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COMMENTARY

Nocturnal heart rate and cerebrovascular disease

Yuichiro Yano

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Many physiological and behavioral events are influenced by circadian rhythms, which are regulated by internal circadian clocks that coordinate biological functions via the cyclic expression of at least 10–20% of the genes in individual tissues.[1] The disruption of circadian rhythms due to aging or an unhealthy lifestyle (for example, high-fat diet, staying up late, shift working) could impact whole-body physiology, resulting in disorders such as hypertension, diabetes, obesity and brain dysfunction.[2,3]

Circadian rhythms impact heart rate (HR) and heart rate variability (HRV: typically calculated from inter-beat or RR interval via electrocardiogram), reducing HR and increasing HRV during sleep. This pattern is established in late infancy or early childhood.[4] The physiological mechanisms remain uncertain, but sympathetic nervous activity during sleep, baroreflex sensitivity, sleep process (for example, rapid eye movement) and quality, and certain organs, including the lungs and liver, may contribute to this phenomenon.[5–7] Behavioral and lifestyle factors, such as drinking, smoking, physical activity, and diet (for example, salt intake), could also influence the circadian rhythm.[5–7]

Higher HR and lower HRV have been linked to adverse prognoses, including cardiovascular disease (CVD) and higher mortality in populations with and without existing cardiovascular risk factors.[7–9] Higher nocturnal HR and/or impaired circadian rhythm of HR (that is, less than normal decline of nocturnal HR, also called 'non-dipper') is closely associated with a higher risk of CVD and/or all-cause mortality.[10–12] Important unanswered questions include whether HR and HRV are causative risk factors for adverse prognoses or merely epiphenomena of pathophysiological conditions (for example, reflecting extrinsic environmental and behavioral changes, impaired intrinsic cardiovascular and neurohumoral systems).[7] In animal studies, HR reduction has led to improved vascular function and prevented atherosclerosis, but evidence in humans is sparse.[7] The recent SIGNIFY study suggests that in those individuals with stable coronary disease without clinical heart failure and a HR $\geqslant$70 b.p.m., the addition of ivabradine, an inhibitor of the I_f (pacemaker) current in the sinoatrial node that reduces HR without affecting blood pressure (BP) or cardiac systolic function, did not improve the outcomes.[13]

In the current issue of *Hypertension Research*, Yamaguchi *et al.*[14] identified a new potential clinical implication of nocturnal HR in community-dwelling, elderly Japanese. Higher nocturnal HRV was associated with a higher risk of cerebral small-vessel disease (SVD) progression but not cognitive decline, and the association was independent of classical cardiovascular risk factors. One hundred ninety people aged 70–72 years were included (45% men, 75% hypertensive individuals, 44% were on antihypertensive medication and 16% had diabetes) in the current study. Nocturnal HR was assessed via 24-h ambulatory BP (measured every 30 min during the day and every 60 min during sleep), and HRV was evaluated as the standard deviation and the root mean square of successive differences. The mean daytime/nocturnal HR was 71/58 b.p.m., respectively, implying that the HR of the participants was lower, especially during sleep, compared with prior reports.[10–12] Brain MRI (0.5 T, 6-mm slice) and cognitive function tests (that is, the mini-mental state examination (MMSE)) were conducted at baseline and 4 years later. New white matter lesions or lacunae at follow-up were defined as a progression of cerebral SVD, and an MMSE score reduction of >2 points at follow-up was defined as cognitive decline. Those with newly developed cerebral SVD (61% of entire population) had higher nocturnal HRV at baseline than those without it, but other clinical characteristics, including a prevalence of hypertension and diabetes, drinking and smoking status, and clinical and 24-h BP values, were similar. The higher prevalence of lacunar infarction and white matter lesions at baseline in those with cerebral SVD progression could be a confounder, although the authors conducted statistical adjustments to account for this. Prior studies[15,16] have shown that nocturnal BP and its variability are associated with cerebral SVD progression risk. However, the small sample size and antihypertensive medication use during follow-up in the Yamaguchi *et al.* study may render the associations null.

Several points should be taken into account in this study. First, we should interpret the findings with caution because the study assessed nocturnal HRV by ambulatory blood pressure monitoring (ABPM). The clinical implication of HRV in ABPM is less clear than with a 24-h Holter electrocardiography (ECG), which has an established clinical utility (for example, quantifying autonomic function via power spectral analysis of HRV) and is the gold standard method of HR assessment.[6] Whether HR measured every other hour accompanied by cuff inflation could reflect true individual HRV remains uncertain. In addition, which clinical characteristics are related to higher nocturnal HRV are unknown, and it therefore remains unclear whether it is biologically plausible that there is an association between higher nocturnal HRV and cerebral SVD risk. Further etiopathophysiological studies on

Y Yano is at Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
E-mail: yyano@jichi.jp or yuichiro.yano@northwestern.edu

nocturnal HRV assessed by ABPM are warranted. Second, although a range of variables were adjusted and findings remained significant, residual confounding due to unknown or incompletely measured factors cannot be excluded. At a minimum, physical activity, sleep apnea or lower sleep quality, and paroxysmal atrial fibrillation are important uncontrolled factors. Third, although the findings were statistically significant, the effect size was small and the clinical meaningfulness, evaluated by NRI (net reclassification improvement) and IDI (integrated discrimination improvement),[17] was unmeasured. From a clinical practice viewpoint, it would be beneficial to conduct cost-effectiveness analyses and assess the availability and invasiveness of nocturnal HR measurement by ABPM (for example, with respect to sleep disturbances, discomfort and restrictions in daily activities).

New technologies are changing our lives, and the medical field has been revolutionized by these rapid and pervasive changes. Until now, assessing nocturnal HR has been difficult. However, new technologies are now allowing researchers to unobtrusively measure nocturnal HR. Technologies such as smartphone-based single-lead ECG, handheld ECG and ECG patch monitoring are swiftly permeating clinical practice.[18] These devices are inexpensive, accessible and easy to use, so people can readily use them even during sleep and over long periods of time. This allows clinicians and researchers to conduct less invasive evaluations and studies. Of course, before their use becomes widespread, we need to consider their advantages and disadvantages and how to incorporate them into clinical practice.

These technologies will start a new era not only in the study of atrial fibrillation but in heart rhythm research overall and begin a transition from population-level health care to personalized preventive medicine. Revealing the novel clinical implications of nocturnal HR, as Yamaguchi *et al.*[14] suggested, are further expected. Ultimately, the most important and challenging issue that lies ahead is to understand whether higher nocturnal HR/HRV and an impaired circadian rhythm of HR are simply markers of concurrent pathophysiology (if so, what is the pathophysiology of these phenomena?) or are causally related to pathogenesis in CVD (if so, what are the treatment options?).[19]

CONFLICT OF INTEREST

The author declares no conflict of interest.

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