Heart rate modulates the relationship of augmented systolic blood pressure with the blood natriuretic peptide levels

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Abstract

Aims Augmented central systolic blood pressure (cSBP), which is known to affect the cardiac afterload, is an independent risk factor for cardiovascular disease. While an inverse relationship is known to exist between the heart rate (HR) and the cSBP, it has not yet been clarified if the HR also modulates the association between the cSBP and the cardiac afterload. The present study was conducted to clarify whether the association of the cSBP with the serum levels of the N-terminal fragment B-type natriuretic peptide (NT-proBNP) differs between subjects with high and low HRs, using data obtained from the same subjects on two occasions (2009 and 2012) so as to confirm their consistency.

Methods and results The radial augmentation index, systolic pressure at the second peak of the radial pressure waveform (SBP2), and serum NT-proBNP levels were measured and analysed in a worksite cohort of 2000 middle-aged men in 2009 and in 2012. The subjects were divided into three groups by the HR (i.e. ≤69, 70–79, and ≥80 b.p.m.). While the serum NT-proBNP levels were similar among the three groups, the radial augmentation index increased (from 61 ± 12% to 72 ± 13%, \( P < 0.01 \) in 2009 and from 61 ± 13% to 73 ± 12%, \( P < 0.01 \) in 2012) and the SBP1-2 decreased (from 18 ± 7 to 13 ± 7 mmHg, \( P < 0.01 \) in 2009 and from 19 ± 7 to 13 ± 6 mmHg, \( P < 0.01 \) in 2012) significantly with decreasing HR. After the adjustment, the SBP2 showed a significant association with the serum NT-proBNP levels in the overall study population \([\text{non-standardized coefficient (B)} = 0.005, \text{standard error (SE)} = 0.001, \text{P} < 0.01 \text{ in } 2009 (n = 2257) \text{ and } B = 0.004, \text{SE} = 0.001, \text{P} < 0.01 \text{ in } 2012 (n = 1986)]\). In subgroup analyses, the SBP2 showed a significant association with the serum NT-proBNP levels \([B = 0.004, \text{SE} = 0.002, P = 0.02 \text{ in } 2009 (n = 1291) \text{ and } B = 0.005, \text{SE} = 0.001, P < 0.01 \text{ in } 2012 (n = 1204)]\) only in the subject group with an HR of ≤69 b.p.m.

Conclusions In middle-aged Japanese men, the relationship between the cSBP and the cardiac afterload appears to differ depending on the HR; the results of our analysis showed that the relationship between the cSBP and the cardiac overload may be more pronounced and strongly significant in patients with low HRs as compared with patients with high HRs.

Keywords Heart rate; Central blood pressure; Natriuretic peptide; Cardiac afterload; Pressure wave

Introduction

Several studies have reported that high heart rates (HRs) are a risk factor for cardiovascular (CV) outcomes, not only in patients with heart disease but also in the general population, acting via several mechanisms.\(^1\)\(^-\)\(^5\) The increased cardiac workload caused by a high HR is thought to be one of the underlying mechanisms.\(^4\)\(^-\)\(^7\) In addition to a high HR, increased cardiac afterload also acts to increase the cardiac workload.\(^8\) Systolic blood pressure (SBP) is one of the major determinants of the cardiac afterload. Although conventionally brachial SBP (bSBP) has been used to assess the cardiac
afterload, recent studies have demonstrated that the central SBP (cSBP) rather than the bSBP may be a more valid tool to assess the cardiac afterload.9,10

The cSBP is estimated by measurement of the augmentation index (AI), a marker of the pressure wave reflection in the arterial tree, and the bSBP.9,10 The AI increases as the HR decreases so that the cSBP is augmented relative to the bSBP at lower HRs.9-11 Thus, while the component of the cardiac workload related to the HR decreases with decreasing HR, the cardiac workload component related to the cSBP may be increased.12 The cSBP is an independent predictor of future CV events13 and increased cardiac afterload is thought to be one of the underlying mechanisms related to poor CV outcomes.9,14 Therefore, it is important to clarify whether the impact of the cSBP on the cardiac afterload differs significantly between subjects with high and low HRs.

The blood natriuretic peptide level is a recognized marker of the CV outcomes, not only in subjects with heart diseases but also in the general population.15,16 Increased blood levels of the peptide are related to increase of the cardiac afterload.17 Previously, our prospective observational study conducted in a worksite cohort reported a significant association of the serum N-terminal fragment B-type natriuretic peptide (NT-proBNP) levels with the central haemodynamic parameters.18,19 In this study, in addition to measurement of the central haemodynamic parameters, measurement of the serum NT-proBNP level was conducted two times (in 2009 and in 2012).19 The present study was conducted in middle-aged Japanese men to clarify whether the association of the cSBP with the serum NT-proBNP levels might differ between subjects with high and low HRs, using data measured in the same subjects on two occasions, that is, in 2009 and, again 3 years later, in 2012, to confirm the consistency of the findings.

Methods

Subjects

The subjects of this prospective study consisted of a cohort of Japanese employees of a single large construction company.18,19 Data were obtained from the annual health check-ups carried out in the subjects in 2009 and 2012. The health check-up examinations, including measurements of the radial AI and serum NT-proBNP, were conducted in the morning after the subjects had fasted overnight. Informed consent was obtained from all of the study participants prior to their participation in this study. The study was conducted in compliance with the Declaration of Helsinki and with the approval of the Ethical Guidelines Committee of Tokyo Medical University (No. 209 and No. 210 in 2003).

In 2009, a total of 3265 subjects who were working at the company headquarters or branch offices underwent annual medical examinations, and in 2012, a total of 2954 subjects underwent the examinations.

From the cohort of 2009, the data of 482 women (because their number was relatively small as compared with the number of men) and 526 men [17 men with atrial fibrillation, 7 men with an ankle/brachial SBP index of <0.90, 54 men with standard deviation of the radial AI of ≥6%, 44 men with a history of treatment for heart disease or stroke, 22 men with serum creatinine levels of >1.5 mg/dL or a history of treatment for renal disease, and 382 men with serum glycosylated haemoglobin A1c (HbA1c) values of >6.5% and/or a history of treatment for hypertension, dyslipidaemia, and/or diabetes mellitus (some of men had more than two abnormalities)] were excluded.

Furthermore, from the cohort of 2012, the data of 425 women and 543 men [6 men with atrial fibrillation, 1 man with an ankle/brachial SBP index of <0.90, 21 men with standard deviation of the radial AI of ≥6%, 39 men with a history of treatment for heart disease or stroke, 13 men with serum creatinine levels of >1.5 mg/dL or a history of treatment for renal disease, and 463 men with serum HbA1c values of >6.5% and/or a history of treatment for hypertension, dyslipidaemia, and/or diabetes mellitus (some of men had more than two abnormalities)] were excluded.

Finally, the data of the remaining 2257 men from the 2009 cohort and 1986 men from the 2012 cohort were included for the analysis.

Measurements

Augmentation index

Measurements of the blood pressure and radial AI were conducted after the subjects had rested for at least 5 min in the sitting position, in a temperature-controlled room (24–26°C) designated exclusively for this purpose. The blood pressure was measured in the right upper arm using the oscillometric method (HEM-907; Omron Healthcare Co., Ltd., Kyoto, Japan). Immediately after this measurement, the left radial arterial waveform was recorded using an arterial applanation tonometry probe equipped with an array of 40 micropiezo-resistive transducers (HEM-9000AI; Omron Healthcare Co., Ltd.).19 Then, the first and second peaks of the peripheral SBP (SP1 and SP2, markers of the cSBP) and peripheral diastolic blood pressure (DBP) were automatically determined using the fourth derivatives for each radial arterial waveform and then averaged. The first peak pulse pressure (PP1) and second peak pulse pressure (PP2, a marker of the central pulse pressure) were calculated as SP1 — brachial DBP and SP2 — brachial DBP, respectively. The radial AI, a marker of the central AI, was then calculated as follows: PP2/PP1 × 100 (%).20 We previously reported a
good reproducibility of the radial AI (Pearson’s correlation coefficient, 0.95; \( P < 0.01 \); coefficient of variation, 3.2%).

**Laboratory measurements**

Fasting serum concentrations of triglyceride, total cholesterol, high-density lipoprotein cholesterol, and creatinine, fasting plasma glucose, and HbA1c concentrations were measured using enzymatic methods (Falco Biosystems Co., Ltd., Tokyo, Japan). Serum NT-proBNP levels were determined using a chemiluminescence immunoassay kit (Roche Diagnostics, Mannheim, Germany). The sensitivity was 88%, and specificity was 92%; the inter-observer and intra-observer coefficients of variation were 1.8% and 1.6%, respectively. All the blood samples were obtained in the morning after the patients had fasted overnight.

**Statistical analyses**

Data are expressed as the means ± standard deviation (figures are shown with error bars). Because the serum NT-proBNP levels were skewed rightward, the values were log transformed for the analyses. The relationships among the variables were assessed by univariate and multivariate linear regression analyses with backward elimination. Concerning the adjustments, the covariates used in the basic adjustment model were the age, body mass index, smoking status, and creatinine.

All the analyses were conducted using the IBM/SPSS software (Version 25.0; IBM/SPSS Inc., Armonk, NY, USA). A \( P \) value of <0.05 was considered as being indicative of a statistically significant difference.

**Results**

*Table 1* shows the clinical characteristics of the study subjects measured in 2009 and 2012. Among the 2374 men whose data were obtained in 2009, 1567 men underwent the same examinations again in 2012. Among men with repeated measurement data, the radial AI (from 68 ± 13% to 71 ± 13%), second peak of the radial pressure waveform (SBP2) (from 105 ± 14 to 106 ± 15 mmHg), and serum NT-proBNP level (from 23 ± 26 to 29 ± 28 pg/mL) increased significantly from 2009 to 2012 (\( P < 0.01 \)).

*Figure 1* shows the measured radial AI, SBP1-2 (SBP1 minus SBP2; i.e. a low SBP1-2 corresponds to augmentation of the cSBP relative to the bSBP), and serum NT-proBNP levels among three groups classified by the HR (i.e. \( \leq 69, 70–79, \) and \( \geq 80 \)) in 2009 and 2012. While the serum NT-proBNP levels were similar among the three groups, the radial AI increased and the SBP1-2 decreased significantly with decreasing HR.

*Table 2* summarizes the results of univariate and multivariate linear regression analyses with backward elimination to examine the association of SBP1 and SBP2 with the serum NT-proBNP levels among the three groups classified by the HR. The SBP2 showed a significant association with the serum NT-proBNP levels in the overall study population. However, in subgroup analyses, the SBP2 showed a significant association with the serum NT-proBNP levels only in subjects with HR \( \leq 69 \) b.p.m.

**Discussion**

The present study was the first to examine the differential association of the cSBP with the serum NT-proBNP levels in subjects with high and low HRS. Augmentation of the cSBP relative to the bSBP was more pronounced in subjects with low HRS as compared with those with high HRS, and significant association of the cSBP with the serum NT-proBNP levels was only observed in subjects with low HRS, but not those with high HRS. These findings were consistent between data obtained in 2009 and those obtained in 2012.

The present study suggested that the cSBP may exert a significant influence on the cardiac afterload in the presence of the condition of low HRS, but not in the presence of under the condition of high HRS. A plausible explanation for this difference in the influence of the cSBP on the cardiac...
afterload depending on the HR might be as follows: (i) the SBP affects the cardiac afterload, and the AI reflects the extent of augmentation of the cSBP relative to the bSBP. In the present study, the AI increased gradually as the HR (classified in intervals of 10 beats) decreased. In addition, the SBP1-2 also decreased gradually as the HR decreased; that is, augmentation of the brachial-to-central SBP increased gradually as the HR decreased.

Figure 1 The radial augmentation index (AI), SBP1 minus SBP2 (SBP1-2; i.e. low SBP1-2 corresponds to augmentation of the central systolic blood pressure relative to the brachial systolic blood pressure; ≤ 69, 70–79, and ≥ 80 = heart rate < 69, 70–79, and ≥ 80 b.p.m.), and serum N-terminal fragment B-type natriuretic peptide (NT-proBNP) levels in the three groups divided by heart rate in 2009 and in 2012. *P < 0.01 vs. heart rate ≤ 69; †P < 0.01 vs. heart rate 70–79.

\[ n = 1291, n = 691, n = 275 \] 2009: total \( n = 2257 \)

\[ n = 1204, n = 558, n = 224 \] 2012: total \( n = 1986 \)
Augmented SBP with the blood natriuretic peptide levels

While the cSBP has been proposed as an independent predictor of adverse CV outcomes,12,13,20,21 the potential clinical significance of the cSBP as a predictor of future CV events has not been fully established. The present study was conducted to verify the proposition that the significant influence on the cardiac outcome is modulated by the HR and that the cSBP could be used as a marker of cardiac afterload.

### Clinical Implications

The findings of the present study are one of the mechanisms underlying the J-shaped relationship of the HR with adverse CV outcomes.2,3 In addition, it is limited to patients with high systolic blood pressure levels.15,16 High HR is a risk factor for adverse CV outcomes.13 Numerous pathophysiological mechanisms underlying the CV risk associated with high HRs (i.e., both high and low HRs could be detrimental outcomes).1,2 The mechanisms underlying the CV risk associated with high HRs (i.e., both high and low HRs could be detrimental outcomes).1,2

A meta-analysis conducted of data obtained from the general population demonstrated a dose–response relationship between the HR and the incidence of adverse CV outcomes.2,21 Moreover, the incidence of adverse CV outcomes was accompanied by an increase in patients with elevated systolic blood pressure levels.12,15 High HR is a risk factor for adverse CV outcomes.13 Numerous pathophysiological mechanisms underlying the CV risk associated with high HRs (i.e., both high and low HRs could be detrimental outcomes).1,2 The mechanisms underlying the CV risk associated with high HRs (i.e., both high and low HRs could be detrimental outcomes).1,2

#### Table 2: Results of univariate and multivariate linear regression analyses performed to assess the differential associations of the central blood pressure with the serum N-terminal fragment B-type natriuretic peptide levels among depending on the heart rate range

| Variable | 2009 Crude Adjustment | 2012 Crude Adjustment |
|----------|------------------------|-----------------------|
|          | B         | SE | β   | P          | B         | SE | β   | P          |
| ≤69 n = 1291 | 0.006 | 0.002 | 0.093 | <0.01 | 0.009 | 0.002 | 0.162 | <0.01 |
| SBP1      | 0.010 | 0.002 | 0.175 | <0.01 | 0.001 | 0.002 | 0.126 | <0.01 |
| SBP2      | 0.011 | 0.002 | 0.220 | <0.01 | 0.004 | 0.002 | 0.069 | <0.01 |
| 70–79 n = 691 | 0.004 | 0.002 | 0.069 | <0.01 | 0.001 | 0.002 | 0.021 | 0.62 |
| SBP1      | 0.007 | 0.003 | 0.123 | <0.01 | 0.007 | 0.003 | 0.132 | <0.01 |
| SBP2      | 0.006 | 0.003 | 0.145 | <0.01 | 0.004 | 0.002 | 0.071 | 0.09 |
| ≥80 n = 227 | 0.009 | 0.001 | 0.111 | <0.01 | 0.006 | 0.001 | 0.107 | <0.01 |
| SBP1      | 0.009 | 0.001 | 0.109 | <0.01 | 0.007 | 0.002 | 0.126 | <0.01 |
| SBP2      | 0.008 | 0.001 | 0.174 | <0.01 | 0.005 | 0.001 | 0.069 | <0.01 |

While the cSBP has been proposed as an independent predictor of future CV events,12,13,20,21 its clinical relevance is not yet fully established. The present study was conducted to verify the proposition that the significant influence on the cardiac outcome is modulated by the HR and that the cSBP could be used as a marker of cardiac afterload.
in men with repeated measurement data (data not shown).

(v) HR variability assessed by 24 h Holter monitoring, which is a marker of autonomic nervous activity, has been reported to be associated with the serum NT-proBNP levels. Autonomic nervous system activity affects the vascular tonus, which in turn affects the cardiac afterload. Therefore, it would be desirable to determine the associations among the cSBP, serum NT-proBNP levels, and HR variability.

Conclusions

In middle-aged Japanese men, the relationship between the cSBP and the cardiac afterload appears to differ depending on the HR; the results of our analysis showed that the relationship between the cSBP and the cardiac overload may be more pronounced and strongly significant in patients with low HRs as compared with patients with high HRs.

Conflict of interest

The sponsor (Omron Healthcare Co., Ltd.) assisted in the data formatting (i.e. the data of the brachial-ankle pulse wave velocity stored in the hard disc of the equipment used for measurement of the brachial-ankle pulse wave velocity were transferred to an Excel file). The authors have no other disclosures to make.

Funding

This study was supported by Omron Healthcare Co., Ltd. (Kyoto, Japan), Asahi Calpis Wellness Company (Tokyo, Japan), and Teijin Pharma Company (Tokyo, Japan), which awarded funds to A.Y. and H.T.

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