Original Article

Brachial-Ankle Pulse Wave Velocity Is an Independent Risk Factor for Microalbuminuria in Patients with Essential Hypertension—A Japanese Trial on the Prognostic Implication of Pulse Wave Velocity (J-TOPP)

Masanori MUNAKATA[1)], Tohru NUNOKAWA[2)], Kaoru YOSHINAGA[2)], and Takayoshi TOYOTA[1)], J-TOPP Study Group*

Brachial-ankle pulse wave velocity is a new measure of arterial stiffness. The clinical significance of brachial-ankle pulse wave velocity as a measure of early vascular damage remains unclear. We examined the hypothesis that higher brachial-ankle pulse wave velocity is associated with a much greater risk of albuminuria by employing a cohort of 718 never-treated hypertensive patients registered in a prospective study. The 718 patients consisted of 500 patients with normoalbuminuria (69.6%), 191 patients with microalbuminuria (26.6%) and 27 patients with macroalbuminuria (3.8%). The prevalence of microalbuminuria increased with a graded increase in brachial-ankle pulse wave velocity (17.6, 22.8, 28.2 and 39.6%, $p<0.0001$). The prevalence of macroalbuminuria remained constant until the third grade group of the brachial-ankle pulse wave velocity but increased significantly in the highest grade group compared with the lower grade groups (2.3, 3.2, 2.3, 9.9%, $p<0.0001$). Age, systolic and diastolic blood pressure, pulse pressure, heart rate, and fasting glucose concentration were also significantly increased with an increase in brachial-ankle pulse wave velocity ($p<0.0001$ for all). Multiple logistic regression analysis has shown that systolic blood pressure, fasting blood glucose, and brachial-ankle pulse wave velocity are significant risk factors for microalbuminuria. After adjusting for other risk factors, the odds ratio for an increase of 200 cm/s in brachial-ankle pulse wave velocity was 1.192 (95% confidence interval: 1.022–1.365; $p<0.05$). These data suggest that brachial-ankle pulse wave velocity is an independent risk factor for microalbuminuria and could be used as a marker for early vascular damage in never-treated hypertensive patients. (*Hypertens Res* 2006; 29: 515–521)

***Key Words*: pulse wave velocity, microalbuminuria, hypertension, diabetes, arterial stiffness**

From the [1)]Preventive Medical Center and [2)]Division of Hypertension and Cardiology, Tohoku Rosai Hospital, Sendai, Japan.

*A list of the J-TOPP study group members is given in the Appendix.

This study was supported in part by Grants-in-Aid from the Miyagi Prefectural Kidney Association, Japan Arteriosclerosis Prevention Fund and Japan Labor Health and Welfare Organization.

Address for Reprints: Masanori Munakata, M.D., Ph.D., Preventive Medical Center, Tohoku Rosai Hospital, 3–21, Dainohara 4, Aoba-ku, Sendai 981–8563, Japan. E-mail: munakata@tohokuh.rofuku.go.jp

Received January 30, 2006; Accepted in revised form March 31, 2006.

Introduction

Atherosclerosis is an essential process in the development of major cardiovascular and cerebrovascular events. Characteristic changes of atherosclerosis are stiffening, thickening and inflammation of the arterial wall (*1–3*). Therefore, early recognition of functional, structural, and biochemical arterial wall changes may identify patients at a high risk of clinical complications from atherosclerosis.

Pulse wave velocity (PWV) is the most widely used measure of arterial stiffness in a wide variety of clinical fields (*4*). The stiffer the arterial wall becomes, the faster the arterial waves travel through the arterial wall. Among the PWV parameters, carotid-femoral PWV, which examines the stiffness of large elastic arteries, is the most widely used measure of arterial stiffness. This is very reasonable, because atherosclerotic changes of the arterial wall begin at the aorta and stiffness of the aorta is deeply involved in the determination of cardiac afterload (*5*). Both cross-sectional and prospective data have shown that carotid-femoral PWV is useful in identifying not only patients with atherosclerosis but also those with a poor prognosis in several cardiovascular diseases (*6–8*).

On the other hand, it is well recognized that arteries in the lower limbs are much more susceptible to atherosclerosis than those in upper limbs. A recent study has shown that muscular artery compliance is deeply involved in the regulation of central systolic blood pressure in humans (*9*). In this context, global approaches to measurement of arterial stiffness, including that of the aorta, which passes over the lower limb arteries, may be of interest (*10*). Brachial-ankle PWV is a new measure of arterial stiffness (*11*, *12*) whose physiological characteristics are closer to carotid-femoral PWV than to femoral-ankle PWV (*13*, *14*). The reproducibility of this measure is good (*11*, *12*, *15*). Recent data have shown that a higher brachial-ankle PWV is associated with more advanced atherosclerotic changes of the arterial wall not only in clinical patients (*16–19*) but also in subclinical individuals (*20*, *21*). Moreover, it has been shown that brachial-ankle PWV is related to microvascular complications in diabetic patients (*22*, *23*). In our preliminary study, higher brachial-ankle PWV was associated with higher urinary albumin excretion in non-diabetic hypertensive patients (*24*). Only a few studies have reported a relation between an arterial stiffness measure and microvascular complications (*25*, *26*). Therefore brachial-ankle PWV is a unique measure which could manifest both macro- and microvascular injuries.

Thus, the important issue is whether brachial-ankle PWV is a better predictor than conventional risk factors of cardiovascular events or subclinical but distinct progression of vascular damage. Recently, Kitahara *et al*. have shown that brachial-ankle PWV has prognostic significance in end-stage renal disease (*27*). However, there is no prospective data on brachial-ankle PWV in patients with essential hypertension. To address this issue we conducted a multicenter cohort study entitled the Japanese Trial on Prognostic Implications of PWV (J-TOPP) (*14*). Between April 2002 and December 2004, 804 never-treated patients with essential hypertension were entered into this study. In the present work, we examined in a cross-sectional manner whether higher brachial-ankle PWV is associated with a much greater risk of albuminuria in this large cohort of untreated hypertensive patients.

Methods

Study Design

The J-TOPP study is a multicenter cohort study that examines the prognostic significance of brachial-ankle PWV in untreated patients with essential hypertension. This study prospectively examines the relationship between brachial-ankle PWV and urinary albumin excretion, one of the most established surrogate markers (*3*) for cardiovascular mortality not only in high risk patients (*28–31*) but also in general populations (*32*, *33*). In uncomplicated hypertension, the risk of cardiovascular events is very low under the current guidelines for hypertensive treatment. Therefore, we need an intermediate endpoint to be able to best predict cardiovascular morbidity and mortality. Urinary albumin excretion can be considered as such a measure. Ibsen *et al*. showed in the LIFE study that reduction in albuminuria during treatment translates into a reduction in cardiovascular events (*34*). In other words, changes in urinary albumin excretion seem to to correlate directly with cardiovascular risk. Fatal and non-fatal cardiovascular events were considered as secondary endpoints in the J-TOPP study.

Fifty-three medical institutions and 73 physicians participated in the present study (see Appendix). Hypertension was defined as an average blood pressure $\geq$140/90 mmHg on at least two different occasions during routine examination. Only never-treated patients with essential hypertension were eligible to participate in this study because previous antihypertensive treatment would likely affect the relationship between brachial-ankle PWV and urinary albumin excretion. Exclusion criteria were secondary causes of hypertension, cancer, atrial fibrillation, severe liver dysfunction, fasting plasma glucose $>$11.1 mmol/l (200 mg/dl), renal insufficiency with plasma creatinine concentration $>$176.8 μmol/l (2.0 mg/dl) and other severe diseases. Patients with peripheral arterial disease were also excluded because precise measurement of brachial-ankle PWV is difficult in these patients. After enrollment, patients underwent measurements of the brachial-ankle PWV and urinary albumin excretion, and were then put on a regimen of an antihypertensive drug, which was an angiotensin II receptor antagonist (ARB), long-acting calcium channel blocker, or angiotensin converting enzyme inhibitor (ACEI) (*14*). This study was started in April 2002. By the end of December 2004, 804 never-treated patients with essential hypertension had been enrolled into this study.

Table 1. Patient Characteristics: Distribution of Risk Factors According to the Grade of Brachial-Ankle PWV

Risk factors	Brachial-ankle PWV (cm/s)				*p* value
	–1,400 (*n*=89)	1,400–1,800 (*n*=311)	1,800–2,200 (*n*=216)	2,200– (*n*=102)	
Age (years)	48±9	57±10	64±11	71±10	<0.0001
Male (%)	50	45	50	43	n.s.
Body mass index (kg/m^2)	25.5±4.0	24.6±3.4	24.0±3.6	23.8±3.6	<0.002
Smoking (%)	35.2	28.4	31.8	31.5	n.s.
Diabetes (%)	4.5	10	10.6	17.6	0.05
Fasting blood glucose (mmol/l)	5.54±1.00	5.77±1.27	5.99±1.55	6.07±1.42	<0.03
Triglyceride (mmol/l)	1.56±1.16	1.50±0.85	1.47±0.83	1.51±0.73	n.s.
Total cholesterol (mmol/l)	5.38±0.97	5.47±1.03	5.35±0.95	5.49±0.96	n.s.
HDL cholesterol (mmol/l)	1.42±0.38	1.49±0.39	1.51±0.45	1.49±0.41	n.s.
Plasma creatinine (mmol/l)	62.2±16.0	61.8±15.6	65.5±14.2	69.4±18.0	<0.0005
Systolic blood pressure (mmHg)	141±15	153±16	161±18	172±21	<0.0001
Diastolic blood pressure (mmHg)	88±10	93±11	95±12	98±13	<0.0001
Pulse pressure (mmHg)	53±9	60±11	66±14	75±14	<0.0001
Heart rate (bpm)	67±10	68±10	71±11	72±12	<0.005
Urinary albumin excretion (mg/g·Cr)	32.4±69.3	46.9±111.5	54.3±142.1	168.6±488	<0.0001

PWV, pulse wave velocity; HDL, high density lipoprotein; n.s., not significant.

Measurement of PWV

Blood pressure and brachial-ankle PWV were studied using a new device, the AT-form PWV/ABI (Colin, Komaki, Japan), which has been described in detail elsewhere (*11–15*). In brief, this device simultaneously records right and left brachial and tibial arterial pressure wave forms, lead I of an electrocardiogram, and a phonocardiogram. Occlusion cuffs, which were connected to both plethysmographic and oscillometric sensors, were placed around both arms and ankles of the patient for pulse wave analysis and blood pressure measurements. The time difference between the brachial and ankle arterial pressure wave (ΔT) was determined by wave front velocity theory. The distance between the arm and ankle (D) was calculated based on anthropometric data for the Japanese population. Finally, the brachial-ankle PWV was calculated as $D/\Delta T$.

Measurement of Urinary Albumin Excretion

Spot urine samples were collected and stored at −20°C until assay. Urinary albumin and creatinine were measured at the Clinical Chemistry Laboratory (SRL Inc., Tokyo, Japan). Urinary albumin concentration was measured by latex agglutination immunoassay on an autoanalyzer (LX-6000; Eiken-kagaku Co., Tokyo, Japan). The sensitivity of this assay was 0.5 mg/l, and the intra-assay and inter-assay coefficients of variation were 1.25% and 2.03%, respectively. Urinary creatinine concentration was measured by an enzymatic method. Urinary albumin excretion was expressed as the ratio of albumin to creatinine excretion. The cut-off values for the presence of microalbuminuria and macroalbuminuria were 30 mg/g·Cr and 300 mg/g·Cr, respectively (*35*). This study was approved by the medical ethics committee of Tohoku Rosai Hospital and all the patients gave informed consent.

Statistical Analysis

Continuous data are expressed as the mean±SD. Differences between groups were assessed with ANOVA. Relationships among variables were assessed by using linear regression analysis and Pearson's correlation coefficient. Comparisons of proportions among groups were performed by using χ^2 analysis. Odds ratios and 95% confidence intervals (CIs) were calculated by exponentiation of the logistic regression analysis. Multiple linear regression analysis was performed to examine the relationship between urinary albumin excretion and other variables. All statistical analyses were performed with commercially available software (Stat Flex version 5.0 for Windows; ARTEC, Osaka, Japan). A value of $p<0.05$ was considered statistically significant.

Results

Of 804 registered patients, 86 were excluded from the analyses because of severe diabetes ($n=13$), an age of greater than 85 years ($n=9$), collagen disease ($n=3$), severe renal failure ($n=3$) and missing data ($n=58$). Consequently, 718 patients were included in the final analysis.

The 718 patients were grouped as 500 with normoalbuminuria (69.6%), 191 with microalbuminuria (26.6%), and 27 with macroalbuminuria (3.8%). Table 1 shows the clinical characteristics of the patient groups according to four grades of brachial-ankle PWV. Urinary albumin excretion increased

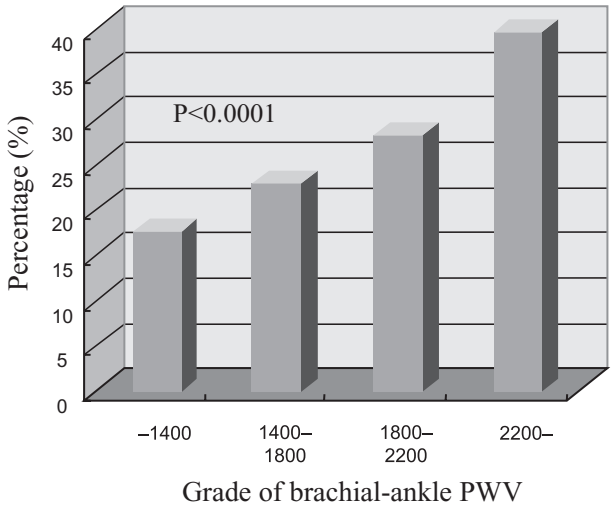

Fig. 1. *Percentage of microalbuminuric patients in each grade of brachial-ankle PWV.*

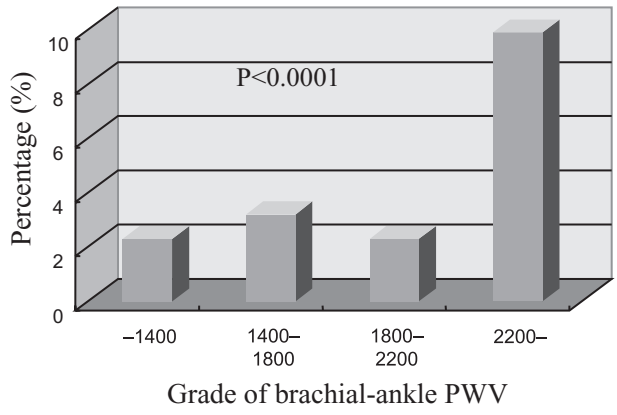

Fig. 2. *Percentage of macroalbuminuric patients in each grade of brachial-ankle PWV.*

with each increase in brachial-ankle PWV ($p<0.0001$). Age ($p<0.0001$), fasting glucose concentration ($p<0.03$), plasma creatinine concentration ($p<0.0005$), systolic and diastolic blood pressure and pulse pressure ($p<0.0001$ for all), and heart rate ($p<0.005$) also increased, whereas body mass index decreased ($p<0.002$) with each increase in brachial-ankle PWV. Among the 718 patients, 76 were diabetics with a fasting plasma glucose concentration of 6.99 mmol/l (126 mg/dl) or over. The frequency of diabetes tended to increase with each increase in brachial-ankle PWV. Gender distribution, smoking status and lipid profiles were similar among the four different brachial-ankle PWV groups.

Figures 1 and 2 show the percentages of microalbuminuria and macroalbuminuria in each group. The frequency of microalbuminuria progressively increased with the graded increase in brachial-ankle PWV (17.6, 22.8, 28.2, and 39.6%, respectively, $p<0.0001$). The frequency of macroalbuminuria remained unchanged until the third grade of the brachial-ankle PWV but increased significantly in the highest grade group compared to the lower grade groups (2.3, 3.2, 2.3, and 9.9%, respectively, $p<0.0001$).

Table 2 compares the risk factors between patients with albuminuria and those without albuminuria. Fasting glucose concentration ($p<0.0005$), systolic and diastolic blood pressure and pulse pressure ($p<0.0001$ for all), heart rate ($p<0.001$), and brachial-ankle PWV ($p<0.0001$) were higher in the group with albuminuria than in the group without albuminuria. Age, gender distribution, smoking status, lipid profile, and plasma creatinine concentration did not differ between the two groups. Multiple logistic regression analysis has shown that the risk of albuminuria increases by 20% with a 1 mmol/l (18 mg/dl) increase in fasting blood glucose, by 24% with a 10 mmHg increase in systolic blood pressure, and by 21% with a 200 cm/s increase in brachial-ankle PWV (Table 3). We performed multiple regression analysis as log [urinary albumin excretion] for dependent variable. Systolic blood pressure ($p<0.05$) and brachial-ankle PWV ($p<0.01$) were significant contributors but fasting plasma glucose was not significant ($p=0.07$). We also examined the risk of microalbuminuria after excluding patients with macroalbuminuria. The odds ratio for a 200 cm/s increase in brachial-ankle PWV was 1.192 (95% CI: 1.022–1.365; $p=0.02$).

Discussion

The J-TOPP study is the first multicenter cohort study that examines the prognostic significance of brachial-ankle PWV in patients with essential hypertension. We examined the relationship between brachial-ankle PWV and the risk of albuminuria using the baseline data of a never-treated hypertensive cohort that was entered into this study.

The pivotal finding of this study was that the frequency of microalbuminuria progressively increased with a graded increase in brachial-ankle PWV. After adjusting for other cardiovascular risk factors, a 200 cm/s increase in brachial-ankle PWV was associated with a 19% increase in the risk of microalbuminuria. This study is the first to show the quantitative risk of brachial-ankle PWV for microalbuminuria in a large cohort of untreated hypertensives.

In our data, the frequency of macroalbuminuria was significantly higher in the highest grade group of the brachial-ankle PWV than in the lower grade groups. Moreover, multiple regression analysis showed that the brachial-ankle PWV was independently and linearly correlated with the log [urinary albumin excretion]. Thus very high brachial-ankle PWV of over 2,200 cm/s may be a risk of overt proteinuria. Our data are consistent with the recent reports showing a close relationship between urinary albumin excretion and either thoracic aortic mechanics (*25*, *26*) or brachial-ankle PWV in a small cohort of hypertensive patients (*36*). It has been shown that the spectrum of albuminuria, from microalbuminuria to

Table 2. Clinical Characteristics of the Patients with or without Albuminuria

Risk factors	Albuminuria (+) (n=218)	Albuminuria (–) (n=500)	p value
Age (years)	64±12	60±12	n.s.
Male (%)	42	49	n.s.
Body mass index (kg/m^2)	24.7±3.8	24.3±3.5	n.s.
Smoking (%)	29.6	31.2	n.s.
Diabetes (%)	16.5	8	<0.0001
Fasting blood glucose (mmol/l)	6.15±1.74	5.73±1.15	<0.0005
Triglyceride (mmol/l)	1.48±0.83	1.51±0.90	n.s.
Total cholesterol (mmol/l)	5.47±1.03	5.40±0.98	n.s.
HDL cholesterol (mmol/l)	1.50±0.44	1.48±0.40	n.s.
Plasma creatinine (mmol/l)	63.2±17.3	64.5±15.0	n.s.
Systolic blood pressure (mmHg)	164±21	154±18	<0.0001
Diastolic blood pressure (mmHg)	97±13	92±11	<0.0001
Pulse pressure (mmHg)	67±15	62±11	<0.0001
Heart rate (bpm)	71±12	69±11	<0.001
Pulse wave velocity (cm/s)	1,948±498	1,769±327	<0.0001

HDL, high density lipoprotein; n.s., not significant.

Table 3. Multiple Logistic Regression Analysis on the Risks of Albuminuria

Variable	Difference	Odds ratio	95% CI	p
Fasting blood glucose	per 1.0 mmol/l increase	1.202	(1.051–1.360)	0.005
Systolic blood pressure	per 10 mmHg increase	1.238	(1.035–1.480)	0.002
Brachial-ankle PWV	per 200 cm/s increase	1.208	(1.056–1.381)	0.02

CI, confidence interval; PWV, pulse wave velocity.

macroalbuminuria, is associated with a linear increase in risk of cardiovascular events (*34*, *37*). The continuous association of higher brachial-ankle PWV with increased urinary albumin excretion is consistent with the nature of the brachial-ankle PWV as an independent marker of cardiovascular risk (*38*). This is further supported by the recent report that brachial-ankle PWV predicted the future cardiovascular deaths in patients with end-stage renal disease (*27*).

Brachial-ankle PWV includes the properties of anatomically and physiologically different parts of the arterial tree, *i.e.*, elastic arteries and muscular arteries. The prognostic significance of muscular artery stiffness has been questioned (*39*), although elastic artery stiffness has been well recognized as having a prognostic value in several cardiovascular diseases (*7*, *8*). So we must carefully establish the clinical significance of the brachial-ankle PWV. In this study, brachial-ankle PWV was closely related to the degree of urinary albumin excretion, possibly because the brachial-ankle PWV has properties more like those of a large elastic artery than a lower limb artery (*13*).

The underlying mechanisms linking albumin excretion in the kidney and systemic arterial stiffness are currently unclear, but endothelial damage may be involved. It has been well recognized that albumin excretion signifies a membrane barrier defect not only in the podocytes and vascular endothelium in the kidney but also in vascular tissues throughout the body (*40*). Because endothelial-derived substances such as NO are involved in the maintenance of large artery compliance, impaired endothelial functions could increase arterial stiffness (*41*).

We found that a 10 mmHg increase in systolic blood pressure and a 1.0 mmol/l (18.0 mg/dl) increase in fasting glucose concentration were associated with a 24% and 20% increase, respectively, in the risk for albuminuria after adjustment for other cardiovascular risk factors. These data suggest strong and independent influences of systemic arterial pressure and plasma glucose concentration on urinary albumin excretion. These data are very consistent with a recent report indicating that the development of microalbuminuria is linked to insufficient blood pressure control and to a progressive increment in blood glucose values in essential hypertension (*42*).

The effects of gender, age, body mass index and smoking on the risk of albuminuria are largely debatable (*43*). In this study, none of those factors were related to the risk of albuminuria. We speculate that the effect of hypertension or hyperglycemia on albumin leakage into the glomerulus was much greater than the other factors in our hypertensive cohort.

Finally, the potential limitations of this study should be mentioned. In a clinical setting, multiple sampling is recommended for evaluation of the severity of albuminuria, because urinary albumin excretion demonstrates a considerable degree of variability (*44*). In this study, we examined only one urine sample, which may have limited the precision of our evaluation of urinary albumin excretion. A single urine sampling, however, is now commonly used in epidemiological studies (*44*) as well as in interventional studies (*45*). It has been shown that microalbuminuria examined from one spot urine sample is well correlated with markers of inflammation (*44*) and predicts cardiovascular mortality (*33*) in the general population. So we believe that single urine sampling did not seriously modify the results.

In conclusion, our study showed, for the first time, that higher brachial-ankle PWV could be a quantitative risk for microalbuminuria in patients with essential hypertension. A 200 cm/s increase in brachial-ankle PWV increased the risk of microalbuminuria by about 19%. Moreover, the brachial-ankle PWV was linearly correlated with the log [urinary albumin excretion]. If brachial-ankle PWV further predicts the behavior of urinary albumin excretion during treatment, this measure could be a powerful tool for stratifying the risk of treated hypertensive patients. Further prospective studies will be needed to confirm this point.

Appendix

The following investigators participated in the J-TOPP study.
Coordinators: M. Munakata and K. Yoshinaga (Tohoku Rosai Hospital).
Investigators: T. Nunokawa, T. Sakuma, H. Kato (Tohoku Rosai Hospital); A. Soyama, T. Nishikawa (Yokohama Rosai Hospital); K. Haruta, M. Nanki (Chubu Rosai Hospital); M. Nomura, Y. Okazaki (Ohsaka Rosai Hospital); M. Kamimatsu, M. Nagata (Kansai Rosai Hospital); H. Kikuoka, A. Kondo (Wakayama Rosai Hospital); K. Ohnishi (Kobe Rosai Hospital); M. Ohke, T. Kishimoto (Okayama Rosai Hospital); K. Ryu (Kyushu Rosai Hospital); Y. Sone (Kagawa Rosai Hospital); M. Takahashi (Hamamatsu Rosai Hospital); H. Onodera, G. Hinata (Aomori Rosai Hospital); T. Nakatsu, E. Mayumi, S. Toyonaga, M. Samukawa (Kagawa Saiseikai Hospital); T. Goto, Y. Suzuki (Yamagata Prefectural Central Hospital); M. Ohta (Ohta Nishinouchi General Hospital); K. Sato (Hanamaki General Hospital); K. Mashima (Yashima General Hospital); T. Kubo (Takeda General Hospital); K. Nagai, T. Ishizuka (Iwate Prefectural Miyako Hospital); S. Morimoto (Ohmihachiman Municipal Hospital); J. Niwa (Hakodate Municipal Hospital); T. Tachiki (Hakodate Bayside Hospital); Y. Tsutsui (Hakodate Central Hospital); T. Naito (Saka General Hospital); A. Ichihara (Keio University); S. Kyogoku (Minaminakayama Clinic); T. Kusakari (Kusakari Medical Clinic); K. Naito (Naito Clinic); H. Madarame (Madarame Clinic); H. Miyashita (Eijinkai Clinic); R. Mori (Mori Ruriko Medical Clinic); S. Watanabe, M. Watanabe (Watanabe Medical Clinic); T. Yambe (Yambe Clinic); H. Fujiya (Fujiya Medical Clinic); N. Ito (Inariyama Medical Welfare Center); N. Uchida (Uchida Clinic); M. Shishido, S. Nakano (Nakano Hospital); T. Sato (Suzuki Clinic); Y. Uchiba (Oookamura Clinic); K. Niikawa (Niikawa Medical Clinic); H. Honnma (Honnma Medical Clinic); C. Murai (Murai Medical Clinic); S. Yagi, T. Yagi, C. Yagi (Yagi Medical Clinic); K. Watanabe (Ikeda Medical Clinic); S. Nagai (Nagai Clinic); K. Shimizu (Shimizu Clinic); M. Kimura (Kimura Clinic); M. Ishibashi (Ishibashi Medical Clinic); S. Nakajima (Nakajima Medical Clinic); T. Honnma (Kensei Hureai Clinic); T. Saito (Saito Medical Clinic); H. Shionoiri (Shionoiri Medical Clinic); D. Katayose (Ekisaikai Hospital).

References

1. Blankenhorn DH, Kramsch DM: Reversal of atherosis and sclerosis. The two components of atherosclerosis. *Circulation* 1989; **79**: 1–7.
2. O'Rourke M: Mechanical principles in arterial disease. *Hypertension* 1995; **26**: 2–9.
3. Labarrere CA, Zaloga GP: C-reactive protein: from innocent bystander to pivotal mediator of atherosclerosis. *Am J Med* 2004; **117**: 499–507.
4. Benetos A, Waeber B, Izzo J, *et al*: Influence of age, risk factors, and cardiovascular and renal disease on arterial stiffness: clinical application. *Am J Hypertens* 2002; **15**: 1101–1108.
5. London GM, Guerin AP, Pannier B, *et al*: Large artery structure and function in hypertension and end-stage renal disease. *J Hypertens* 1998; **16**: 1931–1938.
6. van Popele NM, Grobbee DE, Bots ML, *et al*: Association between arterial stiffness and atherosclerosis: the Rotterdam Study. *Stroke* 2001; **32**: 454–460.
7. Laurent S, Boutouyrie P, Asmar R, *et al*: Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001; **37**: 1236–1241.
8. Blacher J, Guerin AP, Pannier B, *et al*: Impact of aortic stiffness on survival in end-stage renal disease. *Circulation* 1999; **99**: 2434–2439.
9. Hirata K, Vlachopoulos C, Adji A, *et al*: Benefits from angiotensin-converting enzyme inhibitor 'beyond blood pressure lowering' beyond blood pressure or beyond the brachial artery? *J Hypertens* 2005; **23**: 551–556.
10. Woodman RJ, Watts GF: Measurement and application of arterial stiffness in clinical research: focus on new methodologies and diabetes mellitus. *Med Sci Monit* 2003; **9**: RA101–RA109.
11. Munakata M, Ito N, Nunokawa T, *et al*: Utility of automated brachial ankle pulse wave velocity measurements in hypertensive patients. *Am J Hypertens* 2003; **16**: 653–657.
12. Yamashina A, Tomiyama H, Takeda K, *et al*: Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res* 2002; **25**: 359–364.
13. Sugawara J, Hayashi T, Yokoi T, *et al*: Brachial-ankle pulse wave velocity: an index of central arterial stiffness? *J Hum Hypertens* 2005; **19**: 401–406.
14. Munakata M, Nunokawa T, Tayama J, *et al*: Brachial-ankle pulse wave velocity as a novel measure of arterial stiffness: present evidences and perspectives. *Curr Hypertens Rev* 2005; **1**: 223–234.
15. Matsui Y, Kario K, Ishikawa J, *et al*: Reproducibility of

arterial stiffness indices (pulse wave velocity and augmentation index) simultaneously assessed by automated pulse wave analysis and their associated risk factors in essential hypertension. *Hypertens Res* 2004; **27**: 851–857.
16. Munakata M, Sakuraba J, Tayama J, *et al*: The higher brachial-ankle pulse wave velocity is associated with more advanced carotid atherosclerosis in end-stage renal disease. *Hypertens Res* 2005; **28**: 9–14.
17. Yokoyama H, Aoki T, Imahori M, *et al*: Subclinical atherosclerosis is increased in type 2 diabetic patients with microalbuminuria evaluated by intima-media thickness and pulse wave velocity. *Kidney Int* 2004; **66**: 448–454.
18. Kobayashi K, Akishita M, Yu W, *et al*: Interrelationship between non-invasive measurements of atherosclerosis: flow-mediated dilation of brachial artery, carotid intima-media thickness and pulse wave velocity. *Atherosclerosis* 2004; **173**: 13–18.
19. Yambe M, Tomiyama H, Hirayama Y, *et al*: Arterial stiffness as a possible risk factor for both atherosclerosis and diastolic heart failure. *Hypertens Res* 2004; **27**: 625–631.
20. Okamura T, Moriyama Y, Kadowaki T, *et al*: Non-invasive measurement of brachial-ankle pulse wave velocity is associated with serum C-reactive protein but not with alpha-tocopherol in Japanese middle-aged male workers. *Hypertens Res* 2004; **27**: 173–180.
21. Tomiyama H, Arai T, Koji Y, *et al*: The relationship between high-sensitive C-reactive protein and pulse wave velocity in healthy Japanese men. *Atherosclerosis* 2004; **174**: 373–377.
22. Aso K, Miyata M, Kubo T, *et al*: Brachial-ankle pulse wave velocity is useful for evaluation of complications in type 2 diabetic patients. *Hypertens Res* 2003; **26**: 807–813.
23. Yokoyama H, Hirasawa K, Aoki T, *et al*: Brachial-ankle pulse wave velocity measured automatically by oscillometric method is elevated in diabetic patients with incipient nephropathy. *Diabet Med* 2003; **20**: 942–945.
24. Munakata M, Toyota T, Nunokawa T, *et al*: Arterial stiffness and renal damage in hypertension. *J Jpn Soc Dial Ther* 2004; **37**: 205–207 (in Japanese).
25. Tsioufis CP, Lambrou SG, Stefanadis CI, *et al*: Microalbuminuria is associated with abnormal thoracic aortic mechanics in essential hypertension. *Am J Cardiol* 2000; **86**: 797–801.
26. Mule G, Cottone S, Vadala A, *et al*: Relationship between albumin excretion rate and aortic stiffness in untreated essential hypertensive patients. *J Intrern Med* 2004; **256**: 22–29.
27. Kitahara T, Ono K, Tsuchida A, *et al*: Impact of brachial-ankle pulse wave velocity and ankle-brachial blood pressure index on mortality in hemodialysis patients. *Am J Kid Dis* 2005; **46**: 688–696.
28. Rossing P, Hougaard P, Borch-Johnsen K, *et al*: Predictors or mortality in insulin dependent diabetes: 10 year observational follow up study. *BMJ* 1996; **313**: 779–784.
29. Jager A, Kostense PJ, Ruhe HG, *et al*: Microalbuminuria and peripheral arterial disease and independent predictors of cardiovascular and all-cause mortality, especially among hypertensive subjects: five-year follow-up of the Hoorn Study. *Arterioscler Thromb Vasc Biol* 1999; **19**: 617–624.
30. Damsgaard EM, Froland A, Jorgensen OD, *et al*: Microalbuminuria as predictor of increased mortality in elderly people. *BMJ* 1990; **300**: 297–300.
31. Gerstein HC, Mann JF, Pogue J, *et al*: Prevalence and determinants of microalbuminuria in high-risk diabetic and non-diabetic patients in the Heart Outcomes Prevention Evaluation Study: the HOPE Study Investigators. *Diabetes Care* 2000; **23** (Suppl 2): B35–B39.
32. Hillege HL, Fidler V, Diercks GF, *et al*, Prevention of Renal and Vascular End Stage Disease (PREVEND) Study Group: Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 2002; **106**: 1777–1782.
33. Yuyun MF, Khaw KT, Luben R, *et al*: Microalbuminuria independently predicts all-cause mortality in a British population: the European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) population study. *Int J Epidemiol* 2004; **33**: 189–198.
34. Ibsen H, Olsen MH, Wachtell K, *et al*: Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients. *Hypertension* 2005; **45**: 198–202.
35. Roden J: Urinary albumin excretion-lowering the threshold of risk in hypertension. *Hypertension* 2005; **46**: 19–20.
36. Kohara K, Tabara Y, Tachibana R, *et al*: Microalbuminuria and arterial stiffness in a general population: the Shimanami Health Promoting Program (J-SHIPP) study. *Hypertens Res* 2004; **27**: 471–477.
37. Culleton BF, Larson MG, Parfrey PS, Kannel WB, Levy D: Proteinuria as a risk factor for cardiovascular disease and mortality in older people: a prospective study. *Am J Med* 2000; **109**: 1–8.
38. Yamashina A, Tomiyama H, Arai T, *et al*: Brachial-ankle pulse wave velocity as a marker of atherosclerotic vascular damage and cardiovascular risk. *Hypertens Res* 2003; **26**: 615–622.
39. Pannier B, Guerin AP, Marchais SJ, *et al*: Stiffness of capacitive and conduit arteries: prognostic significance for end-stage renal disease patients. *Hypertension* 2005; **45**: 592–596.
40. Bakris G: Proteinuria; a link to undestanding chages in vascular compliance? *Hypertension* 2005; **46**: 473–474.
41. Wilkinson IB, Franklin SS, Cockcroft JR: Nitric oxide and the regulation of large artery stiffness: from physiology to pharmacology. *Hypertension* 2004; **44**: 112–116.
42. Pascual JM, Rodilla E, Gozalez C, *et al*: Long-term impact of systolic blood pressure and glycemia on the development of microalbuminuria in essential hypertension. *Hypertension* 2005; **45**: 1125–1130.
43. Rosa TT, Palatini P: Clinical value of microalbuminuria in hypertension. *J Hypertens* 2000; **18**: 645–654.
44. Barzilay JI, Peterson D, Cushman M, *et al*: The relationship of cardiovascular risk factors to microalbuminuria in older adults with or without diabetes mellitus or hypertension: the cardiovascular health study. *Am J Kid Dis* 2004; **44**: 25–34.
45. Vogt L, Navis G, Koster J, *et al*: The angiotensin II receptor antagonist telmisartan reduces urinary albumin excretion in patients with isolated systolic hypertension: results of a randomized, double-blind, placebo-controlled trial. *J Hypertens* 2005; **23**: 2055–2061.