**Original Article**

# Longitudinal Association of Arterial Stiffness and Pressure Wave Reflection with Decline of the Cardiac Systolic Performance in Healthy Men

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**Aims:** This prospective observational study aimed to examine the individual longitudinal associations of the increases in the arterial stiffness and pressure wave reflection with the decline in the cardiac systolic performance during the study period in healthy middle-aged Japanese men.

**Methods:** In 4016 middle-aged Japanese healthy men ($43 \pm 9$ years), the brachial-ankle pulse wave velocity (baPWV), radial augmentation index (rAI), and pre-ejection period/ejection time (pre-ejection period (PEP)/ET) were measured annually during a 9-year study period.

**Results:** The baPWV, rAI, and PEP/ET showed steady annual increases during the study period. According to the results of multivariate linear regression analyses, both the baPWV and rAI measured at the baseline showed significant independent associations with the PEP/ET measured at the baseline (baPWV: beta=0.17, $p < 0.01$ and rAI: beta=0.11, $p < 0.01$), whereas neither showed any association with the PEP/ET measured at the end of the study period. The results of the mixed-model linear regression analysis of the repeated-measures data collected over the 9-year study period revealed that the baPWV, but not the rAI, showed a significant longitudinal association with the PEP/ET (estimate=0.69 x $10^{-4}$, $p < 0.01$).

**Conclusion:** In apparently healthy middle-aged Japanese men, the annual increase of the arterial stiffness, rather than the annual increase of the pressure wave reflection, appears to be more closely associated with the annual decline of the cardiac systolic performance as assessed by the systolic time interval.

**Key words:** Arterial stiffness, Cardiac systolic function, Pressure wave reflection

## Introduction

Increased arterial stiffness is recognized as one of the key elements involved in the development of heart failure (HF)[1-7]. While several studies have reported that both increased arterial stiffness and augmented pressure wave reflection are independent risk factors for the development of HF[3-7], the individual significances of these parameters in the early stage of development of HF remain unclear. Increased arterial stiffness affects the pressure wave reflection via increasing the traveling speed of the pressure wave along the arterial wall[1, 8, 9]. In addition to arterial stiffness, the pressure wave reflection is also known to be directly affected by the pressure wave reflectance of the small arteries[1, 8, 9]. Thus, arterial stiffness and augmented pressure wave reflection in the arterial tree are thought to be differentially related to some facets of vascular damage. However, the individual associations of changes of the arterial stiffness and pressure wave reflection with the impairment of cardiac systolic performance remain unclear.
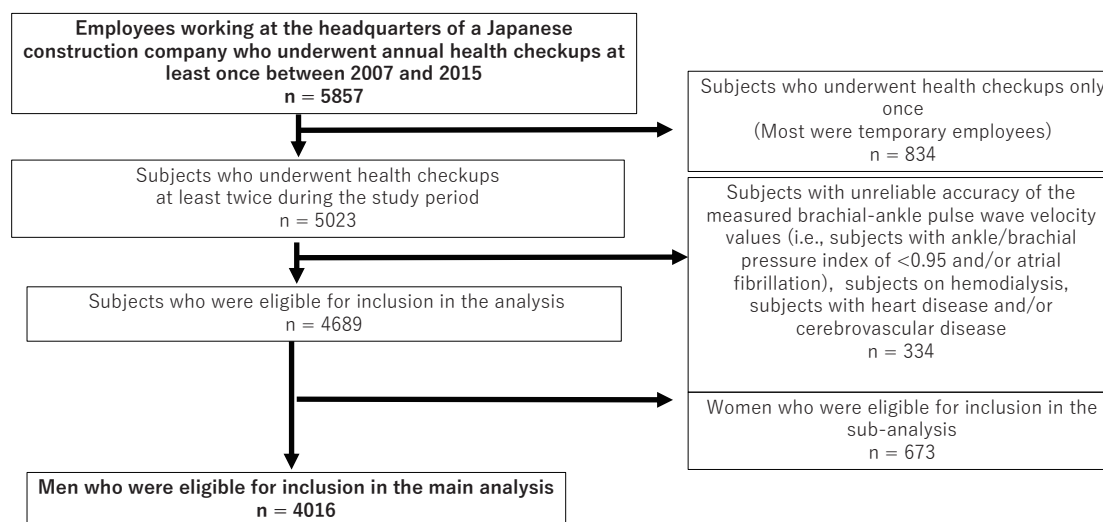
**Fig. 1.** Flow diagram of the subjects enrolled in the study

Prevention of transitioning from preclinical to clinical HF is important[1, 2, 9], and toward achieving that objective, clarification of the associations among arterial stiffness, pressure wave reflection, and impairment of cardiac systolic performance in the preclinical stage of HF is important.

## Aims

From the year 2007 to 2015, Japanese employees (84% were men) of a construction company located in Tokyo underwent annual measurements of the brachial-ankle pulse wave velocity (brachial-ankle PWV) (a marker of arterial stiffness), radial augmentation index (radial AI) (a marker of the pressure wave reflection), and pre-ejection time/ejection time (pre-ejection period (PEP)/ET) (a marker of cardiac systolic function)[10, 11]. Then, the repeated-measures data were analyzed by mixed-model linear (MML) regression analysis with minimization of the effects of time-varying confounders[12], to examine the individual longitudinal associations of increases in the arterial stiffness and pressure wave reflection with the decline in the cardiac systolic performance during the study period in healthy middle-aged Japanese men.

## Methods

### Design and Subjects

This study was conducted in the same cohort as that enrolled in a previously reported prospective observational study[10, 11]. The cohort consisted of employees working at the headquarters of a single large Japanese construction company located in downtown Tokyo. Informed consent for participation in this study was obtained from each of the study participants prior to his/her enrollment in this study. The study was conducted with the approval of the Ethical Guidelines Committee of Tokyo Medical University (No. 209 and No. 210 in 2003).

The health checkup data obtained for the years 2007 through 2015 were used for the present study. Of 5857 subjects working at the headquarters of the construction company who had undergone measurement of the brachial-ankle PWV at least once, the data of 4016 (all men) were included in our analyses for the present study **(Fig. 1)**.

### Measurement of the Brachial-Ankle PWV, Ejection Time (ET), PEP, and Radial Augmentation Index (rAI)

The baPWV was measured using a volume-plethysmographic apparatus (Form/ABI, Omron Healthcare Co., Ltd., Kyoto, Japan), as previously described[10, 11, 13]. The brachial and post-tibial arterial pressures were measured with the oscillometric sensor. The measurements were conducted after the subjects had rested for at least 5 min in the supine position. Data of subjects with ABI < 0.95 and those with atrial fibrillation were excluded from the analyses.

The ET in the right brachial artery pressure waveform was automatically measured from the foot to the dicrotic notch (equivalent to the incisura on the downstroke of the aortic pressure wave contour produced by closure of the aortic valve) of the pulse volume waveform. The total electromechanical systolic interval ($QS_2$) was measured from the onset of the

QRS complex on the electrocardiogram to the first high-frequency vibrations of the aortic component of the second heart sound on the phonocardiogram. The PEP was also automatically calculated by subtracting the ET from the $QS_2$. The PEP/ET obtained by this method has been demonstrated to show an acceptable correlation with the left ventricular ejection fraction measured by echocardiography[14].

Measurements of the blood pressure and rAI were conducted after the subjects had rested for at least 5 min in the seated position. The left radial arterial waveform was recorded using an arterial applanation tonometry probe (HEM-9010AI; Omron Healthcare Co., Ltd.). Then, the first and second peaks of the radial pressure waveform (SP1 and SP2) and brachial diastolic pressure (brDBP) were automatically detected using the fourth derivatives for each radial arterial waveform and then averaged. The rAI was calculated as follows: $(SP2 - brDBP)/(SP1 - brDBP) \times 100$ (%)[15].

Acceptable reproducibility of the baPWV and rAI measurements has been reported elsewhere[13, 15]. In 90 subjects, the ET, PEP, and PEP/ET were determined twice at a 2-min interval. The correlation coefficients between these two measurements were as follows: ET (R=0.96, $P<0.01$), PEP (R=0.94, $p<0.01$), and PEP/ET (R=0.92, $p<0.01$).

### Laboratory Measurements

Serum concentrations of low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), and creatinine, as well as the plasma glycohemoglobin A1c (HbA1c) value, were measured using standard enzymatic methods (Falco Biosystems Co., Ltd., Tokyo).

### Statistical Analysis

Data are expressed as means ± SD, unless otherwise indicated. The differences in the measured values between the baseline and final examinations were assessed by the paired *t*-test for continuous variables and by McNemar's non-parametric test for categorical variables. The values of the variables at the study baseline were compared with those measured annually thereafter during the study period by general linear model univariate analysis.

The association of the variables measured at the baseline of the study period with the PEP/ET measured at the baseline and end of the study period were examined by multivariate linear regression analysis. For the adjustments, variables identified as significant in the univariate linear regression analyses were entered as covariates along with the history of medication for hypertension, dyslipidemia, diabetes

mellitus, and/or hyperuricemia (not receiving medication, 0; receiving medication, 1; for each medication).

The longitudinal associations among the variables were examined by MML regression analysis. In the MML analyses, beta estimates of the interaction between time and each of the explanatory variables were regarded as the annual changes in the values of the outcome variables per unit annual increase of the corresponding explanatory variable. For the adjustments, the variables identified as significant in the univariate mixed-model analyses were entered as fixed effects, and the history of medication for hypertension, dyslipidemia, diabetes mellitus, and/or hyperuricemia (not receiving medication, 0; receiving medication, 1; for each medication) was entered as a random effect.

All analyses were conducted using the SPSS software (version 25.0; IBM/SPSS Inc., Armonk, NY, USA). $P<0.05$ was considered as indicative of a statistically significant difference in all the statistical tests.

### Results

**Table 1** shows the clinical characteristics of the men at the start and end of the study period. "End of the study period" was defined as the last examination of the participants who had undergone at least two annual examinations. The mean number of times that the variables were measured was 5.2 ± 2.1 times, and the mean duration of follow-up was 6.3 ± 2.5 years. The brachial-ankle PWV, radial AI, PEP/ET, and MBP increased from the baseline to the end of the study period **(Table 1)**. **Fig. 2** shows the mean brachial-ankle PWV, mean radial AI, mean PEP/ET values that were measured annually during the 9-year study period, and number of study subjects from the start to the end of the study period. Longitudinal increases of all the brachial-ankle PWV, radial AI, PEP/ET, and MBP were observed during the study period.

In the univariate analysis without adjustments, age, body mass index, heart rate, serum levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, glycohemoglobin A1c, creatinine, and uric acid, smoking status, and the alcohol habit showed significant associations with the PEP/ET. Then, multivariate linear regression analysis was performed with adjustments for these variables plus history of medication for hypertension, dyslipidemia, diabetes mellitus, and/or hyperuricemia (not receiving medication, 0; receiving medication, 1; for each medication) as the covariates. The analysis

**Table 1.** Clinical characteristics of the male study subjects

| Parameter | Start | Final | *P*-value |
| --- | --- | --- | --- |
| number | 4016 | 4016 | |
| Age (years) | 43 ± 9 | 48 ± 9 | |
| BMI (kg/m²) | 24.0 ± 3.1 | 24.2 ± 3.2 | < 0.001 |
| Smoking (current) (%) | 1269 (31.6) | 1004 (25.0) | < 0.001 |
| Alcohol drinking (current) (number [%]) | 3437 (85.6) | 2561 (88.7) | < 0.001 |
| Ethanol g/day | 12.8 ± 11.1 | 14.6 ± 11.8 | |
| SBP (mm Hg) | 124 ± 14 | 123 ± 15 | < 0.001 |
| DBP (mm Hg) | 75 ± 11 | 76 ± 11 | < 0.001 |
| MBP (mm Hg) | 91 ± 11 | 93 ± 11 | < 0.001 |
| Heart rate (beats/min) | 65 ± 9 | 65 ± 10 | 0.104 |
| baPWV (cm/s) | 1289 ± 187 | 1342 ± 215 | < 0.001 |
| rAI (%) | 69 ± 13 | 72 ± 13 | < 0.001 |
| PEP (ms) | 99 ± 12 | 102 ± 12 | < 0.001 |
| ET (ms) | 284 ± 19 | 284 ± 25 | 0.590 |
| PEP/ET | 0.35 ± 0.05 | 0.36 ± 0.05 | < 0.001 |
| LDL (mmol/L) | 3.08 ± 0.81 | 3.17 ± 0.77 | < 0.001 |
| HDL (mmol/L) | 1.61 ± 0.41 | 1.58 ± 0.39 | < 0.001 |
| TG (mmol/L) | 1.41 ± 0.99 | 1.37 ± 0.94 | < 0.001 |
| HbA1c (%) | 5.3 ± 0.6 | 5.5 ± 0.6 | < 0.001 |
| Crnn (μmol/L) | 76 ± 10 | 76 ± 11 | < 0.001 |
| Medications | | | |
| Receiving medication for hypertension (%) | 304 (7.5) | 615 (15.3) | < 0.001 |
| Receiving medication for dyslipidemia (%) | 107 (2.7) | 284 (7.1) | < 0.001 |
| Receiving medication for diabetes mellitus (%) | 96 (2.4) | 172 (4.3) | < 0.001 |

Abbreviations: Start, at the start of the observation period; Final, at the end of the observation period; BMI, body mass index; Smoking, number of current smokers; Alcohol drinking, number of current drinkers; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; baPWV, brachial-ankle pulse wave velocity; rAI, radial augmentation index; PEP, pre-ejection period; ET, ejection time; PEP/ET, ratio of the pre-ejection period to the ejection time; LDL, serum low-density lipoprotein cholesterol; HDL, serum high-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin A1c; Crnn, serum creatinine; Medications, number and percentage of subjects receiving medication(s).

revealed that both the brachial-ankle PWV and radial AI measured at the baseline showed significant independent associations with the PEP/ET measured at the baseline **(Table 2)**. However, after adjustments, including for the PEP/ET measured at the baseline as a covariate, neither the brachial-ankle PWV nor the radial AI measured at the baseline showed any significant association with the PEP/ET measured at the end of the study period **(Table 2)**.

The individual mixed-model analysis without adjustments revealed that the age, heart rate, serum levels of low-density lipoprotein cholesterol, glycohemoglobin A1c, creatinine, and uric acid and the smoking status showed significant longitudinal associations with the PEP/ET. Then, these variables were entered as fixed effects, and the history of medication for hypertension, dyslipidemia, diabetes mellitus, and/or hyperuricemia (not receiving medication, 0; receiving medication, 1; for each medication) at each measurement was entered as a random effect in the MML model. In the crude MML regression analysis, while the brachial-ankle PWV and MBP were found to show a significant positive longitudinal association with the PEP/ET, the radial AI showed a negative relationship with the PEP/ET **(Table 3)**. Then, based on this unexpected result, no further evaluations of the longitudinal association of the radial AI with the PEP/ET were conducted. When the brachial-ankle PWV and MBP were simultaneously entered in the same MML model along with covariates for adjustments, only the brachial-ankle PWV was identified as showing a significant positive longitudinal association with the PEP/ET **(Table 3)**. For the sub-analyses, the study participants were divided by age (under/over 50 years old) and blood pressure (under/over 130/80 mm Hg). Even in these subgroups, the brachial-ankle PWV, but not the radial AI or MBP, was identified as showing a significant positive longitudinal association with the PEP/ET **(Table 3)**.
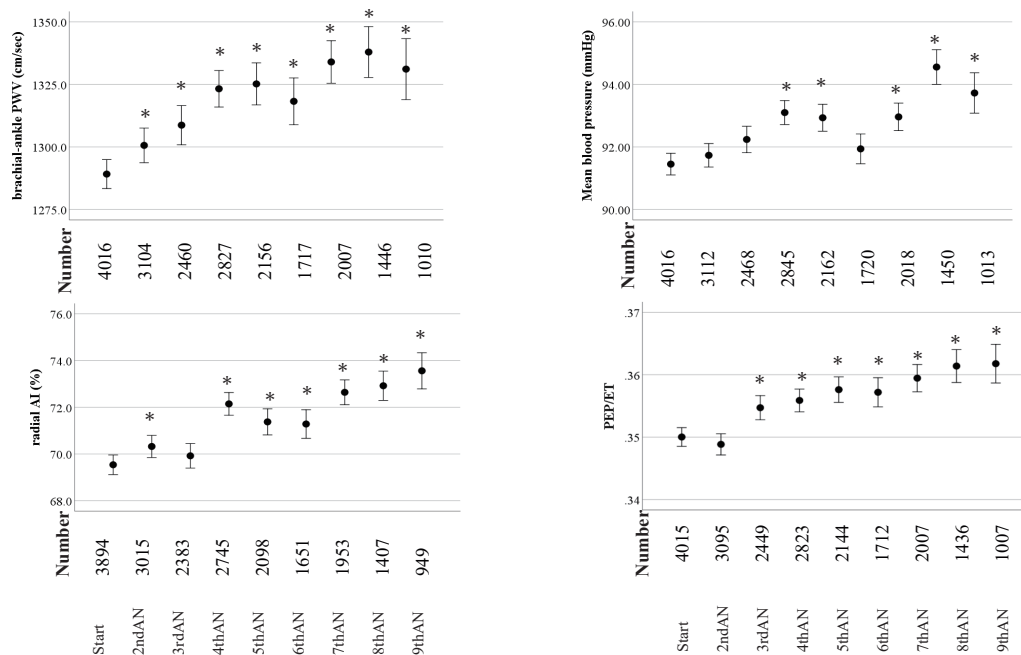
**Fig. 2.** Number of study subjects and annual changes of the brachial-ankle pulse wave velocity, radial augmentation index, and pre-ejection time/ejection time ratio, from the start to the end of the study period

Abbreviations: brachial-ankle PWV, brachial-ankle pulse wave velocity; radial AI, radial augmentation index; PEP/ET, pre-ejection time/ejection time ratio; number, number of study subjects; Start, start of the study period; AN, e.g., 2nd AN, second annual observation; *, $p < 0.05$ vs. Start

**Table 2.** Results of multivariate linear regression analyses to assess the associations of brachial-ankle pulse wave velocity, radial augmentation index and mean blood pressure measured at the baseline with the pre-ejection time/ejection time ratio measured at the baseline and at the end of the study period

| Variable | Crude | | Adjusted | | Simul | | - | |
|---|---|---|---|---|---|---|---|---|
| | Beta | *P*-value | beta | *p*-value | beta | *P*-value | - | - |
| For PEP/ETbase | | | | | | | | |
| baPWVbase | 0.26 | <0.01 | 0.22 | <0.01 | 0.17 | <0.01 | - | - |
| rAIbase | 0.08 | <0.01 | 0.15 | <0.01 | 0.11 | <0.01 | - | - |
| MBPbase | 0.19 | <0.01 | 0.12 | <0.01 | 0.04 | 0.07 | - | - |
| | Crude | | Adjusted | | Simul | | Adjusted + PEP/ETbase | |
| | Beta | *P*-value | beta | *P*-value | beta | *P*-value | beta | *P*-value |
| For PEP/ETend | | | | | | | | |
| baPWVbase | 0.16 | <0.01 | 0.10 | <0.01 | 0.07 | <0.01 | -0.03 | 0.07 |
| rAIbase | 0.07 | <0.01 | 0.11 | <0.01 | 0.09 | <0.01 | 0.02 | 0.24 |
| MBPbase | 0.12 | <0.01 | 0.07 | <0.01 | 0.03 | 0.16 | - | - |

Abbreviations: Variable, explanatory variable; Crude, without adjustment; Adjusted, adjusted with variables identified as significant in the univariate linear regression analyses (i.e., age, body mass index, heart rate, serum levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, glycohemoglobin A1c, crnn, and uric acid, smoking status, alcohol habit) plus history of medication for hypertension, dyslipidemia, diabetes mellitus and/or hyperuricemia (not receiving medication, 0; receiving medication, 1; for each medication; Simul, when any of the brachial-ankle pulse wave velocity, radial augmentation index or mean blood pressure was identified as a significant variable in the multivariate linear regression analysis with adjustments, all of the variables were entered simultaneously in the same model; adjusted + PEP/ETbase, adjusted for the aforementioned covariates plus the pre-ejection time/ejection time ratio measured at the baseline; beta, standardized co-efficient; base, study baseline; end, end of the study period; other abbreviations are as described in the footnote for Table 1.

**Table 3.** Results of mixed-model linear regression analysis conducted to assess the longitudinal associations of vascular functional abnormalities with the pre-ejection period/ejection time

| Whole study subjects ($n=4016$) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | Crude | | | Adjust | | | Simul | | |
| | Estimate | SE | P-value | Estimate | SE | P-value | Estimate | SE | P-value |
| baPWV | $0.80 \times 10^{-4}$ | $0.05 \times 10^{-4}$ | $<0.01$ | $0.64 \times 10^{-4}$ | $0.06 \times 10^{-4}$ | $<0.01$ | $0.69 \times 10^{-4}$ | $0.07 \times 10^{-4}$ | $<0.01$ |
| rAI | $-0.19 \times 10^{-3}$ | $0.09 \times 10^{-3}$ | 0.04 | - | - | - | - | - | - |
| MBP | $0.51 \times 10^{-3}$ | $0.01 \times 10^{-5}$ | $<0.01$ | $0.22 \times 10^{-3}$ | $0.01 \times 10^{-3}$ | $<0.01$ | $0.19 \times 10^{-3}$ | $0.12 \times 10^{-3}$ | 0.10 |

| Sub-analyses by age | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | Crude | | | Adjust | | | Simul | | |
| | Estimate | SE | P-value | Estimate | SE | P-value | Estimate | SE | P-value |
| Age $<50$ ($n=2198$) | | | | | | | | | |
| baPWV | $0.93 \times 10^{-4}$ | $0.71 \times 10^{-4}$ | $<0.01$ | $0.73 \times 10^{-4}$ | $0.08 \times 10^{-4}$ | $<0.01$ | - | - | - |
| rAI | $-0.64 \times 10^{-4}$ | $1.04 \times 10^{-4}$ | 0.54 | - | - | - | - | - | - |
| MBP | $0.49 \times 10^{-3}$ | $0.12 \times 10^{-3}$ | $<0.01$ | $0.23 \times 10^{-3}$ | $0.12 \times 10^{-3}$ | 0.06 | - | - | - |
| Age $>50$ ($n=1818$) | | | | | | | | | |
| baPWV | $0.76 \times 10^{-4}$ | $0.11 \times 10^{-4}$ | $<0.01$ | $0.54 \times 10^{-4}$ | $0.12 \times 10^{-4}$ | $<0.01$ | - | - | - |
| rAI | $-0.96 \times 10^{-3}$ | $0.23 \times 10^{-3}$ | $<0.01$ | - | - | - | - | - | - |
| MBP | $0.60 \times 10^{-3}$ | $0.23 \times 10^{-3}$ | $<0.01$ | $0.16 \times 10^{-3}$ | $0.23 \times 10^{-3}$ | 0.49 | - | - | - |

| Sub-analyses by blood pressure | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | Crude | | | Adjust | | | Simul | | |
| | Estimate | SE | P-value | Estimate | SE | P-value | Estimate | SE | P-value |
| BP $<130/80$ ($n=2869$) | | | | | | | | | |
| baPWV | $0.81 \times 10^{-4}$ | $0.08 \times 10^{-4}$ | $<0.01$ | $0.64 \times 10^{-4}$ | $0.09 \times 10^{-4}$ | $<0.01$ | - | - | - |
| rAI | $-0.61 \times 10^{-4}$ | $1.15 \times 10^{-4}$ | 0.59 | - | - | - | - | - | - |
| MBP | $0.30 \times 10^{-3}$ | $0.16 \times 10^{-5}$ | 0.06 | - | - | - | - | - | - |
| BP $>130/80$ ($n=1147$) | | | | | | | | | |
| baPWV | $0.82 \times 10^{-4}$ | $0.08 \times 10^{-4}$ | $<0.01$ | $0.63 \times 10^{-4}$ | $0.09 \times 10^{-4}$ | $<0.01$ | - | - | - |
| rAI | $-0.34 \times 10^{-3}$ | $0.15 \times 10^{-3}$ | 0.03 | - | - | - | - | - | - |
| MBP | $0.66 \times 10^{-3}$ | $0.17 \times 10^{-3}$ | $<0.01$ | $0.33 \times 10^{-3}$ | $0.17 \times 10^{-3}$ | 0.06 | - | - | - |

Abbreviations: Estimate, Beta estimates of the interaction between time and each of the explanatory variables; SE, standard error of the estimate; Age $<50$ or $>50$, subjects aged under 50 years old or over 50 years old; BP $<130/80$ or $\geq 130/80$ mm Hg, subjects with blood pressure under 130/80 or over 130/80 mm Hg; adjust, adjusted for the variables identified as significant in the univariate mixed-model analyses (i.e., age, heart rate, serum levels of low-density lipoprotein cholesterol, glycohemoglobin A1c, creatinine, and uric acid, smoking status) entered as fixed effects plus history of medication for hypertension, dyslipidemia, diabetes mellitus and/or hyperuricemia (not receiving medication, 0; receiving medication, 1; for each medication) at each measurement entered as a random effect; simul, when any of the brachial-ankle pulse wave velocity, radial augmentation index or mean blood pressure was identified as a significant variable in the mixed model linear regression analysis, all of the variables were entered simultaneously in the same model; other abbreviations are as described in the footnote for Table 1.

## Discussion

To the best of our knowledge, this prospective observational study is the first to examine the longitudinal associations among changes of the brachial-ankle PWV, radial AI, and PEP/ET in apparently healthy Japanese men, based on the analysis of repeated-measures data over a 9-year period. The results of multivariate linear regression analysis revealed that both the brachial-ankle PWV and radial

AI at the study baseline were associated with the PEP/ET measured at the study baseline, but not with that measured at the end of the study period. MML regression analysis of repeated-measures data demonstrated a significant longitudinal association between the change of the arterial stiffness, but not that of the radial AI, and the change of the PEP/ET during the study period.

# Annual Decline of the Cardiac Systolic Performance

While several studies have reported age-related decline of the cardiac diastolic function [16-20], age-related decline of the cardiac systolic performance, which is usually assessed by measurement of the left ventricular ejection fraction, remains unclear. In this study, we confirmed the annual decline in the cardiac systolic performance even in apparently healthy middle-aged Japanese men, by longitudinal measurement of the PEP/ET. Left ventricular ejection fraction is calculated as the left ventricular ejection volume divided by the left ventricular volume at end-diastole and is a standard method for assessing left ventricular systolic function. Determination of the left ventricular ejection fraction requires the availability of imaging modalities, such as echocardiography plain computed tomography, magnetic resonance imaging, etc., and therefore entails the limitation that it cannot be applied to a large study population. On the other hand, PEP/ET allows evaluation of the cardiac systolic performance based on cardiac systolic time intervals [21]. Prolongation of the PEP is caused by a diminished rate of increase of the left ventricular pressure during systole, and a decrease of the ET is associated with a decrease in the stroke volume [21]. Thus, an increase of the PEP/ET has been shown to be associated with a decrease of the cardiac systolic performance and to be closely correlated with a reduced left ventricular ejection fraction [22]. PEP/ET can also be easily measured by pulse recording, electrocardiography, and phonocardiography and is therefore applicable to large study populations. In this study, the mean PEP/ET in the study participants increased from $0.35 \pm 0.05$ to $0.36 \pm 0.05$ during the study period. In our previous study conducted in the same cohort [23], the PEP/ET was higher in subjects with elevated ($\geq 125$ pg/mL) serum NT-pro-BNP levels ($0.38 \pm 0.07$, $n=38$) than in the subjects without elevated serum NT-pro-BNP levels ($0.36 \pm 0.05$, $n=2628$) ($p=0.01$) [24]. Therefore, it appears that PEP/ET does reflect the cardiac systolic performance, and our results suggest that an annual decline of the cardiac systolic performance may be observed even in apparently healthy middle-aged Japanese men.

# Pulse Wave Velocity, Augmentation Index, and Cardiac Systolic Performance

A previous experimental study demonstrated that late, rather than early, cardiac systolic load is the major driver of decline in cardiac performance [25]. Zamani P *et al.* have reported that the amplitude of the pressure wave reflection, which is related to the late cardiac systolic load, is a risk factor for the development of HF [6]. On the other hand, Kim *et al.* reported, from the results of an elderly cohort study, that the carotid-femoral PWV is a risk factor for the development of HF [26]. As mentioned in the Introduction section, increase of the arterial stiffness, as reflected by the PWV, may increase the late cardiac systolic load via augmenting the pressure wave reflection and also directly increase the early cardiac systolic load via countering the forward pressure wave generated by cardiac contraction [7-9]. However, Kim *et al.* could not provide a clear explanation for their finding in the aforementioned study, because they did not measure the PWV and pressure wave reflection simultaneously in the study.

While it was only a cross-sectional study, Bell *et al.* simultaneously measured the carotid-femoral PWV, augmentation index, and cardiac systolic performance in the Framingham heart study cohort [27]. They found a significant negative association between the carotid-femoral PWV and the cardiac mechanical systolic performance, independent of the augmentation index, in both men and women [27]. The findings of the present study were as follows: (1) Significant annual increases of both the brachial-ankle PWV and PEP/ET (i.e., annual increase of the arterial stiffness and decline of cardiac systolic function) were observed during the study period and (2) a significant longitudinal association was observed between the change in the brachial-ankle PWV, but not that of the radial AI, and the change in the PEP/ET during the study period. Thus, the longitudinal increase of the arterial stiffness with age may be directly responsible for a longitudinal decline of the cardiac systolic performance in healthy middle-aged Japanese men, independent of the effect of the pressure wave reflection.

It has been reported that that age-related changes in the augmentation index are more prominent in younger individuals ($<50$ years) [28] and the blood pressure is a major determinant of the PWV [29]. Thus, it seems plausible that age and/or blood pressure affect the associations among arterial stiffness, pressure wave reflection, and cardiac systolic performance. To verify this notion, we conducted subgroup analyses after classifying the subjects into subgroups according to the age and blood pressure levels. The results of these

subgroup analyses also indicated the existence of a significant longitudinal association between reduction of the brachial-ankle PWV decline of the cardiac systolic performance.

Abnormal pressure wave reflection, which is known to be related to the late cardiac systolic load, induces cardiac remodeling, cardiac fibrosis, and cardiac diastolic dysfunction[7, 9]. In turn, cardiac remodeling causes cardiac systolic dysfunction[7, 9]. However, the effect of early cardiac systolic load, related to the arterial stiffness, on the cardiac performance remain unclear. As mentioned above, based on a cross-sectional study conducted in the Framingham heart study cohort, Bell *et al.* proposed that increased arterial stiffness induces impaired cardiac systolic performance through causing mechanical ventricular-arterial coupling (i.e., increased arterial stiffness increases the long-axis left ventricular cardiac load, which decreases the left ventricular systolic long-axis shortening)[27]. These could be some of the plausible mechanisms explaining the findings of the present study.

# Clinical Implications

Several studies have suggested that abnormal pressure wave reflection is one of the important pathophysiological abnormalities underlying new onset of HF[4-7]. Therefore, further studies are needed to clarify the stages in the development of HF at which augmented pressure wave reflection begins to exert harmful effects not only on the cardiac systolic performance but also on the cardiac diastolic performance.

While no strategies have been established yet for de-stiffening of arteries, such a strategy is thought to be one of the potential key elements for preventing the development of CVD[30]. In the aging society, preventing the development of HF is an important issue[31]. The present study demonstrated a significant longitudinal association of age-related progression of arterial stiffness with the decline of left ventricular performance in healthy middle-aged Japanese men. Therefore, arterial de-stiffening may also be important for preventing the development of HF and might be needed even from middle age.

# Study Limitations

This study had some limitations: (1) Gender- and ethnicity-related differences in the association between arterial stiffness and cardiac performance have been reported[17, 18, 27]; therefore, confirmation of the present findings is needed in women and other ethnicities. (2) Brachial-ankle PWV reflects the stiffness of the large- to middle-sized arteries[13].

Stiffness of the large arteries is a key player in the association of the arterial stiffness with the cardiac systolic performance[7, 9]. On the other hand, for assessment of the cardiac systolic performance, left ventricular ejection fraction or left ventricular strain are more commonly used parameters as compared to PEP/ET[14, 32]. Therefore, further study is needed to examine the longitudinal association of the carotid-femoral PWV, a marker of the stiffness of the large arteries, with the cardiac systolic performance assessed by some other methods than by measurement of the PEP/ET. (3) The characteristic impedance is a reliable marker reflecting the early cardiac systolic load[27, 33], but it was not measured in the present study. (4) The associations among vascular functional abnormalities, cardiac diastolic dysfunction, and ventricular morphological abnormalities were not examined in this study.

## Conclusion

In apparently healthy middle-aged Japanese men, the annual increase of the arterial stiffness, rather than the annual increase of the pressure wave reflection, appears to be more closely associated with the annual decline of the cardiac systolic performance as assessed by the systolic time interval.

## Conflict of Interest

The sponsor (Omron Health Care Company) assisted in the data formatting (i.e., the data of the brachial-ankle PWV stored in the hard disc of the equipment used for measurement of the brachial-ankle PWV was transferred to an Excel file). Other than this, however, the company played no role in the design or conduct of the study, i.e., in the data collection, management, analysis or interpretation of the data, or in the preparation, review or approval of the manuscript. The authors have no other disclosure to make.

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