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Association of the second derivative of photoplethysmogram with age, hemodynamic, autonomic, adiposity, and emotional factors

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Abstract

The second derivative of photoplethysmogram (SDPTG) is used as an arterial stiffness marker. This study aimed to examine the associations between SDPTG indices and age, in addition to hemodynamic, autonomic, adiposity, and emotional factors.

This study had a cross-sectional chart review design, and electronic medical records of 262 women outpatients (mean ± SD,|38.57| ± |11.64 years) were reviewed. Among SDPTG measurements, *b/a*, *c/a*, *d/a*, and *(b-c-d)/a* were considered. Hemodynamic measurements included systolic and diastolic blood pressure (SBP and DBP) and cardiac output. Autonomic measurements included low and high frequency (LF and HF) values of the heart rate variability. Adiposity measurements included body mass index (BMI) and waist-hip ratio (WHR). Tension, anger, depression, fatigue, confusion, and vigor scores using the Profile of the Mood States were included as emotional markers. All data were normalized through the Box-Cox transformation, and 4 hierarchical regression models were constructed.

Age was independently predictive of SDPTG, hemodynamic, autonomic, and adiposity factors (β; 0.143–0.648).

After the adjustment for age, SBP and DBP showed negative correlations with *d/a* (r = –0.201, –0.262), whereas BMI, WHR, LF, and HF showed positive correlations with *c/a* (r = 0.126, 0.131, 0.151, 0.234). In the hierarchical regression modeling, age and hemodynamic factors were directly predictive of SDPTG indices (β; 0.103–0.626). Age had moderating effects between diastolic blood pressure, heart rate, depression scores, and SDPTG indices (β; 0.104–0.176).

In conclusion, age, hemodynamic, adiposity, and autonomic factors may be independently associated with SDPTG indices for women. As age has moderating effects between hemodynamic, emotional factors, and SDPTG indices, its moderating effects should be considered when assessing arterial stiffness using SDPTG indices.

Abbreviations: BMI = body mass index, CO = cardiac output, CV = cardiovascular event; DBP = diastolic blood pressure, ECG = electrocardiogram, EMRs = electronic medical recordings, HF = high frequency, HR = heart rate, HRM = hierarchical regression model, HRV = heart rate variability, LF = low frequency, PBF = percentage of the body fat, POMS = profile of the mood states, PP = pulse pressure, PR = peripheral resistance, PTG = photoplethysmogram, PWV = pulse wave velocity, PWA = pulse waveform analysis, RMSSD = squared root of the mean of the sum of the squares of differences between adjacent N-N intervals, SBP = systolic blood pressure, SDNN = standard deviation of N-N intervals, SDPTG = second derivative of photoplethysmogram, VAI = vascular aging index, VIF = variance inflating factor, WHR = waist-to-hip ratio.

Keywords: age factors, photoplethysmography, vascular stiffness

1. Introduction

Arterial stiffness is a potent and independent predictor of cardiovascular (CV) events, including myocardial infarction, stroke, and aortic syndromes.[1] CV risk factors, such as age, hypertension, diabetes mellitus, dyslipidemia, smoking, and secondary lifestyle, have been reported to aggravate arterial stiffness.[2] Although systemic arterial stiffness based on an electrical circuit or Windkessel model has been suggested,[3,4] whether systematic arterial stiffness is independently predictive for CV events remains controversial.[5] Hitherto, regional and local measurements using echo-tracking technique, pulse wave velocity (PWV), and pulse waveform analysis (PWA) may be a primary and practical consideration to estimate arterial stiffness.[2] Among these methods, the measurement of carotid-femoral PWV is robust and reproducible, and is regarded as the gold standard for arterial stiffness.[5]

Together with PWV, PWA based on radial tonometry or fingertip photoplethysmogram (PTG) has been suggested as a marker of arterial stiffness because it is convenient, non-invasive,

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and well tolerated.[5,6] However, challenges in detecting blunted peaks and notches of the original PTG have limited its clinical utility for arterial stiffness. To overcome this limitation, the use of the second derivative of the photoplethysmogram (SDPTG) has been suggested.[6] SDPTG is acquired by 2 mathematical differentiations of the original PTG, and consists of 4 systolic waves (*a, b, c*, and *d*) and a diastolic wave (*e*). The ratios of the amplitudes of the *b*, *c*, *d*, and *e* waves to the amplitude of the *a* wave (*b*/*a*, *c*/*a*, *d*/*a*, and *e*/*a*) are used to estimate arterial stiffness.

SDPTG indices have been shown to be affected by aging,[7,8] and were associated with risk factors of CV diseases in patients with hypertension[6] as well as in the general population.[9] However, SDPTG and PWV measurements taken from the same sample were inconsistent with each other. Hashimoto et al reported that *b*/*a* and *d*/*a* were not related to PWV measurements after adjusting for aging and mean blood pressure,[6] and Bortolotto et al reported that the SDPTG aging index was weakly predictive of atherosclerosis than PWV measurements.[7] For this reason, they suggested that PWV and SDPTG reflect different arterial properties at central and peripheral sites.[6,7] Changes in the stiffness of peripheral arteries are primarily due to changes in smooth muscle tone and are associated with diverse functional factors such as psychological, autonomic, and adiposity-related conditions.[10] Seldenrijk et al reported that depression and anxiety severity were associated with the augmentation index using the PTG of the radial artery, while depression and anxiety severity were not associated with the carotid distensibility coefficient.[11]

In terms of arterial stiffness and autonomic function, Kohjitani et al reported that SDPTG *c*/*a* was related to heart rate variability (HRV) indices.[12] Regarding adiposity-related factors, Majane et al reported that PWV, but not the augmentation index, was related to waist circumference and waist-to-hip ratio (WHR),[13] whereas other studies have reported that SDPTG indices were related to body mass index (BMI).[6] Together with functional factors, hemodynamic factors including blood pressure and heart rate also affect SDPTG indices.[6] Therefore, to expand the clinical utility of SDPTG, the associations of SDPTG indices with age-related, hemodynamic, autonomic, adiposity-related, and emotional factors must be examined. This will allow for a better understanding of the factors that should be adjusted when the SDPTG measurement is used as a marker of CV events.

2. Methods

2.1. Subjects

This study had a cross-sectional chart review design. Among the 414 electronic medical records (EMRs) of female patients who visited the Women's Health Clinic of Kyung Hee University Medical Hospital at Gangdong from April 2011 to February 2012, 148 did not possess SBP and DBP data and 4 did not include the SDPTG data. Therefore, 262 EMRs that were not missing data (mean, 38.57 ± 11.64 years) were finally considered to meet the inclusion criteria. All measurements were conducted on the same day for each patient. On the measurement day, patients were asked to rest for 10 minutes in a quiet room and to complete the Profile of the Mood States (POMS) first in order to prevent other measurements from affecting their moods. After completing the POMS, they underwent hemodynamic, autonomic, SDPTG, and adiposity measurements. The study protocol was approved by the Institutional Review Board of the Kyung Hee University Medical Hospital at Gangdong.

2.2. Measurements

2.2.1. The POMS. The POMS consisted of 65 items that were rated on a 5-point scale: 0 = "not at all," 1 = "a little," 2 = "moderately," 3 = "quite a bit," 4 = "extremely".[14] Among the 6 subscales, tension, depression, anger, fatigue, and confusion were negative mood scales, whereas vigor was a positive mood scale. The Korean version of the POMS has been previously validated.[15] Scores of the 6 subscales were summed to examine the association of one's moods with age and SDPTG indices.

2.2.2. Hemodynamic measurement. Systolic and diastolic blood pressures (SBP and DBP, respectively) were measured in the sitting position. Pulse pressure (PP) was estimated by subtracting DBP from SBP. The patient's cardiac output (CO) was measured using a 3-D Mac, a multi-channel array piezoresistive pressure sensor (DaeyoMedi Co., Ltd., Kyung Gi Do, Korea).[16] Higher systolic amplitude and gradient of the radial pressure waveform were found to be related to the increased stroke volume, and CO was estimated through the multiplication of SV by heart rate (HR).[17] After estimation of the CO, the peripheral resistance (PR) was secondarily estimated by dividing the mean pulse pressure by CO.[18]

2.2.3. Autonomic and SDPTG measurements. Each subject was seated in a comfortable chair, and 3 clip-type electrocardiogram (ECG) leads of a SA-3000P HRV analyzer (Medicore Co., Seoul, Korea) were attached to the patients' wrists and left ankles. The SA-3000P HRV analyzer detects ECG signals at a sampling rate of 500 Hz, and automatically calculates the time- and frequency-domain parameters based on the 5-minute R-R interval data. In this study, the time-domain parameters included the standard deviation of the R-R intervals (SDNN) and the squared root of the mean sum of the squares of differences between adjacent R-R intervals (RMSSD). Frequency-domain parameters included low frequency (LF, 0.04–0.15 Hz) and high frequency (HF, 0.15–0.4 Hz). The PTG was recorded for 90-second periods on the index finger of the left hand using the SA-3000P (Medicore Co., Seoul, Korea). SDPTG consisted of four systolic waves (*a, b, c*, and *d*) and a diastolic wave (*e*) (Fig. 1). As the SA-3000P does not present *e* wave data, we calculated vascular aging index (VAI) as (*b*-*c*-*d*)/*a*, according to the results of a previous study.[19]

2.2.4. Adiposity measurement. Adiposity indices, including BMI, WHR, and percentage of the body fat (PBF) were measured using InBody 720 (Biospace Co., Seoul, Korea). Intra- and extracellular body water, and total body water volumes were estimated according to the impedance levels, which were calculated by administering multi-frequency alternative currents to the body.[20] Lean body mass was estimated as total body water divided by 0.73, while fat mass was calculated as the difference between total body weight and lean body mass.[20] PBF was estimated as a fat mass percentage of the total body weight. WHR was estimated as the ratio of the waist and hip circumferential parameters. However, InBody 720 estimates WHR using the measurement of the visceral fat area.[21]

2.3. Data analysis

Data were checked for multivariate normality. For this, lambda values of all variables were calculated, and Box-Cox transformations were performed based on the lambda levels.[22] Simple regression models for SDPTG, hemodynamic, autonomic, and emotional factors with age as an independent variable were constructed to examine the effects of aging on the variables. After

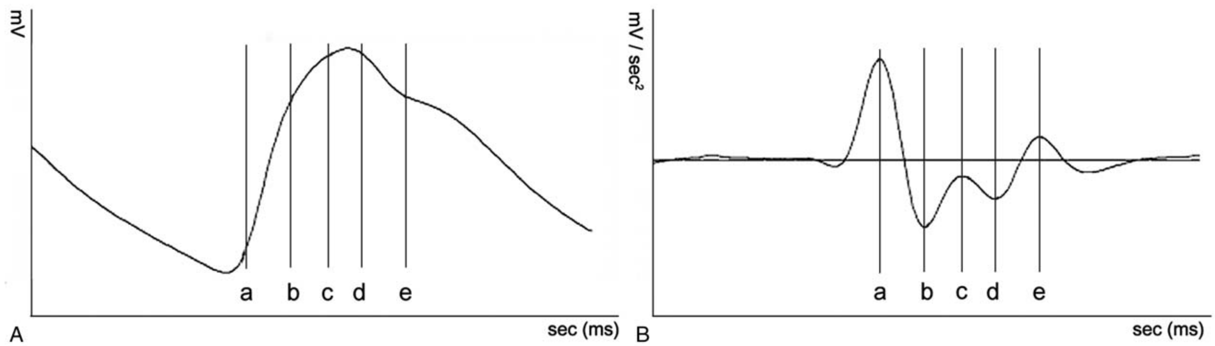

Figure 1. Original photoplethysmogram (A) and the second derivative of photoplethysmogram (B). In A and B, the *x*-axis denotes time (milliseconds). The *y*-axis in A denotes changes in the blood volume that are measured on the patients' left index fingertip and transformed to electric current (millivolts), whereas the *y*-axis of B denotes the results of double differentiations of the changes in blood volume. Wave points of *a*, *b*, *c*, *d*, and *e* on the original photoplethysmogram corresponded equally to those of the second derivative of photoplethysmogram. In this study, the *e* wave point was not considered.

that, Pearson's correlation analyses between SDPTG and other variables were conducted. Finally, 4 hierarchical regression models (HRMs) were constructed, with VAI, *b/a*, *c/a*, and *d/a* variables as dependent variables. In the regression models, all independent variables were inserted in a stepwise method. Age was inserted into the first block, and hemodynamic factors (SBP, DBP, PP, HR, CO, and PR) were inserted into the second block. Autonomic (SDNN, RMSSD, LF, and HF), and adiposity factors (BMI, PBF, and WHR) were inserted into the third and fourth blocks. Emotional factors (depression, vigor, tension, anger, fatigue, and confusion scores) were inserted into the fifth block. Finally, the multiplicative products of the hemodynamic, autonomic, adiposity, and emotional factors with age were calculated, and these variables were inserted into the sixth block of the HRM to examine whether there were moderating effects of age between SDPTG indices and other factors. When performing the multiplications, all factor variables were included by using "mean centering" in order to minimize multicollinearity.[23] In this study, Box-Cox transformations were conducted using the Minitab 16 software (Minitab Inc., State College, PA), and other statistical analyses were conducted using Statistical Package for Social Sciences version 21 (SPSS, Inc., Chicago, IL). Values were presented as means ± standard deviations, and P values $<.05$ were considered statistically significant. In the multiple regression models, a variance inflation factor (VIF) above 10 denoted multicollinearity between the independent variables.[24]

3. Results

Table 1 lists the descriptive characteristics of the women patients. Table 2 lists the effects of age on SDPTG, hemodynamic, autonomic, adiposity, and emotional factors. The standardized beta (β) values of SDPTG indices were 0.543 to 0.658, indicating that age independently and dominantly affected SDPTG indices, which was consistent with the previous results.[9,12,13] SBP and DBP increased with aging, whereas CO decreased, which was consistent with the results of previous studies.[25] As PR, BMI, and WHR variables were transformed to a reciprocal value through the Box-Cox transformation, the decrease in aging were consistent with the results of previous studies.[26,27] Autonomic factors, including SDNN, RMSSD, LF, and HF, showed aging effects, which were consistent with data of a previous study.[28] However, none of the subscale scores of the POMS showed aging effects.

The Pearson's correlation analyses between SDPTG and other variables are shown in Table 3. All variables (hemodynamic, autonomic, and adiposity indices) but emotional factors, showed moderate or weak correlations with the SDPTG indices. Table 4 lists partial Pearson's correlation analyses between SDPTG and other variables with age as a covariate. After adjusting for age, SBP and DBP showed weak correlations with VAI and *d/a*. Among the SDPTG indices, the *c/a* index showed weak correlations with all adiposity and autonomic factors and with vigor score of the POMS. Four HRMs are summarized in Table 5. Age was the most dominant predictor of the VAI, *b/a*, *c/a* and *d/a* indices. Age not only directly affected SDPTG indices, but also had moderating effects on DBP, HR, depression, and vigor factors as well as SDPTG indices. However, the autonomic and adiposity factors did not show direct or moderating effects on SDPTG indices.

4. Discussion

In this study, we examined the effects of age-related, hemodynamic, autonomic, adiposity, and emotional factors on SDPTG indices. The four HRMs showed that aging was the most important determinant factor of the arterial stiffness estimated using the SDPTG. Previously, 2 studies reported age-related effects on SDPTG indices for normotensive subjects. Kohjitani et al reported that the β values of *b/a*, *c/a*, and *d/a* were 0.661, –0.370, and –0.604, respectively, through the multiple regression models,[12] and these values were consistent with the results of our study (β = 0.629, –0.445, and –0.694, respectively). Otsuka et al showed Pearson's correlations of age with *b/a* and *d/a* as 0.52 and –0.51, respectively,[9] and these values were consistent with the adjusted R^2 values of aging effects using the simple regression models of our study (adj. R^2=0.353 and 0.430, respectively). However, another study for the hypertensive patients group reported lower correlations between age, *b/a*, and *d/a* indices than those in the normotensive group (r=0.425 and 0.196, respectively).[6] One possible reason for this difference may be that BP and HR, which are known to contribute to stiffening of the arterial system,[6,25] may have resulted in the acceleration of arterial stiffness in the hypertensive group, and BP and HR in the hypertensive group may have reduced the age-related effect on SDPTG indices more compared to the normotensive group.

Table 1

Descriptive characteristics of the female patients' age, SDPTG, hemodynamic, autonomic, adiposity, and emotional indices and Box-Cox transformations according to the lambda values.

Factor		Mean	SD	λ	Trans.
	Age (year)	38.57	11.64	0.50	$Y^{1/2}$
SDPTG	VAI (ratio)	-58.81	37.88	0.50	$Y^{1/2}$
	b/a (ratio)	-73.15	16.04	0.50	$Y^{1/2}$
	c/a (ratio)	-5.61	14.07	1.00	N.A.
	d/a (ratio)	-27.50	12.01	2.00	Y^2
Hemodynamic	SBP (mmHg)	116.35	12.49	0.50	$Y^{1/2}$
	DBP (mmHg)	71.24	8.23	1.00	N.A.
	PP (mmHg)	45.12	7.24	0.50	$Y^{1/2}$
	CO (L/min)	4.97	0.79	1.00	N.A.
	PR (dyn·sec·cm^{-5})	1577.56	369.56	–1.00	1/Y
	HR (bpm)	66.74	8.83	0.50	$Y^{1/2}$
Autonomic	SDNN (ms)	40.33	20.03	0.00	Ln Y
	RMSSD (ms)	36.78	25.15	0.00	Ln Y
	LF (ms^2)	403.53	736.57	0.00	Ln Y
	HF (ms^2)	372.57	511.19	0.13	Ln Y
	LF/HF (ratio)	1.48	1.78	0.00	Ln Y
Adiposity	BMI (kg/m^2)	21.92	3.05	–1.00	1/Y
	PBF (%)	29.86	6.29	0.50	$Y^{1/2}$
	WHR (ratio)	0.84	0.06	–0.50	$1/(Y^{1/2})$
Emotional	Depression (score)	14.63	13.18	0.23	$Y^{1/4}$
	Tension (score)	11.27	7.07	0.50	$Y^{1/2}$
	Anger (score)	10.55	9.60	0.18	$Y^{1/4}$
	Fatigue (score)	11.82	6.06	0.73	$Y^{1/2}$
	Confusion (score)	9.16	5.09	0.50	$Y^{1/2}$
	Vigor (score)	10.11	6.37	0.50	$Y^{1/2}$

BMI = body mass index, CO = cardiac output, DBP = diastolic blood pressure, HF = high frequency, HR = heart rate, LF = low frequency, Ln = natural logarithm, N.A. = not applicable, PBF = percentage of body fat, PP = pulse pressure, PR = peripheral resistance, RMSSD = squared root of the mean sum of the squares of differences between adjacent NN intervals, SBP = systolic blood pressure, SDNN = standard deviation of NN intervals, SDPTG = second derivative of photoplethysmogram, Trans. = transformation, VAI = vascular aging index = which corresponds to (*b-c-d*)/*a*, WHR = waist-hip ratio, Y = original index.

Table 2

Effects of age on SDPTG, hemodynamic, autonomic, adiposity, and emotional factors.

Factor		Adj. R^2	β	SE	t	P value
SDPTG	VAI (ratio)	0.417	0.648	1.903	13.701	**<.001**
	b/a (ratio)	0.353	0.596	0.850	11.964	**<.001**
	c/a (ratio)	0.292	–0.543	0.779	–10.417	**<.001**
	d/a (ratio)	0.430	–0.658	0.597	–14.076	**<.001**
Hemodynamic	SBP (mmHg)	0.052	0.237	0.065	3.926	**<.001**
	DBP (mmHg)	0.042	0.215	0.043	3.544	**<.001**
	CO (L/min)	0.135	–0.372	0.004	–6.455	**<.001**
	PR (dyn·sec·cm^{-5})	0.181	–0.429*	0.000	–7.662	**<.001**
Autonomic	SDNN (ms)	0.119	–0.349	0.002	–6.011	**<.001**
	RMSSD (ms)	0.177	–0.424	0.003	–7.546	**<.001**
	LF (ms^2)	0.134	–0.371	0.006	–6.432	**<.001**
	HF (ms^2)	0.201	–0.452	0.006	–8.175	**<.001**
	LF/HF (ratio)	0.017	0.143	0.005	2.328	**.021**
Adiposity	BMI (kg/m^2)	0.108	–0.334*	0.000	–5.720	**<.001**
	PBF (%)	0.059	0.251	0.003	4.174	**<.001**
	WHR (ratio)	0.357	–0.600*	0.000	–12.090	**<.001**
Emotional	Depression (score)	–0.004	0.003	0.002	0.043	.965
	Tension (score)	–0.001	0.051	0.005	0.826	.410
	Anger (score)	–0.002	–0.042	0.002	–0.680	.497
	Fatigue (score)	–0.004	–0.008	0.005	–0.127	.899
	Confusion (score)	–0.003	0.020	0.004	0.320	.749
	Vigor (score)	–0.003	0.022	0.005	0.348	.728

Bold letters indicate significant *P* values.

BMI = body mass index, CO = cardiac output, DBP = diastolic blood pressure, HF = high frequency, LF = low frequency, LF/HF = the ratio of LF to HF, PBF = percentage of body fat, PR = peripheral resistance, RMSSD = squared root of the mean sum of the squares of differences between adjacent NN intervals, SBP = systolic blood pressure, SDNN = standard deviation of NN intervals, SDPTG = second derivative of photoplethysmogram, VAI = vascular aging index = that is (*b-c-d*)/*a*, WHR = waist-hip ratio.

* The original values of MBP, PR, BMI, and WHR were transformed to a reciprocal type using the Box-Cox transformation, and the transformed variables show decreased β values with aging.

Table 3

Correlations of the SDPTG indices with the hemodynamic, autonomic, adiposity, and emotional factors.

Factor			SDPTG				Factor			SDPTG			
			VAI	*b/a*	*c/a*	*d/a*				VAI	*b/a*	*c/a*	*d/a*
Hemodynamic	SBP (mmHg)	*r*	0.245	0.229	–0.225	–0.304	Autonomic	SDNN (ms)	*r*	–0.264	–0.219	0.370	0.167
		P	**<.001**	**<.001**	**<.001**	**<.001**			*P*	**<.001**	**<.001**	**<.001**	**.007**
	DBP (mmHg)	*r*	0.219	0.203	–0.136	–0.334		RMSSD (ms)	*r*	–0.288	–0.225	0.401	0.193
		P	**<.001**	**.001**	**.028**	**<.001**			*P*	**<.001**	**<.001**	**<.001**	**.002**
	PP (mmHg)	*r*	0.175	0.164	–0.237	–0.146		LF (ms^2)	*r*	–0.272	–0.227	0.321	0.198
		P	**.005**	**.008**	**<.001**	**.018**			*P*	**<.001**	**<.001**	**<.001**	**.001**
	CO (L/min)	*r*	–0.148	–0.109	0.208	0.187		HF (ms^2)	*r*	–0.321	–0.254	0.423	0.241
		P	**.016**	.078	**.001**	**.002**			*P*	**<.001**	**<.001**	**<.001**	**<.001**
	PR (dyn·sec·cm^{-5})	*r*	–0.189	–0.140	0.252	0.235	Emotional	Depression (score)	*r*	0.005	0.012	–0.015	–0.040
		P	**.002**	**.024**	**<.001**	**<.001**			*P*	.937	.852	.804	.514
	HR (bpm)	*r*	–0.047	–0.114	–0.244	0.168		Tension (score)	*r*	0.052	0.041	–0.039	–0.084
		P	.451	.065	**<.001**	**.007**			*P*	.397	.505	.535	.173
Adiposity	BMI (kg/m^2)	*r*	–0.245	– 0.206	0.283	0.220		Anger (score)	*r*	–0.026	–0.002	0.014	–0.013
		P	**<.001**	**.001**	**<.001**	**<.001**			*P*	.676	.969	.827	.837
	PBF (%)	*r*	0.241	0.198	–0.275	-0.183		Fatigue (score)	*r*	0.023	0.051	0.001	–0.067
		P	**<.001**	**.001**	**<.001**	**.003**			*P*	.710	.411	.993	.277
	WHR (ratio)	*r*	–0.394	–0.331	0.417	0.370		Confusion (score)	*r*	0.020	0.030	–0.009	–0.065
		P	**<.001**	**<.001**	**<.001**	**<.001**			*P*	.745	.631	.879	.297
								Vigor (score)	*r*	–0.040	–0.051	0.091	0.034
									P	.518	.408	.140	.583

Bold values indicate significant *P* values.

BMI = body mass index, CO = cardiac output, DBP = diastolic blood pressure, HF = high frequency, HR = heart rate, LF = low frequency, PBF = percentage of body fat, PP = pulse pressure, PR = peripheral resistance, RMSSD = squared root of the mean sum of the squares of differences between adjacent NN intervals, SBP = systolic blood pressure, SDNN = standard deviation of NN intervals, SDPTG = second derivative of photoplethysmogram, VAI = vascular aging index, WHR = waist-hip ratio.

In terms of hemodynamic effect on arterial stiffness, some study results were not consistent with each other according to the subject groups. For the hypertensive group, Hashimoto et al reported that SBP, like age, was associated with increased *b/a*, and HR was associated with decreased *b/a* and increased *d/a*.[6] In a study with a normotensive population, SBP was associated with decreased *d/a*,[9] while in another study, DBP was associated with decreased *d/a*.[12] In our study, SBP was associated with a

Table 4

Correlations of the SDPTG indices with the hemodynamic, autonomic, adiposity, and emotional factors with age as a covariate.

Factor			SDPTG				Factor			SDPTG			
			VAI	*b/a*	*c/a*	*d/a*				VAI	*b/a*	*c/a*	*d/a*
Hemodynamic	SBP (mmHg)	*r*	0.127	0.114	–0.117	–0.201	Autonomic	SDNN (ms)	*r*	–0.058	–0.017	0.227	–0.099
		P	**.041**	.066	.058	**.001**			*P*	.347	.788	**<.001**	.109
	DBP (mmHg)	*r*	0.110	0.097	–0.022	–0.262		RMSSD (ms)	*r*	–0.028	0.035	0.223	–0.139
		P	.077	.117	.725	**<.001**			*P*	.648	.579	**<.001**	.024
	PP (mmHg)	*r*	0.090	0.083	–0.176	–0.046		LF (ms^2)	*r*	–0.051	–0.012	0.151	–0.076
		P	.145	.0183	**.004**	.458			*P*	.408	.848	**.015**	.220
	CO (L/min)	*r*	0.122	0.147	0.005	–0.093		HF (ms^2)	*r*	–0.049	0.018	0.234	–0.097
		P	**.049**	.018	.940	.136			*P*	.427	.771	**<.001**	.117
	PR (dyn·sec·cm^{-5})	*r*	0.119	0.156	0.022	–0.082	Emotional	Depression (score)	*r*	0.004	0.012	–0.017	–0.052
		P	.055	**.012**	.725	.185			*P*	.948	.842	.789	.399
	HR (bpm)	*r*	–0.029	–0.117	–0.322	0.194		Tension (score)	*r*	0.026	0.014	–0.012	–0.068
		P	.636	.059	**<.001**	**.002**			*P*	.676	.823	.841	.276
Adiposity	BMI (kg/m^2)	*r*	–0.045	–0.012	0.126	–0.008		Anger (score)	*r*	0.001	0.028	–0.012	–0.056
		P	.470	.852	**.043**	.898			*P*	.987	.654	.853	.369
	PBF (%)	*r*	0.110	0.064	–0.170	–0.020		Fatigue (score)	*r*	0.036	0.069	–0.004	–0.098
		P	.076	.302	**.006**	.748			*P*	.560	.268	.943	.113
	WHR (ratio)	*r*	–0.022	0.035	0.131	–0.055		Confusion (score)	*r*	0.010	0.022	0.002	–0.069
		P	.720	.570	**.035**	.373			*P*	.875	.718	.978	.264
								Vigor (score)	*r*	–0.070	–0.079	0.124	0.066
									P	.263	.202	**.046**	.288

Bold values indicate significant *P* values.

BMI = body mass index, CO = cardiac output, DBP = diastolic blood pressure, HF = high frequency, HR = heart rate, LF = low frequency, PBF = percentage of body fat, PP = pulse pressure, PR = peripheral resistance, RMSSD = squared root of the mean sum of the squares of differences between adjacent NN intervals, SBP = systolic blood pressure, SDNN = standard deviation of NN intervals, SDPTG = second derivative of photoplethysmogram, VAI = vascular aging index, WHR = waist-hip ratio.

Table 5

Hierarchical regression models for SDPTG indices with the hemodynamic, autonomic, adiposity, and emotional indices as independent variables.

SDPTG index (Adj. R^2 [*F* value])		VAI (0.413 [62.203])				*b/a* (0.386 [33.778])				*c/a* (0.369 [51.950])				*d/a* (0.522 [96.083])			
		β	*t*	*P* value	VIF	β	*t*	*P* value	VIF	β	*t*	*P* value	VIF	β	*t*	*P* value	VIF
Age (year)		0.612	12.542	**.000**	1.060	0.626	11.651	**.000**	1.225	−0.558	−11.335	**.000**	1.004	−0.613	−13.939	**.000**	1.058
Hemodynamic	SBP (mmHg)	0.103	2.103	**.036**	1.057	0.071	1.406	.161	1.096	0.023	−0.430	.668	1.158	−0.244	−5.410	**.000**	1.109
	DBP (mmHg)	0.000	−0.003	.998	3.297	0.056	1.113	.267	1.070	0.051	0.976	.330	1.110	−0.043	−0.540	.589	3.438
	PP (mmHg)	−0.002	−0.023	.982	2.509	0.054	1.079	.282	1.064	−0.094	−1.852	.065	1.087	−0.026	−0.561	.575	1.149
	HR (bpm)	−0.048	−0.969	.333	1.105	−0.057	−1.168	.244	1.030	−0.274	−5.549	**.000**	1.009	0.198	4.505	**.000**	1.058
	CO (L/min)	0.056	1.066	.287	1.232	0.006	0.058	.954	4.814	0.019	0.361	.719	1.159	−0.006	−0.131	.896	1.202
	PR (dyn·sec·cm^{-5})	0.063	1.185	.237	1.262	0.121	2.246	**.026**	1.228	0.023	0.415	.678	1.230	−0.012	−0.251	.802	1.243
Autonomic	SDNN (ms)	−0.027	−0.529	.597	1.166	−0.032	−0.614	.540	1.168	0.079	1.324	.187	1.472	0.005	0.105	.916	1.477
	RMSSD (ms)	0.009	0.165	.869	1.298	0.017	0.316	.752	1.238	0.045	0.684	.494	1.822	−0.047	−0.817	.415	1.801
	LF (ms^2)	−0.024	−0.467	.641	1.177	−0.026	−0.492	.623	1.189	0.037	0.657	.511	1.311	0.003	0.065	.948	1.311
	HF (ms^2)	−0.015	−0.275	.783	1.312	−0.002	−0.033	.974	1.278	0.095	1.528	.128	1.613	−0.004	−0.070	.944	1.590
Adiposity	BMI (kg/m^2)	−0.025	−0.468	.640	1.227	0.018	0.324	.747	1.353	0.079	1.485	.139	1.175	−0.009	−0.189	.850	1.178
	PBF (%)	0.073	1.460	.146	1.122	0.051	0.982	.327	1.141	−0.098	−1.908	.058	1.114	−0.032	−0.706	.481	1.117
	WHR (ratio)	−0.007	−0.111	.912	1.670	0.046	0.728	.468	1.722	0.083	1.315	.190	1.656	−0.045	−0.822	.412	1.667
Emotional	Depression (score)	−0.005	−0.098	.922	1.012	0.001	0.027	.979	1.005	−0.001	−0.024	.981	1.013	−0.053	−1.233	.219	1.001
	Tension (score)	0.012	0.258	.796	1.020	0.011	0.216	.829	1.018	0.009	0.186	.852	1.022	−0.073	−1.717	.087	1.006
	Anger (score)	−0.011	−0.235	.815	1.019	0.020	0.407	.684	1.011	0.012	0.250	.803	1.022	−0.058	−1.352	.178	1.005
	Fatigue (score)	0.021	0.434	.665	1.015	0.045	0.915	.361	1.023	0.001	0.023	.981	1.014	−0.077	−1.799	.073	1.001
	Confusion (score)	−0.002	−0.052	.959	1.017	0.012	0.241	.810	1.013	0.004	0.085	.932	1.018	−0.057	−1.342	.181	1.002
	Vigor (score)	−0.050	−1.058	.291	1.001	−0.032	−0.651	.516	1.023	0.090	1.835	.068	1.002	0.044	1.037	.301	1.002
Moderating effect of aging	Age × SBP	0.001	0.019	.985	1.018	−0.064	−0.676	.500	3.744	−0.034	−0.683	.495	1.022	−0.026	−0.599	.549	1.010
	Age × DBP	0.024	0.501	.617	1.008	0.104	2.055	**.041**	1.088	−0.055	−1.112	.267	1.007	−0.026	−0.613	.540	1.003
	Age × PP	−0.086	−1.822	.070	1.007	−0.031	−0.567	.571	1.230	0.028	0.563	.574	1.023	0.029	0.666	.506	1.023
	Age × HR	−0.024	−0.495	.621	1.039	−0.176	−3.486	**.001**	1.083	0.004	0.085	.932	1.040	−0.013	−0.301	.764	1.030
	Age × CO	0.048	0.982	.327	1.071	0.022	0.431	.667	1.135	0.023	0.448	.655	1.081	−0.012	−0.278	.781	1.051
	Age × PR	0.015	0.310	.757	1.065	0.002	0.036	.972	1.126	0.047	0.919	.359	1.070	0.005	0.110	.913	1.038
	Age × SDNN	−0.033	−0.680	.497	1.016	−0.103	−1.931	.055	1.219	0.051	1.019	.309	1.018	0.021	0.476	.634	1.015
	Age × RMSSD	−0.020	−0.411	.682	1.003	−0.094	−1.616	.107	1.447	0.039	0.789	.431	1.010	0.009	0.206	.837	1.008
	Age × LF	−0.067	−1.411	.159	1.007	−0.088	−1.755	.080	1.079	0.072	1.448	.149	1.016	0.029	0.675	.500	1.016
	Age × HF	−0.023	−0.488	.626	1.002	−0.074	−1.372	.171	1.247	0.050	1.002	.317	1.013	0.003	0.067	.946	1.013
	Age × BMI	−0.002	−0.049	.961	1.002	−0.009	−0.182	.855	1.110	0.014	0.285	.776	1.001	0.047	1.102	.271	1.001
	Age × PBF	−0.038	−0.795	.427	1.008	−0.059	−1.118	.264	1.176	−0.051	−1.027	.306	1.009	0.005	0.126	.900	1.007
	Age × WHR	0.006	0.133	.894	1.006	−0.006	−0.109	.913	1.129	0.073	1.477	.141	1.006	0.023	0.531	.596	1.010
	Age × depression	0.063	1.163	.246	1.308	0.128	2.617	**.009**	1.022	−0.012	−0.217	.828	1.307	−0.014	−0.322	.747	1.010
	Age × tension	0.066	1.341	.181	1.065	0.032	0.474	.636	1.978	−0.038	−0.757	.450	1.064	0.021	0.479	.632	1.025
	Age × anger	0.030	0.624	.533	1.179	0.010	0.103	.918	3.718	0.026	0.488	.626	1.180	−0.002	−0.057	.955	1.018
	Age × fatigue	.0056	1.087	.278	1.177	0.048	0.682	.496	2.130	0.000	−0.006	.995	1.177	−0.019	−0.438	.662	1.018
	Age × confusion	.0074	1.505	.133	1.069	0.072	0.971	.333	2.310	−0.028	−0.546	.586	1.067	−0.004	−0.092	.927	1.018
	Age × vigor	−0.109	−2.297	**.022**	1.003	−0.063	−1.128	.260	1.327	0.111	2.251	**.025**	1.010	0.056	1.313	.190	1.011

BMI = body mass index, CO = cardiac output, DBP = diastolic blood pressure, HF = high frequency, HR = heart rate, LF = low frequency, PBF = percentage of body fat, PP = pulse pressure, PR = peripheral resistance, RMSSD = squared root of the mean sum of the squares of differences between adjacent NN intervals, SBP = systolic blood pressure, SDNN = standard deviation of NN intervals, SDPTG = second derivative of photoplethysmogram, VAI = vascular aging index, VIF = variance inflation factor, WHR = waist-hip ratio. Bold letters indicate significant *P* values.

decreased *d/a*, while HR was associated with an increased *d/a*. After adjusting for age, SBP and DBP were associated with a decreased *d/a*, while HR was associated with an increased *d/a*, and a decreased *c/a*. The moderating effects of age on DBP and HR were associated with an increased and a decreased *b/a*, respectively. Considering the previous studies and our study results, hemodynamic factors including SBP, DBP, and HR may independently affect *b/a* and *d/a*. Furthermore, age may have a moderating effect on the relationship between hemodynamic factors and SDPTG indices. Therefore, our study results suggest that age, hemodynamic factors, and the moderating effect of age should be considered when estimating arterial stiffness using the SDPTG indices.

It is interesting that the moderating effect of age on depression was associated with increased *b/a*, although none of the emotional factors were directly affected SDPTG indices. The *b* wave period of the SDPTG is related to the first vascular response to blood ejection from the left ventricle.[8] As arteries are stiffer, the reflected wave may overlap with the incident component, resulting in an increase in SBP.[3] Acute mental stress was reported to increase arterial stiffness that was estimated using carotid-femoral PWV.[30] A lifetime diagnosis of depressive or anxiety disorders was associated with central augmentation index, estimated using the radial tonometry.[11] Considering the descriptive characteristics of the POMS scores in our study, it is unlikely that the female subjects may have suffered from moderate or severe emotional problems. Therefore, our study results suggest that depression may have a long-time effect on the early wave reflection from the periphery as aging, and may have secondarily increased *b/a*.

Adiposity markers including BMI and WHR have been reported to have age-related effect.[27] BMI has been suggested to be a predictive factor of SDPTG indices for the hypertensive group.[6] However, another study reported that BMI was not associated with carotid intima-media thickness in the young population.[29] In our study, BMI, PBF, and WHR were associated with all of the SDPTG indices, while these adiposity-related indices were weakly associated with *c/a*, after adjusting for age. These results show that adiposity-related factors may independently affect the SDPTG in normotensive women subjects. In terms of autonomic factors, there were significant Pearson's correlations between SDPTG and autonomic indices, and *c/a* was associated with increased LF and HF after adjusting for age. Previously, 1 study measured SDPTG and HRV indices immediately before oral surgery and reported that *c/a* was associated with an increased LF and a decreased HF.[12] Although the previous study did not document any the subjects' emotions,[12] it is plausible that emotional conditions including tension before oral surgery may have increased sympathetic nervous activity and decreased parasympathetic activity, followed by increased LF and decreased HF. In our study, all of the subjects underwent the measurements after resting for 10 minutes, and it was not possible for the patients to have experienced any acute mental stress. Therefore, it appears that in resting condition, *c/a* may be independently associated with autonomic function related to increased parasympathetic activity.

This study had some limitations. This chart review study included only female subjects. However, women have been reported to exhibit a greater age-related increase in aortic stiffness than men.[31] As mentioned above, CV risk factors such as diabetes mellitus, dyslipidemia, smoking, and secondary lifestyle reportedly aggravate arterial stiffness. Bone mineral density is reportedly related to arterial stiffness in middle-aged and elderly patients.[32] Therefore, we must examine whether one's lifestyle and other factors including bone mineral density and sex hormones may serve as moderating effectors on the relationship between the SDPTG and the hemodynamic, adiposity, autonomic, and emotional factors in male versus female groups. Differences in the predictive factors and their β levels between normotensive and hypertensive groups should be examined in large samples.

In conclusion, findings from our study suggest that for normotensive females, age, hemodynamic, adiposity, and autonomic factors may be independently associated with SDPTG indices. As age had moderating effects between hemodynamic and emotional factors and SDPTG indices, the moderating effects of age as well as age and hemodynamic factors should be considered when assessing arterial stiffness using SDPTG indices. Further studies are needed to address the confounding effects of sex, smoking, secondary lifestyle factors, and bone mineral density on the relationship between the SDPTG indices and hemodynamic, adiposity, autonomic, and emotional factors.

Author contributions

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