

Utility of Second Derivative of the Finger Photoplethysmogram for the Estimation of the Risk of Coronary Heart Disease in the General Population

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Background Increased arterial stiffness has been shown to be associated with coronary heart disease (CHD). However, it remains unclear as to whether the second derivative of the finger photoplethysmogram (SDPTG), a non-invasive method for the assessment of arterial stiffness, is useful for the estimation of risk of CHD in the general population.

Methods and Results The SDPTG in 211 subjects (age: 63±15 years, range: 21–91 years, 93 males) was recorded without apparent atherosclerotic disorders from a community. The relationship between the SDPTG indices (b/a and d/a) and coronary risk factors (n=211) or the Framingham risk score (n=158, age: 60±12 years, range: 30–74 years, 63 males) were analyzed. The SDPTG indices significantly correlated with the Framingham risk score in both genders (b/a; $r_{\text{male}}=0.43$, $r_{\text{female}}=0.54$ and d/a; $r_{\text{male}}=-0.38$, $r_{\text{female}}=-0.58$), as well as several coronary risk factors. In the receiver operating characteristics curve analyses, the b/a discriminated high-risk subjects for CHD, who were in the highest quintile of the Framingham risk score in each gender, with a sensitivity and specificity of 0.85 and 0.58 in males and 0.83 and 0.72 in females, respectively.

Conclusions These results suggest that the SDPTG is useful for the estimation of risk of CHD in the general population. (*Circ J* 2006; 70: 304–310)

Key Words: Arterial stiffness; Cardiovascular preventive medicine; Coronary heart disease; Framingham risk score; Second derivative of the finger photoplethysmogram

Coronary heart disease (CHD) is still one of the major causes of deaths in Japan! Moreover, CHD mortality is expected to increase in the near future because the lifestyles of the Japanese, such as their dietary habits, have become westernized.² Indeed, it has been reported that young Japanese patients with CHD who have multiple coronary risk factors, including hypertension, hyperlipidemia, and obesity, all of which might be associated with their lifestyles, have been increasing.³ Therefore, it is important in the field of cardiovascular preventive medicine to identify those at risk of CHD in general populations.

Increased arterial stiffness has been shown to be associated not only with several coronary risk factors,^{4–11} but also with the future development of CHD!^{12–18} Recently, the second derivative of the finger photoplethysmogram (SDPTG) has been developed as one of the non-invasive and convenient methods for pulse-wave analysis.^{19–21} The SDPTG is obtained from double differentiation of the finger photoplethysmogram (PTG) and is thought to provide structural and functional properties of both central and peripheral arteries.¹⁹ Indeed, an index calculated from the SDPTG showed a significant association with age,^{19,20,22–24} carotid arterial distensibility²⁵ and the aortic augmentation

index (AIx)^{19,21} In addition, the SDPTG indices were independently influenced by several risk factors for atherosclerosis in patients with hypertension²³ and in the general population.²⁴ However, it is still unclear as to whether the SDPTG indices are related to the coronary risk factors, or moreover, the risk for the future development of CHD in apparently healthy individuals.

Thus, we conducted a cross-sectional study in a Japanese community to assess the relationship between the SDPTG indices and coronary risk factors in subjects with no apparent atherosclerotic disorders. Furthermore, we calculated the Framingham risk score,²⁶ which has been used to estimate an individual's risk of CHD, and determined the optimal cut-off points of the SDPTG indices to discriminate individuals at risk of CHD.

Methods

Study Population

In the present study, 211 subjects (age: 63±15 years, range: 21–91 years, 93 males) who underwent both SDPTG recording and blood sampling after an overnight fast were recruited from the annual health examination in a community, Yamanashi, Japan, in 2004 and 2005. Subjects with a history or presence of atherosclerotic disorders, such as CHD, stroke, and peripheral obstructive arterial disease, were excluded from the study. We also excluded subjects with renal dysfunction (serum creatinine ≥1.3 mg/dl) or patients who had taken medications for hypertension, hyperlipidemia, or diabetes mellitus. Subjects with abnormal Q-waves on the 12-lead electrocardiogram at rest were also excluded. This study protocol was approved by the

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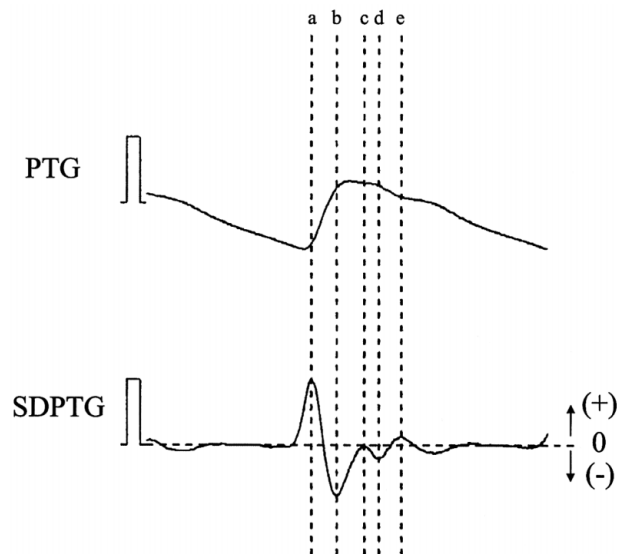


Fig 1. A schema of the finger photoplethysmogram (PTG, Top) and the second derivative of the finger photoplethysmogram (SDPTG, Bottom). The SDPTG consists of 5 waves and each wave is consecutively named 'a', 'b', 'c', 'd', and 'e' wave, respectively. The 'a' and 'b' waves are included in the early systolic phase and the 'c' and 'd' waves in the late systolic phase of the PTG.

ethics committee of Nippon Medical School. Written informed consent was obtained from all participants.

Measurements of the Data

Blood sampling and hemodynamic measurements were conducted in a temperature-controlled room maintained at $24 \pm 2^\circ\text{C}$. Blood samples were collected from the antecubital vein in each participant after an overnight fast. Serum total cholesterol (TC), triglycerides, and plasma glucose were measured by enzymatic reference methods on an automated analyzer. Serum high-density lipoprotein cholesterol (HDL) was analyzed using a direct method based on the selective solubilizing effect. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by means of an automated oscillometric device (USM-700GSi, Elquest Corporation, Chiba, Japan), after the subject had been resting for at least 5 min in a sitting position. Pulse pressure (PP) was defined as the difference between the SBP and DBP. The SDPTG was recorded in the supine position using an SDP-100 instrument (Fukuda Denshi, Tokyo, Japan), when the subject had been resting for at least 5 min in the same position. A transducer was placed on the cuticle of the index finger of the left hand and the signal of the blood volume changes in the peripheral circulation, which indicated PTG, was sent to the SDP-100. The PTG describes the changes in the absorption of light by hemoglobin using a waveform according to the Lambert-Beer law.²⁷ The details of the methodology for the measurement of the PTG and the SDPTG are described elsewhere.²⁸ The double differentiation of the PTG was then performed automatically in the device. The reproducibility of the SDPTG has been previously reported with an intraobserver repeatability of 8%²² according to Bland and Altman²⁹

A schema of the PTG and SDPTG is shown in Fig 1. The SDPTG consists of 4 waves in systole ('a', 'b', 'c', and 'd' waves) and 1 wave in diastole ('e' wave). The 'a' and 'b' waves on the SDPTG are included in the early systolic

Table 1 Clinical Characteristics and SDPTG Indices of Study Subjects (n=211)

Parameters	
Age (years)	63±15
<40	20 (9.5%)
40–49	18 (8.5%)
50–59	34 (16.1%)
60–69	56 (26.5%)
70–79	65 (30.8%)
≥80	18 (8.6%)
Male gender	93 (44.1%)
BMI (kg/m ²)	22.6±3.1
SBP (mmHg)	130±18
DBP (mmHg)	76±12
PP (mmHg)	54±12
TC (mg/dl)	199±37
TG (mg/dl)	96±72
HDL (mg/dl)	59±16
TC/HDL ratio	3.6±1.1
FPG (mg/dl)	93±11
Hypertension	59 (28.0%)
Hyperlipidemia	65 (30.8%)
Obesity	39 (18.5%)
Diabetes mellitus	0 (0%)
Smoking	23 (16.3%)
SDPTG indices	
b/a	-0.46±0.14
d/a	-0.36±0.13

Presented values are the mean±SD or number of subjects (percent of total). Hypertension was defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg. Hyperlipidemia was defined as TC ≥220 mg/dl and/or TG ≥150 mg/dl. Obesity was defined as BMI ≥25 kg/m². Diabetes mellitus was defined as FPG ≥140 mg/dl. Smoking was defined as regularly smoking during the previous 12 months.

SDPTG, second derivative of the finger photoplethysmogram; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein cholesterol; FPG, fasting plasma glucose.

phase of the PTG, whereas the 'c' and 'd' waves are included in the late systolic phase. The height of each wave from the baseline was measured and the ratios of the height of the 'a' wave to that of the 'b' and 'd' waves (b/a and d/a) were calculated and used as the SDPTG indices in the present study.

Assessment of Individual's CHD Risk Level

In 158 subjects who were aged 30 to 74 years (mean age: 60±12 years, 63 males), the individual's CHD risk level was estimated based on the Framingham CHD score sheets presented by Wilson et al.²⁶ This scoring system was applied only to subjects with an age ranging from 30 to 74 years; therefore, 45 subjects over the age of 75 and 8 subjects under the age of 30 were excluded from this assessment. The details of the algorithm for the determination of the risk score are described in the original report.²⁶ In brief, 6 risk factors (age, gender, blood pressure, cholesterol value, smoking status, and presence or absence of diabetes) were changed into the respective scores and the total score was used as the individual's CHD risk level. Diabetes was defined as fasting plasma glucose (FPG) ≥140 mg/dl in the original report,²⁶ and we used the same criterion in the present study. Since subjects who were in the highest quintile of the Framingham risk score could be regarded as 'relatively' high-risk for CHD in a population, we defined them as high-risk subjects in each gender in the present study.

Table 2 Relationship Between the SDPTG Indices (b/a and d/a) and the Coronary Risk Factors

	Pearson's correlation coefficient		Multiple linear regression analysis		
	r	p value	t	p value	
<i>b/a</i>					
Age	0.52	<0.001	0.45	7.49	<0.001
Gender (Female=0, Male=1)	-0.24	<0.001	-0.25	-4.27	<0.001
BMI	0.03	0.67	-		
SBP	0.24	<0.001	0.15	2.49	<0.05
DBP	0.10	0.14	-		
PP	0.26	<0.001	N		
TC	0.01	0.84	-		
TG	0.03	0.64	-		
HDLC	-0.09	0.18	-		
TC/HDLC ratio	0.11	0.10	-		
FPG	0.13	0.06	-		
Smoking (No=0, Yes=1)	-0.09	0.21	-		
					(model R ² =0.33)
<i>d/a</i>					
Age	-0.51	<0.001	-0.43	-6.60	<0.001
Gender (Female=0, Male=1)	0.08	0.26	-		
BMI	-0.02	0.79	-		
SBP	-0.26	<0.001	-0.09	-1.38	0.17
DBP	-0.19	<0.01	N		
PP	-0.21	<0.01	N		
TC	-0.06	0.41	-		
TG	0.00	0.99	-		
HDLC	-0.10	0.15	-		
TC/HDLC ratio	-0.15	<0.05	-0.04	-0.59	0.55
FPG	-0.28	<0.001	-0.11	-1.78	0.08
Smoking (No=0, Yes=1)	0.07	0.30	-		
					(model R ² =0.28)

N, not included in the model. Other abbreviations see in Table 1.

Statistical Analysis

Continuous variables and categorical data were expressed as the mean±SD and the number of subjects (with a percentage), respectively. Statistical analyses were performed by using Dr. SPSS II software (version 11.0.1J, SPSS Japan, Tokyo, Japan) for Windows. The relationship between the SDPTG indices and the coronary risk factors or the Framingham risk score was assessed by means of Pearson's moment correlation coefficient. Thereafter, multiple linear regression analyses were performed with the SDPTG indices as dependent variables and the coronary risk factors that showed significance with Pearson's moment correlation coefficient as independent variables (except for DBP and PP because of a high correlation with SBP). To evaluate as to whether the SDPTG indices were associated with the Framingham risk score independent of age, multiple linear regression analyses were conducted with the Framingham risk score as dependent variables and age and the SDPTG indices as independent variables. Differences in the coronary risk factors contributing to the Framingham risk score (age, SBP, DBP, TC, HDLC, and smoking status) and the SDPTG indices in each quintile were analyzed using one-way analysis of variance (ANOVA) or a chi-square test. Post-hoc Dunnett's tests were performed with the highest quintile as the control group if the ANOVA showed significance. To assess the sensitivity, specificity, and corresponding cut-off values of the SDPTG indices to discriminate the high-risk subjects for CHD, analyses of the receiver operating characteristic (ROC) curves were performed. Significance was assumed when the lower bound of the 95% confidence interval (CI) of the area under the ROC curve (AUC) exceeded 0.5. When the AUC was significant, the corresponding SDPTG index was identified

as a marker for the discrimination of the high-risk subjects for CHD. The point on the ROC curve closest to the upper left-hand corner was defined as the optimal cut-off point. All statistical tests were 2-sided and a p-value less than 0.05 was considered to be significant.

Results

Clinical Characteristics and SDPTG Indices of the Study Subjects

The clinical characteristics and the SDPTG indices of the study subjects are shown in Table 1. The majority of subjects were in the age range of 70 to 79 years. The mean body mass index, SBP, DBP, serum lipid levels, and FPG were within normal range. The prevalence of hypertension and hyperlipidemia was approximately 30%. None of the subjects with diabetes participated in the present study.

SDPTG Indices and Coronary Risk Factors

The relationships between the SDPTG indices and coronary risk factors are noted in Table 2. The b/a showed a significant correlation with age, gender, SBP, and PP. The d/a significantly correlated with age, SBP, DBP, PP, TC/HDLC ratio, and FPG. In the multiple linear regression analyses, the independent variables influencing the b/a were age, gender, and SBP, whereas only age independently influenced the d/a.

Framingham Risk Score and SDPTG Indices

The mean Framingham risk score was 5.8±3.4 in males and 4.8±5.4 in females. The score was distributed more widely in females (-14-16) than in males (-3-13). The correlations between the Framingham risk score and the

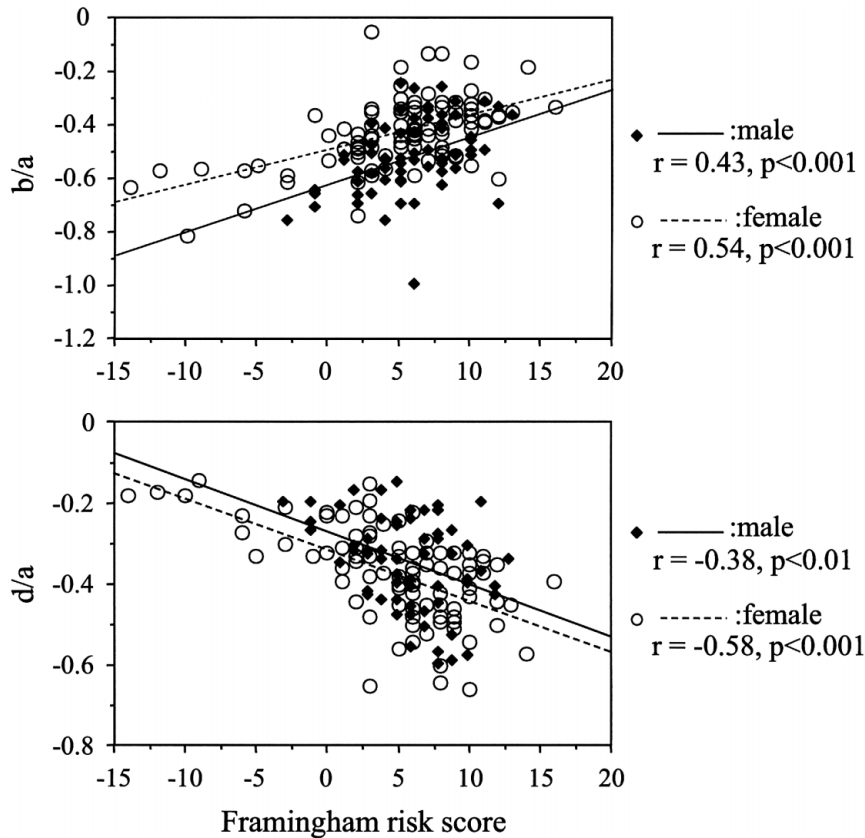


Fig 2. Correlations between second derivative of the finger photoplethysmogram indices and the Framingham risk score in each gender. The b/a was positively correlated (Top), whereas the d/a inversely correlated (Bottom) with the Framingham risk score in both genders.

Table 3 Coronary Risk Factors Contributing to the Framingham Risk Score and SDPTG Indices Based on the Quintile of the Score

	Quintile of the Framingham risk score					p value for trend
	Q1	Q2	Q3	Q4	Q5	
Male	(-3-2)	(3-4)	(5-6)	(7-8)	(9-13)	
Number	10	11	16	13	13	
Age (years)	42±9 [§]	52±9 [§]	61±10	66±4	68±7	<0.001
SBP (mmHg)	124±12 [§]	128±22 [†]	123±12 [§]	134±18*	152±13	<0.001
DBP (mmHg)	75±11*	78±15	73±12 [†]	81±7	89±11	<0.01
TC (mg/dl)	198±20	184±43	186±33	196±46	208±30	0.44
HDLC (mg/dl)	62±8*	63±18*	57±15	53±22	45±7	<0.05
Smoking (Yes/No)	2/8	6/5	8/8	4/9	5/8	0.44
b/a	-0.64±0.08 [†]	-0.55±0.11	-0.53±0.18	-0.45±0.11	-0.46±0.11	<0.001
d/a	-0.25±0.07 [†]	-0.33±0.08	-0.36±0.12	-0.37±0.14	-0.40±0.12	<0.001
Female	(-14-1)	(2-4)	(5-6)	(7-9)	(10-16)	
Number	17	20	21	20	17	
Age (years)	43±7 [§]	60±7*	66±6	66±7	67±7	<0.001
SBP (mmHg)	115±11 [§]	113±10 [§]	121±10 [§]	133±14	140±17	<0.001
DBP (mmHg)	73±9	68±9 [†]	69±6 [†]	75±11	79±11	<0.01
TC (mg/dl)	200±40	213±31	209±26	211±33	204±45	0.79
HDLC (mg/dl)	70±14 [§]	74±13 [§]	66±17 [§]	58±11 [†]	43±9	<0.001
Smoking (Yes/No)	1/16	0/20	0/21	2/18	2/15	0.33
b/a	-0.54±0.11 [§]	-0.47±0.14*	-0.39±0.09	-0.40±0.12	-0.36±0.11	<0.001
d/a	-0.26±0.07 [§]	-0.33±0.11 [†]	-0.40±0.09	-0.44±0.09	-0.44±0.11	<0.001

Presented values are the mean±SD or number of subjects.

The range of the Framingham risk score in each quintile is shown in the parentheses.

[§] $p < 0.001$, [†] $p < 0.01$, and * $p < 0.05$ vs the corresponding values in Q5. See Table 1 for abbreviations.

SDPTG indices in each gender are shown in Fig 2. In both genders, the b/a positively correlated with the Framingham risk score ($r_{\text{male}}=0.43$ and $r_{\text{female}}=0.54$, both $p < 0.001$) and the d/a showed a negative correlation ($r_{\text{male}}=-0.38$, $p < 0.01$ and $r_{\text{female}}=-0.58$, $p < 0.001$). In the multiple linear regres-

sion analysis, such associations were still observed independently of age in females (b/a; $\beta=0.32$, $p < 0.01$, d/a; $\beta=-0.27$, $p < 0.001$), but not in males (b/a; $\beta=0.08$, d/a; $\beta=-0.02$).

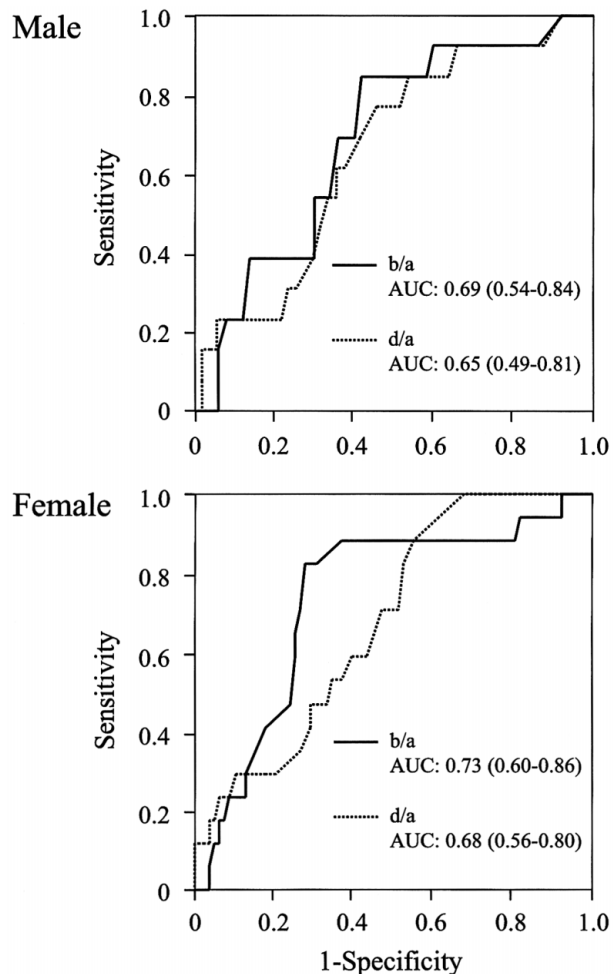


Fig 3. Receiver operating characteristic (ROC) curves of the second derivative of the finger photoplethysmogram indices for the discrimination of high-risk subjects for coronary heart disease in males (Top) and in females (Bottom). The 95% confidence interval of the area under the ROC curve (AUC) are shown in the parentheses. The b/a in both genders and the d/a in females revealed significant discriminatory performance.

Coronary Risk Factors and SDPTG Indices in Each Quintile

The subjects who showed a Framingham risk score of 9 or more points in males ($n=13$) and 10 or more points in females ($n=17$) were classified into the highest quintile and were considered to be high-risk subjects for CHD. The SDPTG indices and the coronary risk factors contributing to the calculation of the risk score (except for diabetes) in each quintile are listed in Table 3. Although TC and smoking did not show a difference in the quintiles, age, SBP, DBP, and HDLC in the lowest and/or second quintile(s) were significantly lower (or higher) than those parameters in the highest quintile in both genders. In regard to the SDPTG indices, both the b/a and d/a in the lowest quintile in males and the lowest and second quintiles in females were significantly different from those in the highest quintile.

Discrimination of High-Risk Subjects for CHD

The ROC curves of the SDPTG indices to discriminate the high-risk subjects in each gender are described in Fig 3. The AUC of the b/a in males was 0.69 (95% CI: 0.54–0.84).

Table 4 Ability of the SDPTG Indices to Discriminate High-Risk Subjects for CHD

	Cut-off value	Sensitivity	Specificity	Accuracy
Male				
b/a	-0.53	0.85	0.58	0.64
Female				
b/a	-0.40	0.83	0.72	0.74
d/a	-0.39	0.59	0.60	0.60

CHD, coronary heart disease. Other abbreviation see in Table 1.

Those of the b/a and d/a in females were 0.73 (95% CI: 0.60–0.86) and 0.68 (95% CI: 0.56–0.80), respectively. In regard to the d/a in males, the AUC (0.65, 95% CI: 0.49–0.81) did not show significance; therefore, its discriminatory ability and corresponding cut-off point were not analyzed. The sensitivity, specificity, and the accuracy for the discrimination of the high-risk subjects for CHD and the corresponding cut-off values are noted in Table 4. The b/a showed discriminatory performance with a sensitivity and specificity of more than 0.8 and 0.7 in females, and more than 0.8 and approximately 0.6 in males, respectively. However, both the sensitivity and specificity of the d/a in females were approximately 0.6. The accuracy of these indices ranged from 0.60 to 0.74.

Discussion

The present study showed that the SDPTG indices independently associated with several coronary risk factors and significantly correlated with the Framingham risk score. Moreover, we found that the b/a, one of the SDPTG indices, might contribute to the discrimination of the high-risk subjects for CHD with an acceptable sensitivity and specificity in the general population. These observations suggest that the SDPTG indices reflect the risk of CHD and that the measurement of these indices might be useful in terms of cardiovascular preventive medicine.

Several investigators have studied the physiological meanings and clinical implications of the SDPTG waveform.^{19–21,25} The ‘b’ wave on the SDPTG mainly expresses the first vascular response to blood ejection from the left ventricle and no reflected components from the periphery interfere. Imanaga et al reported the relationship between the b/a and the distensibility of the carotid artery, suggesting that the b/a reflects the stiffness of large arteries.²⁵ In contrast, the ‘d’ wave mainly represents the intensity of the reflection wave from the periphery, which is determined by the functional vascular tension and arteriosclerosis in the peripheral circulation, thus indicating vascular resistance. Indeed, Takazawa et al reported that the d/a significantly correlated with the aortic AIx, which partially suggests peripheral vascular resistance.^{19,21,30} The d/a, therefore, might represent such vascular properties.

In the present study, the b/a was positively associated with age whereas the d/a was inversely associated with age. Aging increases both large arterial stiffness and vascular resistance.³¹ These results, therefore, suggest that an elevated b/a and a reduced d/a on the SDPTG reflect an increase in large arterial stiffness and peripheral vascular resistance, respectively. In multivariate analyses, however, SBP was an independent determinant of the b/a, but not the d/a. Moreover, gender was also an independent determinant of the b/a, whereas there was no relationship between

gender and the d/a, even in univariate analysis. Recently, Hashimoto et al reported significant associations of both SBP and gender with the d/a, as well as the b/a in the general population²⁴ Although precise reasons for this inconsistency are not clear, one possibility is that the number of subjects that participated in the present study was smaller than that in the study by Hashimoto et al²⁴

It is beyond doubt that a comprehensive risk assessment in each individual for the future development of CHD is important for the primary prevention of cardiovascular disease.³² Therefore, the Framingham risk score has been developed as one of the appropriate tools of the comprehensive risk assessment of CHD in the USA²⁶ Recently, Suka et al reported that the incidence of CHD gradually increased with an increase in the Framingham risk score in the Japanese population.³³ These observations indicate that this score is applicable to the estimation of the individual's CHD risk in Japan. Meanwhile, numerous studies have reported that the pulse-wave velocity (PWV), AIx, and PP, all of which are major surrogate markers of arterial stiffness, are associated with cardiovascular risk^{4–11} and independently predict mortality and morbidity from CHD^{12–18} Furthermore, Yamashina et al recently showed that an increased brachial-ankle PWV was an independent determinant of moderate- to high-risk subjects for CHD based on the Framingham risk score in Japanese subjects⁴ Their report indicates an association between arterial stiffness and the Framingham risk score in the Japanese population. In the present study, the SDPTG indices significantly correlated with the Framingham risk score. Moreover, there were significant differences in the SDPTG indices in the highest and other quintiles of the Framingham risk score. These findings suggest that the measurement of SDPTG has utility for the assessment of an individual's CHD risk in the general population in Japan. However, significant associations between the SDPTG indices and the Framingham risk score were observed independently of age in females, but not in males. These findings suggest that age is a confounding factor for the correlations in males. This point should be evaluated more precisely in further studies.

We were able to determine the optimal cut-off points of the b/a on the ROC curves to discriminate the high-risk subjects for CHD in our study population with a sensitivity of more than 0.8 in both genders and a specificity of more than 0.7 in females. However, the specificity of the b/a in males was lower than that in females. Reduced specificity indicates an increase in the number of false positives. However, false positives would, at first, be subjected to lifestyle modification in terms of the primary prevention of CHD.³² Therefore, we believe that a higher number of false positives with a specificity of 0.58 in males is acceptable, and the b/a could be used for screening subjects at risk of CHD in the general population. In contrast, the d/a discriminated high-risk females with a sensitivity and specificity of approximately 0.6 and it did not discriminate high-risk males. These findings indicate that the d/a might be less useful for screening subjects at risk for CHD in the general population.

The present study has some limitations. First, none of the subjects with diabetes participated in this study. Further studies are needed in populations with glucose intolerance similar to the average Japanese population. Second, this study is not a longitudinal survey, but a cross-sectional survey. It is, therefore, still uncertain as to whether the SDPTG indices truly predict mortality and morbidity from CHD.

Third, the number of subjects that participated in the present study was small for an epidemiological survey. In this regard, the smaller number of male participants might have resulted in a lower specificity of the b/a and the lack of discriminatory ability of the d/a, as well as the lack of associations between the SDPTG indices and the Framingham risk score independent of age, in males. Regardless of these limitations, we believe that the present study deserves to report as the first study, to our knowledge, concerning the association between the SDPTG and the risk of CHD in the general population.

In conclusion, the SDPTG indices significantly associated not only with several coronary risk factors, but also with the Framingham risk score in subjects without apparent atherosclerotic disorders at the time of health examination. Furthermore, the b/a screened subjects at risk of CHD with an acceptable sensitivity and specificity. These results suggest that the measurement of SDPTG is useful for the estimation of the risk of CHD in the general population. However, further studies with a larger number of participants are needed to confirm these results.

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