ORIGINAL RESEARCH

Effect of Wave Reflection and Arterial Stiffness on the Risk of Development of Hypertension in Japanese Men

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***Background*—**We conducted analyses of repeated-measures data to examine whether pressure wave reflection acts additively or synergistically with arterial stiffness in the pathogenesis of hypertension.

***Methods and Results*—**In 3172 middle-aged (42±9 years) healthy Japanese men without hypertension at the study baseline, systolic and diastolic blood pressures, brachial–ankle pulse wave velocity, and radial augmentation index were measured annually during a 9-year study period. Of these, 474 participants (15%) developed hypertension by the end of the study period. Binary logistic regression analysis demonstrated significant individual odds ratios for both baseline brachial–ankle pulse wave velocity and radial augmentation index for the development of hypertension. The rate of onset of hypertension during the study period was highest in the participant group with high values for both brachial–ankle pulse wave velocity and radial augmentation index at study baseline (262 of 965 participants: 27%). The generalized estimating equation analysis revealed that both radial augmentation index (estimate=0.06, SE=0.03, P=0.05) and brachial–ankle pulse wave velocity (estimate=0.07×10^{-1}, SE=0.02×10^{-1}, P<0.01) showed significant longitudinal association with new onset of hypertension, with no significant interaction.

***Conclusions*—**In Japanese men, abnormal wave reflection and increased arterial stiffness may be additively associated with the risk of new onset of hypertension. Abnormal wave reflection and elevated central blood pressure may be longitudinally associated with increase in arterial stiffness, and this longitudinal association may be a mechanism underlying the additive effect of these 2 variables on the risk of new onset of hypertension. **(*J Am Heart Assoc*. 2018;7:e008175. DOI: 10.1161/JAHA.117.008175.)**

Key Words: arterial stiffness • augmentation index • hypertension • pulse wave velocity • wave reflection

Hypertension is known to have high prevalence in the general population. Because it is also a major risk factor for the development of cardiovascular disease,[1] preventing the development of hypertension is of major medical and societal importance.[1,2] Based on the results of several prospective studies, arterial stiffness (ie, macrovascular damage) is recognized to be a key player in the development of hypertension.[3–5] Alternatively, microvascular damage in the arterial tree has also been proposed as an important factor for the development of hypertension.[6,7] In the arterial tree, abnormal wave reflection is caused not only by the increased pressure wave propagation speed on the arterial wall, derived from increased arterial stiffness, but also by elevation of the amplitude of the reflected wave secondary to increased peripheral reflectance, derived from peripheral vascular damage.[8,9] Consequently, it is possible that wave reflection acts additively or synergistically with arterial stiffness to increase the risk of development of hypertension. Detailed clarification of these pathophysiological phenomena is important for developing methods to prevent hypertension.

Generalized estimating equation (GEE) analysis and mixed-model linear (MML) regression analysis of repeated-measures data have been proposed as valid analytical tools for excluding the confounding effects of time-varying variables.[10] Repeated-measures data of blood pressure, arterial stiffness, and pressure wave reflection were obtained over a 9-year observation period for previous prospective observational studies from the employees of a single large Japanese construction company.[5,11–13] Using these data, we conducted this study to examine whether wave reflection acts additively or synergistically with arterial stiffness in the pathogenesis of hypertension.

Methods

The authors declare that all supporting data are available within the article. Informed consent was obtained from study

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Clinical Perspective

What Is New?

- Generalized estimating equation analysis revealed that both radial augmentation index and brachial–ankle pulse wave velocity showed significant longitudinal association, with no significant interaction, with new onset of hypertension.
- When participants were classified into 4 groups according to median values for brachial–ankle pulse wave velocity and radial augmentation index measured at study baseline, the rate of onset of hypertension during the study period was highest in the group with high values for both brachial–ankle pulse wave velocity and radial augmentation index at study baseline.

What Are the Clinical Implications?

- In middle-aged Japanese men, abnormal wave reflection and increased arterial stiffness may be additively associated with the risk of new onset of hypertension.

participants before their participation in the study. The study was conducted with the approval of the ethical guidelines committee of Tokyo Medical University (current: no. 209; 2003: no. 210).

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure, based on the approval of the ethical guidelines committee of Tokyo Medical University (current: no. 209; 2003: no. 210).

Design and Participants

This study was conducted as part of a previous prospective observational study of employees working at the headquarters of a single large Japanese construction company located in downtown Tokyo.[11,12] The participants underwent annual health checkups, including evaluation of atherosclerotic risk factors and measurement of brachial–ankle pulse wave velocity (baPWV) and radial augmentation index (rAI), from 2007 to 2015. The company employs both permanent and temporary workers; however, we included the data of only the permanent employees in our study because annual follow-up temporary employees is difficult. According to the occupational health and safety law in Japan, annual health checkups are mandatory for all company employees. Even so, some data are lost because of dismissal, retirement, or transfer of employees to a branch office. Consequently, we analyzed the data derived from the annual health checkups conducted at the company headquarters from 2007 to 2015 for permanent employees; only those participants who had undergone at least 2 annual health checkups during our study period were included.

Figure 1 shows a flow diagram of the participants enrolled in this study. Of the total 5857 participants, 3908 did not have hypertension at study baseline; of those, all 634 female

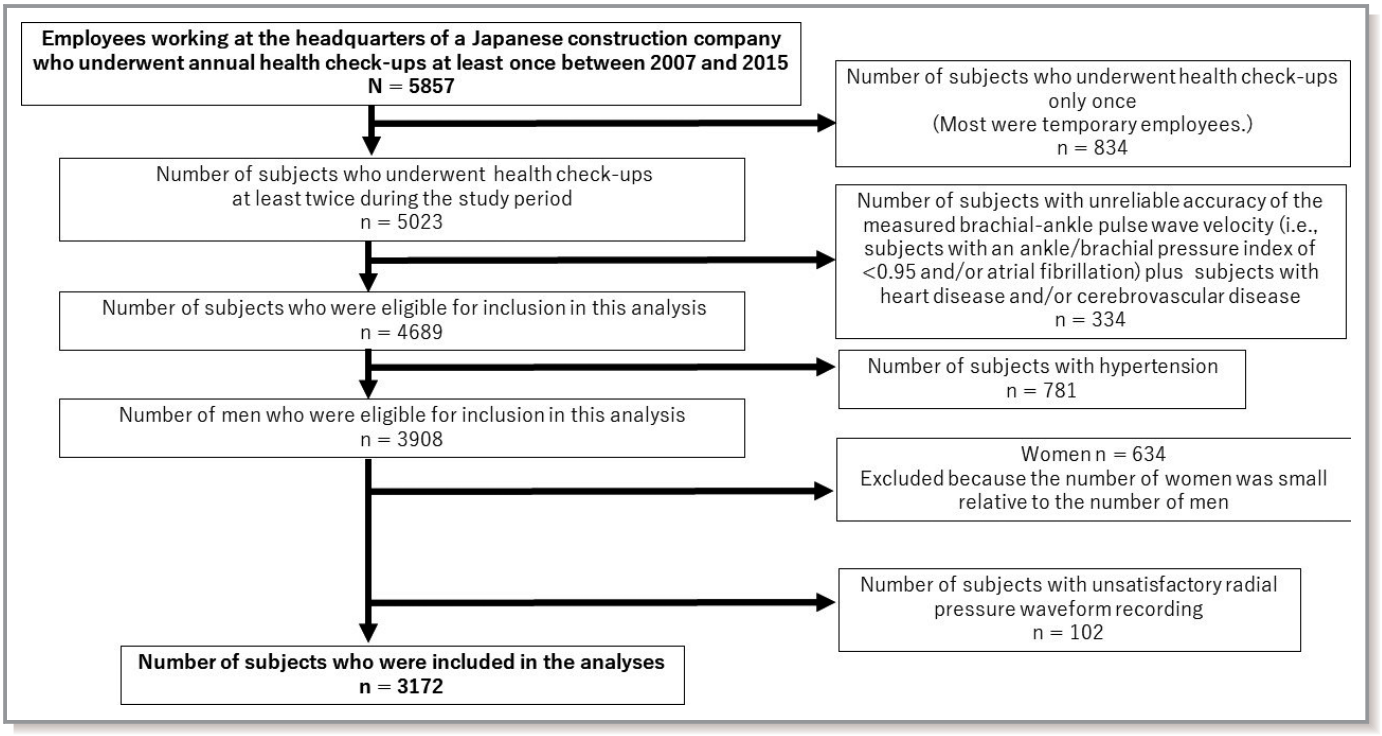

Figure 1. Flow diagram of participants enrolled in the study.

participants (because the number was small relative to the number of male participants) and 102 participants with unsatisfactory radial tonometry recordings (SD >6%; presumed to be from inaccurate pressure waveform recording) were excluded.[13] The present study was conducted in the remaining 3172 men.

Blood Pressure Measurement

Brachial systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured as the mean of 2 measurements obtained in an office setting by the conventional cuff method using a mercury sphygmomanometer. The measurements were conducted by well-trained nurses, with participants in the seated position after they had rested for at least 5 minutes.

Participants with hypertension were defined as those with conventionally measured SBP ≥140 mm Hg and/or DBP ≥90 mm Hg or those receiving antihypertensive medication.

Measurement of rAI

Blood pressure and rAI were measured after participants had rested for at least 5 minutes in the seated position. Blood pressure was measured in the right upper arm using the oscillometric method (SBPosc and DBPosc; HEM-907 [Omron Healthcare). 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-9010AI; Omron Healthcare). Subsequently, the first and second peaks of the radial pressure waveform (SBP1 and SBP2) were automatically detected. The rAI was calculated as follows:

$$(\mathrm{SBP2}-\mathrm{DBPosc})/(\mathrm{SBP1}-\mathrm{DBPosc})\times 100(\%).$$[13]

Measurement of the baPWV

The baPWV was measured once using a volume-plethysmographic apparatus (Form/ABI; Omron Healthcare), as described previously.[14] Briefly, occlusion cuffs connected to both the plethysmographic and oscillometric sensors were tied around both the upper arms and legs of the participants lying in the supine position. The brachial and posttibial arterial pressures were measured by the oscillometric sensor. The measurements were conducted after the participants had rested for at least 5 minutes in the supine position in an air-conditioned room (maintained at 24°C) designated exclusively for this study.

Laboratory Measurements

Serum concentrations of triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and creatinine, as well as the plasma concentrations of glucose and glycohemoglobin A1c, were measured using standard enzymatic methods.

Statistical Analysis

Data are expressed as mean±SD unless otherwise indicated. The differences in the values measured between the baseline and final examinations were assessed using the paired *t* test for continuous variables and the McNemar nonparametric test for categorical variables. The differences in the measured values among the groups were also analyzed using a general linear model with post hoc group comparison.

The basic covariates adjusted for were body mass index, current smoking history, current daily alcohol intake, heart rate, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, glycohemoglobin A1c, creatinine, history of medication use for hypertension, dyslipidemia, and/or diabetes mellitus (not receiving medication=0, receiving medication=1; for each medication), and family history of hypertension. Body mass index and alcohol use were entered into the analyses as categorized variables (ie, body mass index ≥25=1 and <25=0; ethanol intake ≥30 g/day=1 and <30 g/day=0). In the group comparisons, general linear model regression analysis with post hoc comparisons was conducted with and without adjustments.

Logistic regression analysis was performed to identify the variables that were predictive of the development of hypertension. To determine the longitudinal associations of the variables with the new onset of hypertension, GEE analyses were performed. In the GEE analyses, the time effect was entered by the interaction term between time (years from the baseline) and each of the explanatory variables. Beta estimates of the interaction between time and each explanatory variable were regarded as the annual new onset of hypertension per unit of annual increase of the corresponding explanatory variable. In addition, in cases for which the interaction between baPWV and rAI in relation to their longitudinal association with new onset of hypertension was assessed, the interaction term between baPWV and rAI was also added. The GEE analyses were conducted using 4 different model structures (ie, independent, autoregressive [1], exchangeable, and unstructured). Then we used the quasi–likelihood under the independence model criterion to determine the best correlation structure.

To determine the longitudinal associations among the variables, MML analyses were performed. In the MML analyses, the time effect was entered by the interaction term between time (years from baseline) and each of the explanatory variables. Beta estimates of the interaction between time and each explanatory variable were regarded as the annual changes in each of the outcome variables per unit of annual

increase of the corresponding explanatory variable. The MML analyses were conducted using 5 different model structures (ie, autoregressive [1], compound symmetry, diagonal, Toeplitz, and unstructured). Then we used the Akaike information criterion to determine the best model structure.

All analyses were conducted using SPSS software (version 24.0; IBM Corp). $P<0.05$ was considered indicative of a statistically significant difference in all statistical tests.

Results

Table 1 shows the clinical characteristics of the study participants at baseline and at the end of the study period. The relevant parameters were measured a mean of 5.2±2.1 times in the participants, and the mean duration of follow-up was 6.4±2.5 years. Measured SBPcon, DBPcon, baPWV, rAI, and SBP2 increased significantly in the participants during the study period.

Of the participants included in the analysis, 474 (15%) developed hypertension by the end of the study period (of those, 152 were receiving antihypertensive medication by the end of the study period; Table 1). Furthermore, 110 of 1882 participants (6%) developed hypertension by the third year of the study period, and 140 of 1662 participants (8%) developed hypertension by the fifth year of the study period. Binary logistic regression analysis, with baPWV and rAI entered simultaneously in the same model, revealed significant odds ratios (per 1-SD increase), independent of both baseline baPWV and baseline rAI, for the development of hypertension by the third year, the fifth year, and the end of the study period, even after adjustments for the basic covariates measured at study baseline plus the SBP measured at the study baseline (Table 2).

Sensitivity analyses were conducted to determine the significance of both baseline baPWV and baseline rAI for the development of hypertension among the groups divided by age (ie, age ≥50 or <50 years), severity of hypertension (outcomes at the end of the study period: grade 1 hypertension or grade 2 hypertension[15]/receiving antihypertensive medication), and blood pressure categories at baseline (ie, optimal, normal, and high-normal blood pressure).[15] The numbers of participants in these blood pressure categories at baseline are depicted in Table 3. The baPWV and the rAI were associated with significant adjusted odds ratios for the development of hypertension in all subgroups divided by age or blood pressure category at the baseline. When outcome variable was defined as grade 1 hypertension or grade 2 hypertension[15]/receiving antihypertensive medication at the end of the study period, the adjusted odds ratio of the rAI for grade 1 hypertension was marginally significant (Table 3).

As shown in Figure 2, participants were classified into 4 groups according to the median values of baPWV and rAI measured at study baseline (high baPWV: ≥1227 cm/s; low baPWV: <1227 cm/s; high rAI: ≥68.5%; low rAI: <68.5%). Table 4 shows the clinical characteristics of the 4 groups. Age, prevalence of family history of hypertension, prevalence of smoking, prevalence of alcohol intake, blood pressure, serum low-density lipoprotein cholesterol, serum triglyceride, glycohemoglobin A1c, and medication rates for diabetes mellitus and/or dyslipidemia were highest in the participant group with high values of both baPWV and rAI at baseline. The results of the general linear model analysis revealed that the

Table 1. Clinical Characteristics of the Study Participants

Parameter	At Study Baseline	At the End of the Observation Period	*P* Value
Number	3172	3172	
Age, y	42±9	48±9	
BMI, kg/m^2	23.7±2.9	23.9±3.0	<0.01
Smoking (current), n (%)	1020 (32)	814 (26)	<0.01
Alcohol drinking (current), n (%)	2701 (85)	2812 (89)	<0.01
Daily alcohol intake, g/d	12.1±10.7	14.2±11.7	<0.01
SBPcon, mm Hg	119±10	123±11	<0.01
DBPcon, mm Hg	72±8	75±10	<0.01
Hypertension, n (%)	0	474 (15)	
Heart rate, beats/min	67±9	67±9	0.23
baPWV, cm/s	1245±144	1303±187	<0.01
SBPosc, mm Hg	120±12	121±13	0.08
DBPosc, mm Hg	73±9	74±10	0.01
rAI, %	68±13	72±13	<0.01
SBP2, mm Hg	105±13	107±15	<0.01
LDL, mmol/L	3.06±0.80	3.18±0.78	<0.01
HDL, mmol/L	1.61±0.40	1.58±0.39	<0.01
TG, mmol/L	1.36±0.96	1.34±0.91	0.28
HbA1C, %	5.2±0.5	5.3±0.6	<0.01
Family history, n (%)	935 (30)	935 (30)	
Cr, μmol/L	75±9	76±10	<0.01
Medication history			
Hypertension, n (%)	0	152 (5)	<0.01
Dyslipidemia, n (%)	55 (2)	157 (5)	<0.01
Diabetes mellitus, n (%)	43 (1)	89 (3)	<0.01

baPWV indicates brachial–ankle pulse wave velocity; BMI, body mass index; Cr, serum creatinine; DBPcon, brachial diastolic blood pressure measured by the conventional cuff method; DBPosc, diastolic blood pressure measured by the oscillometric method at the time of rAI measurement; HbA1c, glycosylated hemoglobin A1c; HDL, serum high-density lipoprotein cholesterol; LDL, serum low-density lipoprotein cholesterol; rAI, radial augmentation index; SBP2, second peak of the radial pressure waveform; SBPcon, brachial systolic blood pressure measured by the conventional cuff method; SBPosc, systolic blood pressure measured by the oscillometric method at the time of rAI measurement; TG, serum triglyceride.

Table 2. Results of Logistic Regression Analysis Performed to Examine the Predictive Value of rAI and baPWV for New Onset of Hypertension by the Third Year, the Fifth Year, and the End of the Study Period

Parameter	OR (Per 1-SD Increase)	95% CI	*P* Value
By the third year (HBP: 110/1882)			
Crude			
rAI	1.42	1.17–1.72	<0.01
baPWV	2.25	1.90–2.66	<0.01
Covariates adjusted for (rAI and baPWV were entered individually)			
rAI	1.47	1.11–1.95	<0.01
baPWV	1.77	1.41–2.22	<0.01
Covariates adjusted for (rAI and baPWV were entered simultaneously)			
rAI	1.30	0.97–1.74	0.07
baPWV	1.70	1.35–2.15	<0.01
By the fifth year (HBP: 140/1662)			
Crude			
rAI	1.46	1.22–1.74	<0.01
baPWV	2.32	1.97–2.74	<0.01
Covariates adjusted for (rAI and baPWV were entered individually)			
rAI	1.46	1.14–1.86	<0.01
baPWV	1.70	1.40–2.08	<0.01
Covariates adjusted for (rAI and baPWV were entered simultaneously)			
rAI	1.25	0.97–1.62	0.08
baPWV	1.63	1.33–2.00	<0.01
By the end (HBP: 474/3172)			
Crude			
rAI	1.58	1.43–1.75	<0.01
baPWV	2.17	1.97–2.40	<0.01
Covariates adjusted for (rAI and baPWV were entered individually)			
rAI	1.64	1.41–1.91	<0.01
baPWV	1.53	1.35–1.73	<0.01
Covariates adjusted for (rAI and baPWV were entered simultaneously)			
rAI	1.50	1.28–1.76	<0.01
baPWV	1.42	1.25–1.62	<0.01

Adjustment was for basic covariates (age, body mass index, current smoking, current daily alcohol intake, heart rate, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, serum triglyceride, glycosylated hemoglobin A1c and serum creatinine measured at baseline, medication history for dyslipidemia and/or diabetes mellitus, and family history of hypertension; nobody had medication for hypertension at baseline) plus systolic blood pressure measured at study baseline. For HBP, the numerator shows the number of participants who developed hypertension and the denominator shows the number of participants for whom data were available. baPWV indicates brachial–ankle pulse wave velocity; CI, confidence interval; HBP, high blood pressure; OR, odds ratio; rAI, radial augmentation index.

rates of new onset of hypertension by the third year, the fifth year, and the end of the study period were highest in the participant group with high values of both baPWV and rAI at

Table 3. Results of Logistic Regression Analysis Performed With Adjustments to Examine the Predictive Value of rAI and baPWV for Outcomes by the End of the Study Period Among the Subgroups

Parameter	Adjusted OR (Per 1-SD Increase)	95% CI	*P* Value
Subgroups divided by age			
Participants aged <50 y (n=2460)			
Covariates adjusted (rAI and baPWV were entered individually)			
rAI	1.61	1.34–1.93	<0.01
baPWV	1.42	1.20–1.67	<0.01
Participants aged ≥50 y (n=712)			
rAI	1.57	1.18–2.09	<0.01
baPWV	1.71	1.41–2.07	<0.01
Subgroups divided by outcomes			
Grade 1 HTN by the end of the study period (n=276 for outcome)			
Covariates adjusted (rAI and baPWV were entered individually)			
rAI	1.18	0.99–1.40	0.07
baPWV	1.17	1.02–1.34	0.03
Grade 2 HTN/receiving antihypertensive medication by the end of the study period (n=198 for outcome)			
Covariates adjusted for (rAI and baPWV were entered individually)			
rAI	2.34	1.87–2.94	<0.01
baPWV	1.59	1.35–1.87	<0.01
Subgroups divided by BP categories			
Optimal BP (n=1363)			
Covariates adjusted (rAI and baPWV were entered individually)			
rAI	1.82	1.29–2.57	<0.01
baPWV	1.77	1.29–2.44	<0.01
Normal BP (n=1054)			
Covariates adjusted (rAI and baPWV were entered individually)			
rAI	1.64	1.27–2.13	<0.01
baPWV	1.31	1.06–1.63	0.01
High-normal BP (n=755)			
Covariates adjusted (rAI and baPWV were entered individually)			
rAI	1.51	1.21–1.90	<0.01
baPWV	1.53	1.28–1.82	<0.01

Adjustment was for basic covariates (age, body mass index, current smoking, current daily alcohol intake, heart rate, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, serum triglyceride, glycosylated hemoglobin A1c and serum creatinine measured at baseline, medication history for dyslipidemia and/or diabetes mellitus, and family history of hypertension; nobody had medication for hypertension at baseline) plus systolic blood pressure measured at study baseline. Subgroups were divided for outcomes by the outcome variables of grade 1 hypertension or grade 2 hypertension/receiving antihypertensive medication at the end of study period. baPWV indicates brachial–ankle pulse wave velocity; BP, blood pressure; CI, confidence interval; HTN, hypertension; OR, odds ratio; rAI, radial augmentation index.

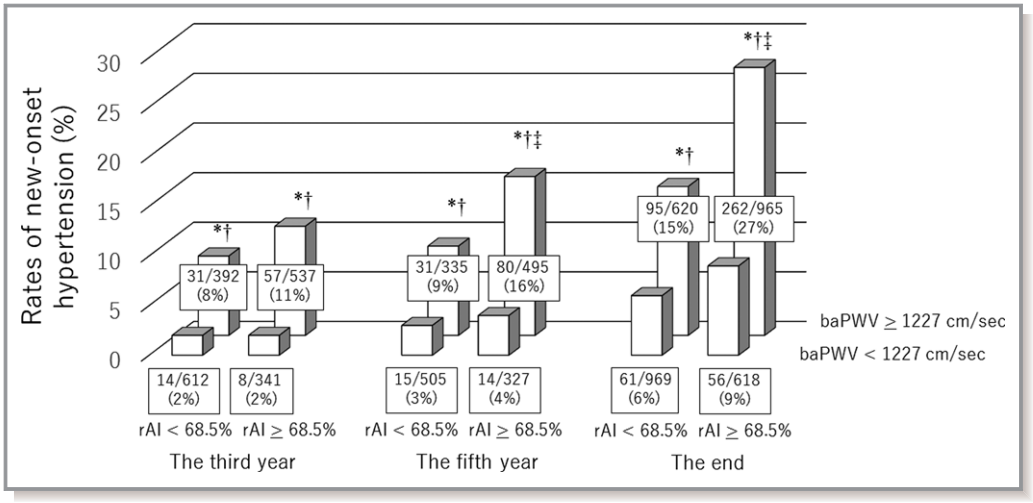

Figure 2. Incidence of hypertension by the third year, the fifth year, and the end of the study period in participants classified into 4 groups according to the median values of the brachial–ankle pulse wave velocity (baPWV) and radial augmentation index (rAI) measured at study baseline. Numbers in boxes indicate the numbers of participants who developed hypertension (numerator) and the total number of participants in each group (denominator). **P*<0.05 vs participants with baPWV <1227 cm/s and rAI <68.5%; †*P*<0.05 vs participants with baPWV <1227 cm/s and rAI ≥68.5%; ‡*P*<0.05 vs participants with baPWV ≥1227 cm/s & rAI <68.5%.

baseline, even after adjustments for basic covariates plus SBP at baseline and duration of follow-up.

The significant longitudinal associations of rAI and baPWV with new onset of hypertension were confirmed by the results of the GEE analyses (Table 5). In the absence of the addition of an interaction term to the model, rAI and baPWV were found to show independent longitudinal associations with the new onset of hypertension (Table 5). Analysis with entry of the interaction term into the model revealed no significant interaction of rAI and baPWV in their longitudinal association with new onset of hypertension (Table 5).

Table 6 shows the results of the MML analysis conducted to assess the longitudinal associations of rAI and SBP2 with baPWV, which was revealed. Conversely, baPWV showed a significant longitudinal association with SBP2 but not with rAI.

Discussion

To the best of our knowledge, this study was the first observational study using GEE and MML analysis of repeated-measures data to examine the mutual association between arterial stiffness and wave reflection in the development of hypertension.

Several studies have demonstrated that increased arterial stiffness is a predictor of the development of hypertension.[2–5] A plausible mechanism is that increased arterial stiffness increases the amplitude of the forward pressure wave originating from the left ventricle. Wave reflection has also been reported as a risk factor for the development of hypertension.[3,5,16] In addition to arterial stiffness, which increases the speed of propagation of the pressure wave originating from the left ventricle along the arterial wall, peripheral wave reflectance also affects the wave reflection; thus, arterial stiffness and wave reflection may reflect partially different facets of damage in the arterial tree.[7–9] The findings of the present study suggest that both baPWV, a marker of arterial stiffness, and rAI, a marker of wave reflection, are independent predictors of the risk of development of hypertension. Furthermore, the rates of new onset of hypertension by the third year, the fifth year, and the end of the study period were the highest in the participant group with the high values for both baPWV and rAI at baseline; therefore, abnormalities of both parameters were associated with an enhanced risk of development of hypertension.

Although the relationship of age with an increase of pulse wave velocity has been shown to be linear,[4] age-related increase of the augmentation index showed an attenuated curve in participants aged ≥50 years.[13] The presence of white-coat hypertension and/or masked hypertension could have affected the findings of the present study. Consequently, sensitivity analyses were conducted as part of the logistic regression analyses in the following subgroups; (1) divided by age at baseline; (2) divided by the outcome of the analyses as having developed grade 1 hypertension or grade 2 hypertension/receiving antihypertensive medication, because grade 1 hypertension could include white-coat hypertension; (3) divided by the blood pressure categories at baseline (optimal,

Table 4. Clinical Characteristics of the Study Participants Among the 4 Groups Classified According to Median Values of the baPWV and rAI Measured at Study Baseline

Parameter	baPWV <1227 cm/s and rAI <68.5%	baPWV <1227 cm/s and rAI ≥68.5%	baPWV ≥1227 cm/s and rAI <68.5%	baPWV ≥1227 cm/s and rAI ≥68.5%
Number	970	618	620	964
Duration of follow-up, y	6.3±2.5	6.5±2.4*	6.5±2.4*	6.3±2.4†‡
Age, y	37±7	43±9*	40±8*†	47±9*†‡
BMI, kg/m^2	23.7±3.1	23.4±2.8*	24.1±3.1*†	23.7±2.6‡
Smoking (current), n (%)	276 (29)	206 (33)*	199 (32)	337 (35)*†‡
Alcohol drinking (current), n (%)	803 (83)	531 (86)*	531 (86)*	837 (87)*†‡
Daily alcohol intake, g/d	9.7±9.1	12.1±10.6	12.8±11.5	14.1±11.5
SBPcon, mm Hg	117±10	116±10	122±10*†	123±10*†
DBPcon, mm Hg	70±8	71±8	74±9*†	75±8*†‡
Heart rate, beats/min	68±9	63±8*	73±9*†	67±9*†‡
baPWV, cm/s	1130±69	1152±58*	1327±104*†	1369±125*†‡
SBPosc, mm Hg	116±10	116±10	123±11*†	126±13*†‡
DBPosc, mm Hg	69±8	71±8*	75±9*†	79±10*†‡
rAI, %	57±8	78±7*	59±7*†	80±8*†‡
SBP2, mm Hg	95±9	106±10*	103±10*†	116±13*†‡
LDL, mmol/L	3.00±0.83	3.05±0.79	3.09±0.82*	3.12±0.77*
HDL, mmol/L	1.61±0.40	1.63±0.39	1.60±0.39	1.62±0.41
TG, mmol/L	1.23±0.93	1.27±0.89	1.44±0.98*†	1.48±0.98*†
HbA1C, %	5.1±0.4	5.2±0.4*	5.2±0.7*	5.3±0.6*†‡
Family history, n (%)	218 (23)	182 (29)*	199 (32)*†	336 (35)*†‡
Cr, μmol/L	76±9	75±9*	75±10*	75±10*
Medication history				
Dyslipidemia, n (%)	10 (1)	10 (2)	11 (2)	24 (3)*
Diabetes mellitus, n (%)	5 (1)	7 (1)	12 (2)*	19 (3)*

baPWV indicates brachial–ankle pulse wave velocity; BMI, body mass index; Cr, serum creatinine; DBPcon, brachial diastolic blood pressure measured by the conventional cuff method; DBPosc, diastolic blood pressure measured by the oscillometric method at the time of rAI measurement; HbA1c, glycosylated hemoglobin A1c; HDL, serum high-density lipoprotein cholesterol; LDL, serum low-density lipoprotein cholesterol; rAI, radial augmentation index; SBP2, second peak of the radial pressure waveform; SBPcon, brachial systolic blood pressure measured by the conventional cuff method; SBPosc, systolic blood pressure measured by the oscillometric method at the time of rAI measurement; TG, serum triglyceride.
*P<0.05 vs participants with baPWV <1227 cm/s and rAI <68.5%.
†P<0.05 vs participants with baPWV <1227 cm/s and rAI ≥68.5%.
‡P<0.05 vs participants with baPWV ≥1227 cm/s and rAI <68.5%.

normal, and high-normal blood pressure),[15] because high-normal blood pressure might include cases of masked hypertension. In these analyses, baPWV and rAI showed significant odds ratios for the outcomes, except for the odds ratio of rAI for grade 1 hypertension (ie, this was marginally significant: P=0.07). The wide blood pressure variability in white-coat hypertension[17] could be responsible for the attenuated significance of the association of rAI with grade 1 hypertension. Thus, even considering the effects of age, white-coat hypertension and/or masked hypertension, abnormalities of arterial stiffness and pressure wave reflection were significantly associated with an enhanced risk of development of hypertension.

Until now, most clinical studies carried out to examine the association of vascular abnormalities with blood pressure elevation have been prospective 2-point assessment studies[3,5,16]; therefore, the effects of time-varying explanatory variables/covariates during the study period on the outcome variable have not been evaluated precisely.[10] Accordingly, we considered that GEE analysis and/or MML analysis of repeated-measures data obtained over a longitudinal time course would be more appropriate to verify the association of arterial stiffness and wave reflection with the risk of development of hypertension.[10] AlGhatrif et al reported the existence of a longitudinal association between the carotid–femoral pulse wave velocity and blood pressure, based on the

Table 5. Results of Generalized Estimating Equation Analysis Without or With Entering the Interaction Term to Assess the Longitudinal Association of Pressure Wave Reflection and Arterial Stiffness With New Onset of Hypertension

Explanatory Variable	Estimate*	SE	*P* Value
Crude (rAI and baPWV were entered individually)			
rAI	0.04	0.04×10^{-1}	<0.01
baPWV	0.06×10^{-1}	0.03×10^{-2}	<0.01
Covariates adjusted for (rAI and baPWV were entered simultaneously without the interaction term)			
rAI	0.03	0.08×10^{-1}	0.04
baPWV	0.05×10^{-1}	0.05×10^{-2}	<0.01
Covariates adjusted for (rAI and baPWV were entered simultaneously with the interaction term)			
rAI	0.06	0.03	0.05
baPWV	0.07×10^{-1}	0.02×10^{-1}	<0.01
Interaction	-0.02×10^{-3}	0.02×10^{-3}	0.30

Adjustment for basic covariates (age, body mass index, current smoking, current daily alcohol intake, heart rate, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, serum triglyceride, glycosylated hemoglobin A1c and serum creatinine measured at the baseline, medication history for dyslipidemia and/or diabetes mellitus, and family history of hypertension; nobody had medication for hypertension at baseline). baPWV indicates brachial–ankle pulse wave velocity; rAI, radial augmentation index.
*β estimates of interaction between time and each of the explanatory variables.

results of MML analysis of repeated-measures data[4]; however, to date, no study has examined the longitudinal association between wave reflection and blood pressure. In the present study, GEE analysis of repeated-measures data revealed the existence of significant, independent, longitudinal associations of arterial stiffness and pressure wave reflection with new onset of hypertension. Thus, arterial stiffness and pressure wave reflection may be independently involved in the pathogenesis of hypertension.

Table 6. Results of Mixed-Model Linear Regression Analysis Performed to Assess the Longitudinal Association Between Wave Reflection and Arterial Stiffness

Outcome Variable	Explanatory Variable	Estimate*	SE	*P* Value
Crude				
rAI	baPWV	-0.09×10^{-2}	$0.\ 14\times10^{-2}$	0.51
SBP2	baPWV	0.04	0.02×10^{-1}	<0.01
baPWV	rAI	1.14	0.25	<0.01
baPWV	SBP2	5.42	0.19	<0.01
Covariates adjusted				
rAI	baPWV	…	…	…
SBP2	baPWV	0.04	0.02×10^{-1}	<0.01
baPWV	rAI	2.62	0.26	<0.01
baPWV	SBP2	5.15	0.19	<0.01

Adjustment for basic covariates (age, body mass index, current smoking, current daily alcohol intake, heart rate, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, serum triglyceride, glycosylated hemoglobin A1c and serum creatinine measured at baseline, medication history for dyslipidemia and/or diabetes mellitus, and family history of hypertension: nobody had medication for hypertension at baseline). baPWV indicates brachial–ankle pulse wave velocity; rAI, radial augmentation index; SBP2, second peak of the radial pressure waveform.
*β estimates of interaction between time and each of the explanatory variables.

In the present study, the GEE analysis revealed no significant interaction of longitudinal associations with new onset of hypertension between baPWV and rAI. The rates of new onset of hypertension by the third year, the fifth year, and the end of the study period were highest in the participant group with the high values of both baPWV and rAI at baseline. In addition, MML analyses also revealed longitudinal associations of rAI and SBP2 with baPWV. Apart from arterial stiffness, as mentioned, increased peripheral reflectance related to peripheral vascular damage may also worsen pressure wave reflection, which could functionally increase arterial stiffness via elevation of central blood pressure.[7–9] Consequently, arterial stiffness and pressure wave reflection may be additively associated with the development of hypertension.

In the present study, no significant longitudinal association of baPWV with rAI was observed. Impedance mismatch might break down the association of increased arterial stiffness with augmented wave reflection via a distal shift of the reflection point[18] and, in the Framingham study, the significant inverse (not positive) relationship of the carotid–femoral pulse wave velocity at study baseline with augmentation index at the end of the study period.[3] Usually, impedance mismatch is observed in older participants,[18] and the mean age of the participants in the Framingham study was 60 years.[3] However, because the mean age of the participants in the present study was only 42 years, the effect of impedance mismatch might not be significant. A plausible explanation for the findings of the present study might be that the effect of the increased peripheral reflectance derived from microvascular damage on the wave reflection masks the interaction of arterial stiffness with wave reflection.

This study had some limitations. First, although the reported rate of new onset of hypertension in previous prospective studies is in the range of 30% to 50%,[3,4] the incidence of hypertension during the study period in the present study was only 15%. It is possible that the participants in this study were more motivated to maintain a healthy lifestyle; Their mean body mass index was 23.2 and the percentage of current smokers was only ≈30%. When interpreting the data, the profile of the study participants should be taken into account. Further studies are needed to confirm the present findings in women, in other ethnicities, and in the general population. Second, baPWV actually reflects the stiffness of the large- to medium-sized arteries[11,12,14]; therefore, the importance of aortic stiffness

in blood pressure elevation could not be examined precisely in this study. Third, the effect of habitual exercise, which is well known to affect the blood pressure and arterial stiffness,[19] was not examined in the present study. Fourth, we could not examine the mechanism underlying the etiological basis of development of hypertension (ie, primary or secondary). Fifth, white-coat hypertension and masked hypertension were not evaluated in the present analyses.

Conclusion

In middle-aged Japanese men, abnormal pressure wave reflection and increased arterial stiffness may be additively associated with new onset of hypertension. Abnormal wave reflection or elevated central blood pressure may be longitudinally associated with an increase in arterial stiffness, and this longitudinal association may be a mechanism underlying the additive effect of the 2 variables on the development of hypertension.

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Disclosures

None.

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