ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 3957–3963
Published online 28 July 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13540

ORIGINAL RESEARCH ARTICLE

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

Hirofumi Tomiyama*, Hiroki Nakano, Takamichi Takahashi, Masatsune Fujii, Kazuki Shiina, Chisa Matsumoto, Taishiro Chikamori and Akira Yamashina

Department of Cardiology and Division of Preemptive Medicine for Vascular Damage, Tokyo Medical University, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo, 160-0023, Japan

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 [non-standardized coefficient (B) = 0.005, standard error (SE) = 0.001, $P < 0.01$ in 2009 (n = 2257) and B = 0.004, SE = 0.001, $P < 0.01$ in 2012 (n = 1986)]. In subgroup analyses, the SBP2 showed a significant association with the serum NT-proBNP levels [B = 0.004, SE = 0.002, P = 0.02 in 2009 (n = 1291) and B = 0.005, SE = 0.001, $P < 0.01$ 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

Received: 18 December 2020; Revised: 1 June 2021; Accepted: 13 July 2021
**Correspondence to: Professor Hirofumi Tomiyama, Department of Cardiology and Division of Preemptive Medicine for Vascular Damage, Tokyo Medical University, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan. Tel: +81-3-3342-6111; Fax: +81-3-5381-6652. Email: tomiyama@tokyo-med.ac.jp*

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 events,[13] 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 $\geq 6\%$, 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 $\geq 6\%$, 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%).[20]

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).[21] (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. ≤69, 70–79, and ≥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 1 Clinical characteristics of the study subjects

Examination time	2009	2012
Number of subjects	2257	1986
Age (years)	44 ± 9	45 ± 9
BMI	23.9 ± 3.0	24.0 ± 3.0
Smoking history (not/current) (%)	1592/665 (29)	1464/522 (26)
SBP1 (mmHg)	122 ± 14	119 ± 14
SBP2 (mmHg)	107 ± 16	105 ± 15
SBP1-2 (mmHg)	14 ± 7	15 ± 7
HR (b.p.m.)	69 ± 10	68 ± 10
Radial AI (%)	69 ± 13	70 ± 13
TC (mmol/L)	5.4 ± 0.9	5.4 ± 0.9
HDL (mmol/L)	1.6 ± 0.4	1.7 ± 0.4
TG (mmol/L)	1.4 ± 1.2	1.3 ± 0.9
FPG (mmol/L)	5.0 ± 0.5	4.9 ± 0.4
Cr (μmol/L)	76 ± 9	74 ± 9
HbA1c (%)	5.1 ± 0.3	5.0 ± 0.3
NT-proBNP (pg/mL)	25 ± 29	29 ± 46

2009, examination conducted in 2009; 2012, examination conducted in 2012; AI, augmentation index; BMI, body mass index; Cr, serum creatinine level; FPG, fasting plasma glucose; HbA1c, serum glycosylated haemoglobin A1c; HDL, serum high-density lipoprotein cholesterol level; HR, heart rate; NT-proBNP, serum level of the N-terminal fragment of B-type natriuretic peptide; SBP1, first peak of the radial pressure waveform; SBP2, second peak of the radial pressure waveform; SBP1-2, SBP1 minus SBP2; smoking, not = not current smoker and current = current smoker; TC, serum total cholesterol level; TG, serum triglyceride level.

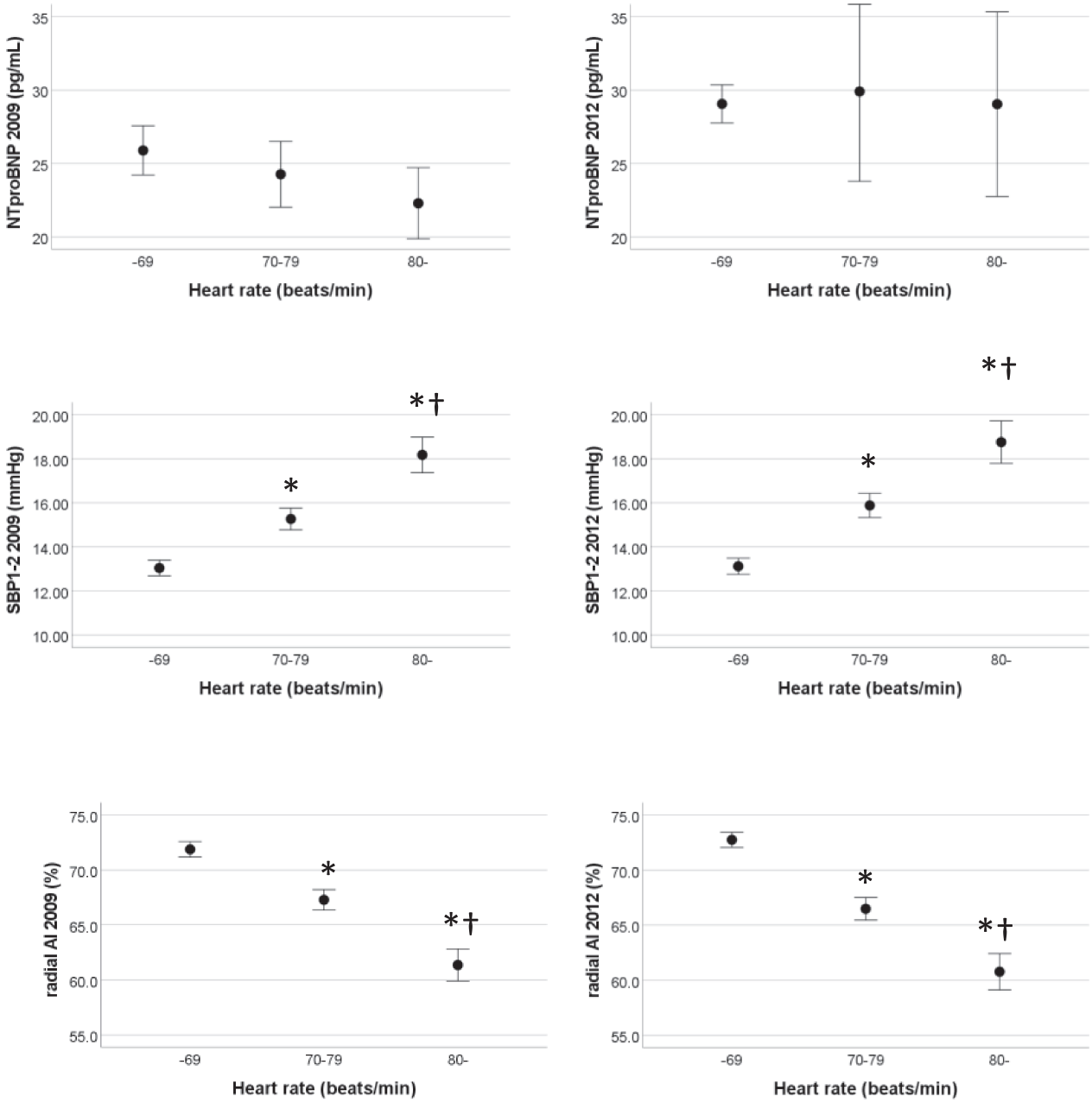
Table 2 summarizes the results of univariate and multivariate linear regression analyses with backward elimination to examine the association of SBP1 and SBP2 with the serum NT-proBNP levels among the three groups classified by the HR. The SBP2 showed a significant association with the serum NT-proBNP 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 ≤ 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 under 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

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.



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.[10,14,20,22] 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. While

DOI: 10.1002/ehf2.13540

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

	2009								2012							
	B	SE	*β*	*P*	*B*	SE	*β*	*P*	*B*	SE	*β*	*P*	*B*	SE	*β*	*P*
Variable	Crude				Adjustment				Crude				Adjustment			
≤69	*n* = 1291				R^2 = 0.112				*n* = 1204				R^2 = 0.100			
SBP1	0.006	0.002	0.093	<0.01	—	—	−0.031	0.15	0.009	0.002	0.161	<0.01	—	—	0.018	0.23
SBP2	0.009	0.001	0.162	<0.01	0.004	0.002	0.069	0.02	0.010	0.001	0.213	<0.01	0.005	0.001	0.116	<0.01
70–79	*n* = 691				R^2 = 0.135				*n* = 558				R^2 = 0.090			
SBP1	0.010	0.002	0.175	<0.01	0.007	0.002	0.126	<0.01	0.001	0.002	0.021	0.62	—	—	0.023	0.60
SBP2	0.011	0.002	0.220	<0.01	—	—	0.006	0.28	0.004	0.002	0.071	0.09	—	—	0.006	0.89
≥80	*n* = 275				R^2 = 0.103				*n* = 224				R^2 = 0.132			
SBP1	0.007	0.003	0.123	0.04	0.007	0.003	0.132	0.04	0.006	0.003	0.122	0.07	—	—	0.105	0.15
SBP2	0.007	0.003	0.145	0.02	—	—	−0.072	0.16	0.009	0.003	0.182	<0.01	—	—	0.103	0.12
Total	*n* = 2257				R^2 = 0.112				*n* = 1986				R^2 = 0.098			
SBP1	0.006	0.001	0.110	<0.01	—	—	−0.011	0.98	0.006	0.001	0.107	<0.01	—	—	−0.010	0.18
SBP2	0.009	0.001	0.174	<0.01	0.005	0.001	0.089	<0.01	0.008	0.001	0.171	<0.01	0.004	0.001	0.084	<0.01

≤69, subjects with heart rate ≤69 b.p.m.; ≥80, subjects with heart rate ≥80 b.p.m.; 70–79, subjects with heart rates in the range of 70–79 b.p.m.; Adjustment, analysis in which the variables (SBP1 and SBP2) were entered simultaneously in the same model with adjustments; *B*, non-standardized coefficient; Crude, univariate analysis in which each variable (SBP1 or SBP2) was entered individually in the model without adjustment; *n*, number of study subjects; SE, standard error; Total, entire study population; *β*, standardized coefficient.

the bSBP is a major determinant of the cardiac afterload regardless of the HR, the augmented SBP represented by the cSBP may exert a significant additive influence on the cardiac afterload in the presence of a low HR, but not that of a high HR. (ii) A time-varying myocardial load, affected by the pressure wave reflection, has been proposed.[23] Kobayashi *et al*. reported that sustained late systolic loading due to an augmented arterial wave reflection was accompanied by an increased cardiac afterload caused by concentric hypertrophy. While the extent of late systolic cardiac load was not evaluated in this study, increased AI, which reflects elevated cSBP, may increase the time-varying myocardial load.[24]

In subjects with elevated CV risk reflected by elevated blood natriuretic peptide levels,[15,16] high HR is a risk factor for adverse CV outcomes.[1–3] Numerous pathophysiological studies have identified atherosclerosis, ventricular remodelling, hypertension, and heart failure as the potential mechanisms underlying the CV risk associated with high HRs.[4,5,25] A meta-analysis conducted of data obtained from the general population demonstrated a dose–response relationship of the HR with the incidence of hypertension and heart failure.[26] Therefore, the aforementioned pathophysiological abnormalities associated with high HRs could be attenuated in subjects with low HRs. However, some studies have proposed a J-shaped relationship of the HR with adverse CV outcomes (i.e. both high and low HRs could be detrimental for CV outcomes).[27,28] In addition, although it is limited to patients with heart failure or coronary artery disease, the beneficial effects of pharmacological lowering of the HR by ivabradine on the CV outcomes were limited to patients with HRs of 70 b.p.m. or greater.[29–31] The mechanisms underlying such HR-dependent limitation of the beneficial effect of pharmacological lowering of HR have not yet been fully clarified. In patients with heart failure or coronary artery disease, cardiac workload may be one of the major factors affecting their CV outcomes.[4–8] Therefore, based on the findings of the present study, as one of the mechanisms underlying the J-shaped relationship of the HR with adverse CV outcomes and for the previously mentioned HR-dependent limitation of the beneficial effects of pharmacological lowering of the HR, it is plausible that augmented cSBP in subjects with HR $\leq$ 69 b.p.m. counteracts the beneficial effect of reduced cardiac workload associated with low HR, including pharmacologically lowered HR.

Clinical implications

While the cSBP has been proposed as an independent predictor of future CV events,[9,13,14,22] its clinical relevance is not yet fully established. The present study was conducted to verify the proposition that the significance of the cSBP as a predictor of the CV outcomes is modulated by the HR and that the cSBP could be used as a marker of cardiac afterload,

independent of the bSBP, especially in subjects with low HRs (i.e. ≤69 b.p.m.) in middle-aged Japanese men. Recently, a cuff-based measurement method for the cSBP has become available,[32] and this simple method is applicable for first-line assessment of the CV risk. From our findings, in such assessment of the CV risk based on the cSBP, modulation by the HR might also need to be considered.

As the next step, it would be of interest to clarify whether augmented cSBP caused by pharmacological lowering HR overrides the benefits of HR-lowering therapy in patients with CV disease. For example, the importance of pharmacological lowering of the HR in patients with heart failure and/or coronary heart disease has been proposed.[1,2,5,12] The only parameter that can be used for monitoring the efficacy of HR-lowering therapy is the HR. However, the present study proposed the importance of monitoring of the cSBP, which might be useful to prevent adverse outcomes, such as heart failure caused by elevated cSBP associated with lowering of the HR.

Study limitations

The present study had several limitations: (i) in the present study, we did not determine the significance of the impact of augmented cSBP in subjects with low HRs on the cardiac afterload in subjects with CV diseases, such as hypertension, diabetes, dyslipidaemia, heart failure, or coronary artery disease. (ii) The significance of modulation by the HR of other cSBP-mediated harmful effects on the CV outcomes, such as insufficiency of the coronary blood supply or pulsatile vasculopathy, also needs to be clarified.[9,13,14,22] (iii) Gender differences and differences among ethnicities in the AI have been reported[20,33] so that our findings need to be confirmed in women and other ethnicities. (iv) To confirm the consistency of our findings, the analyses were conducted using data obtained on two occasions: in 2009 and, then 3 years later, in 2012. While data on both occasions could only be obtained in 1567 of 2374 men (66%), consistent results were obtained 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.[34] Autonomic nervous system activity affects the vascular tonus, which in turn affects the cardiac afterload.[35] 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.

References

1. Böhm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L, SHIFT Investigators. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. *Lancet* 2010; **376**: 886–894.
2. Vitale C, Iellamo F, Volterrani M, Lombardi M, Fini M, Banach M, Rosano GM. Heart rate control in an unselected consecutive population of outpatients with stable coronary artery disease: analysis of the CARDIf Study Cohort. *Angiology* 2010; **61**: 763–767.
3. Woodward M, Webster R, Murakami Y, Barzi F, Lam TH, Fang X, Suh I, Batty GD, Huxley R, Rodgers A, from the Asia Pacific Cohort Studies Collaboration. The association between resting heart rate, cardiovascular disease and mortality: evidence from 112,680 men and women in 12 cohorts. *Eur J Prev Cardiol* 2014; **21**: 719–726.
4. Tadic M, Cuspidi C, Grassi G. Heart rate as a predictor of cardiovascular risk. *Eur J Clin Invest* 2018; **48**.
5. Bielecka-Dabrowa A, von Haehling S, Rysz J, Banach M. Novel drugs for heart rate control in heart failure. *Heart Fail Rev* 2018; **23**: 517–525.
6. Singh BN. Increased heart rate as a risk factor for cardiovascular disease. *Eur Heart J* 2003; **5**: G3–G9.
7. Magder SA. The ups and downs of heart rate. *Crit Care Med* 2012; **40**: 239–245.

8. Little RC, Little WC. Cardiac preload, afterload, and heart failure. *Arch Intern Med* 1982; **142**: 819–822.
9. Weber T, Chirinos JA. Pulsatile arterial haemodynamics in heart failure. *Eur Heart J* 2018; **39**: 3847–3854.
10. Nichols WW. Clinical measurement of arterial stiffness obtained from noninvasive pressure waveforms. *Am J Hypertens* 2005; **18**: 3S–10S.
11. Laurent P, Albaladejo P, Blacher J, Rudnichi A, Smulyan H, Safar ME. Heart rate and pulse pressure amplification in hypertensive subjects. *Am J Hypertens* 2003; **16**: 363–370.
12. Messerli FH, Rimoldi SF, Bangalore S, Bavishi C, Laurent S. When an increase in central systolic pressure overrides the benefits of heart rate lowering. *J Am Coll Cardiol* 2016; **68**: 754–762.
13. Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. *Eur Heart J* 2010; **31**: 1865–1871.
14. O'Rourke MF, Hashimoto J. Mechanical factors in arterial aging: a clinical perspective. *J Am Coll Cardiol* 2007; **50**: 1–13.
15. Gopal DJ, Iqbal MN, Maisel A. Updating the role of natriuretic peptide levels in cardiovascular disease. *Postgrad Med* 2011; **123**: 102–113.
16. Di Angelantonio E, Chowdhury R, Sarwar N, Ray KK, Gobin R, Saleheen D, Thompson A, Gudnason V, Sattar N, Danesh J. B-type natriuretic peptides and cardiovascular risk: systematic review and meta-analysis of 40 prospective studies. *Circulation* 2009; **120**: 2177–2187.
17. Maeder MT, Mariani JA, Kaye DM. Hemodynamic determinants of myocardial B-type natriuretic peptide release: relative contributions of systolic and diastolic wall stress. *Hypertension* 2010; **56**: 682–689.
18. Odaira M, Tomiyama H, Matsumoto C, Yoshida M, Shiina K, Nagata M, Yamashina A. Strength of relationships of the pulse wave velocity and central hemodynamic indices with the serum N-terminal fragment B-type natriuretic peptide levels in men: a worksite cohort study. *Circ J* 2012; **76**: 1928–1933.
19. Tomiyama H, Nishikimi T, Matsumoto C, Kimura K, Odaira M, Shiina K, Yamashina A. Longitudinal changes in late systolic cardiac load and serum NT-proBNP levels in healthy middle-aged Japanese men. *Am J Hypertens* 2015; **28**: 452–458.
20. Tomiyama H, Yamazaki M, Sagawa Y, Teraoka K, Shirota T, Miyawaki Y, Yamashina A. Synergistic effect of smoking and blood pressure on augmentation index in men, but not in women. *Hypertens Res* 2009; **32**: 122–126.
21. Yeo KT, Wu AH, Apple FS, Kroll MH, Christenson RH, Lewandrowski KB, Sedor FA, Butch AW. Multicenter evaluation of the Roche NT-proBNP assay and comparison to the Biosite Triage BNP assay. *Clin Chim Acta* 2003; **338**: 107–115.
22. Tomiyama H, Yamashina A. Non-invasive vascular function tests: their pathophysiological background and clinical application. *Circ J* 2010; **74**: 24–33.
23. Chirinos JA, Segers P, Gillebert TC, Gupta AK, De Buyzere ML, De Bacquer D, St John-Sutton M, Rietzschel ER, Asklepios Investigators. Arterial properties as determinants of time-varying myocardial stress in humans. *Hypertension* 2012; **60**: 64–70.
24. Kobayashi S, Yano M, Kohno M, Obayashi M, Hisamatsu Y, Ryoke T, Ohkusa T, Yamakawa K, Matsuzaki M. Influence of aortic impedance on the development of pressure-overload left ventricular hypertrophy in rats. *Circulation* 1996; **94**: 3362–3368.
25. Nikolovska Vukadinović A, Vukadinović D, Borer J, Cowie M, Komajda M, Lainscak M, Swedberg K, Böhm M. Heart rate and its reduction in chronic heart failure and beyond. *Eur J Heart Fail* 2017; **19**: 1230–1241.
26. Shi Y, Zhou W, Liu X, Ping Z, Li YQ, Wang C, Lu J, Mao ZX, Zhao J, Yin L, Zhang D, Li L. Resting heart rate and the risk of hypertension and heart failure: a dose–response meta-analysis of prospective studies. *J Hypertens* 2018; **36**: 995–1004.
27. Bangalore S, Messerli FH, Ou FS, Tamis-Holland J, Palazzo A, Roe MT, Hong MK, Peterson ED. CRUSADE InvestigatorsThe association of admission heart rate and in-hospital cardiovascular events in patients with non-ST-segment elevation acute coronary syndromes: results from 135 164 patients in the CRUSADE quality improvement initiative. *Eur Heart J* 2010; **31**: 552–560.
28. Kolloch R, Legler UF, Champion A, Cooper-Dehoff RM, Handberg E, Zhou Q, Pepine CJ. Impact of resting heart rate on outcomes in hypertensive patients with coronary artery disease: findings from the INternational VErapamil-SR/trandolapril STudy (INVEST). *Eur Heart J* 2008; **29**: 1327–1334.
29. Fox K, Ford I, Steg PG, Tardif JC, Tendera M, Ferrari R, SIGNIFY Investigators. Ivabradine in stable coronary artery disease without clinical heart failure. *N Engl J Med* 2014; **371**: 1091–1099.
30. Fox K, Ford I, Steg PG, Tendera M, Ferrari R, BEAUTIFUL Investigators. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; **372**: 807–816.
31. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L, SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010; **376**: 875–885.
32. Sharman JE, Avolio AP, Baulmann J, Benetos A, Blacher J, Blizzard CL, Boutouyrie P, Chen CH, Chowienczyk P, Cockcroft JR, Cruickshank JK, Ferreira I, Ghiadoni L, Hughes A, Jankowski P, Laurent S, McDonnell BJ, McEniery C, Millasseau SC, Papaioannou TG, Parati G, Park JB, Protogerou AD, Roman MJ, Schillaci G, Segers P, Stergiou GS, Tomiyama H, Townsend RR, Van Bortel LM, Wang J, Wassertheurer S, Weber T, Wilkinson IB, Vlachopoulos C. Validation of non-invasive central blood pressure devices: ARTERY Society task force consensus statement on protocol standardization. *Eur Heart J* 2017; **38**: 2805–2812.
33. Chirinos JA, Kips JG, Roman MJ, Medina-Lezama J, Li Y, Woodiwiss AJ, Norton GR, Yasmin, Van Bortel L, Wang JG, Cockcroft JR, Devereux RB, Wilkinson IB, Segers P, McEniery CM. Ethnic differences in arterial wave reflections and normative equations for augmentation index. *Hypertension* 2011; **57**: 1108–1116.
34. Lorgis L, Moreau D, Mock L, Daumas B, Potard D, Touzery C, Cottin Y, Zeller M. High N-terminal pro-B-type natriuretic peptide levels are associated with reduced heart rate variability in acute myocardial infarction. *PLoS ONE* 2012; **7**: e44677.
35. Dampney RA, Horiuchi J, Tagawa T, Fontes MA, Potts PD, Polson JW. Medullary and supramedullary mechanisms regulating sympathetic vasomotor tone. *Acta Physiol Scand* 2003; **177**: 209–218.