Circadian Clocks, Autonomic Rhythms, and Blood Pressure Dipping

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Blood pressure does not fluctuate in random fashion but follows characteristic rhythmic patterns. A blood pressure rhythm of ~0.1 Hz (~6 cycles/min) is easily recognizable when blood pressure is monitored continuously and was first independently recognized in the late 1800s by Traube, Hering, and Mayer. This pattern can be analyzed using spectral analysis of the low-frequency range in the frequency domain. There is controversy about the genesis of this rhythm. Two theories have been proposed. The pacemaker theory suggests that the rhythm is generated from oscillators within the central nervous system, either located in discrete pacemaker neurons or originating in neuronal networks. Alternatively, this rhythm may result from a resonance phenomenon because the baroreflex inhibits sympathetic tone after every increase in blood pressure. There is some disagreement about the utility of using the power of the low-frequency blood pressure variability as a measure of sympathetic modulation of vascular tone. However, there is little doubt that information modulating rhythmic blood pressure fluctuation is transmitted through efferent autonomic nerves because it is greatly reduced in patients with pure autonomic failure and is abolished by blockade of autonomic ganglia neurotransmission. It has been argued that rhythmic sympathetic discharge is beneficial because it provides a more effective mechanism to regulated cardiovascular tone.

In this regard, it is important to note that increasing the frequency of sympathetic activation much above ~0.1 Hz would not translate into more effective neurovascular coupling because of the relatively low-frequency response of vascular contraction.

Blood pressure also fluctuates with a pattern that follows a circadian rhythm, with a peak in the early morning hours and a trough during sleep. This rhythm originates in a “master oscillator,” located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus. The SCN receives input through the retinohypothalamic tract in the optical nerve. Circadian rhythms are generated within the SCN by the regulated expression of clock genes in discrete neuronal populations. Most of the 16 000 to 20 000 SCN neurons (and some cells that act as peripheral clocks) can independently generate a self-sustained circadian rhythm when grown in vitro, but molecular feedback loops and neuronal networks explain the expression of these genes in a circadian organized pattern. Furthermore, blood pressure is only one of many biological signals that follow a circadian pattern, but not all follow the same pattern with an early morning peak. The different timing of peak activity of these circadian rhythms appears to originate from distinct subpopulation of cells within the SCN.

The neuronal activity originating in the SCN translates into circadian rhythms either through hormones released from the hypothalamus or through efferent neural pathways. The autonomic nervous system itself follows a circadian pattern, which is apparent when measuring sympathetic nerve activity, muscle sympathetic nerve activity during the night without altering sleep. Other studies have shown that the normal nighttime decrease in sympathetic activity (assessed by urinary norepinephrine) and increase in parasympathetic activity are blunted in nondippers. However, it is important to note that patients with primary autonomic failure and very low sympathetic and parasympathetic activities also have high incidence of nondipping, suggesting that it is not the inability to inhibit sympathetic activity during the night, but...
the inability to modulate autonomic tone that is responsible for the nondipping phenomenon.

Nonetheless, the finding by Grassi et al that nondippers have increased sympathetic activity is of importance. It raises the possibility that this mechanism, rather than nondipping itself, contributes to the worsening in end-organ damage observed in these patients. A large number of patients would be required to test this hypothesis, making it impossible to use the careful recordings of sympathetic activity performed by Grassi et al. Low-frequency variability of blood pressure could offer an alternative method to estimate sympathetic activity, but it is limited by large interindividual variability.

Cardiovascular events occur more frequently in the morning and have been associated with increased sympathetic activity. Therefore, it is possible that the morning increase in sympathetic activity observed by Grassi et al also contributes to the poor prognosis of nondippers. An early morning increase in muscle sympathetic nerve activity has not been documented in all studies, but this could be because its association with nondipping had not been examined previously. In addition to nondipping, an excessive early morning surge in blood pressure, defined as an exaggerated increase in postawake morning blood pressure compared with 2-hour preawake blood pressure, is also associated with increased cardiovascular events. This observation presents us with an apparent paradox. By definition, dippers would be more likely to have an early morning surge. Indeed, extreme dippers have been associated with increased cardiovascular events in some studies. One potential explanation for this apparent paradox is that both early morning surge and nondipping are characterized by an exaggerated increase in sympathetic activity in the morning. However, this remains hypothetical, and it would have been of interest if Grassi et al had examined this possibility in their patient population.

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**References**

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