CLINICAL STUDY

Blood Pressure Increases Before Pulse Rate During the Nocturnal Period in Hypertensive Patients
Age and Gender Dependency

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Summary
Ambulatory blood pressure monitoring (ABPM) is used for the evaluation of out-of-office blood pressure (BP), however, knowledge concerning the detailed behavior of nocturnal blood pressure (BP) and pulse rate (PR) is limited.

A total of 190 participants (64 ± 15 years, 46.3% males) underwent ABPM for diagnosis of hypertension or evaluation of hypertensive therapy. BP and PR were measured automatically by the oscillometric method. From the hourly average ABPM values, the nocturnal time courses (0 AM to 6 AM) of SBP and PR were determined and compared to each other.

In general, SBP fell to the lowest level at around midnight and started to increase progressively towards dawn while PR stayed unchanged until 7 AM. Age and gender affected the time course of SBP, most distinctly in the female patients aged ≥ 60 years. The time course of the increase of SBP was very similar in the patients, with BP dipping and non-dipping. The cardiothoracic ratio (CTR) slightly and renal dysfunction modestly facilitated the increase of nocturnal SBP. The nocturnal increase in SBP was not accompanied by an increase of PR in any group or subgroup. The pathophysiology and clinical significance of the early and exclusive increase in nocturnal BP need to be investigated.

Average ABPM values in these hypertensive patients showed that BP starts to increase toward dawn without an increase in PR and that this discrepant behavior between BP and PR was most distinct in females 60 or older. The mechanism and clinical significance of such a discordant variation in BP and PR need to be elucidated.

(Int Heart J 2020; 61: 579-584)

Key words: Ambulatory blood pressure monitoring, Hypertension, Nocturnal variability of hemodynamics

Ambulatory blood pressure monitoring (ABPM) is used for diagnosing hypertension and evaluating antihypertensive therapy.1-3) Altered diurnal variability of blood pressure (BP) and pulse rate (PR) has been suggested to be a risk factor for cardiovascular events in hypertensive patients and in subjects in the general population.4-9)

Variations of BP and PR decline during the nighttime when physical and mental activities are at a minimum,10-12) but the details of BP and PR time courses have not yet been fully investigated during the nocturnal period. This is mainly due to marked fluctuations in BP in individual ABPM records, however, determining the precise time courses of BP and PR may provide information for understanding the regulatory mechanism of hemodynamics during the nighttime.

To characterize hemodynamics in the nocturnal period, we analyzed the time course of BP in relation to that of PR using average ABPM values. After plotting hourly average BP and PR values, the time courses of nocturnal BP and HR were analyzed in hypertensive patients in all groups and when the patients were divided according to their dipping pattern, and by the clinical parameters of age, gender, cardiothoracic ratio (CTR), and estimated glomerular filtration rate (eGFR).13)

Methods

This was a retrospective cross-sectional study of ABPM data from 190 patients who visited our clinic and were diagnosed with hypertension or were evaluated for treatment in the previous 5 years. All patients underwent clinical evaluations, including electrocardiography (ECG), chest X-rays, and routine CBC and blood chemistry tests.

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Received for publication December 17, 2019. Revised and accepted February 12, 2020.

Released in advance online on J-STAGE May 15, 2020.

doi: 10.1536/ihj.19-695

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Exclusion criteria were as follows: previous myocardial infarction, idiopathic cardiomyopathy and valvular heart disease with overt heart failure, atrial fibrillation, sick sinus syndrome, or frequent premature beats. Patients with eGFR < 40 mL/minute/1.73 m², sleep dyspnea, or beta-blocker therapy were also excluded.

**ABPM:** ABPM was performed after obtaining informed consent from the patients. The cuff of the ABPM system (Digital Walk FM-800, Fukuda Denshi Co., Tokyo) was placed on the nondominant arm of the patient, and BP was recorded every 30 minutes during the daytime (10 AM to 10 PM) and every 1 hour during the nighttime (10 PM to 10 AM). The patients were asked to maintain a motionless state during BP measurements when they were awake and to maintain a diary to record their daily activities during the ABPM period. PR was determined during oscillometric BP measurements and was used as an alternative to heart rate expressed in beats per minute (bpm). In patients receiving medication for hypertension or other concomitant diseases, ABPM was performed under these same conditions, but patients on beta-blocker therapy were excluded as mentioned above.

**Data analysis:** We averaged the ABPM data and obtained hourly systolic SBP (SBP) measurements between 9 PM and 9 AM. Next, we plotted the SBP data from 9 PM to 9 AM, and the time course of SBP was traced during the nocturnal period.

SBP values from 12 AM to 2 AM were averaged and defined as the midnight SBP, and the time when SBP started to increase and the time when SBP significantly exceeded the midnight SBP were determined. The timing of PR changes was evaluated in a similar manner.

The time courses of nocturnal changes in BP and PR were analyzed in all patients and in subgroups divided by age (≥ 60 years old versus < 60 years old), gender (male versus female), CTR (≥ 50% versus < 50%), eGFR (≤ 60 mL/minute/1.73 m² versus > 60 mL/minute/1.73 m²).

According to previous studies, dipping and nondipping were defined by the ratio of mean nocturnal BP to mean daytime BP, with a ratio > 0.9 indicating nondipping.

The sample size was determined based on the assumption of a detection rate of 80% and BP changes from midnight (120-125 mmHg) to dawn (130-135 mmHg) at a 5% level of statistical significance and calculated (nQuary Advisor software); Result: 30-50 patients. Among the subgroups, only the <60 year-old female patient group was below this range: 27 patients, but the results were presented for a comparison.

Correlations between SBP and PR during the daytime (10 AM to 10 pm) and during the nocturnal period (0 AM to 6 AM) were obtained to see if there were concordant behaviors between them.

**Statistical analysis:** Numerical data are presented as the mean ± standard deviation, and categorical parameters are presented as an absolute number or percentage. The data were compared among subgroups using the unpaired t-test or chi-squared test when appropriate. The serial changes in nocturnal SBP and RP were compared using the paired t-test. JMP software (Statistical Discovery Software, version 5.0.1J, SAS Institute, NC, USA) was used to perform the statistical analyses. Two-sided nominal P < 0.05 was considered significant. Informed consent was obtained from each patient before the study, and the study protocol was approved by the Institutional Review Board of Tachikawa Medical Center.

**Results**

**Clinical characteristics:** The mean age of the 190 patients was 64 ± 15 years, and 88 patients (46.3%) were male. Hypertension was diagnosed in 177 (93.2%) patients. Other comorbidities included dyslipidemia, diabetes mellitus, hyperuricemia, ischemic heart disease and valvular diseases. Hypertension was treated most often by calcium channel blockers (CCBs) with or without angiotensin receptor blockers (ARBs) or diuretics, and the patients were maintained under good control. No patient was in a state of New York Heart Association functional class III or IV.

**Age and gender and nocturnal BP and PR variations:**

In all the patients, SBP increased progressively towards dawn: starting to increase at 4 AM and reaching a significantly higher level than the midnight SBP at 5 AM, while PR started to increase at 6 AM and became higher at 7 AM than the midnight PR. The time courses of SBP and PR were then analyzed in subgroups divided according to clinical characteristics.

Female patients (n = 102) showed an increase of SBP 1-2 hours earlier than male patients (n = 88) while PR exhibited a slight decline at 3 to 5 AM followed by a significant increase at 7 AM (Table). Different time courses between SBP and PR were observed between patients aged ≥ 60 years (n = 129, 77 ± 5 years) and those aged < 60 years (n = 61, 47 ± 11 years), and the SBP increased earlier in the patients aged ≥ 60 years.

Next, the age-dependent nocturnal variation of SBP was analyzed in each gender. In female patients aged ≥ 60 years, SBP started to increase at 3 AM and was significantly higher than the midnight SBP at 4 AM (P = 0.0051) while SBP was significantly higher at 7 AM in female patients < 60 years of age (Figure 1A). In male patients ≥ 60 years and those < 60 years, the starting time and the time of significant increase in SBP were 3 AM and 5 AM, and 5 AM and 7 AM, respectively (P = 0.0379) (Figure 1B). PR significantly increased at 7 AM in the two genders for both age groups (Figure 1C, D).

**BP dipping/non-dipping and nocturnal BP and PR:** Patients were divided into two groups, dipping (n = 104) and non-dipping (n = 86).

Diabetes mellitus was more frequent in the patients with BP dipping compared to the patients with non-dipping: 20.5% versus 10.3% (P = 0.0319), but other clinical data, comorbidities and medication were comparable between the two groups.

A higher daytime SBP (143 ± 17 mmHg versus 133 ± 16 mmHg, P < 0.0001) and a lower midnight SBP (119 ± 17 mmHg versus 127 ± 16 mmHg, P = 0.0021) were observed in the dipping group compared to the non-dipping group. A progressive increase toward dawn was observed in SBP in the two subgroups. SBP started to increase at 4 AM to reach a higher level at 6 AM and there-
The timing of the increase of nocturnal SBP was dependent on age, gender, and eGFR, but not on CTR or BP dipping pattern, and the earliest increase in SBP was observed in female patients aged ≥ 60 years. However, a significant increase in PR was observed after dawn. The mechanism of the discrepant time course between SBP and PR during the nocturnal period was not apparent and needs further investigation.

**Discussion**

In the averaged ABPM data from hypertensive patients, SBP was observed to increase and to reach a significantly higher level above the midnight SBP while PR declined or remained unchanged, revealing discrepant time courses between the two measurements. The timing of the increase of nocturnal SBP was dependent on age, gender, and eGFR, but not on CTR or BP dipping pattern, and the earliest increase in SBP was observed in female patients aged ≥ 60 years. However, a significant increase in PR was observed after dawn. The mechanism of the discrepant time course between SBP and PR during the nocturnal period was not apparent and needs further investigation.

**ABPM enabled us to evaluate diurnal variations of BP, and a fall of nocturnal BP compared to the daytime BP less than 10% was defined as a non-dipping pattern which has been shown to be a risk for cardiovascular events in hypertensive patients and in subjects in the general population.** High home nighttime BP was also shown to be associated with a higher cardiovascular event rate. The pathophysiology involved in elevated BP in patients with a non-dipping pattern has been investigated thus far.

For elevated nocturnal BP, enhanced sympathetic activity with or without attenuated parasympathetic nerve activity was shown to be responsible. Sleep apnea induces enhancement of adrenergic nervous activity and may be associated with elevation of nocturnal BP. In addition, a state of body fluid accumulation like that occurring in salt-sensitive hypertension or primary aldosteronism is known to elevate nocturnal BP. Cardiovascular or renal dysfunction may be associated with body fluid accumulation.
male patients aged CTR or dipping pattern of nocturnal BP (Figure 2). Feder (Figure 1), modestly by eGFR, and only slightly by clinical characteristics, markedly affected by age and genetic factor. Moreover, the time courses toward dawn and was then followed minimum at around midnight in all patients and took a characteristic time course: SBP started to increase soon after midnight and reached a significantly higher level at the earliest point among the subgroups.

Of note, PR remained unchanged or even declined slightly from the midnight level while SBP was increasing, and PR became significantly higher than the midnight level at 7:00 AM (Figures 1, 2). This time course of nocturnal PR was common to all subgroups divided according to clinical characteristics (Figures 1, 2).

Since adrenergic stimuli are the main cause of SBP and PR variation, BP and PR are expected to increase to- dial hypertension (12 AM to 6 AM) was absent: relative coefficient $r = 0.015$, $P = 0.9183$, while a good positive correlation was observed during the daytime (10 AM to 10 PM): $r = 0.55$, $P = 0.0494$. The mechanism of the discrepant behavior between nocturnal BP and PR needs to be elucidated.

**Mechanism and clinical implication:** The mechanism responsible for the exclusive increase in BP was not apparent from the present study. We may be able to postulate

**cumulation and a non-dipping pattern.** After correction of abnormal fluid accumulation by pressure-diuresis, the non-dipping pattern was observed to change to the dipping pattern. These studies addressed the mechanisms for elevated nocturnal BP or non-dipping, but detailed analysis of the time course of BP (and PR) remains to be addressed.

**Time course of hemodynamics:** In individual records of ABPM, we may observe cases who show a rapid and progressive increase in BP during the nocturnal period toward dawn. However, precise analysis of the time course of nocturnal BP is limited because of marked fluctuations in individual ABPM records. We then attempted to analyze the time courses of BP and PR during the nocturnal period using the averaged ABPM data.

By this method, our study revealed that SBP fell to a minimum at around midnight in all patients and took varying time courses toward dawn and was then followed by a morning surge.

The time course of increase in SBP was affected by clinical characteristics, markedly affected by age and gender (Figure 1), modestly by eGFR, and only slightly by CTR or dipping pattern of nocturnal BP (Figure 2). Female patients aged ≥ 60 years showed the most distinct characterisic time course: SBP started to increase soon after midnight and reached a significantly higher level at the earliest point among the subgroups.

Of note, PR remained unchanged or even declined slightly from the midnight level while SBP was increasing, and PR became significantly higher than the midnight level at 7:00 AM (Figures 1, 2). This time course of nocturnal PR was common to all subgroups divided according to clinical characteristics (Figures 1, 2).

Since adrenergic stimuli are the main cause of SBP and PR variation, BP and PR are expected to increase to-
mechanisms which predominantly increase BP: an increased vascular reactivity with/without depressed cardiac reactivity to adrenergic stimuli,4,35) endogenous vasopressor substances which might be released during the nighttime,36) and altered vascular/cardiac reactivity to neurohumoral stimuli, but studies to prove or disprove their roles are needed.

Elucidation of the mechanism responsible for the exclusive increase in nocturnal BP would improve our knowledge of nighttime blood pressure regulation.

The time course of nocturnal BP was observed to be affected by clinical characteristics, most distinctly in aged females, but the mechanism is not apparent and further study is needed. Furthermore, we should determine whether specific time courses of nocturnal BP have clinical significance or not. Recent studies have showed that high nighttime home BP can be a hallmark of organ damage,14-16) and nighttime BP measurements have been recommended. However, when the BP is changing, we have to specify the best timing of BP measurements during the nighttime. Thus, confirming the precise nocturnal time course of BP and factors involved in nocturnal BP regulation would have clinical implications.

Limitations: Early and exclusive increases in BP during the nocturnal period have not been stressed in previous studies, mainly due to the fact that previous ABPM studies treated younger hypertensive patients, in which simultaneous increases in BP and PR are common as observed in the present study.17,30) Sleep apnea or frequent urination enhance sympathetic activity,22,23) but none of the patients complained of sleep disorders or pollakisuria in the present study. Physical activity such as urination is known to increase BP as well as PR.24,31) Cases of extreme dipping or reverse dipping were observed in 11 or 13 patients, respectively, but the exclusion of these patients did not alter the time course of BP during the nocturnal period or the conclusion of the present study.

Conclusion

The average ABPM data from hypertensive patients showed that BP starts to increase toward dawn without a simultaneous increase in PR and that this discrepant behavior between BP and PR was most distinct in female patients over 60 years of age. The mechanism and clinical significance of such a discordant variation in BP and HR during the nighttime should be elucidated.

Disclosure

Conflicts of interest: All authors declare that they have no competing interests.

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