

A Population-based Study of Arterial Stiffness Index in Relation to Cardiovascular Risk Factors

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We investigated the relation of arterial stiffness, considered an independent predictor of cardiovascular events, to cardiovascular risk factors in a population-based study of 1023 subjects. An Arterial Stiffness Index (ASI) was developed to evaluate arterial stiffness based on an analysis of the pulse wave amplitude pattern acquired from measurements of brachial blood pressure. In control subjects ($n = 266$) without any major risk factors, the ASI was 46 ± 11 , and increased with age ($r = 0.346$). The ASI was significantly higher in women ranging from 50 to 54 years of age than in age-matched men. The ASI rose in correlation with the number of risk factors. Subjects with two risk factors showed a significantly higher ASI than those without any risk factors (54 ± 26 vs. 46 ± 11). The ASI was significantly increased in diabetic subjects with hypertension in comparison to those without hypertension. Furthermore, hyperlipidemic subjects with hypertension showed significantly higher values than those without hypertension. ASI could be a useful predictor of cardiovascular events in hypertensive subjects with multiple risk factors. *J Atheroscler Thromb*, 2005; 12: 175–180.

Key words: Oscillometry, Aging, Gender, Hypertension

Introduction

Most epidemiologic studies have shown that high systolic blood pressure (SBP) is a risk factor for stroke and coronary heart disease (1–3). Recent studies have determined brachial pulse pressure (PP) as a strong determinant for coronary heart disease (4, 5), stroke (6), and cardiovascular events in the general population (7–10). Increased brachial PP is considered to augment cardiovascular morbidity and mortality, since elevated SBP raises left ventricular afterload while decreased diastolic blood pressure (DBP) reduces coronary perfusion (3, 4, 8–10). A major clinical determinant of PP is arterial stiffness, which is an arteriosclerotic change that progresses

under the influence of several risk factors (4, 11–14). Arterial stiffness commonly is assessed by measuring the aortic pulse wave velocity (PWV) between the carotid and femoral arteries (6, 7, 15), which can be used to evaluate the elastic properties of the aorta. The brachial-femoral PWV, another useful indicator (15, 16), requires less measurement time than aortic PWV but cannot be applied to patients with arteriosclerosis obliterans. Recently several noninvasive, reproducible methods have been developed for measuring brachial artery stiffness. The arterial stiffness index (ASI), a useful measure of brachial artery stiffness, is obtained simultaneously with the measurement of brachial arterial blood pressure (15, 17, 18) by computer-assisted oscillometry at the arm. ASI has been reported to show a good correlation with pulse wave velocity between the carotid and femoral arteries, and has been considered valuable for evaluating arterial stiffness in hypertensive patients (15). However, its relation to coronary risk factors has not been investigated in a large population. The method for evaluating ASI is simple

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Received August 24, 2004.

Accepted for publication February 4, 2005.

and convenient, requiring only a few minutes for a measurement with the subject in a sitting position. ASI enables repeated measurements of arterial stiffness in large populations. We investigated factors affecting ASI in healthy subjects, as well as correlations of ASI with cardiovascular risk factors in a general population.

Materials and Methods

Subjects

After obtaining informed consent, we studied 1023 subjects who were undergoing medical checkups in the Health and Medical Center. Ages ranged from 22 to 85 years (mean \pm SD, 52 \pm 11). Subjects were classified into five groups based on their medical history (Table 1). Subjects without disease were assigned to the control group, while subjects with any disease were placed in the disease group. Hyperlipidemia was defined as total serum cholesterol (TC) > 220 mg/dl, and/or low-density lipoprotein cholesterol (LDL-C) > 140 mg/dl, and/or triglyceride (TG) > 150 mg/dl. Diabetes mellitus was defined as fasting blood sugar (FBS) concentrations exceeding 110 mg/dl and/or hemoglobin A1c (HbA1c) values above 5.9%. Hypertension was defined as SBP exceeding 140 mm Hg and/or DBP exceeding 90 mm Hg. Smoking was defined as regular cigarette smoking.

The 266 subjects without any of the four major risk factors (hyperlipidemia, diabetes mellitus, hypertension, and smoking) were assigned to the control group (109 men, 157 women; 22 to 84 years; mean age, 49 \pm 12 years). The 757 subjects (522 men, 235 women; 23 to 85 years; mean age, 53 \pm 11 years) with one or more risk factors were assigned to the disease group.

Measurement of arterial stiffness index

An Arterial stiffness index (ASI) was measured in all subjects using CardioVision (MS-2000; IMDP, Las Vegas, NV, USA), a device that utilizes a new method for evaluating arterial stiffness while measuring blood pressure. This computer-assisted oscillometric method enables the measurement of ASI based on the pulse wave amplitude pattern acquired from a brachial blood pressure measurement (17).

The device occludes the brachial artery by increasing cuff pressure to a point above SBP. After occluding the artery, the cuff is slowly deflated automatically, and a pressure sensor attached to the blood pressure cuff measures small volumetric changes in the subject's arm, resulting in increases in the amplitude of the pulse waves, as the volume in the brachial artery slowly increases. The amplitude of these volumetric changes slowly increases, becoming maximal when the cuff pressure is near the mean arterial pressure. At this point the elastic properties of the artery also are maximal. After the pulse wave peaks, the amplitudes of volume variation decrease as the cuff pressure returns to zero and the brachial artery is fully opened.

In calculating the ASI, the flat upper part of the pulse wave pattern was defined as the region between the highest point (100%) and 80% of the amplitude. The ASI then was calculated as the pressure range (mm Hg \times 10) of the oscillometric curve corresponding with the length of the upper 5% of this flat area (Fig. 1). Arrhythmia influences the pulse wave pattern, so measurements in the presence of premature beats or atrial fibrillation were excluded.

The ASI measurement was repeated five times per sub-

Table 1. Background data for study subjects

		Number of risk factors				
		Normal (<i>n</i> = 266)	1 (<i>n</i> = 402)	2 (<i>n</i> = 260)	3 (<i>n</i> = 80)	4 (<i>n</i> = 15)
Age		49 \pm 12	52 \pm 11	54 \pm 10	56 \pm 9	53 \pm 9
SBP	[mm Hg]	115 \pm 12	123 \pm 14	131 \pm 17	144 \pm 15	142 \pm 14
DBP	[mm Hg]	73 \pm 8	77 \pm 10	82 \pm 11	90 \pm 11	90 \pm 9
PP	[mm Hg]	43 \pm 7	45 \pm 9	49 \pm 11	54 \pm 12	52 \pm 16
T-Cho	[mg/dl]	184 \pm 22	209 \pm 34	225 \pm 37	224 \pm 32	218 \pm 33
LDL-C	[mg/dl]	106 \pm 20	130 \pm 30	140 \pm 34	141 \pm 30	133 \pm 43
HDL-C	[mg/dl]	63 \pm 12	60 \pm 16	56 \pm 16	52 \pm 14	49 \pm 14
TG	[mg/dl]	71 \pm 27	106 \pm 60	149 \pm 91	167 \pm 102	232 \pm 171
FBS	[mg/dl]	93 \pm 7	96 \pm 16	109 \pm 44	136 \pm 58	140 \pm 37
HbA1c	[%]	5.0 \pm 0.3	5.3 \pm 0.8	5.7 \pm 1.5	6.3 \pm 1.6	6.6 \pm 1.2
BMI	[kg/m ²]	22.5 \pm 3.2	23.4 \pm 3.1	24.0 \pm 2.8	25.7 \pm 3.7	24.7 \pm 3.2

SBP: systolic blood pressure, DBP: diastolic blood pressure, PP: pulse pressure, T-Cho: total cholesterol, LDL-C: LDL cholesterol, HDL-C: HDL cholesterol, TG: triglyceride, FBS: fasting blood sugar, BMI: body mass index.

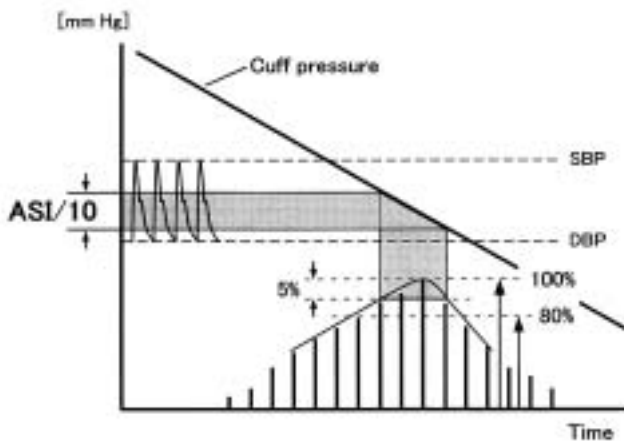


Fig. 1. The relationship between cuff pressure during actual blood pressure measurements and the pulse wave pattern. An Arterial Stiffness Index (ASI) was calculated based on computer-assisted oscillometry.

ject. After excluding the maximum and minimum values from these five measurements, the mean of the remaining three values was taken as representative for the subject.

Statistical analysis

Data are expressed as the mean \pm 1 standard deviation (SD). When comparing means between two groups and of multiple groups, we used an unpaired *t*-test and Bonferroni/Dunn test, respectively. Simple regression analysis was used to assess the correlation of ASI with age or blood pressure. In all analyses, a *p* value below 0.05 was considered significant.

Results

Influence of aging and gender on ASI

The ASI in the control group was 46 ± 11 . It gradually increased with age. The correlation coefficient of the ASI for age was 0.346 ($p < 0.0001$; Fig. 2). The ASI was significantly higher in women than in men (48 ± 12 vs. 43 ± 8 ; $p < 0.01$). To determine whether the gender difference is affected by aging, the group was divided into subgroups of 5-year intervals. The greatest gender difference in ASI was observed between the ages of 50–54 (42 ± 6 in men vs. 49 ± 9 in women, $p < 0.01$; Fig. 3).

Influence of blood pressure on ASI

In the control group, a significant positive correlation was noted between age and SBP ($y = 0.361x + 97.74$, $r = 0.372$, $p < 0.0001$), and between age and DBP ($y = 0.163x + 64.63$, $r = 0.231$, $p < 0.0001$). To adjust for aging and

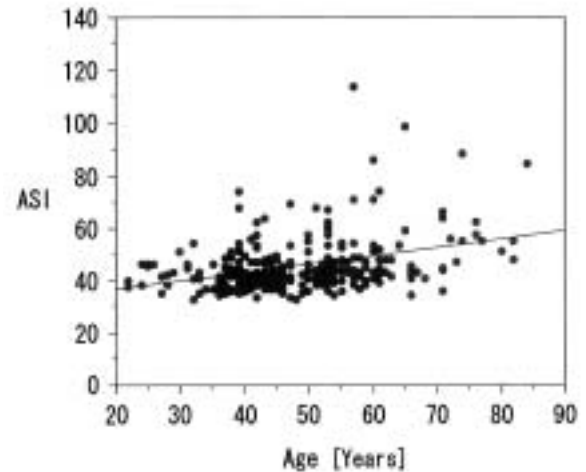


Fig. 2. A significant correlation between the Arterial Stiffness Index (ASI) and aging is shown. The linear regression equation and the Pearson correlation coefficients were $y = 0.31x + 30.709$ and $r = 0.346$ ($p < 0.0001$).

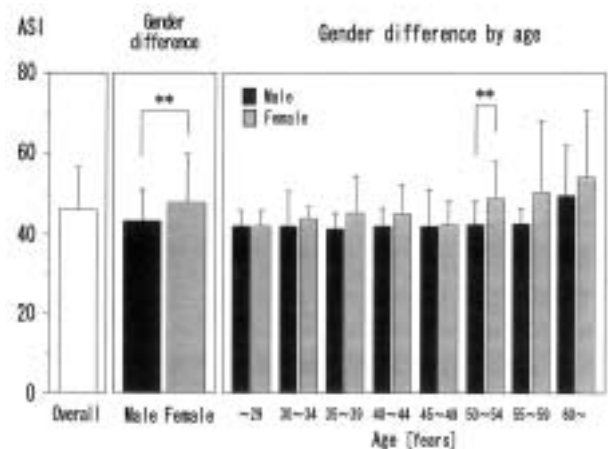


Fig. 3. Gender differences overall and determined within 5-year subgroups from the third to the fifth decade. **: $p < 0.01$.

gender, relationships between blood pressure and the ASI were analyzed in the subgroup of control subjects (less than 50 years of age). No significant correlations were found between either ASI and SBP or ASI and DBP. In contrast, a positive correlation was indicated between PP and ASI ($r = 0.174$, $p < 0.05$; Fig. 4).

Influence of risk factors on ASI

The ASI was significantly higher in the disease group ($n = 757$) than in the control group (51 ± 23 vs. 46 ± 11 , $p < 0.05$). In the 402 subjects with one risk factor, the ASI was 49 ± 19 , which was not significantly different from that in the control group (Fig. 5). However, the 260 subjects with two risk factors had a significantly higher

ASI than control subjects (54 ± 26 vs. 46 ± 11 , $p < 0.01$; Fig. 5). Subjects with three risk factors had a significantly higher ASI than those in the control group (64 ± 38 vs. 46 ± 11 , $p < 0.01$; Fig. 5). Subjects with four risk factors had also a significantly higher ASI than the controls (64 ± 52 vs. 46 ± 11 , $p < 0.01$; Fig. 5).

Subjects with both hyperlipidemia and hypertension had a significantly higher ASI than control subjects (67 ± 35 vs. 46 ± 11 , $p < 0.01$; Fig. 6). While an increase in the ASI was not indicated in diabetic subjects with hyperlipidemia, an increase was indicated in diabetic subjects

with hypertension (64 ± 37 , vs. 46 ± 11 ; $p < 0.05$; Fig. 6).

Among subjects with three risk factors, hyperlipidemic patients with hypertension and diabetes mellitus had significantly higher ASI values than control subjects (69 ± 41 vs. 46 ± 11 , $p < 0.01$; Fig. 7). An increased ASI was also indicated in hyperlipidemic subjects with hypertension and cigarette smoking (59 ± 29 vs. 46 ± 11 , $p < 0.05$; Fig. 7). However, in hyperlipidemic subjects without hypertension, an increased ASI was not indicated (Fig. 7).

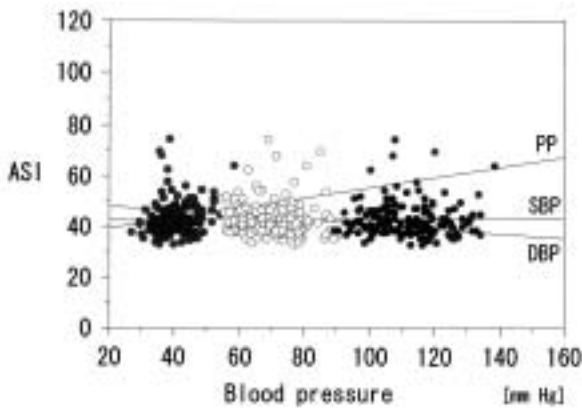


Fig. 4. Relationship between blood pressure and the Arterial Stiffness Index (ASI) in normal subjects under 50 years old. No correlation was evident between the ASI and the systolic blood pressure (SBP; closed circles, $r = 0.007$) or diastolic blood pressure (DBP; open circles, $r = 0.133$). A significant correlation was found between the ASI and pulse pressure (PP; shaded circles, $y = 0.201x + 34.819$, $r = 0.174$, $p < 0.05$).

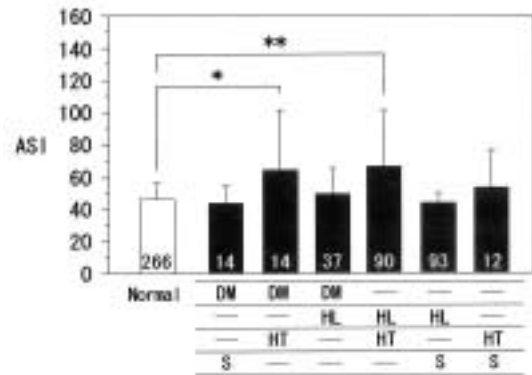


Fig. 6. The Arterial Stiffness Index (ASI) in subjects with two risk factors. Those with both diabetes mellitus (DM) and hypertension (HT; $n = 14$) had a higher ASI than subjects with no risk factors ($n = 262$). The combination of hyperlipidemia (HL) with HT also increased the ASI significantly compared to normal subjects. The addition of cigarette smoking (S) to other risk factors did not increase the ASI. Bars represent the mean \pm 1 SD. *: $p < 0.05$, **: $p < 0.01$.

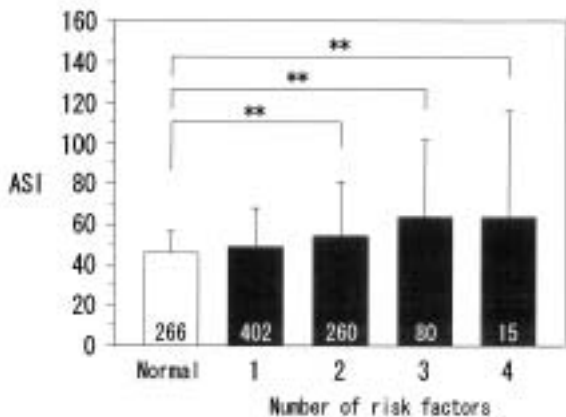


Fig. 5. Effects of accumulation of risk factors on the Arterial Stiffness Index (ASI), which increased significantly as risk factors accumulated. **: $p < 0.01$.

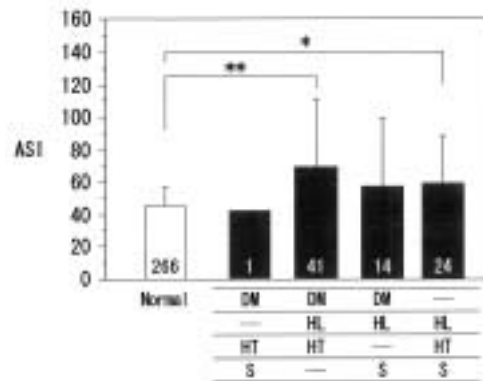


Fig. 7. The Arterial Stiffness Index (ASI) in subjects with multiple risk factors. Among subgroups with three risk factors, groups with hyperlipidemia (HL) plus hypertension (HT) plus either diabetes mellitus (DM; $n = 41$) or cigarette smoking (S; $n = 24$) had a higher ASI than the normal group with none of these risk factors ($n = 266$). Bars represent the mean \pm 1 SD. *: $p < 0.05$, **: $p < 0.01$.

Discussion

The normal range of the ASI commonly accepted in North America and Europe is a value below 70 (18). The mean value \pm 1 SD in healthy Japanese subjects ranging from 22 to 84 years of age was found to be 46 ± 11 . To our knowledge, this is the first paper to report a normal range of the ASI in Japanese subjects. In healthy Japanese subjects, the ASI was positively correlated with age. The data suggest that ASI is a useful marker with which to evaluate aging-related arterial stiffness in subjects without risk factors.

The risk of cardiovascular disease is well known to increase in postmenopausal women (19), and epidemiologic evidence has suggested that estrogen replacement therapy may reduce cardiovascular risk by improving the lipid profile (20, 21). Recently, estrogen supplementation has been reported to reduce the age-associated increase in arterial stiffness as determined based on pulse wave velocity (PWV) (22–24), systemic arterial compliance (22, 25), or the augmentation index (25). The female subjects in the control group in a present study had a significantly higher ASI than the male subjects, particularly between the ages of 50–54. The average age of menopause in Japan is 50 years. The gender difference in ASI may partly due to an estrogen deficiency near menopause. Measuring ASI in middle-aged women may be important in assessing menopause-related arterial stiffness.

Brachial pulse pressure, a surrogate index of arterial stiffness, has been identified as an independent predictor of future cardiovascular events (4, 8–10, 26), and increased arterial stiffness has been associated with a poor cardiovascular prognosis (5–7). However, the influence of cardiovascular risk factors on arterial stiffness had not been determined in a population-based sample. In our population-based study of 1023 subjects, we found that arterial stiffness increased in correlation with the number of risk factors. Hypertensive subjects with hyperlipidemia or diabetes mellitus had a greatly increased ASI. In subjects with three or more risk factors, hypertension also contributed to an increased ASI. These results indicate that high blood pressure is a leading contributor to arterial stiffness.

The present study suggests that ASI could be a useful predictor of future cardiovascular events in hypertensive patients with metabolic disorders.

Acknowledgments: We thank Mr. Toshiaki Takeichi for excellent technical assistance, and Professor Minoru Yamamoto for important advice concerning this study.

References

- (1) Vogel RA and Benitez RM: Noninvasive assessment of cardiovascular risk: From Framingham to the fu-

- ture. *Rev Cardiovasc Med*, 1: 34–42, 2000
- (2) Benitez RM and Vogel RA: Assessment of subclinical atherosclerosis and cardiovascular risk. *Clin Cardiol*, 24: 642–650, 2001
- (3) White WB: Systolic versus diastolic blood pressure versus pulse pressure. *Curr Cardiol Rep*, 4: 463–467, 2002
- (4) Safar ME, Levy BI, and Struijker-Boudier H: Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. *Circulation*, 107: 2864–2869, 2003
- (5) Weber T, Auer J, O'Rourke MF, Kvas E, Lassnig E, Berent R, and Eber B: Arterial stiffness, wave reflections, and the risk of coronary artery disease. *Circulation*, 109: 184–189, 2004
- (6) Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, and Benetos A: Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension*, 37: 1236–1241, 2001
- (7) Amar J, Ruidavets JB, Chamontin B, Drouet L, and Ferrieres J: Arterial stiffness and cardiovascular risk factors in a population-based study. *J Hypertens*, 19: 381–387, 2001
- (8) Darne B, Girerd X, Safar M, Cambien F, and Guize L: Pulsatile versus steady component of blood pressure: a cross-sectional analysis and a prospective analysis on cardiovascular mortality. *Hypertension*, 13: 392–400, 1989
- (9) Madhavan S, Ooi WL, Cohen H, and Alderman MH: Relation of pulse pressure and blood pressure reduction to the incidence of myocardial infarction. *Hypertension*, 23: 395–401, 1994
- (10) Benetos A, Rudnichi A, Safar M, and Guize L: Pulse pressure and cardiovascular mortality in normotensive and hypertensive subjects. *Hypertension*, 32: 560–564, 1998
- (11) Schram MT, Henry RM, van Dijk RA, Kostense PJ, Dekker JM, Nijpels G, Heine RJ, Bouter LM, Westerhof N, and Stehouwer CD: Increased central artery stiffness in impaired glucose metabolism and type 2 diabetes: The Hoorn Study. *Hypertension*, 43: 176–181, 2004
- (12) Mahmud A and Feely J: Effect of smoking on arterial stiffness and pulse pressure amplification. *Hypertension*, 41: 183–187, 2003
- (13) Mackey RH, Sutton-Tyrrell K, Vaitkevicius PV, Sakkinen PA, Lyles MF, Spurgeon HA, Lakatta EG, and Kuller LH: Correlates of aortic stiffness in elderly individuals: a subgroup of the Cardiovascular Health Study. *Am J Hypertens*, 15: 16–23, 2002
- (14) Benetos A, Adamopoulos C, Bureau JM, Temmar M, Labat C, Bean K, Thomas F, Pannier B, Asmar R, Zureik M, Safar M, and Guize L: Determinants of accelerated progression of arterial stiffness in nor-

- motensive subjects and in treated hypertensive subjects over a 6-year period. *Circulation*. 105: 1202–1207, 2002
- (15) Kaibe M, Ohishi M, Komai N, Ito N, Katsuya T, Rakugi H, and Ogihara T: Arterial stiffness index: A new evaluation for arterial stiffness in elderly patients with essential hypertension. *Geriatrics and Gerontology International*, 2: 199–205, 2002
- (16) Yokoyama H, Shoji T, Kimoto E, Shinohara K, Tanaka S, Koyama H, Emoto M, and Nishizawa Y: Pulse wave velocity in lower-limb arteries among diabetic patients with peripheral arterial disease. *J Atheroscler Thromb*, 10: 253–258, 2003
- (17) Shimazu H, Kawarada A, Ito H, and Yamakoshi K: Electric impedance cuff for the indirect measurement of blood pressure and volume elastic modulus in human limb and finger arteries. *Med Biol Eng Comput*, 27: 477–483, 1989
- (18) Sharma GK, Prisant LM, Oracion A, Jupin D, and Gudapati SB: Assessment of immediate test repeatability of arterial stiffness index measured by CardioVision(r) MS-2000. *Am J Hypertens*, 15 (4 Pt 2): 64A, 2002
- (19) Colditz GA, Willett WC, Stampfer MJ, Rosner B, Speizer FE, and Hennekens CH: Menopause and the risk of coronary heart disease in women. *N Engl J Med*, 316: 1105–1110, 1987
- (20) Stampfer MJ, Colditz GA, Willett WC, Manson JE, Rosner B, Speizer FE, and Hennekens CH: Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the Nurses' Health Study. *N Engl J Med*, 325: 756–762, 1991
- (21) Sack MN, Rader DJ, and Cannon RO: Oestrogen and inhibition of oxidation of low-density lipoproteins in postmenopausal women. *Lancet*, 343: 269–270, 1994
- (22) Ahimastos AA, Formosa M, Dart AM, and Kingwell BA: Gender differences in large artery stiffness pre- and post puberty. *J Clin Endocrinol Metab*, 88: 5375–5380, 2003
- (23) Miura S, Tanaka E, Mori A, Toya M, Takahashi K, Nakahara K, Ohmichi M, and Kurachi H: Hormone replacement therapy improves arterial stiffness in normotensive postmenopausal women. *Maturitas*, 45: 293–298, 2003
- (24) Scuteri A, Lakatta EG, Bos AJ, and Fleg JL: Effect of estrogen and progestin replacement on arterial stiffness indices in postmenopausal women. *Aging Clin Exp Res*, 13: 122–130, 2001
- (25) Berry KL, Cameron JD, Dart AM, Dewar EM, Gatzka CD, Jennings GL, Liang YL, Reid CM, and Kingwell BA: Large-artery stiffness contributes to the greater prevalence of systolic hypertension in elderly women. *J Am Geriatr Soc*, 52: 368–373, 2004
- (26) Sorensen KE, Kristensen IB, and Celermajer DS: Atherosclerosis in the human brachial artery. *J Am Coll Cardiol*, 29: 318–322, 1997