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Second Derivative of the Finger Arterial Pressure Waveform: An Insight into Dynamics of the Peripheral Arterial Pressure Pulse

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Summary

The study investigated second derivative of the finger arterial pressure waveform (SDFAP) in 120 healthy middle-aged subjects and in 24 subjects with essential hypertension. SDFAP consists of 5 sequential waves 'a'-'e'. Their normalized magnitudes (B/A, C/A, D/A, and E/A) were calculated. In multivariate regression analysis, B/A and C/A correlated only with age. D/A independently correlated with age, heart period, mean blood pressure (MBP), body height, and gender. E/A independently correlated with age and MBP. D/A and E/A were higher (0.42±0.16 vs. 0.33±0.14, p=0.05 and 0.63±0.15 vs. 0.45±0.14, p<0.001), while B/A and C/A were lower (1.04±0.16 vs. 1.20±0.17, p=0.002 and 0.09±0.15 vs. 0.26±0.20, p=0.001) in hypertensives compared to sex- and age-matched controls. After the adjustment for MBP, heart period, and body mass index (ANCOVA), independent discriminative power was preserved only for indices B/A and C/A (p = 0.001 and 0.021, respectively). Therefore, B/A and C/A provide additional information about simple clinical characteristics and might reflect the structural alteration of the arterial wall in hypertensive subjects.

Key words

Pulse wave analysis • Finapres • Second derivative • Essential hypertension • Aging • Augmentation index

Introduction

Increased arterial stiffness is one of the important markers of arteriosclerosis. Arteries stiffen progressively even in the earliest stages of arteriosclerosis, prior to the first clinical manifestation and anatomical evidence of the disease (Arnett *et al.* 1994). Therefore, it is believed that the measurement of arterial stiffness might provide a useful clinical tool for the assessment of cardiovascular risk. Two surrogates of arterial stiffness, namely aortic pulse wave velocity and aortic augmentation index, were associated with cardiovascular burden in several studies (Nurnberger *et al.* 2002, Asmar *et al.* 2001, Laurent *et al.* 2001, Blacher *et al.* 1999, Bortolotto *et al.* 2000, Hayashi *et al.* 2002).

Alternative method for the assessment of arterial

elastic properties has recently been introduced that was based on the analysis of the second derivative of the finger photoplethysmogram waveform (SDPTG) (Takazawa *et al.* 1998). Although obtained from the periphery of the circulation, SDPTG provides information about both central and peripheral arterial properties. It was shown that some SDPTG quantifiers closely correlated with the ascending aortic augmentation index and distensibility of the common carotid artery (Takazawa *et al.* 1998, Imanaga *et al.* 1998), age and other atherosclerotic risk factors (Takazawa *et al.* 1998, Hashimoto *et al.* 2002, Takada *et al.* 1997, Millasseau *et al.* 2003).

While the finger photoplethysmogram signal closely reflects digital volume pulse (Dillon *et al.* 1941, Lund 1986), the use of the same signal in the Peňáz volume clamping technique enables to measure finger arterial pressure waveform (FAP) (Boehmer 1987). Since the FAP possibly provides additional information on peripheral hemodynamics compared to photoplethysmogram signal alone, we hypothesized that the second derivative of the FAP (SDFAP) might provide comparable or even more valuable indices than SDPTG.

This study has investigated whether SDPTG analytical approach can be applied to FAP. The main objective of the study was to define descriptors of the SDFAP waveform and to explore their relationship to the simple clinical characteristics in a group of healthy normotensive subjects. The second objective of the study was to investigate the discriminative power of SDFAP indices between hypertensive subjects and healthy normotensive controls.

Methods

Subjects

Healthy subjects (n=120) and subjects with moderate to severe essential hypertension (n=24) were recruited from the outpatient department of preventative medicine and hypertension unit at the General University Hospital. Healthy subjects were non-smoking normotensives (office blood pressure <140/90 mm Hg), had no previous history of cardiovascular disease, and none of them was receiving any drugs. Hypertensive subjects had no clinical evidence of cardiovascular disease other than hypertension. All chronic antihypertensive therapy likely to interfere with laboratory investigation of secondary forms of hypertension was discontinued >14 days prior to examination. When necessary, alpha blockers (n=10) and/or calcium channel blockers (n=14) were administered to prevent symptomatic or excessive increase in blood pressure. Secondary forms of hypertension were excluded by laboratory testing and imaging techniques, when appropriate. The study was approved by the local Ethical Committee and all participants gave a signed informed consent.

Pulse wave analysis

All subjects underwent 5-min recording of ECG (single precordial lead) and continuous FAP (Finapres, Ohmeda, Englewood, CO, USA) from the middle phalanx of the middle finger of the right hand. Recordings were performed in the supine position after 20-min resting period. Both signals were sampled at 1000 Hz with 12-bit resolution and stored digitally for off-line analysis. The signal processing was performed semiautomatically by the purpose-made software. QRS complexes were automatically detected using combination of threshold and derivative method. ECG and pressure signals were carefully inspected to confirm all detected QRS complexes, to remove all non-sinus beats, and to exclude incidental noise. All non-distorted FAP waveforms belonging to sinus RR intervals were signal-averaged using R waves of QRS complexes as triggers. SDFAP with respect to time was obtained by double-differentiation of the signal-averaged FAP waveforms with 10-ms time constant. SDFAP waveform consists of ‘a’, ‘b’, and ‘c’ waves in early and ‘d’, ‘e’, and ‘f’ waves in late systole (Fig. 1). Positive waves ‘a’, ‘c’, and ‘e’ express instant accelerations of blood pressure throughout heart period. The reverse applies to the waves ‘b’, ‘d’, and ‘f’, i.e. they represent deceleration waves. By analogy to the SDPTG analytical approach (Takada *et al.* 1997, Takazawa *et al.* 1998, Iketani Y *et al.* 2000, Miyai *et al.* 2001, Hashimoto *et al.* 2002), the magnitude of these waves was measured and normalized to that of the ‘a’ wave, thus obtaining ratios B/A, C/A, D/A, and E/A. As the wave ‘f’ was not regularly expressed, the ratio F/A was not analyzed. For more comprehensible interpretation, ratios B/A and D/A were analyzed in negative values.

Systolic and diastolic blood pressure (SBP, DBP) was measured in the left arm using an automated oscillometric method (Omron HEM-703C, Omron Healthcare, The Netherlands) at the end of the examination. Venous blood sample for biochemical analyses was collected in the morning after overnight

fasting. Plasma total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured by commercially available kits.

The reproducibility of SDFAP indices was assessed in a subgroup of healthy subjects (15 men, aged 27.4±3.7 years). Two measurements within 2±4 days were performed under identical conditions.

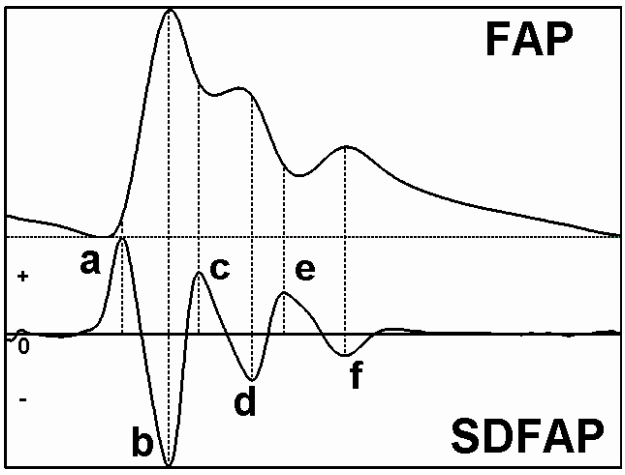

Fig. 1. Typical signal-averaged finger arterial pressure waveform (FAP) and its second derivative (SDFAP). The SDFAP consist of six successive waves 'a'-'f'.

Statistical analysis

Relationship between SDFAP indices and age, body height, body mass index (BMI), brachial SBP, DBP, mean blood pressure (MBP; calculated as DBP + [SBP-DBP]/3), and mean heart period was studied in a control group using least squares univariate regression analysis. All factors, which were significantly univariately associated with SDFAP indices, were investigated using multiple stepwise linear regression analysis. Because of co-linearity of SBP, DBP, and MBP and because SBP is influenced by arterial stiffness, only MBP was entered into the multivariate regression model. Gender was entered as a categorical variable. The strength of correlations was quantified by the correlation coefficients of univariate (r) and multiple (β) regression analyses.

To compare normotensive and hypertensive subjects, the sex- and age-matched subgroup of healthy controls was composed from the cohort of healthy subjects. SDFAP indices in hypertensive and normotensive subjects were compared by the unpaired, two-tailed t-test and by an analysis of covariance (ANCOVA) with all clinical variables, which were found to be significantly different between both groups, entered as covariates.

Reproducibility of SDFAP quantifiers was expressed as the mean within-subject standard deviation (SD_{WS}) in pairs of repeated measurements. For SDFAP quantifiers, which were significantly correlated with age, the SD_{WS} was also expressed in equivalent years of vascular aging as determined from the slope of the regression line between age and SDFAP quantifiers (Millasseau *et al.* 2000). The differences between two repeated measurements were assessed by the paired, two-tailed t-test.

Statistical analysis was performed using Statistica 5.1 for Windows (StatSoft, Inc., Tulsa, USA). $P<0.05$ value was considered as significant.

Results

Characteristics of healthy subjects

The clinical characteristics and SDFAP indices in healthy subjects are shown in Table 1. The mean age of 120 healthy subjects (83 men) was 38.0±10.7 years. The distribution of age was similar among men (range 20-63 years) and women (range 20-60 years). The brachial arterial blood pressures, body height, BMI, and serum triglycerides levels were higher in men than in women. Both genders were comparable in mean heart period, plasma total cholesterol, and HDL-cholesterol levels.

Reproducibility of SDFAP indices

Data are summarized in Table 2. There was no significant bias between the first and the second measurement of SDFAP indices. All native indices and their vascular-age counterparts were highly (and comparably) reproducible.

Clinical factors influencing SDFAP indices

The female subjects had a slightly higher D/A ratio than males ($p = 0.04$), but there were no gender differences in other SDFAP indices. In univariate regression analysis, all SDFAP indices correlated significantly with age (Fig. 2). The correlation coefficients for ratios B/A, C/A, D/A, and E/A were –0.24 ($p = 0.008$), –0.43 ($p<0.001$), 0.55 ($p<0.001$) and 0.68 ($p<0.001$), respectively. B/A and C/A ratios correlated significantly with age only. The D/A ratio also correlated significantly with body height ($r = –0.26$, $p<0.01$), heart period ($r = 0.20$, $p<0.05$), SBP ($r = 0.23$, $p<0.05$), DBP ($r = 0.27$, $p<0.01$), and MBP ($r = 0.28$, $p<0.01$). The E/A ratio also correlated significantly with

BMI ($r = 0.28$, $p<0.01$), SBP ($r = 0.29$, $p<0.01$), DBP ($r = 0.42$, $p<0.001$) and MBP ($r = 0.40$, $p<0.001$). There was no significant relationship between SDFAP indices and serum lipid levels.

The results of stepwise multivariate linear regression analysis are shown in Table 3. Because the B/A and C/A ratios were significantly correlated only with age in univariate regression analysis, the multiple regression analysis was only performed for the D/A and E/A ratios. The D/A ratio independently correlated with age, heart period, MBP, body height, and gender. The model explained 51 % of the observed D/A variability. Independent factors influencing the E/A ratio were age and MBP, which explained 50 % of the observed E/A variability.

Table 1. Clinical characteristics of the healthy subjects

	Males (n = 83)	**Females (n = 37)**	**All (n = 120)**
Age (years)	38.4 ± 10.2	37.0 ± 11.7	38.0 ± 10.7
Body height (cm)	181.7 ± 6.7	167.8 ± 5.8***	177.4 ± 9.1
BMI (kg/m^2)	25.0 ± 3.6	23.1 ± 3.5**	24.4 ± 3.6
SBP (mmHg)	115.6 ± 10.8	108.6 ± 9.4***	113.4 ± 10.9
DBP (mmHg)	70.1 ± 9.4	63.7 ± 8.3***	68.1 ± 9.5
MBP (mmHg)	85.3 ± 9.2	78.7 ± 8.1***	83.2 ± 9.3
Heart period (ms)	983 ± 113	935 ± 125*	969 ± 119
Total cholesterol (mmol/l)	5.34 ± 0.91	4.91 ± 0.88	5.20 ± 0.92
HDL cholesterol (mmol/l)	1.29 ± 0.38	1.47 ± 0.31	1.35 ± 0.37
Triglycerides (mmol/l)	1.31 ± 0.53	0.89 ± 0.44**	1.17 ± 0.53
B/A	1.25 ± 0.18	1.21 ± 0.18	1.24 ± 0.18
C/A	0.32 ± 0.15	0.30 ± 0.16	0.32 ± 0.15
D/A	0.20 ± 0.17	0.26 ± 0.14*	0.22 ± 0.17
E/A	0.38 ± 0.12	0.37 ± 0.15	0.37 ± 0.13

Data are mean ± SD. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; HDL, high-density lipoproteins; B/A, C/A, D/A, and E/A, normalized magnitudes of 'b', 'c', 'd', and 'e' waves of SDFAP, respectively; * P < 0.05, ** P < 0.01, *** P < 0.001, versus males.

Table 2. Reproducibility of SDFAP indices (n = 15)

	Mean*	**SDWS**	**SDWS/age**
B/A	1.26	0.07	1.11
C/A	0.37	0.07	2.11
D/A	0.09	0.06	1.95
E/A	0.30	0.03	1.89

* Mean of two repeated measurements; SDWS, mean within subject standard deviation; SDWS/age, mean within subject standard deviation for indices transformed to equivalent years of vascular aging; B/A, C/A, D/A, and E/A, normalized magnitudes of 'b', 'c', 'd', and 'e' waves of SDFAP, respectively. Differences in SDFAP indices between hypertensive and normotensive subjects

The results are shown in Table 4. In addition to expectedly higher SBP, DBP, and MBP, hypertensive subjects had significantly higher BMI and mean heart rate. Body height was comparable in both groups. Significant differences between both groups were observed for all SDFAP indices. B/A and C/A ratios were significantly lower, while D/A and E/A ratios were significantly higher in hypertensive subjects compared to normotensive ones (Fig. 2). After the adjustment for MBP, heart period, and BMI (ANCOVA), independent discriminative power was preserved only for indices B/A and C/A. Hypertensive subjects in a lower quartile of age (22-43 years) had B/A and C/A ratios (1.11±0.15 and 0.22±0.09, respectively) comparable to normotensive subjects in an upper quartile of age (47-63 years; 1.19±0.19 and 0.24±0.19 for B/A and C/A ratios, respectively). Hypertensive subjects with and without antihypertensive medication had comparable clinical characteristics and SDFAP descriptors (data not shown).

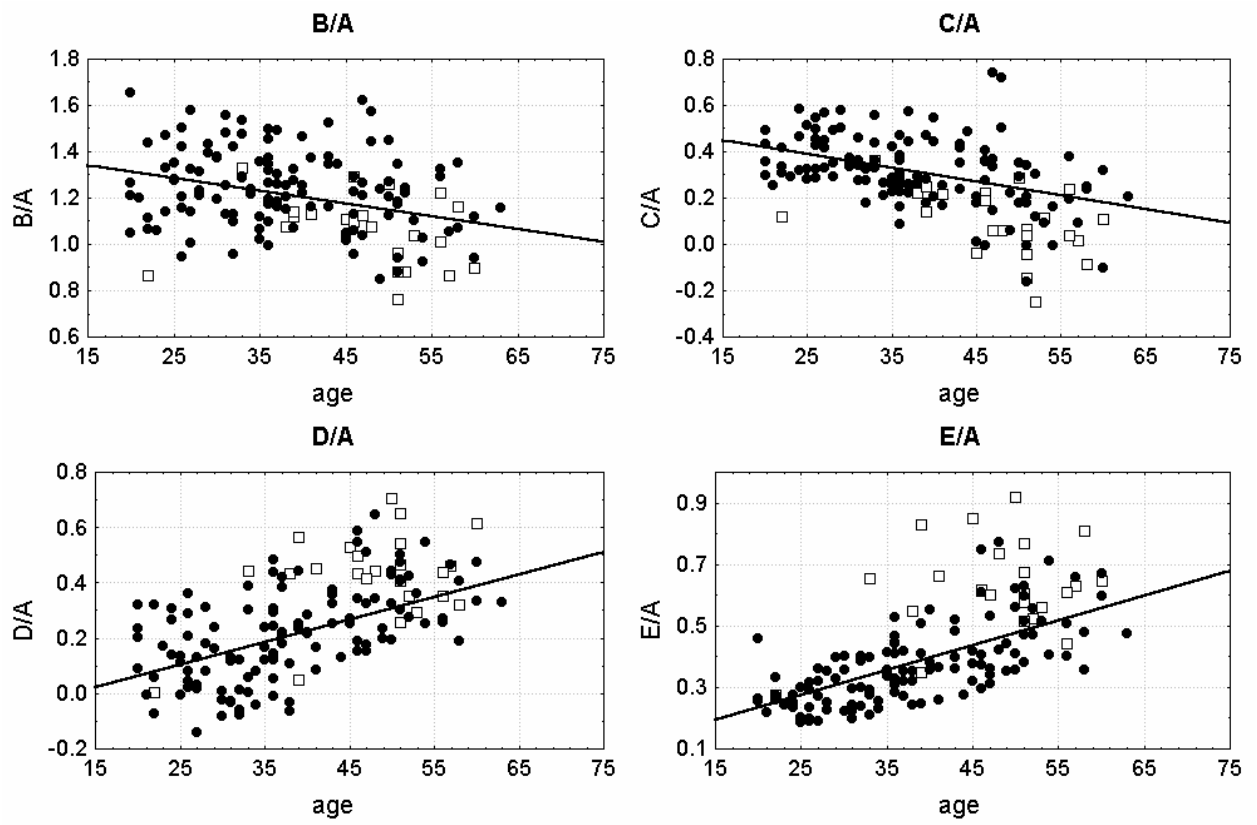

Fig. 2. Correlation between the indices of second derivative of finger arterial pressure (SDFAP) and age. B/A, C/A, D/A, and E/A, normalized magnitudes of 'b', 'c', 'd', and 'e' waves of SDFAP, respectively; closed circles, normotensive subjects; open squares, hypertensive patients. Regression lines are plotted for normotensive subjects. Corresponding regression equations are as follows: B/A = -0.0038.age + 1.39, C/A = -0.0060.age + 0.54, D/A = 0.0085.age – 0.10, and E/A = 0.0081.age + 0.64.

Table 3. Multiple stepwise linear regression analysis of second derivative of the finger arterial pressure indices (n=120)

		β	SE	t	P
D/A	*age (years)*	0.421	0.073	5.76	< 0.001
	heart period (ms)	0.372	0.073	5.11	< 0.001
	MBP (mm Hg)	0.342	0.079	4.31	< 0.001
	height (cm)	-0.240	0.102	-2.36	0.020
	gender (f = 0, m = 1)	-0.235	0.101	-2.33	0.022
E/A	*age (years)*	0.660	0.076	8.71	< 0.001
	MBP (mm Hg)	0.219	0.074	2.96	0.004

D/A and E/A, normalized magnitudes of 'd' and 'e' waves of SDFAP, respectively; D/A, model R2 = 0.51, F = 22.8, model probability P<0.0001; E/A, model R2= 0.50, F = 38.1, P < 0.0001; The coefficient β provides a measure of the relative strength of the association independent of the units of measurement. Parameters listed in descending value of β. MBP, mean blood pressure; SE, standard error.

Discussion

The second derivative method has recently been used for the analysis of the finger photoplethysmogram waveform. This is the first study investigating this approach for the analysis of finger arterial pressure contour. We found that SDFAP, as well as SDPTG, consisted of 5 consecutive waves. We demonstrated that SDFAP indices were highly reproducible and independently discriminated between hypertensive patients and healthy normotensive controls.

Although the physiological explanation of the SDFAP ratios is not known, several suggestions can be made. Primarily, an analogy with the SDPTG indices can

be drawn. Age-related changes of the B/A ratio are characterized by shallowing of the 'b' wave in relation to the 'a' wave (Takazawa *et al.* 1998). Because the early systolic 'a' and 'b' waves are not influenced by the reflection wave, it was suggested that the B/A ratio might reflect the large arterial stiffness. Indeed, the B/A ratio correlated significantly with the distensibility of the common carotid artery and was also proportional to the intima-media thickness (Imanaga *et al.* 1998). On the contrary, 'd' wave occurs in the late systolic period and D/A ratio was shown to be closely correlated with aortic augmentation index (Takazawa *et al.* 1998). Therefore, it is believed that D/A ratio is a surrogate of the intensity of pulse wave reflection (Takazawa *et al.* 1998, Iketani T *et al.* 2000).

Table 4. Differences between hypertensives and healthy controls, matched for age and gender

	Hypertensives	**Normotensives**	**t-test (p-value)**	**ANCOVA (p-value)**
Age (years)	47.5 ± 8.8	47.5 ± 8.8	-	-
Gender (M/F)	15/9	15/9	-	-
Height (cm)	175.2 ± 8.7	175.8 ± 10.5	0.84	0.45
BMI (kg/m^2)	31.0 ± 4.0	24.7 ± 2.5	<0.001	-
SBP (mm Hg)	158.7 ± 21.3	112.1 ± 8.7	<0.001	0.18
DBP (mm Hg)	94.9 ± 13.7	67.2 ± 8.7	<0.001	0.18
MBP (mm Hg)	116.1 ± 15.3	82.2 ± 8.0	<0.001	-
Heart period (ms)	899 ± 125	976 ± 96	0.021	-
B/A	1.04 ± 0.16	1.20 ± 0.17	0.002	0.001
C/A	0.09 ± 0.15	0.26 ± 0.20	0.001	0.021
D/A	0.42 ± 0.16	0.33 ± 0.14	0.048	0.25
E/A	0.63 ± 0.15	0.45 ± 0.14	<0.001	0.43

Data are means ± S.D. Statistical comparison was performed by unpaired t-test and by analysis of covariance (ANCOVA), with BMI, MBP, and heart period as covariates. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; B/A, C/A, D/A, and E/A, normalized magnitudes of 'b', 'c', 'd', and 'e' waves of SDFAP, respectively.

Since FAP is related to the digital volume pulse by a simple linear relation that remains constant across a wide age range and that is not influenced by hypertension or nitroglycerine administration (Millasseau *et al.* 2000), it might be hypothesized that SDFAP and SDPTG indices can be interpreted in a similar way. If this hypothesis is true, both SDFAP and SDPTG indices should exhibit similar relationship to simple clinical characteristics. Unfortunately, there were several discrepancies between our observations and the previous reports on SDPTG. In our study, the strongest and the weakest correlation with age was observed in the E/A and B/A ratios, respectively. This observation is just opposite to that found for SDPTG indices (Takazawa *et al.* 1998). This study also found an inverse correlation between E/A ratio and age, while it was positive in our study. Women had higher D/A ratio than men in our study. This is consistent with the finding of another study that investigated SDPTG indices in a large adolescent population (Miyai *et al.* 2001). In contrast, no gender difference in D/A ratio, but higher B/A ratio in women was reported in an adult Japanese population (Takazawa *et al.* 1998). Thus, the SDFAP approach provides, at least in part, different information than SDPTG. Further direct comparative studies are needed to clarify the differences between SDPTG and SDFAP indices.

SDFAP quantifiers of the peripheral arterial pressure dynamics in an early and late systolic period have different relationship to simple clinical variables. The correlations between age and descriptors of an early (B/A, C/A) and late (D/A, E/A) systolic phase were negative and positive, respectively, and the strength of this correlation increased gradually from early to late systole. While B/A and C/A ratios were related significantly only to age, D/A and E/A ratios were independently associated with age and MBP. The D/A ratio was also independently related to the heart period, body height, and gender. It is noteworthy that all clinical

determinants of D/A ratio were identical to those, influencing aortic augmentation index (Yasmin and Brown 1999). Consequently, the physiological background of both D/A ratio and aortic augmentation index may be the same and D/A ratio might serve as a surrogate of aortic augmentation index. In this respect, the inverse correlation of D/A ratio with body height can be explained by earlier reflection of pressure wave in shorter subjects, resulting in increased augmentation of the primary systolic pulse (Smulyan *et al.* 1998). The presumable relationship between D/A and aortic augmentation indices is also consistent with the finding that height was the most powerful determinant of D/A ratio during the growth period in an adolescent population (Miyai *et al.* 2001). Similarly, higher values of D/A ratio in women can be attributed to smaller body stature that is associated with reflection sites closer to heart, smaller arterial diameters, higher pulse wave velocity, and earlier return of reflected pressure waves to central aorta (Smulyan *et al.* 1998, Yasmin and Brown 1999, Gatzka *et al.* 2001). Finally, positive correlation between D/A ratio and the heart period can be explained by a prolongation of ejection period at slower heart rate, which shifts the reflected wave into systole and results in increase of pressure augmentation (Wilkinson *et al.* 2000).

We did not find any correlation between SDFAP descriptors and serum lipid levels. However, this observation was made within a rather narrow range of serum lipid levels and, consequently, this does not necessarily mean that hyperlipidemia has no effect on SDFAP indices.

As expected, essential hypertensives and matched normotensive controls differed significantly in all descriptors of SDFAP. Our study clearly demonstrated that aging and hypertension had concurrent impact on the peripheral blood pressure waveform. Interestingly, their effect on the dynamics of blood pressure in a period of early and late systole was just opposite. Early systolic SDFAP quantifiers were significantly higher in younger or normotensive subjects than in the elderly or hypertensives. The reverse was true for SDFAP descriptors in a late systolic period.

Despite profound differences between hypertensive individuals and matched normotensive subjects in all SDFAP descriptors, after adjustment for confounding variables, the independent discriminative power was preserved only for B/A and C/A ratios. Being independent of blood pressure, alteration of these descriptors might reflect structural vessel properties rather than raised blood pressure alone and might be useful for the assessment of accelerated vascular aging in subjects with essential hypertension. Conversely, significantly higher late systolic descriptors of SDFAP in hypertensive subjects can be almost entirely attributed to the elevated blood pressure and do not convey any independent information.

SDFAP is a non-invasive, reproducible, operator-independent, and easy-to-perform method, which does not require any special training. It offers an accurate recognition of the inflection points on the original waveform and, hence, enables to analyze delicate morphologic features. Nevertheless, several relevant issues need to be addressed before introducing the SDFAP method as a research or clinical tool. First, SDFAP and SDPTG indices should be compared directly. Second, it is not known whether the derivative approach can supplement anything to the already validated techniques of pulse wave analysis based on simple wave magnitudes. In particular, D/A ratio should be compared with the aortic augmentation index obtained by the use of radial artery applanation tonometry, which represents an increasingly used non-invasive and reproducible technique (Wilkinson *et al.* 1998, Filipovský *et al.* 2000). Third, the effect of vasoactive agents on SDFAP has to be investigated.

There are some limitations of the present study. First, continuous measurement of arterial pressure by Penaz volume clamping method (Penaz 1973) is significantly influenced by local effects that might considerably distort the pressure waveform (Imholz *et al.* 1998, Avolio 2002). These effects must be taken into account when relating FAP contour to central large artery properties. As our experiments were performed under strict procedural standards, we believe that this unavoidable source of measurement error was minimized. Second, it should be emphasized that the comparison of SDFAP and SDPTG was made indirectly using previously published data. While we studied central European population of healthy normotensive subjects, the SDPTG indices were studied in an adult Japanese population with 20 % hypertensive subjects (Takazawa *et al.* 1998) and in a Japanese population of adolescents (Miyai *et al.* 2001). These differences might account for observed dissimilarities between SDFAP and SDPTG descriptors in terms of their relation to clinical variables. Finally, a relatively small number of hypertensive subjects were involved. Larger sample of subjects would

increase the statistical power of the study and consequently, might reveal that also D/A and E/A ratios are significant and independent discriminators between normotensive and hypertensive subjects.

In conclusion, both aging and hypertension decrease peripheral arterial pressure dynamics in a period of early systole and increase it in a period of late systole. Early systolic indices (B/A and C/A ratios) discriminate independently between subjects with essential hypertension and healthy controls. They provide additional information on simple clinical characteristics and might reflect the structural alteration of arterial wall in subjects with essential hypertension. On the other hand, late systolic indices (D/A and E/A ratios), which predominantly reflect pressure augmentation, do not convey independent information.

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