biol Rhythms*. 2006;21:458–469. doi: 10.1177/0748730406293854
41. Dickmeis T. Glucocorticoids and the circadian clock. *J Endocrinol*. 2009;200:3–22. doi: 10.1677/JOE-08-0415
42. Williams LR, Leggett RW. Reference values for resting blood flow to organs of man. *Clin Phys Physiol Meas*. 1989;10:187–217. doi: 10.1088/0143-0815/10/3/001
43. Claassen J, Thijssen DHJ, Panerai RB, Faraci FM. Regulation of cerebral blood flow in humans: physiology and clinical implications of autoregulation. *Physiol Rev*. 2021;101:1487–1559. doi: 10.1152/physrev.00022.2020
44. Faraci FM, Mayhan WG, Heistad DD. Segmental vascular responses to acute hypertension in cerebrum and brain stem. *Am J Physiol*. 1987;252(4 Pt 2):H738–H742. doi: 10.1152/ajpheart.1987.252.4.H738
45. Lee YK, Rothwell PM, Payne SJ, Webb AJS. Reliability, reproducibility and validity of dynamic cerebral autoregulation in a large cohort with transient ischaemic attack or minor stroke. *Physiol Meas*. 2020;41:095002. doi: 10.1088/1361-6579/abad49
46. Yang S, Webb AJS. Associations between neurovascular coupling and cerebral small vessel disease: a systematic review and meta-analysis. *Eur Stroke J*. 2023;8:895–903. doi: 10.1177/23969873231196981
47. Molina C, Sabin JA, Montaner J, Rovira A, Abilleira S, Codina A. Impaired cerebrovascular reactivity as a risk marker for first-ever lacunar infarction: a case-control study. *Stroke*. 1999;30:2296–2301. doi: 10.1161/01.str.30.11.2296
48. Schubert T, Santini F, Stalder AF, Bock J, Meckel S, Bonati L, Markl M, Wetzel S. Dampening of blood-flow pulsatility along the carotid siphon: does form follow function? *AJNR Am J Neuroradiol*. 2011;32:1107–1112. doi: 10.3174/ajnr.A2426
49. Ogoh S, Brothers RM, Barnes Q, Eubank WL, Hawkins MN, Purkayastha S, O-Yurvati A, Raven PB. The effect of changes in cardiac output on middle cerebral artery mean blood velocity at rest and during exercise. *J Physiol*. 2005;569:697–704. doi: 10.1113/jphysiol.2005.095836
50. Brown CM, Dutsch M, Hecht MJ, Neundorfer B, Hilz MJ. Assessment of cerebrovascular and cardiovascular responses to lower body negative pressure as a test of cerebral autoregulation. *J Neurol Sci*. 2003;208:71–78. doi: 10.1016/s0022-510x(02)00438-0
51. Levine BD, Giller CA, Lane LD, Buckey JC, Blomqvist CG. Cerebral versus systemic hemodynamics during graded orthostatic stress in humans. *Circulation*. 1994;90:298–306. doi: 10.1161/01.cir.90.1.298
52. Rajagopalan B, Raine AE, Cooper R, Ledingham JG. Changes in cerebral blood flow in patients with severe congestive cardiac failure before and after captopril treatment. *Am J Med*. 1984;76:86–90. doi: 10.1016/0002-9343(84)90891-x
53. Gruhn N, Larsen FS, Boesgaard S, Knudsen GM, Mortensen SA, Thomsen G, Aldershvile J. Cerebral blood flow in patients with chronic heart failure before and after heart transplantation. *Stroke*. 2001;32:2530–2533. doi: 10.1161/hs1101.098360
54. Barnett CH, Marsden CD. Functions of the mammalian carotid rete mirabile. *Nature*. 1961;191:88–89. doi: 10.1038/191088a0
55. Webb AJS, Wartolowska KA, Li L, Rothwell PM. Low heart rate is associated with cerebral pulsatility after TIA or minor stroke. *Ann Neurol*. 2022;92:909–920. doi: 10.1002/ana.26480
56. Webb AJ, Simoni M, Mazzucco S, Kuker W, Schulz U, Rothwell PM. Increased cerebral arterial pulsatility in patients with leukoaraiosis: arterial stiffness enhances transmission of aortic pulsatility. *Stroke*. 2012;43:2631–2636. doi: 10.1161/STROKEAHA.112.655837
57. Webb AJS, Lawson A, Wartolowska K, Mazzucco S, Rothwell PM, Cohort OS. Aortic stiffness, pulse pressure, and cerebral pulsatility progress despite best medical management: the OXVASC cohort. *Stroke*. 2022;53:1310–1317. doi: 10.1161/STROKEAHA.121.035560
58. Harper SL, Bohlen HG, Rubin MJ. Arterial and microvascular contributions to cerebral cortical autoregulation in rats. *Am J Physiol*. 1984;246(1 Pt 2):H17–H24. doi: 10.1152/ajpheart.1984.246.1.H17
59. Heistad DD, Marcus ML, Abboud FM. Role of large arteries in regulation of cerebral blood flow in dogs. *J Clin Invest*. 1978;62:761–768. doi: 10.1172/JCI109187
60. Heistad DD, Marcus ML, Piegors DJ, Armstrong ML. Regulation of cerebral blood flow in atherosclerotic monkeys. *Am J Physiol*. 1980;239:H539–H544. doi: 10.1152/ajpheart.1980.239.4.H539
61. Sundgreen C, Larsen FS, Herzog TM, Knudsen GM, Boesgaard S, Aldershvile J. Autoregulation of cerebral blood flow in patients resuscitated from cardiac arrest. *Stroke*. 2001;32:128–132. doi: 10.1161/01.str.32.1.128
62. Dinsdale HB. Hypertensive encephalopathy. *Neurol Clin*. 1983;1:3–16. PMID: 6687306
63. Webb AJ, Rothwell PM. Physiological correlates of beat-to-beat, ambulatory, and day-to-day home blood pressure variability after transient ischemic attack or minor stroke. *Stroke*. 2014;45:533–538. doi: 10.1161/STROKEAHA.113.003321

Downloaded from http://ahajournals.org by on April 3, 2025

64. Lewis NC, Atkinson G, Lucas SJ, Grant EJM, Jones H, Tzeng YC, Horsman H, Ainslie PN. Diurnal variation in time to presyncope and associated circulatory changes during a controlled orthostatic challenge. *Am J Physiol Regul Integr Comp Physiol*. 2010;299:R55–R61. doi: 10.1152/ajpregu.00030.2010
65. Tiecks FP, Lam AM, Aaslid R, Newell DW. Comparison of static and dynamic cerebral autoregulation measurements. *Stroke*. 1995;26:1014–1019. doi: 10.1161/01.str.26.6.1014
66. Aaslid R, Lindegaard KF, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. *Stroke*. 1989;20:45–52. doi: 10.1161/01.str.20.1.45
67. Claassen JA, Meel-van den Abeelen AS, Simpson DM, Panerai RB; International Cerebral Autoregulation Research Network (CARNet). Transfer function analysis of dynamic cerebral autoregulation: a white paper from the International Cerebral Autoregulation Research Network. *J Cereb Blood Flow Metab*. 2016;36:665–680. doi: 10.1177/0271678X15626425
68. Eames PJ, Blake MJ, Dawson SL, Panerai RB, Potter JF. Dynamic cerebral autoregulation and beat to beat blood pressure control are impaired in acute ischaemic stroke. *J Neurol Neurosurg Psychiatry*. 2002;72:467–472. doi: 10.1136/jnnp.72.4.467
69. Beishon L, Clough RH, Kadicheeni M, Chithiramohan T, Panerai RB, Haunton VJ, Minhas JS, Robinson TG. Vascular and haemodynamic issues of brain ageing. *Pflugers Arch*. 2021;473:735–751. doi: 10.1007/s00424-020-02508-9
70. Rashid P, Weaver C, Leonardi-Bee J, Bath F, Fletcher S, Bath P. The effects of transdermal glyceryl trinitrate, a nitric oxide donor, on blood pressure, cerebral and cardiac hemodynamics, and plasma nitric oxide levels in acute stroke. *J Stroke Cerebrovasc Dis*. 2003;12:143–151. doi: 10.1016/S1052-3057(03)00037-5
71. Ainslie PN, Duffin J. Integration of cerebrovascular CO_2 reactivity and chemoreflex control of breathing: mechanisms of regulation, measurement, and interpretation. *Am J Physiol Regul Integr Comp Physiol*. 2009;296:R1473–R1495. doi: 10.1152/ajpregu.91008.2008
72. Webb A, Werring D, Dawson J, Rothman A, Lawson A, Wartolowska K. Design of a randomised, double-blind, crossover, placebo-controlled trial of effects of sildenafil on cerebrovascular function in small vessel disease: Oxford haemodynamic adaptation to reduce pulsatility trial (OxHARP). *Eur Stroke J*. 2021;6:283–290. doi: 10.1177/23969873211026698
73. Dineen NE, Brodie FG, Robinson TG, Panerai RB. Continuous estimates of dynamic cerebral autoregulation during transient hypocapnia and hypercapnia. *J Appl Physiol (1985)*. 2010;108:604–613. doi: 10.1152/japplphysiol.01157.2009
74. Blair GW, Appleton JP, Flaherty K, Doubal F, Sprigg N, Dooley R, Richardson C, Hamilton I, Law ZK, Shi Y, et al. Tolerability, safety and intermediary pharmacological effects of cilostazol and isosorbide mononitrate, alone and combined, in patients with lacunar ischaemic stroke: The LACunar Intervention-1 (LACI-1) trial, a randomised clinical trial. *EClinicalMedicine*. 2019;11:34–43. doi: 10.1016/j.eclinm.2019.04.001
75. Blair GW, Janssen E, Stringer MS, Thrippleton MJ, Chappell F, Shi Y, Hamilton I, Flaherty K, Appleton JP, Doubal FN, et al. Effects of cilostazol and isosorbide mononitrate on cerebral hemodynamics in the LACI-1 randomized controlled trial. *Stroke*. 2022;53:29–33. doi: 10.1161/STROKEAHA.121.034866
76. Zhu WM, Neuhaus A, Beard DJ, Sutherland BA, DeLuca GC. Neurovascular coupling mechanisms in health and neurovascular uncoupling in Alzheimer's disease. *Brain*. 2022;145:2276–2292. doi: 10.1093/brain/awac174
77. Maggio P, Salinet AS, Panerai RB, Robinson TG. Does hypercapnia-induced impairment of cerebral autoregulation affect neurovascular coupling? A functional TCD study. *J Appl Physiol (1985)*. 2013;115:491–497. doi: 10.1152/japplphysiol.00327.2013
78. Staessen JA, Bieniaszewski L, O'Brien E, Gosse P, Hayashi H, Imai Y, Kawasaki T, Otsuka K, Palatini P, Thijs L, et al. Nocturnal blood pressure fall on ambulatory monitoring in a large international database. The "Ad Hoc' Working Group. *Hypertension*. 1997;29(1 Pt 1):30–39. doi: 10.1161/01.hyp.29.1.30
79. O'Brien E, Parati G, Stergiou G, Asmar R, Beilin L, Bilo G, Clement D, de la Sierra A, de Leeuw P, Dolan E, et al; European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension position paper on ambulatory blood pressure monitoring. *J Hypertens*. 2013;31:1731–1768. doi: 10.1097/HJH.0b013e328363e964
80. O'Brien E, Sheridan J, O'Malley K. Dippers and non-dippers. *Lancet*. 1988;2:397. doi: 10.1016/s0140-6736(88)92867-x
81. Dolan E, Stanton A, Thijs L, Hinedi K, Atkins N, McClory S, Den Hond E, McCormack P, Staessen JA, O'Brien E. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. *Hypertension*. 2005;46:156–161. doi: 10.1161/01.HYP.0000170138.56903.7a
82. Mancia G, Kreutz R, Brunstrom M, Burnier M, Grassi G, Januszewicz A, Lorenza Muiesan M, Tsioufis K, Agabiti-Rosei E, Abd Elhady Algharably E, et al. 2023 ESH guidelines for the management of arterial hypertension. The task force for the management of arterial hypertension of the European Society of Hypertension: endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). *J Hypertens*. 2023;41:1874–2071. doi: 10.1097/HJH.0000000000003480
83. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71:1269–1324. doi: 10.1161/HYP.0000000000000066
84. Siennicki-Lantz A, Reinprecht F, Axelsson J, Elmstahl S. Cerebral perfusion in the elderly with nocturnal blood pressure fall. *Eur J Neurol*. 2007;14:715–720. doi: 10.1111/j.1468-1331.2007.01805.x
85. Sindrup JH, Kastrup J, Christensen H, Jorgensen B. Nocturnal variations in peripheral blood flow, systemic blood pressure, and heart rate in humans. *Am J Physiol*. 1991;261(4 Pt 2):H982–H988. doi: 10.1152/ajpheart.1991.261.4.H982
86. Bray MS, Shaw CA, Moore MW, Garcia RAP, Zanquetta MM, Durgan DJ, Jeong WJ, Tsai JY, Bugger H, Zhang D, et al. Disruption of the circadian clock within the cardiomyocyte influences myocardial contractile function, metabolism, and gene expression. *Am J Physiol Heart Circ Physiol*. 2008;294:H1036–H1047. doi: 10.1152/ajpheart.01291.2007
87. Narkiewicz K, Somers VK. Interactive effect of heart rate and muscle sympathetic nerve activity on blood pressure. *Circulation*. 1999;100:2514–2518. doi: 10.1161/01.cir.100.25.2514
88. Narkiewicz K, Winnicki M, Schroeder K, Phillips BG, Kato M, Cwalina E, Somers VK. Relationship between muscle sympathetic nerve activity and diurnal blood pressure profile. *Hypertension*. 2002;39:168–172. doi: 10.1161/hy1201.097302
89. Dodt C, Breckling U, Derad I, Fehm HL, Born J. Plasma epinephrine and norepinephrine concentrations of healthy humans associated with nighttime sleep and morning arousal. *Hypertension*. 1997;30(1 Pt 1):71–76. doi: 10.1161/01.hyp.30.1.71
90. Kario K, Pickering TG, Umeda Y, Hoshide S, Hoshide Y, Morinari M, Murata M, Kuroda T, Schwartz JE, Shimada K. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. *Circulation*. 2003;107:1401–1406. doi: 10.1161/01.cir.0000056521.67546.aa
91. Noriega de la Colina A, Badji A, Robitaille-Grou MC, Gagnon C, Boshkovski T, Lamarre-Cliche M, Joubert S, Gauthier CJ, Bherer L, Cohen-Adad J, et al. Associations between relative morning blood pressure, cerebral blood flow, and memory in older adults treated and controlled for hypertension. *Hypertension*. 2021;77:1703–1713. doi: 10.1161/HYPERTENSIONAHA.120.16124
92. Jenkins DJA, Sahye-Pudaruth S, Khodabandehlou K, Liang F, Kasmani M, Wanyan J, Wang M, Selvaganesh K, Paquette M, Patel D, et al. Systematic review and meta-analysis examining the relationship between postprandial hypotension, cardiovascular events, and all-cause mortality. *Am J Clin Nutr*. 2022;116:663–671. doi: 10.1093/ajcn/nqac158
93. Munakata M, Kameyama J, Kanazawa M, Nunokawa T, Moriai N, Yoshinaga K. Circadian blood pressure rhythm in patients with higher and lower spinal cord injury: simultaneous evaluation of autonomic nervous activity and physical activity. *J Hypertens*. 1997;15(12 Pt 2):1745–1749. doi: 10.1097/00004872-199715120-00083
94. Goldstein DS, Holmes C, Cannon RO 3rd, Eisenhofer G, Kopin IJ. Sympathetic cardioneuropathy in dysautonomias. *Adv Pharmacol*. 1998;42:615–619.
95. Aoki K, Stephens DP, Johnson JM. Diurnal variation in cutaneous vasodilator and vasoconstrictor systems during heat stress. *Am J Physiol Regul Integr Comp Physiol*. 2001;281:R591–R595. doi: 10.1152/ajpregu.2001.281.2.R591
96. Mozdzan M, Mozdzan M, Chalubinski M, Wojdan K, Broncel M. The effect of melatonin on circadian blood pressure in patients with type 2 diabetes and essential hypertension. *Arch Med Sci*. 2014;10:669–675. doi: 10.5114/aoms.2014.44858
97. Portaluppi F, Cortelli P, Provini F, Plazzi G, Manfredini R, Lugaresi E. Alterations of sleep and circadian blood pressure profile. *Blood Press Monit*. 1997;2:301–313. PMID: 10234133
98. Cho MC. Clinical significance and therapeutic implication of nocturnal hypertension: relationship between nighttime blood pressure and quality of sleep. *Korean Circ J*. 2019;49:818–828. doi: 10.4070/kcj.2019.0245

Downloaded from http://ahajournals.org by on April 3, 2025

99. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambar S, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet*. 2009;373:1275–1281. doi: 10.1016/S0140-6736(09)60566-3
100. Hermida RC, Crespo JJ, Dominguez-Sardina M, Otero A, Moyá A, Ríos MT, Sineiro E, Castiñeira MC, Callejas PA, Pousa L, et al; Hygia Project Investigators. Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia Chronotherapy Trial. *Eur Heart J*. 2020;41:4565–4576. doi: 10.1093/eurheartj/ehz754
101. Mackenzie IS, Rogers A, Poulter NR, Williams B, Brown MJ, Webb DJ, Ford I, Rorie DA, Guthrie G, Grieve JWK, et al; TIME Study Group. Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study): a prospective, randomised, open-label, blinded-endpoint clinical trial. *Lancet*. 2022;400:1417–1425. doi: 10.1016/S0140-6736(22)01786-X
102. Poulter NR, Savopoulos C, Anjum A, Apostolopoulou M, Chapman N, Cross M, Falaschetti E, Fotiadis S, James RM, Kanellos I, et al. Randomized crossover trial of the impact of morning or evening dosing of antihypertensive agents on 24-hour ambulatory blood pressure. *Hypertension*. 2018;72:870–873. doi: 10.1161/HYPERTENSIONAHA.118.11101
103. Mia S, Sonkar R, Williams L, Latimer MN, Rawnsley DR, Rana S, He J, Dierickx P, Kim T, Xie M, et al. Novel roles for the transcriptional repressor E4BP4 in both cardiac physiology and pathophysiology. *JACC Basic Transl Sci*. 2023;8:1141–1156. doi: 10.1016/j.jacbts.2023.03.016
104. Yamashita T, Sekiguchi A, Iwasaki YK, Sagara K, Iinuma H, Hatano S, Fu LT, Watanabe H. Circadian variation of cardiac K+ channel gene expression. *Circulation*. 2003;107:1917–1922. doi: 10.1161/01.CIR.0000058752.79734.F0
105. Young ME, Latimer MN. Circadian rhythms in cardiac metabolic flexibility. *Chronobiol Int*. 2023;40:13–26. doi: 10.1080/07420528.2021.1939366
106. Nonaka H, Emoto N, Ikeda K, Fukuya H, Rohman MS, Raharjo SB, Yagita K, Okamura H, Yokoyama M. Angiotensin II induces circadian gene expression of clock genes in cultured vascular smooth muscle cells. *Circulation*. 2001;104:1746–1748. doi: 10.1161/hc4001.098048
107. Durgan DJ, Hotze MA, Tomlin TM, Egbejimi O, Graveleau C, Abel ED, Shaw CA, Bray MS, Hardin PE, Young ME. The intrinsic circadian clock within the cardiomyocyte. *Am J Physiol Heart Circ Physiol*. 2005;289:H1530–H1541. doi: 10.1152/ajpheart.00406.2005
108. Ding M, Wang R, Kalpouzos G, Laukka EJ, Li Y, Johnell K, Fratiglioni L, Qiu C. Cerebral small vessel disease associated with atrial fibrillation among older adults: a population-based study. *Stroke*. 2021;52:2685–2689. doi: 10.1161/STROKEAHA.120.031573
109. Speed C, Arneil T, Harle R, Wilson A, Karthikesalingam A, McConnell M, Phillips J. Measure by measure: resting heart rate across the 24-hour cycle. *PLOS Digit Health*. 2023;2:e0000236. doi: 10.1371/journal.pdig.0000236
110. Young ME, Razeghi P, Cedars AM, Guthrie PH, Taegtmeyer H. Intrinsic diurnal variations in cardiac metabolism and contractile function. *Circ Res*. 2001;89:1199–1208. doi: 10.1161/hh2401.100741
111. Bigger JT Jr, Steinman RC, Rolnitzky LM, Fleiss JL, Albrecht P, Cohen RJ. Power law behavior of RR-interval variability in healthy middle-aged persons, patients with recent acute myocardial infarction, and patients with heart transplants. *Circulation*. 1996;93:2142–2151. doi: 10.1161/01.cir.93.12.2142
112. Tong M, Watanabe E, Yamamoto N, Nagahata-Ishiguro M, Maemura K, Takeda N, Nagai R, Ozaki Y. Circadian expressions of cardiac ion channel genes in mouse might be associated with the central clock in the SCN but not the peripheral clock in the heart. *Biol Rhythm Res*. 2013;44:519–530. doi: 10.1080/09291016.2012.704801
113. Hablitz LM, Pla V, Giannetto M, Vinitsky HS, Stæger FF, Metcalfe T, Nguyen R, Benrais A, Nedergaard M. Circadian control of brain glymphatic and lymphatic fluid flow. *Nat Commun*. 2020;11:4411. doi: 10.1038/s41467-020-18115-2
114. Ben-Dov IZ, Kark JD, Ben-Ishay D, Mekler J, Ben-Arie L, Bursztyn M. Blunted heart rate dip during sleep and all-cause mortality. *Arch Intern Med*. 2007;167:2116–2121. doi: 10.1001/archinte.167.19.2116
115. Northcote RJ, Canning GP, Ballantyne D. Electrocardiographic findings in male veteran endurance athletes. *Br Heart J*. 1989;61:155–160. doi: 10.1136/hrt.61.2.155
116. Shusterman V, Warman E, London B, Schwartzman D. Nocturnal peak in atrial tachyarrhythmia occurrence as a function of arrhythmia burden. *J Cardiovasc Electrophysiol*. 2012;23:604–611. doi: 10.1111/j.1540-8167.2011.02263.x
117. Muhling J, Dehne MG, Sablotzki A, Hempelmann G. Cerebral blood flow velocity during isovolemic hemodilution and subsequent autologous blood retransfusion. *Can J Anaesth*. 1999;46:550–557. doi: 10.1007/BF03013545
118. Seaman GV, Engel R, Swank RL, Hissen W. Circadian periodicity in some physicochemical parameters of circulating blood. *Nature*. 1965;207:833–835. doi: 10.1038/207833a0
119. Convertino VA. Blood volume response to physical activity and inactivity. *Am J Med Sci*. 2007;334:72–79. doi: 10.1097/MAJ.0b013e318063c6e4
120. Huamaní C, Bayona-Pancorbo W, Sarmiento W, Córdova-Heredia G, Cruz-Huanca L, Damián-Saavedra P, Requena N, Oré-Montalvo V, Pérez-Alviz C, Acuña-Mamani JC. Does blood viscosity affect cerebral blood flow? A study in a population living in a high-altitude city. *medRxiv*. 2023. doi: 10.1101/2023.01.15.23284577
121. Tomiyama Y, Brian JE Jr, Todd MM. Plasma viscosity and cerebral blood flow. *Am J Physiol Heart Circ Physiol*. 2000;279:H1949–H1954. doi: 10.1152/ajpheart.2000.279.4.H1949
122. Song SH, Kim JH, Lee JH, Yun YM, Choi DH, Kim HY. Elevated blood viscosity is associated with cerebral small vessel disease in patients with acute ischemic stroke. *BMC Neurol*. 2017;17:20. doi: 10.1186/s12883-017-0808-3
123. Li RY, Cao ZG, Li Y, Wang RT. Increased whole blood viscosity is associated with silent cerebral infarction. *Clin Hemorheol Microcirc*. 2015;59:301–307. doi: 10.3233/CH-131760
124. Lee H, Heo J, Lee IH, Kim YD, Nam HS. Association between blood viscosity and early neurological deterioration in lacunar infarction. *Front Neurol*. 2022;13:979073. doi: 10.3389/fneur.2022.979073
125. Etsuda H, Takase B, Uehata A, Kusano H, Hamabe A, Kuhara R, Akima T, Matsushima Y, Arakawa K, Satomura K, et al. Morning attenuation of endothelium-dependent, flow-mediated dilation in healthy young men: possible connection to morning peak of cardiac events? *Clin Cardiol*. 1999;22:417–421. doi: 10.1002/clc.4960220610
126. Panza JA, Epstein SE, Quyyumi AA. Circadian variation in vascular tone and its relation to alpha-sympathetic vasoconstrictor activity. *N Engl J Med*. 1991;325:986–990. doi: 10.1056/NEJM199110033251402
127. Reilly DF, Curtis AM, Cheng Y, Westgate EJ, Rudic RD, Paschos G, Morris J, Ouyang M, Thomas SA, FitzGerald GA. Peripheral circadian clock rhythmicity is retained in the absence of adrenergic signaling. *Arterioscler Thromb Vasc Biol*. 2008;28:121–126. doi: 10.1161/ATVBAHA.107.152538
128. Davidson AJ, London B, Block GD, Menaker M. Cardiovascular tissues contain independent circadian clocks. *Clin Exp Hypertens*. 2005;27:307–311. PMID: 15835394
129. Rudic RD, McNamara P, Reilly D, Grosser T, Curtis AM, Price TS, Panda S, Hogenesch JB, FitzGerald GA. Bioinformatic analysis of circadian gene oscillation in mouse aorta. *Circulation*. 2005;112:2716–2724. doi: 10.1161/CIRCULATIONAHA.105.568626
130. Tunctan B, Weigl Y, Dotan A, Peleg L, Zengil H, Ashkenazi I, Abacioğlu N. Circadian variation of nitric oxide synthase activity in mouse tissue. *Chronobiol Int*. 2002;19:393–404. doi: 10.1081/cbi-120002915
131. Palmer MJ. Endothelin receptor antagonists: status and learning 20 years on. *Prog Med Chem*. 2009;47:203–237. doi: 10.1016/S0079-6468(08)00205-1
132. Viswambharan H, Carvas JM, Antic V, Marecic A, Jud C, Zaugg CE, Ming XF, Montani JP, Albrecht U, Yang Z. Mutation of the circadian clock gene Per2 alters vascular endothelial function. *Circulation*. 2007;115:2188–2195. doi: 10.1161/CIRCULATIONAHA.106.653303
133. Wang CY, Wen MS, Wang HW, Hsieh IC, Li Y, Liu PY, Lin FC, Liao JK. Increased vascular senescence and impaired endothelial progenitor cell function mediated by mutation of circadian gene Per2. *Circulation*. 2008;118:2166–2173. doi: 10.1161/CIRCULATIONAHA.108.790469
134. Xie Z, Su W, Liu S, Zhao G, Esser K, Schroder EA, Lefta M, Stauss HM, Guo Z, Gong MC. Smooth-muscle BMAL1 participates in blood pressure circadian rhythm regulation. *J Clin Invest*. 2015;125:324–336. doi: 10.1172/JCI76881
135. Kunieda T, Minamino T, Miura K, Katsuno T, Tateno K, Miyauchi H, Kaneko S, Bradfield CA, FitzGerald GA, Komuro I. Reduced nitric oxide causes age-associated impairment of circadian rhythmicity. *Circ Res*. 2008;102:607–614. doi: 10.1161/CIRCRESAHA.107.162230
136. Nernpermpisooth N, Qiu S, Mintz JD, Suvitayavat W, Thirawarapan S, Rudic DR, Fulton DJ, Stepp DW. Obesity alters the peripheral circadian clock in the aorta and microcirculation. *Microcirculation*. 2015;22:257–266. doi: 10.1111/micc.12192
137. Thosar SS, Berman AM, Herzig MX, McHill AW, Bowles NP, Swanson CM, Clemons NA, Butler MP, Clemons AA, Emens JS, et al. Circadian rhythm of vascular function in midlife adults. *Arterioscler Thromb Vasc Biol*. 2019;39:1203–1211. doi: 10.1161/ATVBAHA.119.312682

Downloaded from http://ahajournals.org by on April 3, 2025

138. Endo Y, Jinnai K, Endo M, Fujita K, Kimura F. Diurnal variation of cerebral blood flow in rat hippocampus. *Stroke*. 1990;21:1464–1469. doi: 10.1161/01.str.21.10.1464
139. Wauschkuhn CA, Witte K, Gorbey S, Lemmer B, Schilling L. Circadian periodicity of cerebral blood flow revealed by laser-Doppler flowmetry in awake rats: relation to blood pressure and activity. *Am J Physiol Heart Circ Physiol*. 2005;289:H1662–H1668. doi: 10.1152/ajpheart.01242.2004
140. Droste DW, Berger W, Schuler E, Krauss JK. Middle cerebral artery blood flow velocity in healthy persons during wakefulness and sleep: a transcranial Doppler study. *Sleep*. 1993;16:603–609. PMID: 7904769
141. Conroy DA, Spielman AJ, Scott RQ. Daily rhythm of cerebral blood flow velocity. *J Circadian Rhythms*. 2005;3:3. doi: 10.1186/1740-3391-3-3
142. Meyer JS, Ishikawa Y, Hata T, Karacan I. Cerebral blood flow in normal and abnormal sleep and dreaming. *Brain Cogn*. 1987;6:266–294. doi: 10.1016/0278-2626(87)90127-8
143. Madsen PL, Holm S, Vorstrup S, Friberg L, Lassen NA, Wildschiodtz G. Human regional cerebral blood flow during rapid-eye-movement sleep. *J Cereb Blood Flow Metab*. 1991;11:502–507. doi: 10.1038/jcbfm.1991.94
144. Hajak G, Klingelhofer J, Schulz-Varszegi M, Sander D, Ruther E. Sleep apnea syndrome and cerebral hemodynamics. *Chest*. 1996;110:670–679. doi: 10.1378/chest.110.3.670
145. Strohm J, Duffin J, Fisher JA. Circadian cerebrovascular reactivity to CO_2. *Respir Physiol Neurobiol*. 2014;197:15–18. doi: 10.1016/j.resp.2014.03.003
146. Shariffi B, Lloyd IN, Cessac ME, Harper JL, Limberg JK. Reproducibility and diurnal variation in middle cerebral artery blood velocity in healthy humans. *Exp Physiol*. 2023;108:692–705. doi: 10.1113/EP090873
147. Labrecque L, Burma JS, Roy MA, Smirl JD, Brassard P. Reproducibility and diurnal variation of the directional sensitivity of the cerebral pressure-flow relationship in men and women. *J Appl Physiol (1985)*. 2022;132:154–166. doi: 10.1152/japplphysiol.00653.2021
148. Diamant M, Harms MP, Immink RV, Van Lieshout JJ, Van Montfrans GA. Twenty-four-hour non-invasive monitoring of systemic haemodynamics and cerebral blood flow velocity in healthy humans. *Acta Physiol Scand*. 2002;175:1–9. doi: 10.1046/j.1365-201X.2002.00953.x
149. Cummings KJ, Swart M, Ainslie PN. Morning attenuation in cerebrovascular CO_2 reactivity in healthy humans is associated with a lowered cerebral oxygenation and an augmented ventilatory response to CO_2. *J Appl Physiol (1985)*. 2007;102:1891–1898. doi: 10.1152/japplphysiol.01437.2006
150. Lewis NC, Atkinson G, Lucas SJ, Grant EJM, Jones H, Tzeng YC, Horsman H, Ainslie PN. Is there diurnal variation in initial and delayed orthostatic hypotension during standing and head-up tilt? *Chronobiol Int*. 2011;28:135–145. doi: 10.3109/07420528.2010.536283
151. Lewis NC, Ainslie PN, Atkinson G, Jones H, Grant EJ, Lucas SJ. The effect of time-of-day and sympathetic alpha1-blockade on orthostatic tolerance. *Chronobiol Int*. 2012;29:882–890. doi: 10.3109/07420528.2012.699121
152. Lidington D, Wan H, Dinh DD, Ng C, Bolz SS. Circadian rhythmicity in cerebral microvascular tone influences subarachnoid hemorrhage-induced injury. *Stroke*. 2022;53:249–259. doi: 10.1161/STROKEAHA.121.036950
153. Ainslie PN, Murrell C, Peebles K, Swart M, Skinner MA, Williams MJA, Taylor RD. Early morning impairment in cerebral autoregulation and cerebrovascular CO_2 reactivity in healthy humans: relation to endothelial function. *Exp Physiol*. 2007;92:769–777. doi: 10.1113/expphysiol.2006.036814
154. Ameriso SF, Mohler JG, Suarez M, Fisher M. Morning reduction of cerebral vasomotor reactivity. *Neurology*. 1994;44:1907–1909. doi: 10.1212/wnl.44.10.1907
155. Hajjar I, Selim M, Novak P, Novak V. The relationship between nighttime dipping in blood pressure and cerebral hemodynamics in nonstroke patients. *J Clin Hypertens (Greenwich)*. 2007;9:929–936. doi: 10.1111/j.1524-6175.2007.07342.x
156. Burma JS, Copeland P, Macaulay A, Khatra O, Smirl JD. Comparison of diurnal variation, anatomical location, and biological sex within spontaneous and driven dynamic cerebral autoregulation measures. *Physiol Rep*. 2020;8:e14458. doi: 10.14814/phy2.14458
157. Claassen JA, Levine BD, Zhang R. Dynamic cerebral autoregulation during repeated squat-stand maneuvers. *J Appl Physiol (1985)*. 2009;106:153–160. doi: 10.1152/japplphysiol.90822.2008
158. Abadjiev DS, Toschi-Dias E, Salinet AS, Gaykova NN, Lo MT, Nogueira RC, Hu K. Daily rhythm of dynamic cerebral autoregulation in patients after stroke. *J Cereb Blood Flow Metab*. 2023;43:989–998. doi: 10.1177/0271678X231153750
159. Makino M, Hayashi H, Takezawa H, Hirai M, Saito H, Ebihara S. Circadian rhythms of cardiovascular functions are modulated by the baroreflex and the autonomic nervous system in the rat. *Circulation*. 1997;96:1667–1674. doi: 10.1161/01.cir.96.5.1667
160. Chalmers JA, Martino TA, Tata N, Ralph MR, Sole MJ, Belsham DD. Vascular circadian rhythms in a mouse vascular smooth muscle cell line (Movas-1). *Am J Physiol Regul Integr Comp Physiol*. 2008;295:R1529–R1538. doi: 10.1152/ajpregu.90572.2008
161. Pulido RS, Munji RN, Chan TC, Quirk CR, Weiner GA, Weger BD, Rossi MJ, Elmsaouri S, Malfavon M, Deng A, et al. Neuronal activity regulates blood-brain barrier efflux transport through endothelial circadian genes. *Neuron*. 2020;108:937–952.e7. doi: 10.1016/j.neuron.2020.09.002
162. Zhang SL, Lahens NF, Yue Z, Arnold DM, Pakstis PP, Schwarz JE, Sehgal A. A circadian clock regulates efflux by the blood-brain barrier in mice and human cells. *Nat Commun*. 2021;12:617. doi: 10.1038/s41467-020-20795-9
163. Mastrullo V, van der Veen DR, Gupta P, Matos RS, Johnston JD, McVey JH, Madeddu P, Velliou EG, Campagnolo P. Pericytes' circadian clock affects endothelial cells' synchronization and angiogenesis in a 3D tissue engineered scaffold. *Front Pharmacol*. 2022;13:867070. doi: 10.3389/fphar.2022.867070
164. Carver KA, Lourim D, Tryba AK, Harder DR. Rhythmic expression of cytochrome P450 epoxygenases CYP4x1 and CYP2c11 in the rat brain and vasculature. *Am J Physiol Cell Physiol*. 2014;307:CC989–CC998. doi: 10.1152/ajpcell.00401.2013
165. Hodkinson DJ, O'Daly O, Zunszain PA, Pariante CM, Lazurenko V, Zelaya FO, Howard MA, Williams SCR. Circadian and homeostatic modulation of functional connectivity and regional cerebral blood flow in humans under normal entrained conditions. *J Cereb Blood Flow Metab*. 2014;34:1493–1499. doi: 10.1038/jcbfm.2014.109
166. Blautzik J, Vetter C, Peres I, Gutyrchik E, Keeser D, Berman A, Kirsch V, Mueller S, Pöppel E, Reiser M, et al. Classifying fMRI-derived resting-state connectivity patterns according to their daily rhythmicity. *Neuroimage*. 2013;71:298–306. doi: 10.1016/j.neuroimage.2012.08.010
167. Schroeter ML, Bucheler MM, Scheid R. Circadian variability is negligible in primary visual cortices as measured by fNIRS. *Int J Psychophysiol*. 2006;62:9–13. doi: 10.1016/j.ijpsycho.2005.11.003
168. Della Corte V, Tuttolomondo A, Pecoraro R, Di Raimondo D, Vassallo V, Pinto A. Inflammation, endothelial dysfunction and arterial stiffness as therapeutic targets in cardiovascular medicine. *Curr Pharm Des*. 2016;22:4658–4668. doi: 10.2174/1381612822666160510124801
169. Markus HS, Lythgoe DJ, Ostegaard L, O'Sullivan M, Williams SC. Reduced cerebral blood flow in white matter in ischaemic leukoaraiosis demonstrated using quantitative exogenous contrast based perfusion MRI. *J Neurol Neurosurg Psychiatry*. 2000;69:48–53. doi: 10.1136/jnnp.69.1.48
170. Scheer FA, Van Montfrans GA, van Someren EJ, Mairuhu G, Buijs RM. Daily nighttime melatonin reduces blood pressure in male patients with essential hypertension. *Hypertension*. 2004;43:192–197. doi: 10.1161/01.HYP.0000113293.15186.3b
171. Tochikubo O, Minamisawa K, Miyakawa T, Miyajima E, Fujiki Y, Ishii M. Blood pressure during sleep: antihypertensive medication. *Am J Cardiol*. 1991;67:18B–25B. doi: 10.1016/0002-9149(91)90816-4
172. Oxlund CS, Henriksen JE, Tarnow L, Schousboe K, Gram J, Jacobsen IA. Low dose spironolactone reduces blood pressure in patients with resistant hypertension and type 2 diabetes mellitus: a double blind randomized clinical trial. *J Hypertens*. 2013;31:2094–2102. doi: 10.1097/HJH.0b013e3283638b1a
173. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, Fetsch T, van Gelder IC, Haase D, Haegeli LM, et al; EAST-AFNET 4 Trial Investigators. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med*. 2020;383:1305–1316. doi: 10.1056/NEJMoa2019422
174. Bath PM, Mhlanga I, Woodhouse LJ, Doubal F, Oatey K, Montgomery AA, Wardlaw JM; LACI-2 Trial Investigators. Cilostazol and isosorbide mononitrate for the prevention of progression of cerebral small vessel disease: baseline data and statistical analysis plan for the Lacunar Intervention Trial-2 (LACI-2) (ISRCTN14911850). *Stroke Vasc Neurol*. 2023;8:134–143. doi: 10.1136/svn-2022-001816
175. Hankey GJ. CSPS.com Trial of adding cilostazol to antiplatelet therapy to reduce recurrent stroke. *Stroke*. 2020;51:696–698. doi: 10.1161/STROKEAHA.119.028409
176. Shinohara Y, Katayama Y, Uchiyama S, Yamaguchi T, Handa S, Matsuoka K, Ohashi Y, Tanahashi N, Yamamoto H, Genka C, et al; CSPS 2 Group. Cilostazol for prevention of secondary stroke (CSPS 2): an aspirin-controlled, double-blind, randomised non-inferiority trial. *Lancet Neurol*. 2010;9:959–968. doi: 10.1016/S1474-4422(10)70198-8
177. Kim BJ, Kwon SU, Park JH, Kim YJ, Hong KS, Wong LKS, Yu S, Hwang YH, Lee JS, Lee J, et al; PICASSO Investigators. Cilostazol versus aspirin in ischemic stroke patients with high-risk cerebral

Downloaded from http://ahajournals.org by on April 3, 2025

hemorrhage: subgroup analysis of the PICASSO trial. *Stroke*. 2020;51:931–937. doi: 10.1161/STROKEAHA.119.023855
178. Han SW, Lee SS, Kim SH, Lee JH, Kim GS, Kim OJ, Koh IS, Lee JY, Suk SH, Lee SI, et al. Effect of cilostazol in acute lacunar infarction based on pulsatility index of transcranial Doppler (ECLIPse): a multicenter, randomized, double-blind, placebo-controlled trial. *Eur Neurol*. 2013;69:33–40. doi: 10.1159/000338247
179. Kopczak A, Stringer MS, van den Brink H, Kerkhofs D, Blair GW, van Dinther M, Onkenhout L, Wartolowska KA, Thrippleton MJ, Duering M, et al. The EffecTs of amlodipine and other blood PREssure lowering agents on microvascular FuncTion in Small Vessel Diseases (TREAT-SVDs) trial: study protocol for a randomised crossover trial. *Eur Stroke J*. 2023;8:387–397. doi: 10.1177/23969873221143570
180. Pauls MMH, Binnie LR, Benjamin P, Betteridge S, Clarke B, Dhillon MK, Ghatala R, Hainsworth FAH, Howe FA, Khan U, et al. The PASTIS trial: Testing tadalafil for possible use in vascular cognitive impairment. *Alzheimers Dement*. 2022;18:2393–2402. doi: 10.1002/alz.12559
181. Bath PM, Woodhouse LJ, Krishnan K, Appleton JP, Anderson CS, Berge E, Cala L, Dixon M, England TJ, Godolphin PJ, et al. Prehospital transdermal glyceryl trinitrate for ultra-acute intracerebral hemorrhage: data from the RIGHT-2 trial. *Stroke*. 2019;50:3064–3071. doi: 10.1161/STROKEAHA.119.026389
182. Suzuki M, Guilleminault C, Otsuka K, Shiomi T. Blood pressure "dipping" and "non-dipping" in obstructive sleep apnea syndrome patients. *Sleep*. 1996;19:382–387. doi: 10.1093/sleep/19.5.382
183. Thomas J, Jezzard P, Webb AJS. Low-frequency oscillations in the brain show differential regional associations with severity of cerebral small vessel disease: a systematic review. *Front Neurol*. 2023;17:1254209. doi: 10.3389/fnins.2023.1254209
184. Enevoldsen EM, Jensen FT. Autoregulation and CO2 responses of cerebral blood flow in patients with acute severe head injury. *J Neurosurg*. 1978;48:689–703. doi: 10.3171/jns.1978.48.5.0689
185. Agrawal S, Placek MM, White D, Daubney E, Cabeleira M, Smielewski P, Czosnyka M, Young A, Watson S, Maw A, et al. Studying Trends of Auto-Regulation in Severe Head Injury in Paediatrics (STARSHIP): protocol to study cerebral autoregulation in a prospective multicentre observational research database study. *BMJ Open*. 2023;13:e071800. doi: 10.1136/bmjopen-2023-071800

Downloaded from http://ahajournals.org by on April 3, 2025