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ORIGINAL ARTICLE

Arterial stiffness index: A new evaluation for arterial stiffness in elderly patients with essential hypertension

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Background: Arterial stiffness is one of the predictors of cardiovascular event. Arterial stiffness is commonly measured by pulse wave velocity between the carotid and femoral arteries. Recently the arterial stiffness index which is measured by computerized oscillometry at the upper arm was developed. As this procedure is a convenient means of measuring pulse wave velocity, we considered it suitable to evaluate arterial stiffness in elderly patients. We evaluated this arterial stiffness index and compared it with other methods of evaluating arterial stiffness in hypertensive patients, including the elderly.

Methods: Forty-two patients with essential hypertension, including 26 subjects over 60 years old were enrolled. We evaluated the arterial stiffness index by computerized oscillometry, and also evaluated arterial stiffness between the carotid-femoral artery and the brachial-tibial artery, the second derivative of photoplethysmogram, the forearm vasodilator response to reactive hyperemia by strain-gauge plethysmography.

Results: Arterial stiffness index was positively correlated with pulse wave velocity between the carotid-femoral artery ($P<0.0001$; $r=0.579$), the heart-carotid artery ($r=0.454$) and right brachial-tibial artery ($r=0.549$). It was also correlated with b/a ($r=0.474$) and d/a ($r=0.568$) by a second derivative of photoplethysmogram, but not correlated with a reactive vasodilator response. In elderly patients, arterial stiffness index was also correlated with carotid-femoral pulse wave velocity ($P<0.05$; $r=0.456$) but not correlated with a vasodilator response to reactive hyperemia.

Conclusion: These data suggest that arterial stiffness index is correlated to common pulse wave velocity between the carotid and femoral arteries, so this index might be useful to evaluate arterial stiffness in hypertensive patients including the elderly.

Keywords: arterial stiffness index, hypertension in the elderly, pulse wave velocity, second derivative of photoplethysmogram.

Introduction

In the present study, the functional changes that occur to arteries during aging were observed. Arterial stiffness is one of these arteriosclerotic changes that occurs during aging[1] as well as high blood pressure – they are both measured by pulse wave velocity (PWV).[2] Aortic PWV between the carotid and femoral arteries is commonly used to evaluate arterial stiffness, and population-based studies[3] have reported that this parameter predicts the presence of cardiovascular events and mortality in hypertensive patients,[4–6] end-stage renal disease patients[7,8] and elderly subjects.[9] Much evidence has been arisen from the use of this method, however, as it

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takes a long time to measure PWV by this procedure, it is not convenient for elderly subjects. Recently, the automatic procedure of brachial-femoral PWV was developed, and this, in contrast, is convenient. However, this procedure cannot evaluate arterial PWV in patients with arteriosclerosis obliterans. The second derivative of photoplethysmogram (SD-PTG) is another procedure which evaluates arterial functional changes. After analyzing this waveform, Takazawa *et al*. suggest that the b/a index might reflect large arterial stiffness and the d/a index indicates peripheral reflection.[10] These parameters are different to arterial stiffness measured by PWV and there is little evidence regarding their clinical usefulness. The forearm vasodilator response to reactive hyperemia using strain-gauge plethysmography is another method which partially evaluates endothelial function (another important early atherosclerotic change). Many reports have suggested that endothelial dysfunction is a useful predictor for cardiovascular events, however, this procedure takes a long time and requires a special machine for measurement.

Recently, several non-invasive devices have been developed for measuring brachial artery stiffness. The arterial stiffness index (ASI) measured by computerized oscillometry is one of these devices and it enables us to measure brachial artery stiffness at the upper arm for a few minutes. This device is a convenient method of clinically evaluating arterial stiffness because it takes only a few minutes and it enables the measurement of the upper arm only. However, its usefulness and its relationship with other evaluations has not been established yet.

Therefore, to clarify the usefulness of ASI measured by computerized oscillometry, we investigated the correlation of ASI to other methods of evaluating functional arterial changes, such as carotid-femoral PWV, brachial-tibial PWV, SD-PTG and the forearm vasodilator response to reactive hyperemia in patients with essential hypertension including the elderly.

Methods

Subjects

Forty-two patients with mild essential hypertension (60 ± 12 years old), defined as stage I by the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI) were enrolled. We excluded from this study, hypertensive patients who had severe complications (stage III of World Health Organization) and secondary hypertension, subjects with diabetes mellitus, dyslipidemia, arrhythmia, or cerebrovascular disease by routine physical and laboratory examinations. We classified patients over 60 years old ($n=26$; 68 ± 6 years old) as 'elderly' patients and those under 59 years ($n=16$; 47 ± 8 years old) as 'younger patients with essential hypertension'. Twenty-three patients had no medication and 14 patients were treated with single antihypertensive drugs (calcium antagonist for nine patients, angiotensin-converting enzyme inhibitor for three, angiotensin II receptor antagonist for two). Five patients were treated with more than two different drugs (calcium antagonist and angiotensin-converting enzyme inhibitor for two patients, calcium antagonist and angiotensin II receptor antagonist for two, and angiotensin-converting enzyme inhibitor, beta-blocker and diuretics for one patient). The protocol of this study was approved by the hospital ethics committee, and written informed consent was obtained from all the patients. Patients' characteristics are shown in Table 1.

Table 1 Characteristics of subjects

	All patients	Younger patients	Elderly patients
Number	42	16	26
Sex (male/female)	25/17	13/3	12/14
Age (years)	60 ± 12	47 ± 8	68 ± 6
BMI (kg/m^2)	24.5 ± 3.4	25.2 ± 3.1	24.1 ± 3.5
T-chol (mg/dL)	218 ± 46	234 ± 42	212 ± 46
Triglyceride (mg/dL)	147 ± 87	155 ± 90	143 ± 87
LDL-chol (mg/dL)	131 ± 42	139 ± 42	127 ± 43
HDL-chol (mg/dL)	62 ± 21	71 ± 25	59 ± 19
FBS (mg/dL)	104 ± 22	94 ± 8	109 ± 25
HbA_{1C} (%)	5.6 ± 1.2	4.8 ± 0.3	6.0 ± 1.3*
Systolic BP (mmHg)	136 ± 20	136 ± 21	137 ± 19
Diastolic BP (mmHg)	82 ± 13	84 ± 15	81 ± 11

BMI, body mass index; FBS, fasting blood sugar; HDL-chol, high-density lipoprotein cholesterol; LDL-chol, low-density lipoprotein cholesterol; T-chol, total cholesterol.
*$P < 0.05$ *vs* young patients.

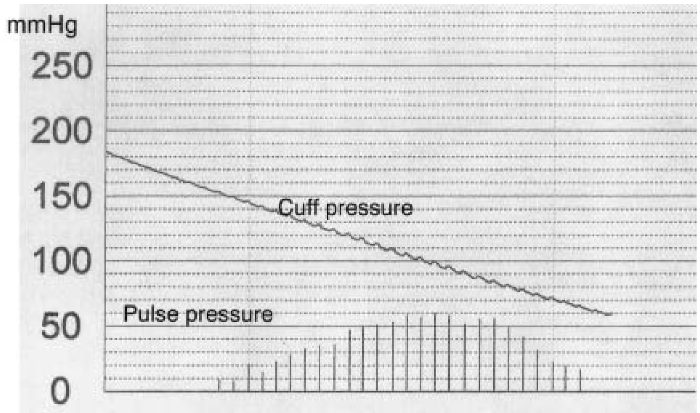

Figure 1 Computerized oscillometry. A typical computerized oscillometry pattern. In this case, the ASI was 113.

Arterial stiffness index

The arterial stiffness index was measured and calculated by computerized oscillometry (Cardiovision, International Medical Devices, Las Vegas, NV, USA). In this procedure, a pressure sensor is attached to the blood pressure cuff to enable the measurement of small volumetric changes of the arm as the cuff pressure is gradually reduced (as shown in Fig. 1). After subtraction of mean cuff pressure, highly elastic brachial arteries generate sharply peaked oscillometric curves, whereas stiff brachial arteries produce rounded oscillometric curves. Using this principle, this device calculates an ASI as the oscillometric curve width in each 10 mmHg at 80% of the mean arterial pressure.

After 10 min rest in the sitting position, we measured ASI using this device on the left upper arm. After five measurements, we excluded the highest and lowest ASI, and then calculated the mean ASI. The intraobserver coefficient of variation was 2.2% and interobserver coefficient of variation was 4.9%.

Pulse wave velocity

To evaluate PWV which is a maker of another arterial stiffness, we used two different devices: one for carotid-femoral PWV (FCP-4731; Fukuda Denshi, Tokyo, Japan) and one for brachial-tibial PWV (AT-Form; Colin, Komaki, Japan).

To measure carotid-femoral PWV, the pulse waveforms of the right carotid and femoral arteries were recorded non-invasively using a TY-306-Fukuda pressure-sensitive transducer (Fukuda Denshi), and the heart sound was recorded at the same time. A preprocessing automatically analyzed the gain in each waveform and adjusted it for equality of the two signals. This procedure has been published in detail.[11] The intraobserver coefficient of variation was 2.8% and the interobserver coefficient was 3.7%.

To measure brachial-tibial PWV, we recorded pressure waveforms of the brachial and tibial arteries using an automatic waveform analyzer (AT-Form, Colin, Komaki, Japan) as previously reported.[12] After 10 min of bed rest, cuffs with tonometry were settled at both right and left upper arm and lower limbs. Additionally, to measure heart-carotid or heart-femoral PWV, we placed pressure-sensitive transducers on the carotid and femoral arteries and a microphone on the right edge of the sternum at the second intercostal space. The pressure waveforms obtained at each site were simultaneously recorded to determine the time interval between the initial rise in the brachial, carotid, femoral and tibial pressure waveforms. After each distance was automatically calculated, PWV was calculated as distance divided time interval between each site. This procedure automatically measured each PWV twice and calculated the mean of the velocity as the final PWV index.

Second derivative of photoplethysmogram

SD-PTG was performed by a Fukuda FCP-4731 with a model IB-70, as described previously.[13] The IB-70 performs an automatic analysis of each SD-PTG waveform, which consists of four waves in systole (a, b, c and d) and one in diastole (e) (as shown in Fig. 2). The b/a ratio was defined as the ratio of the height of the b-wave to that of the a-wave, and the d/a ratio as the height of the d-wave to that of the a-wave. Takazawa *et al.* suggest that the b/a index might reflect large arterial stiffness and the d/a index indicates peripheral reflection.[10] The intraobserver coefficient of variation was 2.2% and the interobserver coefficient was 2.4%.

Vasodilator response to reactive hyperemia

We measured forearm blood flow by strain-gauge plethysmography (EC5R, DE Horkkanson, USA). The

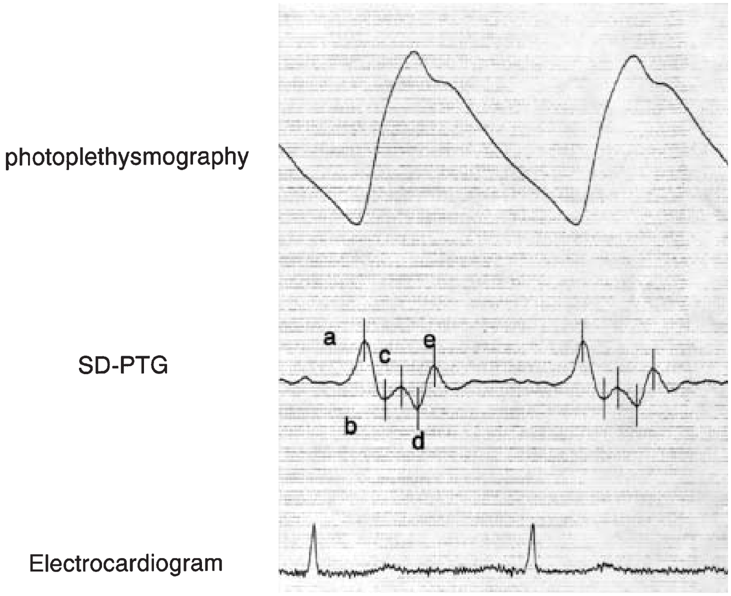

Figure 2 The second derivative of photoplethysmogram. A typical SD-PTG. The height of a, b, c, d or e was measured by the distance from the baseline.

procedure has been previously published in detail.[14–16] We calculated the reactive hyperemia/baseline value of forearm blood flow as reactive hyperemia ratio, partly reflecting endothelium-dependent vasodilatation. The intraobserver coefficient of variation was 3.4% and the interobserver coefficient was 5.1%.

Statistical analysis

Data were analyzed with StatView version 4.51 (SAS Institute Inc., NC, USA) and presented as mean ± SD. A simple regression analysis was used to compare ASI with the parameters of PWV, SD-PTG or the forearm vasodilator response to reactive hyperemia. The unpaired *t*-test was used to compare characteristics of subjects and baseline data of PWV, SD-PTG, reactive hyperemia and ASI. A value of $P<0.05$ was taken as statistically significant.

Results

Baseline data of arterial PWV, SD-PTG and the forearm vasodilator response to reactive hyperemia are shown in Table 2. We could not find any statistical difference in blood pressure, PWV, ASI or reactive hyperemia between younger and elderly patients. The b/a in elderly patients was significantly higher than that in younger patients ($P<0.01$) and the d/a in elderly patients was significantly lower than that in younger patients ($P<0.05$). The correlation between ASI and other evaluations are shown in Table 3. Compared with ASI and carotid-femoral PWV measured by FCP-4731, ASI was significantly correlated with carotid-femoral PWV in all patients ($P<0.0001$; $r=0.579$), moreover, the significantly positive correlation with ASI and carotid-femoral PWV was found in the younger ($P=0.0021$; $r=0.728$) and the elderly patients ($P=0.0252$; $r=0.456$). To compare with arterial PWV measured by AT-Form, ASI was positively correlated with heart-carotid ($P<0.005$; $r=0.454$), heart-brachial ($P<0.05$; $r=0.380$), heart-femoral ($P<0.01$; $r=0.426$), right femoral-tibial ($P<0.0005$; $r=0.560$), left femoral-tibial ($P<0.0005$; $r=0.539$), right brachial-tibial ($P<0.0005$; $r=0.549$) and left branchial-femoral PWV ($P<0.001$; $r=0.511$) in all patients. In elderly patients, ASI was positively correlated with right femoral-tibial ($P<0.05$; $r=0.489$), left femoral-tibial ($P<0.05$; $r=0.449$) and right brachial-tibial ($P<0.05$; $r=0.477$) PWV. Evaluated by SD-PTG, b/a ($P<0.005$; $r=0.474$) and d/a ($P<0.0001$; $r=0.568$) were positively correlated with ASI in all patients, and d/a ($P<0.05$; $r=0.460$) was also significantly correlated with ASI in the elderly patients. In the evaluation of endothelial dysfunction measured by the forearm vasodilator response to reactive hyperemia, we could not find any correlation between ASI and reactive hyperemia in all or elderly patients.

The correlation with carotid-femoral PWV and other evaluations including ASI is shown in Table 4. As we showed in Table 3, the correlation coefficient of ASI and carotid-femoral PWV was 0.579 in all patients and 0.456 the elderly patients. Compared with brachial-femoral PWV, which has been recently used to evaluate arterial stiffness, the correlation coefficient was 0.585 for right and 0.572 for left in all patients, and 0.603 for right and 0.575 for left in elderly patients.

Table 2 Blood pressure, arterial pulse wave velocity, SD-PTG, reactive hyperemia and arterial stiffness index

	All patients	Younger patients	Elderly patients
Right upper arm			
Systolic BP (mmHg)	136 ± 21	139 ± 23	135 ± 19
Diastolic BP (mmHg)	83 ± 12	86 ± 15	81 ± 9
Right lower limb			
Systolic BP (mmHg)	158 ± 25	160 ± 27	156 ± 24
Diastolic BP (mmHg)	83 ± 14	87 ± 17	81 ± 12
Left upper arm			
Systolic BP (mmHg)	135 ± 20	135 ± 23	135 ± 20
Diastolic BP (mmHg)	81 ± 14	84 ± 15	79 ± 13
Left lower limb			
Systolic BP (mmHg)	158 ± 24	160 ± 26	156 ± 23
Diastolic BP (mmHg)	84 ± 13	87 ± 17	82 ± 11
Carotid-femoral PWV (m/s)	8.72 ± 1.83	8.3 ± 1.8	8.98 ± 1.82
Heart-carotid PWV (cm/s)	1144 ± 366	1114 ± 422	1164 ± 331
Heart-brachial PWV (cm/s)	648 ± 93	647 ± 101	636 ± 80
Heart-femoral PWV (cm/s)	1086 ± 209	1083 ± 241	1087 ± 190
Right femoral-tibial PWV (cm/s)	1099 ± 151	1083 ± 171	1109 ± 138
Left femoral-tibial PWV (cm/s)	1117 ± 147	1089 ± 165	1136 ± 134
Right brachial-tibial PWV (cm/s)	1615 ± 332	1544 ± 299	1669 ± 356
Left brachial-tibial PWV (cm/s)	1640 ± 345	1537 ± 288	1718 ± 372
SD-PTG			
b/a	–0.49 ± 0.17	–0.59 ± 0.19	–0.43 ± 0.13**
d/a	–0.35 ± 0.16	–0.27 ± 0.19	–0.39 ± 0.11*
Reactive hyperemia	1.92 ± 0.56	1.89 ± 0.43	1.94 ± 0.63
ASI	77.2 ± 58.3	55.7 ± 51.0	90.5 ± 59.3

ASI, arterial stiffness index; b/a, b wave divided by a wave; BP, blood pressure; d/a, d wave divided by a wave; SD-PTG, second derivative of photoplethysmogram. Data express mean ± SD. *$P < 0.05$, **$P < 0.01$ *vs* young patients.

Table 3 The correlation between ASI and other evaluations

	All patients		Younger patients		Elderly patients	
	P-value	Correlation coefficient	*P*-value	Correlation coefficient	*P*-value	Correlation coefficient
Carotid-femoral PWV	<0.0001	0.579	0.0021	0.728	0.0252	0.456
Heart-carotid PWV	0.0032	0.454	0.0002	0.799	0.4255	0.171
Heart-brachial PWV	0.0171	0.380	0.0005	0.788	0.6101	0.110
Heart-femoral PWV	0.0062	0.426	0.0459	0.505	0.0624	0.386
Right femoral-tibial PWV	0.0002	0.560	0.0065	0.649	0.0153	0.489
Left femoral-tibial PWV	0.0003	0.539	0.0107	0.618	0.0276	0.449
Right brachial-tibial PWV	0.0003	0.549	0.0112	0.634	0.0184	0.477
Left brachial-tibial PWV	0.0009	0.511	0.0081	0.654	0.0536	0.399
b/a by SD-PTG	0.0020	0.474	0.0060	0.654	0.3496	0.200
d/a by SD-PTG	<0.0001	0.568	0.0090	0.629	0.0238	0.460
Reactive hyperemia	0.0554	–0.309	0.0964	–0.445	0.2430	–0.248

b/a, b wave divided by a wave; d/a, d wave divided by a wave; PWV, pulse wave velocity; SD-PTG, second derivative photoplethysmogram.

Table 4 The correlation between carotid-femoral PWV and other evaluations

	All patients		Younger patients		Elderly patients	
	P-value	Correlation coefficient	*P*-value	Correlation coefficient	*P*-value	Correlation coefficient
ASI	<0.0001	0.579	0.0021	0.728	0.0252	0.456
Heart-carotid PWV	<0.0001	0.606	<0.0001	0.893	0.1089	0.336
Heart-brachial PWV	0.0030	0.469	0.0075	0.680	0.6101	0.110
Heart-femoral PWV	0.0002	0.564	0.0195	0.594	0.0058	0.545
Right femoral-tibial PWV	0.0007	0.519	0.1090	0.431	0.0041	0.565
Left femoral-tibial PWV	0.0013	0.497	0.1150	0.424	0.0087	0.523
Right brachial-tibial PWV	0.0001	0.585	0.0620	0.511	0.0018	0.603
Left brachial-tibial PWV	0.0002	0.572	0.0543	0.524	0.0033	0.575
b/a by SD-PTG	0.0617	0.302	0.0560	0.503	0.9256	0.020
d/a by SD-PTG	0.0310	0.346	0.0940	0.448	0.4319	0.168
Reactive hyperemia	0.0222	–0.370	0.1391	–0.416	0.3252	–0.210

ASI, arterial stiffness index; b/a, b wave divided by a wave; d/a, d wave divided by a wave; PWV, pulse wave velocity; SD-PTG, second derivative photoplethysmogram.

Discussion

This is the first report to evaluate the usefulness of ASI compared with other parameters of arterial stiffness and endothelial dysfunction in patients with hypertension. The computerized oscillometry was a convenient procedure and ASI measured by this method was strongly correlated to arterial stiffness evaluated by other methods. Therefore, ASI would be a useful and convenient index to evaluate arterial stiffness in hypertensive patients, including the elderly.

Arterial stiffness measured by PWV was widely used to evaluate arterial aging[1] and to predict the presence of cardiovascular event[3–8] even in elderly subjects over 70 years old.[9] These reports were based on the measurement of carotid-femoral PWV, which was measured using pressure-sensitive transducer and heart sound recorder. If the pressure-sensitive transducer was placed on the wrong point of the carotid and femoral artery, pressure wave form was not clearly recorded accuracy was lost. Therefore, pressure-sensitive transducers should be settled completely on the carotid and femoral arteries. However, it required a mature technique and took about 10 minutes. To stay in the same position for a long time may be difficult for elderly patients for reasons including lumber pain, poor realization or dementia. To measure arterial stiffness more conveniently, a new procedure was developed from Colin Co. – AT-Form. To evaluate only brachial-tibial PWV by this procedure, we should perform both left and right upper arm and ankle blood pressure measurement at the same time using an automatic waveform analyzer. This procedure was quite convenient, however, if patients have arterial stenosis between the brachial and tibial artery (such as arteriosclerosis obliterans) this PWV loses its accuracy. Moreover, if heart-carotid PWV measurement was required as in this study, we should place the pressure-sensitive transducer on the carotid and femoral artery like carotid-femoral PWV, so it should also take about 10 min to measure. However, it took only couple of minutes to complete via ASI. In comparison with these two procedures, ASI measured by computerized oscillometry was more convenient, and as we could measure arterial stiffness at the upper arm, ASI was evaluated in patients with arteriosclerosis obliterans.

Another major arterial change is endothelial dysfunction. The forearm vasodilator response to reactive hyperemia was a post-ischemic vasodilator reaction of the radial artery. However, this reaction was strongly correlated to the vasodilator response to acetylcholine infusion from artery. Therefore, the forearm vasodilator response to reactive hyperemia was partially expressed endothelial function. In this study, ASI was not strongly correlated to reactive hyperemia. The endothelial dysfunction is considered to reflect earlier functional responses caused by atherosclerosis, however, arterial stiffness measured by PWV reflects a constitutive stiffened change of artery. Arerial stiffness index measured by computerized oscillometry did not express endothelial function, but would express arterial stiffness.

The present paper indicates that carotid-femoral PWV is related to cardiovascular disease and mortality, however, the brachial-tibial PWV showed little relation to atherosclerotic diseases or mortality. Moreover, we could not find any report about the clinical meanings of ASI. In this report, we showed a strong correlation between ASI and carotid-femoral PWV which was considered to be one of the predictors of the presence of cardiovascular disease. As we speculated from this evidence, further large cohort studies may show that ASI might possibly predict the presence of cardiovascular diseases.

It would seem that ASI is a new and convenient method of evaluating arterial stiffness in hypertensive patients including the elderly.

Study limitations

The present paper has several limitations. A small number of patients were enrolled and analyzed in this study. Forty-two patients is not a sufficient number to analyze and make conclusions regarding the usefulness and convenience of this procedure. We should also emphasize the large number of cohort studies with primary endpoints including the presence of cardiovascular diseases and mortality should re required using the computerized oscillometry.

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References

1 Machey R, Stutton-Tyrrell K, Vaitkevicius P *et al.* Correlates of aortic stiffness in elderly individuals: a subgroup of the Cardiovascular Health Study. *Am J Hypertens* 2002; **15:** 16–23.
2 Benetos A, Adamopoulos C, Bureau J *et al.* Determinants of accelerated progression of arterial stiffness in normotensive subjects and in treated hypertensive subjects over a 6-year period. *Circulation* 2002; **105:** 1202–1207.
3 Amar J, Ruidavets J, Chamontin B, Drouet L, Ferrieres J. Arterial stiffness and cardiovascular risk factors in a population-based study. *J Hypertens* 2001; **19:** 381–387.
4 Asmar R, Rudnichi A, Blacher J, London G, Safar M. Pulse pressure and aortic pulse wave are markers of cardiovascular risk in hypertensive populations. *Am J Hypertens* 2001; **14:** 91–97.
5 Boutouyrie P, Tropeano A, Asmar R *et al.* Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. *Hypertension* 2002; **39:** 10–15.
6 Laurent S, Boutouyrie P, Asmar R *et al.* Aortic stiffness is an independent predictor of all-case and cardiovascular mortality in hypertensive patients. *Hypertension* 2001; **37:** 1236–1241.
7 Blacher J, Guerin A, Pannier B, Marchais S, London G. Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. *Hypertension* 2001; **38:** 938–942.
8 London G, Blacher J, Pannier B, Guerin A, Marchais S, Safar M. Arterial wave reflections and survival in end-stage renal failure. *Hypertension* 2001; **38:** 434–438.
9 Meaume S, Rudnichi A, Lynch A *et al.* Aortic pulse wave velocity as a marker of cardiovascular disease in subjects over 70 years old. *J Hypertens* 2001; **19:** 871–877.
10 Takazawa K, Tanaka N, Fujita M *et al.* Assessment of vasoactive agents and vascular aging by the second derivative of photoplethysmogram waveform. *Hypertension* 1998; **32:** 365–370.
11 Asmar R, Benetos A, Topouchian J *et al.* Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. *Hypertension* 1995; **26:** 485–490.
12 Suzuki E, Kashiwagi A, Nishio Y *et al.* Increased arterial wall stiffness limits flow volume in the lower extremities in type 2 diabetic patients. *Diabetes Care* 2001; **24:** 2107–2111.
13 Komai N, Ohishi M, Moriguchi A *et al.* Low-dose doxazosin improved aortic stiffness and endothelial dysfunction measured by non-invasive evaluation. *Hypertens Res* 2002; **25:** 5–10.
14 Komai N, Ohishi M, Morishita R *et al.* Serum hepatocyte growth factor concentration is correlated with the forearm vasodilator response in hypertensive patients. *Am J Hypertens* 2002; **15:** 499–506.
15 Higashi Y, Sasaki S, Nakagawa K *et al.* A comparison of angiotensin-converting enzyme inhibitors, calcium antagonists, beta-blockers and diuretic agents on reactive hyperemia in patients with essential hypertension: a multicenter study. *J Am Coll Cardiol* 2000; **35:** 284–291.
16 Iwatsubo H, Nagano M, Sakai T *et al.* Converting enzyme inhibitor improves forearm reactive hyperemia in essential hypertension. *Hypertension* 1997; **29:** 286–290.