

*Original Article*

# Independent Determinants of Second Derivative of the Finger Photoplethysmogram among Various Cardiovascular Risk Factors in Middle-Aged Men

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The second derivative of the finger photoplethysmogram (SDPTG) has been used as a non-invasive examination for arterial stiffness. The present study sought to elucidate independent determinants of the SDPTG among various cardiovascular risk factors in middle-aged Japanese men. The SDPTG was obtained from the cuticle of the left-hand forefinger in 973 male workers (mean age:  $44 \pm 6$  years) during a medical checkup at a company. The SDPTG indices (*b/a* and *d/a*) were calculated from the height of the wave components. Multiple logistic regression analyses revealed that the independent determinants of an increased *b/a* (highest quartile of the *b/a*) were age (odds ratio [OR]: 1.12 per 1-year increase, 95% confidence interval [CI]: 1.09–1.15), hypertension (OR: 1.65, 95% CI: 1.03–2.65), dyslipidemia (OR: 1.51, 95% CI: 1.09–2.09), impaired fasting glucose/diabetes mellitus (OR: 2.43, 95% CI: 1.16–5.07), and a lack of regular exercise (OR: 2.00, 95% CI: 1.29–3.08). Similarly, independent determinants of a decreased *d/a* (lowest quartile of the *d/a*) were age (OR: 1.11 per 1-year increase, 95% CI: 1.08–1.14), hypertension (OR: 3.44, 95% CI: 2.20–5.38), and alcohol intake 6 or 7 days per week (OR: 2.70, 95% CI: 1.80–4.06). No independent association was observed between the SDPTG indices and blood leukocyte count or serum C-reactive protein levels. In conclusion, the SDPTG indices reflect arterial properties affected by several cardiovascular risk factors in middle-aged Japanese men. The association between inflammation and the SDPTG should be evaluated in further studies. (*Hypertens Res* 2007; 30: 1211–1218)

**Key Words:** arterial stiffness, cardiovascular preventive medicine, finger photoplethysmogram, risk factors

## Introduction

The measurement of arterial stiffness has become an important diagnostic modality in various clinical and epidemiological settings, because increased arterial stiffness is associated with an increased risk of cardiovascular disease (CVD) (1–4). The second derivative of the finger photoplethysmogram (SDPTG), which is obtained from the double differentiation of the finger photoplethysmogram (PTG), has been used,

mainly in Japan, as a non-invasive method for pulse wave analysis (5). The indices calculated from the SDPTG waveforms are reported to correlate closely with both the distensibility of the carotid artery (6) and the central augmentation index (AIx) (5), suggesting the SDPTG indices may be a surrogate measure of arterial stiffness. Several previous studies showed that the SDPTG indices are associated with age (5, 7–10), blood pressure (BP) (7, 8, 10), the estimated risk of coronary heart disease (8), and the presence of atherosclerotic disorders (11). However, there is still less information on the

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SDPTG than on other modalities to measure arterial stiffness. Moreover, to our knowledge, there are no reports on the association between the SDPTG and various cardiovascular risk factors including inflammation, excessive alcohol drinking, and a lack of regular exercise.

The present study is a cross-sectional evaluation of the independent determinants of the SDPTG among various risk factors for CVD in middle-aged Japanese men.

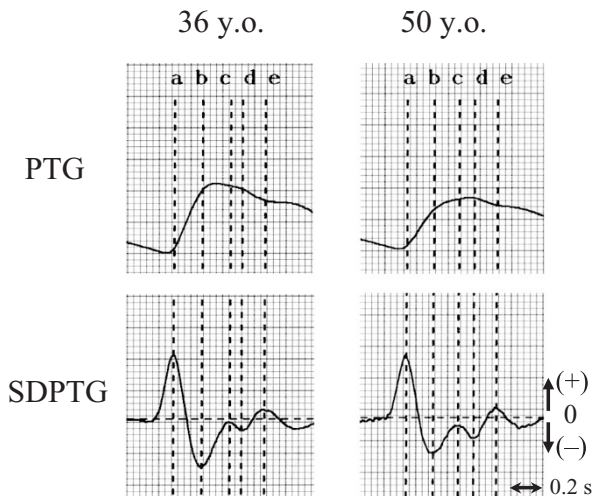
## Methods

### Study Population

This study was conducted during an annual medical checkup at a company that develops precision equipment in Kanagawa, Japan, in 2005. A total of 1,074 male employees between 35 and 60 years of age received the medical checkup. All employees were engaged in daytime, desk work. Among them, the following were excluded: those on medication for hypertension, dyslipidemia, or diabetes mellitus ( $n=60$ ); and those with acute or chronic inflammatory disorders including infectious disease ( $n=8$ ), the presence or history of CVD ( $n=5$ ), or an incomplete recording of the SDPTG ( $n=2$ ). In addition, subjects with C-reactive protein (CRP)  $\geq 10.0$  mg/L ( $n=15$ ) or leukocyte count  $\geq 10.0 \times 10^9/L$  ( $n=11$ ) were also excluded because the presence of an infection or inflammation was suspected. Finally, 973 subjects participated in the present study. The study protocol was approved by the ethics committee of Nippon Medical School, and all participants gave their written informed consent.

### Biochemical and Physical Measurements

All anthropometric and hemodynamic measurements and blood sampling were conducted between 9 AM and 11 AM in a temperature-controlled room maintained at  $22 \pm 2^\circ\text{C}$ . Blood samples were obtained from the antecubital vein after overnight fasting. Standard enzymatic methods were used to measure the serum total cholesterol, triglycerides, and plasma glucose with an automated analyzer (Model 7170, Hitachi High-Technologies, Tokyo, Japan). The serum high-density lipoprotein (HDL) cholesterol was measured using the direct method. The low-density lipoprotein (LDL) cholesterol level was calculated by using Friedewald's formula in 962 participants with serum triglyceride levels  $< 400$  mg/dL. Blood leukocytes were counted by an automatic cell counter (SE9000, Sysmex, Kobe, Japan). The serum CRP level was measured using a latex turbidimetric immunoassay kit (LPIA CRP-H, Mitsubishi Kagaku Iatron, Tokyo, Japan) with an automated analyzer (Model 7170). The lower detection limit of this assay is 0.1 mg/L. The intra-assay coefficient of variation is reported to be  $\leq 3.4\%$  (12). The systolic and diastolic BP were measured twice by well-trained staff members using the right arm of a seated subject, after at least 5 min of rest, using a mercury sphygmomanometer with the optimal cuff size for



**Fig. 1.** Representative waveforms of PTG (top) and SDPTG (bottom) in a 36-year-old man and a 50-year-old man who participated in the present study. The SDPTG consists of five waves named a, b, c, d, and e. The a and b waves are in the early systolic phase, the c and d waves in the late systolic phase, and the e wave in the diastolic phase of the PTG. The b and d waves in participants who were 50 years of age were shallower and deeper, respectively, than in those who were 36 years of age. PTG, finger photoplethysmogram; SDPTG, second derivative of the finger photoplethysmogram.

each subject's arm circumference. The first and fifth Korotkoff sounds were recorded to determine the systolic and diastolic BP, respectively.

Hypertension was defined as systolic BP  $\geq 140$  mmHg and/or diastolic BP  $\geq 90$  mmHg. Dyslipidemia was defined as LDL cholesterol  $\geq 140$  mg/dL, triglycerides  $\geq 150$  mg/dL, and/or HDL cholesterol  $< 40$  mg/dL according to the updated Japanese Atherosclerosis Society criteria (13). Obesity was defined as body mass index  $\geq 25$  kg/m<sup>2</sup>. Impaired fasting glucose (IFG)/diabetes mellitus (DM) was defined as fasting plasma glucose  $\geq 110$  mg/dL. Current smoking was defined as regularly smoking during the previous 12 months. The frequency of alcohol intake was categorized as follows: 0 to 1 day per week, 2 to 5 days per week, or 6 to 7 days per week. Regular exercise was defined as continuous exercise for at least 15 min 2 days or more per week for at least 1 year. Elevated leukocyte count and CRP were defined as the highest quartile of each parameter ( $\geq 6.3 \times 10^9/L$  and  $\geq 0.6$  mg/L, respectively).

### SDPTG Measurement

The SDPTG was recorded in the sitting position using an SDP-100 instrument (Fukuda Denshi, Tokyo, Japan), with the subject having rested for at least 5 min after BP measurement. A transducer was placed on the cuticle of the forefinger of the

left hand at the same height as the subject's heart. The signal of the blood volume changes in the peripheral circulation, which indicated the 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 (14). The PTG measurement methodology is described in detail elsewhere (15). Multiple waveforms of the PTG were obtained during 5-s recordings. The PTG waveforms were then averaged, and the double differentiation of the averaged PTG (*i.e.*, SDPTG) was performed automatically by the device.

Representative waveforms of the PTG and SDPTG in 2 participants, aged 36 and 50 years old, are described in Fig. 1. The SDPTG consists of four waves in systole (*a*, *b*, *c*, and *d* waves) and one wave in diastole (*e* wave). The *a* and *b* waves on the SDPTG are included in the early systolic phase of the PTG, while the *c* and *d* waves are included in the late systolic phase. The height of each wave from the baseline was measured, with the values above the baseline being positive and those under it negative. The ratios of the height of the *b* and *d* waves to that of the *a* wave (*b/a* and *d/a*) were calculated from the SDPTG waveform. These ratios were used as the SDPTG indices in this study, according to the report by Takazawa *et al.* (5). The acceptable reproducibility of these indices has been reported (11, 16). An increased *b/a* and a decreased *d/a* have been thought to represent increased arterial stiffness (5).

## Statistical Analysis

Continuous variables were expressed as mean $\pm$ SD, mean (95% confidence interval), or median (interquartile range), as appropriate. Categorical data were expressed as percentages. Since the values of CRP were skewed to the left, its log-transformed data were used for a simple correlation analysis. All analyses were conducted using the SPSS software program version 11.0.1 (SPSS, Chicago, USA). Pearson's moment correlation coefficient was used to evaluate the simple correlations between the SDPTG indices and the clinical parameters. Differences in the mean SDPTG indices between the groups with and without each cardiovascular risk factor were compared using an analysis of covariance with age, height, and heart rate as covariates. To detect independent determinants of the SDPTG indices, logistic regression analyses were performed. First, the odds ratios of each cardiovascular risk factor for an increased *b/a* ( $\geq -0.56$ , highest quartile of the *b/a*) and a decreased *d/a* ( $\leq -0.34$ , lowest quartile of the *d/a*) were calculated using univariate analysis. The variables with a *p* value of less than 0.10 in that analysis were entered into multivariate analysis. All statistical tests were two-sided, and a *p* value of less than 0.05 was considered significant.

## Results

The baseline characteristics of the study subjects are shown in Table 1. The mean age was 44 $\pm$ 6 years. The mean values of

**Table 1. Characteristics of the Study Subjects (n=973)**

Age (years)	44 $\pm$ 6
35–40 (%)	35.1
41–50 (%)	49.9
51–60 (%)	15.0
Height (m)	1.71 $\pm$ 0.06
Body mass index (kg/m <sup>2</sup> )	23.3 $\pm$ 2.9
Obesity (%)	23.5
Heart rate (bpm)	69 $\pm$ 10
Systolic BP (mmHg)	119 $\pm$ 13
Diastolic BP (mmHg)	76 $\pm$ 10
Hypertension (%)	11.3
Total cholesterol (mg/dL)	200 $\pm$ 32
Triglycerides (mg/dL)	115 $\pm$ 106
HDL cholesterol (mg/dL)	56 $\pm$ 14
LDL cholesterol (mg/dL) (n=962)	122 $\pm$ 28
Dyslipidemia (%)	43.5
Fasting plasma glucose (mg/dL)	91 $\pm$ 11
IFG/DM (%)	4.1
Leukocyte count ( $\times 10^9/L$ )	5.6 $\pm$ 1.3
CRP (mg/L)	0.3 (0.2, 0.6)
Current smoking (%)	28.5
Family history of CVD (%)	23.0
Lack of regular exercise (%)	79.1
Frequency of alcohol intake	
0 to 1 day per week (%)	39.2
2 to 5 days per week (%)	37.2
6 to 7 days per week (%)	23.6
SDPTG index	
<i>b/a</i>	-0.64 $\pm$ 0.11
<i>d/a</i>	-0.26 $\pm$ 0.12

The value of CRP is expressed as the median (interquartile range). Other values are the mean $\pm$ SD or % of total. BP, blood pressure; CRP, C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; HDL, high-density lipoprotein; IFG, impaired fasting glucose; LDL, low-density lipoprotein; SDPTG, second derivative of a finger photoplethysmogram.

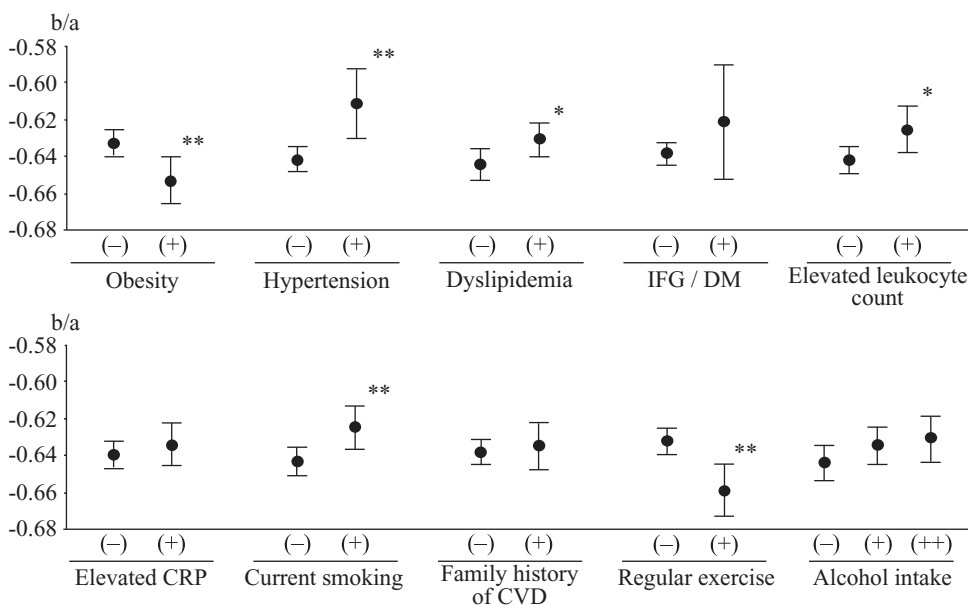
body mass index, systolic BP, diastolic BP, total cholesterol, triglycerides, HDL and LDL cholesterol, and fasting plasma glucose were within the normal ranges. While IFG/DM was present in less than 5% of study subjects, dyslipidemia was present in more than 40%. The mean leukocyte count was 5.6  $\times 10^9/L$ , and the median CRP level was 0.3 mg/L. The prevalence among subjects who did not exercise regularly or who drank alcohol 6 to 7 days per week was 79.1% and 23.6%, respectively.

Correlations between the SDPTG indices and clinical parameters are noted in Table 2. Both SDPTG indices correlated substantially with age. Height, heart rate, total and LDL cholesterol, fasting plasma glucose, and leukocyte count also significantly correlated with both SDPTG indices. The systolic and diastolic BP appeared to correlate considerably bet-

**Table 2. Correlation Coefficients of the SDPTG Indices with the Clinical Parameters**

	<i>b/a</i>		<i>d/a</i>	
	<i>r</i>	<i>p</i> value	<i>r</i>	<i>p</i> value
Age	0.40	<0.001	-0.41	<0.001
Height	-0.23	<0.001	0.17	<0.001
Body mass index	-0.02	0.470	-0.08	0.019
Systolic BP	0.10	0.003	-0.27	<0.001
Diastolic BP	0.09	0.004	-0.29	<0.001
Heart rate	-0.17	<0.001	0.09	0.007
Total cholesterol	0.09	0.005	-0.10	0.002
Triglycerides	0.02	0.583	-0.05	0.159
HDL cholesterol	-0.03	0.425	-0.02	0.475
LDL cholesterol	0.10	0.003	-0.07	0.035
Fasting plasma glucose	0.09	0.007	-0.10	0.002
Leukocyte count	0.09	0.006	-0.08	0.011
log CRP	0.02	0.448	-0.07	0.039

BP, blood pressure; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SDPTG, second derivative of a finger photoplethysmogram.



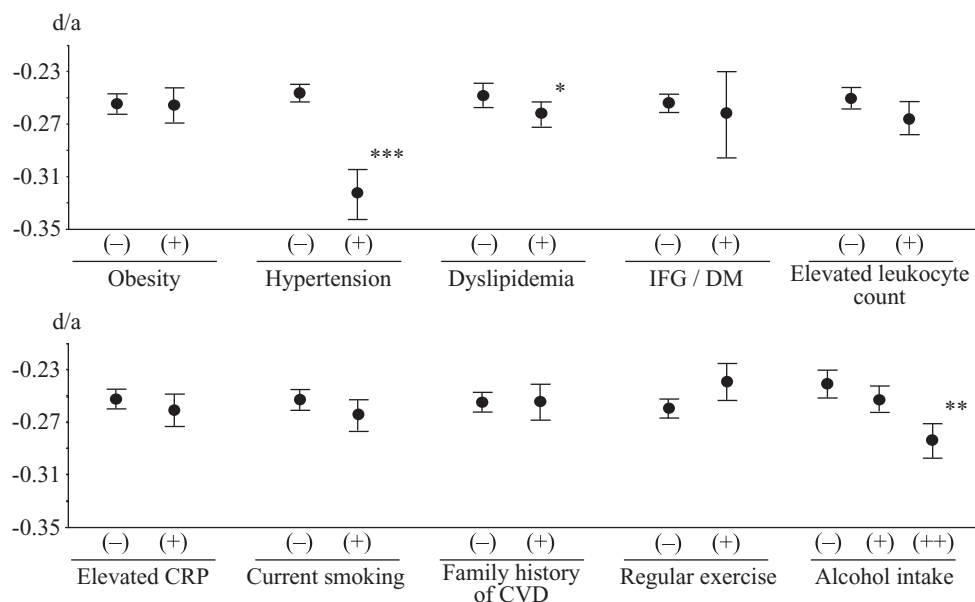
**Fig. 2.** Comparison of the mean *b/a* between the groups with and without each cardiovascular risk factor. The mean values were adjusted for age, height, and heart rate. Error bars indicate 95% confidence intervals. CRP, C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; IFG, impaired fasting glucose. \**p*<0.05, \*\**p*<0.01. Alcohol intake: (-), 0 to 1 day per week; (+), 2 to 5 days per week; (++) , 6 to 7 days per week.

ter with the *d/a* than with the *b/a*. A weak correlation between the CRP level and the *d/a* was observed, but no correlation with the *b/a* was observed.

The differences in the adjusted means of the *b/a* and *d/a* between the groups with and without each cardiovascular risk factor are shown in Figs. 2 and 3, respectively (detailed values not shown). The *b/a* was significantly higher in the group with hypertension, dyslipidemia, elevated leukocyte count,

and current smoking, while it was significantly lower in the group with obesity and regular exercise than in the group without. On the other hand, the *d/a* was significantly lower in the group with hypertension and dyslipidemia than in the group without. Alcohol intake 6 to 7 days per week was significantly associated with a decreased *d/a*.

The odds ratios of each cardiovascular risk factor for an increased *b/a* and a decreased *d/a* are noted in Tables 3 and 4,



**Fig. 3.** Comparison of the mean d/a between the groups with and without each cardiovascular risk factor. The mean values were adjusted for age, height, and heart rate. Error bars indicate 95% confidence intervals. CRP, C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; IFG, impaired fasting glucose. \*p < 0.05, \*\*p < 0.01 vs. (+) and p < 0.001 vs. (-), \*\*\*p < 0.001. Alcohol intake: (-), 0 to 1 day per week; (+), 2 to 5 days per week; (++) 6 to 7 days per week.

**Table 3. Odds Ratio of Each Cardiovascular Risk Factor for an Increased b/a**

Variables	Univariate		Multivariate	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Age (per 1-year increase)	1.13 (1.10–1.16)	<0.001	1.12 (1.09–1.15)	<0.001
Height (per 0.01-m increase)	0.93 (0.90–0.95)	<0.001	0.94 (0.91–0.97)	<0.001
Heart rate (per 1-bpm increase)	0.97 (0.96–0.99)	0.003	0.96 (0.94–0.98)	<0.001
Obesity	0.84 (0.59–1.20)	0.337	—	
Hypertension	1.81 (1.19–2.76)	0.006	1.65 (1.03–2.65)	0.038
Dyslipidemia	1.70 (1.27–2.28)	<0.001	1.51 (1.09–2.09)	0.014
IFG/DM	3.24 (1.71–6.13)	<0.001	2.43 (1.16–5.07)	0.018
Elevated CRP	0.97 (0.70–1.35)	0.852	—	
Elevated leukocyte count	1.34 (0.97–1.85)	0.079	0.92 (0.63–1.34)	0.650
Current smoking	1.47 (1.08–2.01)	0.016	1.27 (0.89–1.83)	0.189
Family history of CVD	1.23 (0.88–1.72)	0.234	—	
Lack of regular exercise	1.54 (1.05–2.28)	0.028	2.00 (1.29–3.08)	0.002
Alcohol intake*				
2 to 5 days per week	1.17 (0.83–1.64)	0.365	—	
6 to 7 days per week	1.27 (0.87–1.85)	0.221	—	

Variables with a p value of less than 0.10 in the univariate analysis were entered into the subsequent multivariate analysis. \*Zero to 1 day per week as a reference. CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; IFG, impaired fasting glucose.

respectively. Multiple logistic regression analyses revealed the independent determinants of an increased b/a to be age, height, heart rate, hypertension, dyslipidemia, IFG/DM, and a lack of regular exercise. Similarly, the independent determi-

nants of a decreased d/a were age, height, hypertension, and an alcohol intake of 6 to 7 days per week. Hypertension appeared to more strongly influence the d/a than the b/a (odds ratio: 1.65 for the b/a and 3.44 for the d/a).

**Table 4. Odds Ratio of Each Cardiovascular Risk Factor for a Decreased  $d/a$** 

Variables	Univariate		Multivariate	
	Odds ratio (95% CI)	<i>p</i> value	Odds ratio (95% CI)	<i>p</i> value
Age (per 1-year increase)	1.13 (1.11–1.16)	<0.001	1.11 (1.08–1.14)	<0.001
Height (per 0.01-m increase)	0.95 (0.93–0.98)	<0.001	0.96 (0.93–0.99)	0.003
Heart rate (per 1-bpm increase)	0.99 (0.98–1.01)	0.473	—	—
Obesity	1.06 (0.75–1.49)	0.759	—	—
Hypertension	4.02 (2.68–6.05)	<0.001	3.44 (2.20–5.38)	<0.001
Dyslipidemia	1.50 (1.12–2.01)	0.007	1.29 (0.93–1.80)	0.131
IFG/DM	1.90 (0.98–3.67)	0.056	0.96 (0.47–1.97)	0.908
Elevated CRP	1.32 (0.96–1.82)	0.090	1.25 (0.87–1.79)	0.228
Elevated leukocyte count	1.28 (0.92–1.77)	0.144	—	—
Current smoking	1.27 (0.93–1.74)	0.140	—	—
Family history of CVD	1.20 (0.86–1.69)	0.291	—	—
Lack of regular exercise	1.00 (0.70–1.43)	0.980	—	—
Alcohol intake*				
2 to 5 days per week	1.24 (0.87–1.77)	0.241	1.33 (0.90–1.96)	0.148
6 to 7 days per week	2.71 (1.87–3.92)	<0.001	2.70 (1.80–4.06)	<0.001

Variables with a *p* value of less than 0.10 in the univariate analysis were entered into the subsequent multivariate analysis. \*Zero to 1 day per week as a reference. CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; IFG, impaired fasting glucose.

## Discussion

The novel feature of the present study is to evaluate the independent determinants of the SDPTG among various risk factors for CVD by means of multiple logistic regression analysis in a relatively large population. The results indicate that several risk factors for CVD, such as age, hypertension, dyslipidemia, IFG/DM, a lack of regular exercise, and excessive drinking (6 to 7 days per week), were significantly associated with the SDPTG indices. In contrast, the present study failed to identify any independent association between the SDPTG indices and serum CRP levels or the blood leukocyte count.

The  $b/a$  and  $d/a$  were used as the SDPTG indices in the present study. Because the  $b$  wave on the SDPTG is included in the early systolic phase of the PTG, it is only slightly affected by the reflected components from the periphery. Imanaga *et al.* reported that the  $b/a$  is correlated with the distensibility of the carotid artery (6), a surrogate measure of large arterial stiffness. In contrast, because the  $d$  wave is included in the late systolic phase of the PTG, it should be enhanced by the backward wave from the periphery. Takazawa *et al.* reported that the  $d/a$  is significantly correlated with the central AIX (5), which represents the structural and functional properties of the systemic arterial tree including the peripheral circulation.

The present study showed that the SDPTG indices were robustly related to age. The SDPTG was originally proposed as an assessment tool for “vascular aging” (5), and a number of previous studies have shown a considerable association

between the SDPTG and age (5, 7–10). The present results therefore support these earlier observations.

Hypertension was significantly associated with both the  $b/a$  and  $d/a$  in the present study, which is also consistent with previous reports (7, 8, 10). Elevated BP is thought to increase arterial stiffness (17, 18). Therefore, the association of hypertension with the SDPTG in both the present and the previous studies is a plausible observation. Importantly, the odds ratios of hypertension for a decreased  $d/a$  was more than twice that for an increased  $b/a$  even after adjusting for multiple potential confounders. As mentioned above, the  $d/a$  at least partially reflects the functional properties of peripheral circulation, which also indicates the peripheral vascular resistance. The impact of hypertension on the  $d/a$  may therefore be greater than that on the  $b/a$ .

This study demonstrated, for the first time to our knowledge, that dyslipidemia was independently associated with the  $b/a$ . The results of several clinical studies investigating the association between lipid profiles and arterial stiffness are still controversial (19–22), possibly because of the difference in the duration of vascular exposure to the dyslipidemic state (23, 24). However, the relationship between the duration in those suffering from dyslipidemia and the SDPTG cannot be discussed because this information was not available in the present study.

The present study also showed that other risk factors for CVD such as IFG/DM, a lack of regular exercise, and excessive alcohol drinking were independent determinants of an increased  $b/a$  or a decreased  $d/a$ . In experimental studies, hyperglycemia (and related hyperinsulinemia and increased advanced glycation endproducts) and chronic ethanol admin-

istration were reported to decrease the contents of elastin in the vessel wall and/or to elevate vascular tone (25, 26), which in turn increases arterial stiffness. These mechanisms may contribute at least partially to the associations between the SDPTG and these factors. On the other hand, recent experimental studies showed that exercise had a negligible effect on arterial stiffness (27, 28), whereas in human studies regular exercise is thought to have a favorable effect on arterial properties (29–31). The present results showing the association between exercise and the SDPTG indices are in line with the results of the human studies.

Recently, numerous studies have indicated that inflammation increases arterial stiffness (32–36). However, in the current study the SDPTG indices were not independently associated with the blood leukocyte count or serum CRP levels. Although it is not possible to clearly explain this discrepancy, the current results may be influenced by some biases, such as the healthy worker effect, because this study was conducted at a certain company. To our knowledge, no other reports have investigated the association between the SDPTG and inflammation. Further studies are needed to evaluate their association in community-based populations.

This study has some limitations. First, heart rate and height were selected as independent determinants of the SDPTG indices. Particularly, an elevated heart rate ameliorates the SDPTG indices, although resting tachycardia is thought to be a cardiovascular risk factor (37, 38). These confounders must be considered when measuring and evaluating the SDPTG. However, this limitation is not specific to the SDPTG but is common to other representative measures of arterial stiffness (2). Second, the population of this study consisted of only middle-aged Japanese men. Therefore, the present results may not extrapolate to other populations including women, the elderly, or other ethnic groups.

In conclusion, the present study showed that several risk factors for CVD, such as age, hypertension, dyslipidemia, IFG/DM, a lack of regular exercise, and excessive alcohol drinking, were independently associated with the SDPTG indices in middle-aged Japanese men. These findings suggest that SDPTG measurement is efficient for evaluating the arterial properties affected by these risk factors. The application of the SDPTG to epidemiological settings is anticipated because of its simplicity and easy accessibility (39). The present results may therefore indicate the usefulness of the SDPTG in the field of cardiovascular preventive medicine.

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