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Abstract—To evaluate the clinical application of the second derivative of the fingertip photoplethysmogram waveform, we performed drug administration studies (study 1) and epidemiological studies (study 2). In study 1, ascending aortic pressure was recorded simultaneously with the fingertip photoplethysmogram and its second derivative in 39 patients with a mean±SD age of 54±11 years. The augmentation index was defined as the ratio of the height of the late systolic peak to that of the early systolic peak in the pulse. The second derivative consists of an a, b, c, and d wave in systole and an e wave in diastole. Ascending aortic pressure increased after injection of 2.5 μg angiotensin from 126/74 to 160/91 mm Hg and decreased after 0.3 mg sublingual nitroglycerin to 111/73 mm Hg. The d/a, the ratio of the height of the d wave to that of the a wave, decreased after angiotensin from −0.40±0.13 to −0.62±0.19 and increased after nitroglycerin to −0.25±0.12 ($P<0.001$ and $P<0.001$, respectively). The negative d/a increased with increases in plethysmographic and ascending aortic augmentation indices ($r=0.79$, $P<0.001$, and $r=0.80$, $P<0.001$, respectively). The negative d/a reflects the late systolic pressure augmentation in the ascending aorta and may be useful for noninvasive evaluation of the effects of vasoactive agents. In study 2, the second derivative of the plethysmogram waveform was measured in a total of 600 subjects (50 men and 50 women in each decade from the 3rd to the 8th) in our health assessment center. The b/a ratio increased with age, and c/a, d/a, and e/a ratios decreased with age. Thus, the second derivative aging index was defined as b-c-d-e/a. The second derivative wave aging index (y) increased with age (x) ($r=0.80$, $P<0.001$, $y=0.023x-1.515$). The second derivative aging index was higher in 126 subjects with any history of diabetes mellitus, hypertension, hypercholesterolemia, and ischemic heart disease than in age-matched subjects without such a history (−0.06±0.36 versus −0.22±0.41, $P<0.01$). Women had a higher aging index than men ($P<0.01$). The b-c-d-e/a ratio may be useful for evaluation of vascular aging and for screening of arteriosclerotic disease. **(*Hypertension*. 1998;32:365-370.)**

Key Words: photoplethysmography ■ second derivative wave ■ augmentation index ■ vasoactive agents ■ vascular aging ■ angiotensin ■ nitroglycerin

Noninvasive pulse wave analysis is useful for evaluation of vascular load and vascular aging.[1] It is usually measured at the palpable artery, including carotid, femoral, and radial arteries.[2] These pulse wave tracings provide more precise information concerning blood pressure changes than systolic and diastolic pressures only.[3] The basic idea of the augmentation index was first described by Murgo et al[4] in 1980 in relation to the reflection return point in the ascending aorta. Kelly et al[2] first used the term "augmentation index" in their 1989 study evaluating age-related changes in AIs. They showed age-related increase in AIs at carotid and radial arteries. Ascending aortic pressure can be divided into 2 components at the anacrotic notch, where maximal flow velocity is observed.[2] The early systolic component is caused mainly by left ventricular ejection, and the second component is augmented by peripheral reflection wave.[5] PTG detects the changes in the amount of light absorbed by hemoglobin, which reflects changes in blood volume. Wiederhelm et al[6] showed pulsatile pressure changes in vessel down to metaarteriole size that corresponded to pulse tracing. PTG has been used to evaluate arterial compliance in relation to changes in the amplitude of wave,[7] but the wave contour itself is not usually used. The SDPTG has been developed to allow more accurate recognition of the inflection points on the original plethysmographic wave, ie, anacrotic or dicrotic notches. In 1972, Ozawa recorded the first and second derivative waves of PTG and reported (in Japanese) that the first derivative wave had characteristic wave contours. In 1978, he further reported that the second derivative wave had characteristic contours that facilitated the interpretation of the original waves. The conventional PTG measurements came to be performed less frequently because of difficulties in analysis and reading, and most clinicians made recordings of the second derivative wave alone because of the simplicity of evaluating the heights of each wave and the ease of recognition of the changes in the waveforms. The purpose of the

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Selected Abbreviations and Acronyms

AGT = angiotensin
AI = augmentation index
NTG = nitroglycerin
PTG = photoplethysmography
SDPTG = second derivative wave of fingertip photoplethysmography

present studies was to determine the wave changes in SDPTG immediately after administration of vasoactive agents (study 1) and age-related changes in different age groups (study 2).

Methods

Study 1

Thirty-nine patients (34 men, 5 women) with a mean±SD age of 54±11 years who underwent diagnostic cardiac catheterization were studied: there were 19 cases of myocardial infarction, 17 cases of angina pectoris, and 3 cases of chest pain syndrome without organic cardiac abnormalities. Ascending aortic pressure was measured by a microtip catheter (SPC or SVPC series, Millar Instruments), and PTG and SDPTG were measured by a photoplethysmograph equipped with double differentiation circuits (PT-400, Fukuda Denshi), with the sensor located at the cuticle of the second digit of the left hand. Measurements were performed in the control state and when systolic blood pressure was increased by ≈30% after intravenous injection of 2.5 μg AGT. After systolic pressure returned to control levels, 0.3 mg sublingual NTG was administered; measurement was made 5 minutes later. Figure 1 shows the analysis of each wave. The negative d/a (−d/a) was used for adjustment of polarity to be compared with the AI.

All procedures were approved by the ethics committee of Tokyo Medical College Hospital. Informed consent was obtained from all patients.

Study 2

The study included a total of 600 subjects (50 men and 50 women in each decade from the 3rd to the 8th) in our health assessment center. PTG and SDPTG were measured in subjects in the sitting position at the cuticle of the second digit of the left hand by digital PTG (FCP-3166 Fukuda Denshi). The FCP-3166 contained automatic analyses of each SDPTG wave, and total frequency response was adjusted to 10 Hz for the PT-400 model used in study 1. Some subjects had a history of disease: diabetes mellitus (n=12), hypertension (n=117), ischemic heart disease (n=4), and hypercholesterolemia (n=12).

Results

Study 1

Figure 2 shows a sample tracing. Results are shown in Table 1, with descriptive statistics of ANOVA and Scheffé's F test. Compared with the control state, b/a, c/a, and e/a ratios did not change significantly after AGT or NTG. The d/a ratio decreased significantly after AGT and increased after NTG ($P<0.001$ and $P<0.001$, respectively). Figure 3 shows the relationship between AIs and the negative d/a. The negative d/a (−d/a) increased with increasing PTG AI and aortic pressure AI ($r=0.79$, $P<0.001$, and $r=0.81$, $P<0.001$, respectively). PTG AI increased with increasing aortic pressure AI ($r=0.86$, $P<0.001$).

Study 2

Figure 4 shows age-related changes for each SDPTG ratio. The b/a ratio increased with age ($r=0.75$, $P<0.001$); c/a ($r=-0.67$, $P<0.001$), d/a ($r=-0.72$, $P<0.001$), and e/a ($r=0.25$, $P<0.001$) ratios decreased with age. From the above results, the equation of b-c-d-e/a was defined as the SDPTG aging index. Figure 5 shows the relationship between SDPTG aging index and age. SDPTG aging index (y) increased with age (x) ($r=0.80$, $P<0.001$; $y=0.023x-1.515$). The SDPTG aging index was higher in 126 subjects with any history of the diseases listed above than in age-matched subjects without any such history (−0.06±0.36 versus −0.22±0.41, $P<0.01$).

Table 2 shows the gender difference of parameters. Women had a higher b/a ratio than men (−0.59±0.18 versus

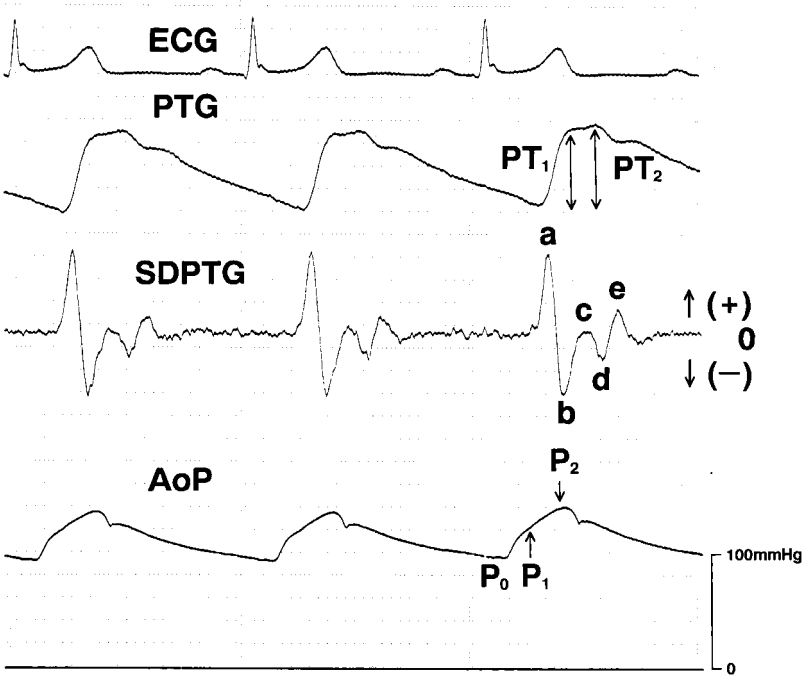

Figure 1. Measurement of wave. Ascending aortic pressure (AoP) AI was defined as P_2-P_0/P_1-P_0, where P_2 is ascending aortic late peak systolic pressure, P_0 is ascending aortic diastolic pressure, and P_1 is ascending aortic early peak systolic pressure. The AI of PTG was defined as PT_2/PT_1, where PT_2 is amplitude of the late systolic component, and PT_1 is amplitude of the early systolic component. SDPTG includes 4 systolic waves and 1 diastolic wave: a wave, initial positive wave; b wave, early negative wave; c wave, re-increasing wave; d wave, re-decreasing wave; and diastolic e wave. The ratios of the height of each wave to that of the a wave were measured (b/a, c/a, d/a, and e/a).

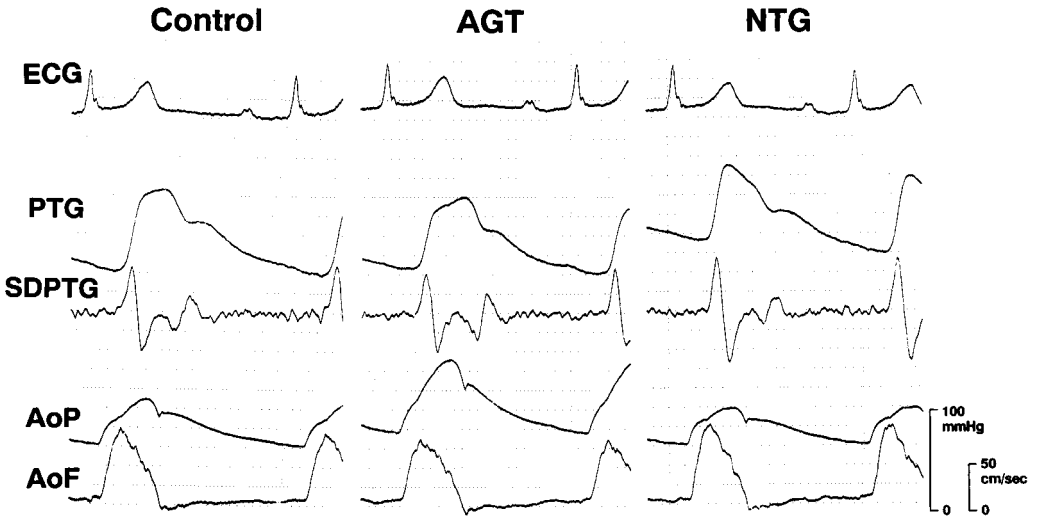

Figure 2. Tracings show results of administration of vasoactive agents. An increase in the late systolic component of aortic pressure (AoP) and PTG after intravenous injection of 2.5 μg AGT and a deepened d wave in relation to the height of the a wave (decreased d/a) are seen in SDPTG. On the other hand, NTG produces marked reduction in late systolic components of aortic pressure and PTG, with d wave becoming shallower in relation to the height of a wave (increased d/a). AoF indicates ascending aortic flow velocity.

−0.64±0.18, $P<0.001$). The e/a ratio was lower in women than men (0.16±0.07 versus 0.19±0.09, $P<0.001$). PTG AI was higher in women than men (1.11±0.22 versus 1.07±0.21, $P<0.05$). SDPTG aging index was higher in women than men (−0.32±0.47 versus −0.43±0.47, $P<0.01$).

Discussion

In study 1, we found marked changes in the d/a ratio of SDPTG before and after administration of vasoactive agents without any significant changes in b/a, c/a, and e/a ratios. This may have been caused by changes in the reflection wave, which increased with vasoconstriction produced by AGT and decreased through vasodilation produced by NTG. AGT produced a marked increase in both systolic and diastolic pressures in the ascending aorta through vasoconstriction of peripheral arteriole,[8] which elevated the mean pressure and increased pulse wave velocity, resulting in early return of peripheral reflection wave. Increase in reflection wave after administration of AGT caused the increase in aortic pressure AI and PTG AI. On the other hand, after NTG administration, marked reductions were observed in the AIs for aortic pressure and PTG. Vasodilation by NTG produced a marked reduction in the ascending aortic late systolic component without significant change in diastolic pressure, which was brought about by reduction in peripheral reflection wave through dilation of muscular arteries.[9] Despite the PTG representing a flow/volume pulse measured from an extremity, a similarity between the aortic pressure AI and the PTG AI was observed both at baseline and after hemodynamic alterations. The values of PTG AI from our data would appear to fall between values of radial and carotid AIs obtained from the studies of Kelly et al.[2] The late systolic component of PTG is relatively higher than that of the radial artery, and this

TABLE 1. Descriptive Statistics and Results of ANOVA and Scheffé's F Test

	Control	After AGT	After NTG
P_0, mm Hg	74±11	91±12*	73±10
P_1, mm Hg	108±12	125±13†	104±12*
P_2, mm Hg	126±16	160±20*	111±16*
AoP AI	1.53±0.24	2.10±0.43*	1.25±0.27*
PT_1, mm	29±11	22±8*	42±16*
PT_2, mm	34±13	31±12	38±17‡
PTG AI	1.17±0.13	1.43±0.17*	0.92±0.14*
b/a	−0.61±0.22	−0.57±0.17	−0.69±0.14
c/a	−0.06±0.22	−0.00±0.17	−0.12±0.17
d/a	−0.40±0.13	−0.62±0.19*	−0.25±0.12*
e/a	0.27±0.08	0.31±0.09	0.28±0.09
SV, mL	77±16	76±17	71±15†
CO, L/min	5.2±1.1	5.1±1.4	5.1±1.1
HR, bpm	69±11	68±11	73±12†

P_0 indicates ascending aortic diastolic pressure; P_1, ascending aortic early systolic peak pressure; P_2, ascending aortic late systolic peak pressure; AoP AI, ascending aortic augmentation index; PT_1, amplitude of early systolic wave of PTG; PT_2, amplitude of late systolic wave of PTG; b/a, ratio of height of b wave to that of a wave of SDPTG; c/a, ratio of height of c wave to that of a wave; d/a, ratio of height of d wave to that of a wave; e/a, ratio of height of e wave to that of a wave; SV, stroke volume; CO, cardiac output; and HR, heart rate.

*$P<0.001$, †$P<0.01$, ‡$P<0.05$ vs control.

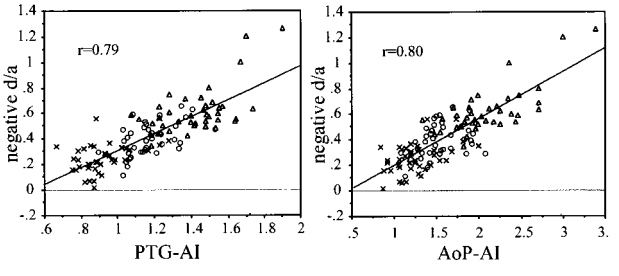

Figure 3. Relationship between the negative d/a and AIs. Negative d/a increased with increases in PTG AI (left) and aortic pressure (AoP) AI (right). ○ indicates control; △, after AGT; and ×, after NTG.

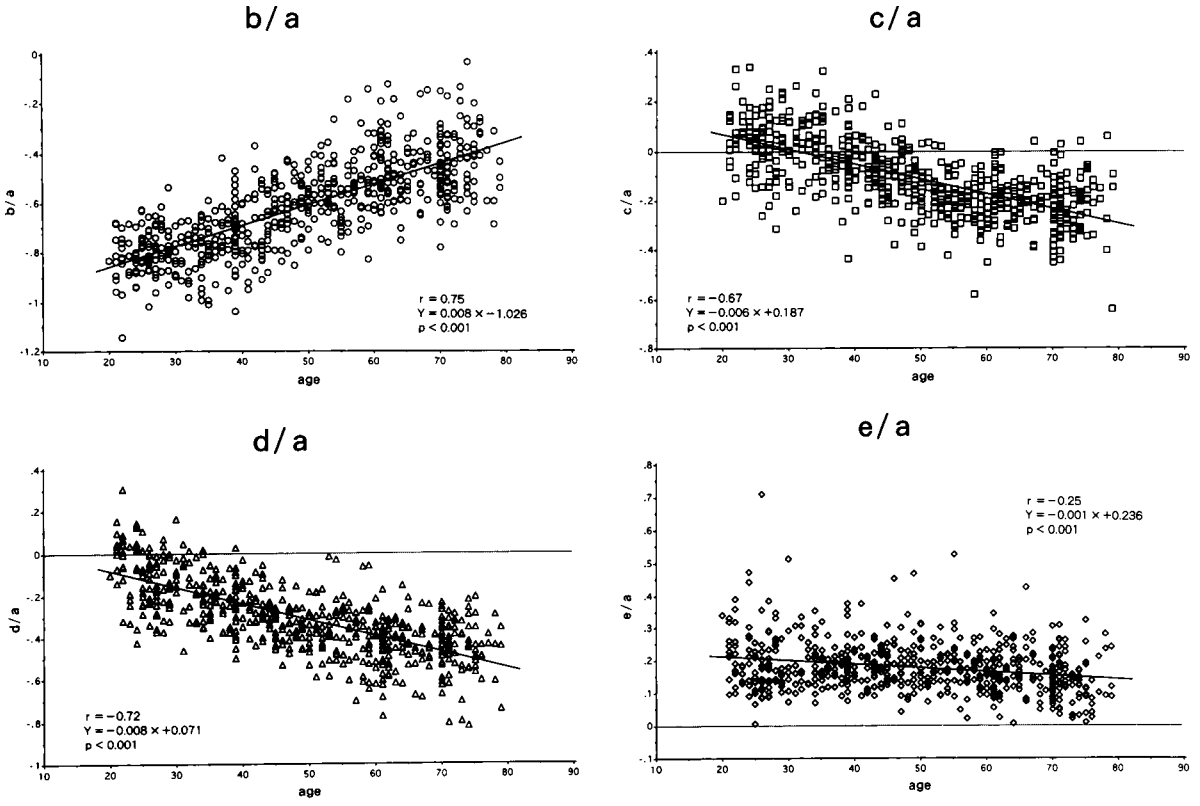

Figure 4. Relationship between each wave ratio and age. The b/a ratio increased with age, and c/a, d/a, and e/a ratios decreased with age.

may reflect the complex anatomy of arterioles in which the timing of wave propagations can vary. Another important issue is that the signal from the device is a function of red cell density, with the relation between blood volume and signal output being more likely a logarithmic function according to the Lambert-Beer equation.[10]

In study 2, SDPTG shows the increase in b/a and decrease in c/a, d/a and e/a ratios. Each wave ratio had significant age-related change. The b wave became shallower in relation to the a wave (increased b/a), and the a and b waves are included in the early systolic component where the effect of reflection wave is less; therefore, the b/a ratio may reflect the

TABLE 2. Demographics of Study 2 Subjects With Results of Student's Unpaired *t* Test

	3rd Decade		4th Decade		5th Decade		6th Decade	
Demographic	M	F	M	F	M	F	M	F
Subjects, n	50	50	50	50	50	50	50	50
Age, y	26.0±2.2	24.4±2.6*	34.7±3.2	35.9±2.5‡	44.7±2.8	44.7±2.7	54.6±2.8	54.5±3.2
Height, m	1.72±0.05	1.57±0.07*	1.72±0.05	1.58±0.04*	1.70±0.06	1.56±0.06*	1.66±0.06	1.56±0.05*
Weight, kg	65±9	48±7*	69±10	53±7	68±8	53±8*	64±9	54±7*
SBP, mm Hg	113±10	98±8*	114±13	102±9*	116±11	104±10*	116±13	108±16†
DBP, mm Hg	61±8	59±5	69±10	63±7*	74±11	67±8*	77±8	70±10*
PP, mm Hg	52±11	40±8*	45±11	39±8†	42±8	37±8*	39±10	38±10
MBP, mm Hg	79±7	72±5*	84±10	76±7*	88±10	79±8*	90±9	83±11*
PR, bpm	70±12	73±10	68±10	73±10‡	68±11	69±11	66±10	69±10
b/a	−0.79±0.08	−0.80±0.11	−0.81±0.11	−0.72±0.11*	−0.72±0.11	−0.60±0.11*	−0.57±0.13	−0.54±0.11
c/a	0.01±0.13	0.07±0.10‡	0.01±0.12	−0.01±0.12	−0.08±0.13	−0.10±0.07	−0.18±0.11	−0.20±0.08
d/a	−0.10±0.13	−0.10±0.16	−0.17±0.15	−0.24±0.09†	−0.29±0.11	−0.30±0.08	−0.38±0.14	−0.36±0.12
e/a	0.21±0.12	0.19±0.08	0.21±0.09	0.17±0.05†	0.22±0.08	0.17±0.05*	0.19±0.08	0.17±0.05
SDPTG AI	−0.91±0.23	−0.95±0.31	−0.86±0.28	−0.64±0.26*	−0.57±0.28	−0.36±0.23*	−0.20±0.30	−0.16±0.27
PTG AI	0.87±0.14	0.88±0.18	0.92±0.14	1.02±0.14*	1.03±0.12	1.12±0.16†	1.16±0.19	1.13±0.13

SBP indicates systolic blood pressure at arm; DBP, diastolic blood pressure; PP, pulse pressure; MBP, mean blood pressure; and PR, pulse rate. Other abbreviations are defined in Table 1.

*$P<0.001$, †$P<0.01$, ‡$P<0.05$ (M vs F in each decade).

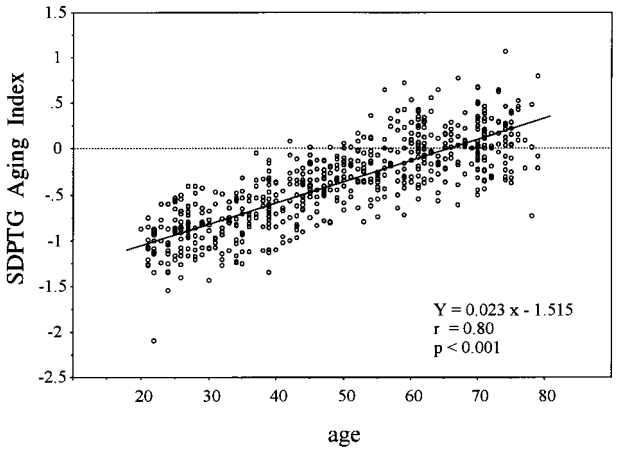

Figure 5. Relationship between SDPTG aging index and age. SDPTG aging index (b-c-d-e/a) (Y) increased with age (X); Y=0.023X−1.515 ($P<0.001$, $r=0.80$).

large arterial stiffness. The b/a ratio was higher in women than in men. The epidemiological study on pulse wave velocity reported by London et al[11] showed that pulse wave velocity in women was higher than that in men. Similar data were reported by Hayward et al[12]: the AI obtained by carotid pulse was also higher in women than in men. In both of these studies, it was assumed that the body structure (ie, relatively short limbs and small diameter of ascending aorta) in women contributed to the results. In our study, women were also shorter than men in height. Age-related changes in the shallower b wave relative to the a wave might be caused by decreasing distensibility of the aorta. On the other hand, deepened d wave relative to a wave is caused mainly by increased reflection wave from the periphery. The reflection wave from the periphery increases with age because of arterial stiffness and early return of wave reflection as a consequence of increased pulse wave velocity. The meaning of the c/a ratio was not understood; c/a ratio usually moves with association with the b or the d wave. The e wave reflects the initial rise of the diastolic wave. The e/a ratio decreased with age and was lower in women than in men. The subjects who had any history of arteriosclerotic disease showed a higher SDPTG aging index. Characteristic arterial waveforms of patients with arteriosclerosis were reported by Lax and Feiburg[13] and Dawber et al.[14] Both reports focused on diminution of the dicrotic notch. Lax and Feiburg also found diminution of the dicrotic notch in the characteristic arterial pulse of young diabetic subjects, which might be related to our findings of an age-related decrease in the e wave.

Limitations

The amplitude of PTG was thought to reflect the volume of blood, but it really reflects the changes in blood volume. The amplitude of PTG reflects blood volume changes from the basal to highest; if the basal blood volume is different, the amplitude of height does not indicate the same amount of blood. Kawarada et al[15] introduced quantitative PTG volume signals in conjunction with calibration counter-pressure to derive elastic modulus curves as a function of transmural pressure. We used the relative ratio of PTG and SDPTG waves for comparison of each subject, which gave us more accurate information on pulse wave contours in relation to ascending aortic pressure wave. The other important issue is frequency response of PTG and SDPTG. We recorded a final frequency response of 10 Hz in SDPTG. This relatively lower frequency of derivative method is convenient for tracing pulse wave contour and eliminating noise, but it is not used for the determination of rate of wave rise such as dP/dt.

TABLE 2. Continued

7th Decade		8th Decade		All Decades	
M	F	M	F	M	F
50	50	50	50	300	300
63.3±2.6	63.5±2.6	73.0±2.8	72.3±2.1	49.4±16.4	49.2±1.5
1.66±0.05	1.53±0.05*	1.63±0.06	1.50±0.05*	1.68±0.06	1.55±0.06*
64±8	54±7*	62±9	50±7*	65±9	52±7*
126±20	119±22	124±17	118±16‡	118±15	108±16*
77±12	74±12	73±7	70±8	72±11	67±10*
49±13	45±14	51±14	47±15	46±12	41±11*
93±14	89±15	90±10	86±9‡	87±11	81±11*
64±9	72±12*	64±11	71±11†	67±11	71±11*
−0.48±0.12	−0.45±0.13	−0.48±0.13	−0.40±0.12*	−0.64±0.18	−0.59±0.18*
−0.20±0.10	−0.20±0.07	−0.20±0.14	−0.24±0.09	−0.10±0.15	−0.12±0.14
−0.44±0.11	−0.43±0.12	−0.45±0.13	−0.46±0.13	−0.30±0.18	−0.32±0.17
0.17±0.07	0.16±0.06	0.16±0.07	0.12±0.07†	0.19±0.09	0.16±0.07*
−0.01±0.27	0.03±0.26	0.00±0.32	0.18±0.29†	−0.43±0.47	−0.32±0.47†
1.20±0.15	1.26±0.24	1.25±0.20	1.27±0.20	1.07±0.21	1.11±0.22‡

The acute effect of vasoconstriction and vasodilation with increase and decrease in blood pressure could be assessed by the d/a ratio. Nichols et al[16] reported an increase in fundamental impedance (impedance at one harmonic), which is one of the potent indicators of left ventricular afterload, associated with increasing pressure augmentation. The negative d/a increased with increases in the AIs of PTG and ascending aortic pressure wave, which indicates that the negative d/a ratio should be a useful index for the evaluation of vasoactive agents, as well as an index of left ventricular afterload. The SDPTG aging index may be useful for evaluation of vascular aging and screening of arteriosclerotic patients.

Acknowledgments

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