Have a safe night: intimate protection against cerebral hyperperfusion during REM sleep

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STUDIES using a variety of methods (transcranial Doppler ultrasonography, \(^{133}\)Xe inhalation, and single-photon emission computerized tomography) have shown a reduction (\( \sim 10–20\% \)) in cerebral blood flow (CBF) during non-rapid-eye-movement (NREM) sleep and an increase (\( \sim 20–35\% \)) during rapid-eye-movement (REM) sleep compared with wakeful state in healthy humans (5, 6). The close coupling between cerebral activity and cerebral perfusion in REM sleep indicates that metabolic mechanisms of CBF regulation are more important in REM compared with NREM sleep. In REM sleep, high levels of cortical activity are accompanied by increases in CBF; thus CBF regulation has been thought to be heavily influenced by metabolic rate (6). The mechanisms, however, that regulate CBF during sleep are poorly understood and are likely to differ from those during wakefulness. For example, during wakefulness, powerful regulatory influences such as cerebral autoregulation, neuronal activation, cerebrovascular CO\(_2\) reactivity, and, potentially, cardiac output all interact to regulate CBF in a complex and likely nonlinear manner (9). Although there is little evidence in humans that sympathetic nervous activity (SNA) directly regulates CBF during wakefulness, perhaps masked by these other more powerful factors, there is a certain amount of autonomic influence over cerebral auto-regulation (10). However, as illustrated in Fig. 1, it seems likely that cerebral autoregulation (4), neuronal activation (6), and cerebrovascular CO\(_2\) reactivity (8) are reduced during NREM sleep. It should be noted, however, that alterations in cerebrovascular CO\(_2\) reactivity during sleep are unclear; the finding in humans of a marked reduction in cerebrovascular CO\(_2\) reactivity during NREM sleep (8) has not been recently confirmed in the highly controlled lamb model (2). Moreover, in this animal study, it was reported that cerebral SNA is withdrawn during REM sleep and, because of this, the CBF response to hypercapnia is augmented (2). Nevertheless, the sleep-related redundancies of these normal powerful regulatory systems highlight the need for other processes to become operant to help maintain CBF within relatively narrow limits. When CBF is reduced below a critical limit, and oxygen extraction is maximized, global ischemia is imminent. Cerebral perfusion pressures above a critical level may result in breakthrough edema, hemorrhage, seizures, and posterior leukoencephalopathy. The importance of CBF regulation during sleep is underscored by the common (10–40\%) nighttime occurrence of strokes (7).

Dramatic fluctuations in blood pressure are common in a range of situations such as exercise, postural change, coughing, defecation, and sexual activity. Nevertheless, at least in humans free of pathology, such alterations in blood pressure can be well tolerated because of powerful autoregulatory mechanisms that help maintain CBF within safe limits (9). Somewhat surprisingly, marked fluctuations in arterial blood pressure (up to 100\%) also occur during transition from NREM into REM sleep; such changes from NREM into REM sleep, in humans, have been associated with even more marked changes in muscle sympathetic nerve activity (11). Despite intensive study, and the presence of a rich extrinsic sympathetic innervation in the cerebral vessels (reviewed in Ref. 10), the importance of SNA in regulating CBF in humans is not well understood and has been the subject of a recent point-by-point debate in this Journal (12, 13).

In this issue of the Journal of Applied Physiology, Cassaglia and colleagues (3) demonstrate an impressive data set that, via the novel continuous recording of SNA in the superior cervical ganglion, adds substantial information to the field of cerebrovascular physiology and sheds light on the potential role of SNA in the regulation of CBF. The findings from this elegant study indicate that marked elevations in SNA to the cerebral vessels occur in anticipation of large elevations in blood pressure during phasic REM sleep; it seems logical that such changes in SNA activation may act to protect otherwise vulnerable cerebral microvessels against excessive elevations in perfusion pressure. The basis of this work follows from a previous study during wakefulness (2) in which SNA directed to cerebral vessels increases with acute hypertension, but not with hypotension, indicating that it serves a protective function for the cerebral microcirculation, and not a regulatory role for maintenance of systemic arterial pressure. Their most recent study extends these findings and shows that the protective role of SNA might be particularly important during sleep, especially during REM sleep where fluctuations in blood pressure are most marked (11). Thus cerebral hyperperfusion or hyperperfusion that is not corrected by SNA might be a critical “trigger,” underlining the high incidence of ischemic or hemorrhagic strokes during sleep, respectively (7).

Another important finding from the study by Cassaglia and colleagues (3) is support of the concept of a very differential control of regional SNA outflow between the brain and other vascular beds (e.g., during REM sleep, elevations in cerebral SNA are apparent whereas SNA is reduced in both lumbar and renal regions). Although it seems that comparable sleep-related REM elevations in brain and muscle SNA might occur (11), the findings of Cassaglia et al. underscore a key difference in that skeletal muscle SNA is terminated during the surges in blood pressure (11), whereas the elevations in brain SNA precede the surge in blood pressure. Although the mechanisms for this protective “anticipatory” response of cerebral SNA require further study, interactions between sleep state with barore-
flex control of the cerebral circulation, neuronal activation, and cerebral autoregulation are likely complex mediators.

In summary, the present findings (3) add substantial support to the concept that sympathetic perivascular nerves can provide intimate protection of the brain against cerebral hyperperfusion, especially during sleep, a situation in which the brain would otherwise be most prone to such a hypertensive insult. The teleological relevance of why the brain is more sensitive in protecting itself against potential overperfusion is not clear but might, in part, explain why the incidence of sleep-associated ischemic stroke is more common than hemorrhagic strokes (7). The extent to which the regulation of cerebral SNA might also be adversely altered during pathological states (e.g., sleep apnea, hypertension) and special populations (e.g., elderly and cognitive impairment) is not known. Future studies are needed to provide insight into the high prevalence of cerebrovascular events in such patients groups.

REFERENCES