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COMMENT

Potential impact of non-dipping pulse rate pattern and nocturnal high pulse rate variability on target organ damage in patients with cardiovascular risk

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Hypertension is a critical public health issue because of its close association with numerous major diseases and adverse outcomes [1]. A non-dipping blood pressure (BP) pattern, which is BP < 10% lower at night than during the day, is associated with cardiovascular events and hypertensive organ damage [2]. The non-dipping pulse rate (PR) pattern is also associated with cardiovascular events [3]. In contrast, an association between the standard deviation (SD) of systolic BP (SBP), short-term BP variability assessed using ambulatory BP monitoring (ABPM), and cardiovascular events has been reported [4]. However, the association between nocturnal PR, short-term PR variability (PRV), and hypertensive organ damage has not yet been clarified.

In the current issue of *Hypertension Research*, Kabutoya et al. [5] report on an observational study to determine whether there is an association between the SD of the SBP, PRV assessed by ABPM, and brain natriuretic peptide (BNP) levels as part of the J-HOP (Japan Morning Surge-Home Blood Pressure) study [6], a general practice-based national home BP registry of outpatients with cardiovascular risk factors. In their study, Kabutoya et al. [5] enrolled 1439 patients with cardiovascular disease (CVD) risk factors who underwent ABPM every 30 min for 24 h, and evaluated BNP levels at baseline. The SDs of PR (PR-SD) at night were divided into quartiles (Q1–Q4). Non-dipping PR was defined as (awake PR-sleep PR/awake PR) < 0.1. When analyzing the association between BNP and the various combinations of dipping/non-dipping PR and PR-SD quartiles, the median BNPs in the dipping PR/PR-SD Q1–Q3, dipping PR/PR-SD Q4, non-dipping PR/PR-SD Q1–Q3, and non-dipping PR/PR-SD Q4 group were 17.7 (9.3–34.2), 16.4 (7.8–32.6), 21.9 (10.2–57.0), and 37.8 (13.0–83.0) pg/mL (ANOVA $p < 0.001$, Fig. 1A), respectively. BNP levels were significantly higher in participants in the non-dipping PR/PR-SD Q4 combination than in those in the non-dipping PR/PR-SD Q1–Q3 combination ($p = 0.041$). The percentage of participants with BNP ≥ 100 pg/mL in the dipping PR/PR-SD Q1–Q3, dipping PR/PR-SD Q4, non-dipping PR/PR-SD Q1–Q3, and non-dipping PR/PR-SD Q4 groups were 5.2%, 4.8%, 13.0%, and 20.0%, respectively (ANOVA, $p < 0.001$, Fig. 1B).

On a related topic, the term "heart rate variability" (HRV), which seems similar to PRV, refers to the fact that the duration of the cardiac cycle varies from one heart beat to the next and the extent of variability is determined by the ECG signal [7]. HRV has been considered to be a useful tool to assess the direct relationship between cardiac rhythm and the activity of the sympathetic and parasympathetic nervous systems. Indeed, a decrease in the SD of normal-to-normal (NN) intervals (SDNN), the variability of the RR interval as evaluated by Holter electrogram, is known to be associated with decreased autonomic function in patients with diabetes and in other patients, and it is also associated with increased mortality [8]. Reduced HRV has also been shown to be correlated with the risk of cardiac events such as myocardial infarction, congestive heart failure and sudden cardiac death. However, the relationship between PRV and HRV is not entirely understood, and the effects of cardiovascular changes have not been fully elucidated [7, 9]. Importantly, PRV is obtained based on the varying length of pulse cycles, not cardiac cycles and several methods such as ABPM, photoplethysmography, and continuous

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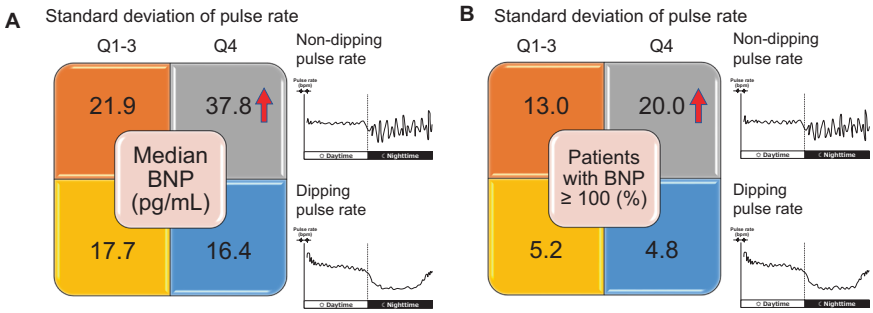

Fig. 1 The median BNP (**A**) and patients with BNP ≥ 100 pg/mL (%) (**B**) according to the combinations of dipper/non-dipper pulse rate (PR) and PR-SD quartiles. BNP brain natriuretic peptide, SD standard deviation

blood pressure monitoring have been used to evaluate PRV [5, 8, 9]. In the paper by Kabutoya et. al. [5], they demonstrated that PR and PRV assessed by ABPM are useful indices for heart failure. As discussed in their paper, the PR assessed by ABPM is the moving average and the PRV is the variation of PR across several measurement points; thus, the PRV is essentially different from the HRV variables such as SDNN. In this regard, the visit-to-visit variation in PR shown by Zhao et al. was also a variability between measurement points [10] and may be methodologically similar to the variation detected using 30 min intervals in the study by Kabutoya et al. Regarding the mechanism underlying the increase in PR and PRV, respiration-induced changes in intrathoracic pressure and subsequent blood flow variations in the venous system, as well as in the arterial circulatory system, might be pivotal factors [8]. Namely, such passive changes in cardiovascular loading would likely cause spontaneous oscillations of small arteries leading to blood flow and PR variations [8]. Kabutoya et al. speculated that irregular hypoxemia might cause sympathetic activation, resulting in increased BP and PR during sleep apnea and the nocturnal increase in venous perfusion associated with the supine position might be accompanied by an increase in PR and PRV in patients with heart failure. Also, an increase in nocturnal sympathetic activity might cause not only nocturnal PRV every 30 min but also an increase in the nocturnal PR itself, which might be the cause of non-dipper PR. Furthermore, sleep apnea syndrome may also cause increased PRV owing to increased sympathetic activity at night; in this regard, further studies will be necessary to examine the relationship between sleep apnea syndrome and PRV.

In conclusion, investigation of the factors that cause increased nocturnal PRV will likely advance healthcare technologies that control not only absolute BP and PR, but also BP and PR variability, especially at night. Future studies are needed to assess the association between nocturnal BP and PR variability and cardiovascular events for healthy longevity in hypertensive patients.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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