—**Original**—

Clinical Usefulness of Measuring Pulse Wave Velocity in Predicting Cerebrovascular Disease: Evaluation from a Cross-Sectional and Longitudinal Follow-up Study

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Abstract

The present study was designed both as a cross-sectional and longitudinal follow-up study to evaluate the association between pulse wave velocity (PWV) and cardiovascular disease.

The subjects in this study included a total 260 patients (134 men and 126 women) ranging from 25 to 91 years (mean, 67.6 ± 11.0 years). Carotid to femoral PWV was measured in all patients. The subsequent development of a cerebrovascular or coronary event was defined as a cardiovascular event. The longitudinal follow-up study was conducted with the occurrence of a cardiovascular event as the endpoint. The patients were classified into two groups: an L group with a PWV of less than 10 m/sec and an H group with a PWV of 10 m/sec or higher.

Cross-sectional study at baseline: The H group patients were significantly older than the L group patients. The prevalence of hypertension, cardiovascular disease, ischemic heart disease, and cerebrovascular disease were significantly higher in the H group. Systolic blood pressure and serum uric acid were significantly higher in the H group than in the L group. However, there were no significant differences between the two groups with respect to other risk factors. Multivariate analysis using the prevalence of cardiovascular disease as the dependent variable showed "age" and "H group" to be independent variables. When the prevalence of ischemic heart disease or cerebrovascular disease was used as dependent variable, only "age" was an independent variable.

Longitudinal follow-up study: The prevalence of cardiovascular event and cerebrovascular event were significantly higher in the H group than in the L group. The prevalence of coronary event in the H group tended to be higher than in the L group, but the difference was not statistically significant. Multivariate analysis using the cardiovascular event rate or coronary event rate as the dependent variable showed only "age" to be an independent variable. When the cerebrovascular event rate was used as the dependent variable,"uric acid" and "H group" were independent variables.

The results of this study suggest a higher rate of cerebrovascular disease in patients with high PWV. (J Nippon Med Sch 2001; 68: 490—497)

Key words: pulse wave velocity, cardiovascular disease, longitudinal follow-up study, atherosclerosis, cerebral infarction

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Introduction

Measurement of pulse wave velocity (PWV) is a relatively simple and noninvasive means of evaluating atherosclerosis. Several studies have described an association between various risk factors for atherosclerosis and PWV[1-5]. Multivariate analyses in these studies have generally shown a relationship between age and PWV. Most of the studies relating PWV to cholesterol and/or dyslipidemia found minimal or inconsistent correlations[6,7]. However, several reports differ in their conclusions regarding the association between other risk factors and PWV[5,8,9]. There has also been a lack of consensus regarding the association between PWV and cardiovascular disease[1-5]. We believe that one reason for this discrepancy has been the fact that all these previous investigations were cross-sectional studies. Therefore, the present study was designed both as a cross-sectional and longitudinal follow-up study to investigate the clinical usefulness of measuring PWV and the relationship of these findings to cardiovascular disease.

Materials and Methods

The present study included 260 patients (134 men and 126 women) treated by the Division of Geriatric Medicine at Nippon Medical School Hospital between March 1993 and November 1997. The patients ranged from 25 to 91 years (mean, 67.6 ± 11.0 years). Each patient fasted overnight, and early the next morning, blood pressure was measured, blood samples were drawn from forearm vein, and PWV was then measured. Patients with known atrial fibrillation, patients with any arrhythmia detected during measurement of PWV, and patients on hemodialysis were excluded.

A diagnosis of angina pectoris was based on symptoms and typical changes on electrocardiography (ECG). A diagnosis of myocardial infarction was based on a history of acute myocardial infarction in association with ECG and serum enzyme changes. If there were suspected changes on ECG, further cardiac ultrasound or radioisotope studies were performed to confirm the presence of an infarct lesion. ECGs were assessed in accordance with the Minnesota code. Any patient diagnosed with myocardial infarction and/or angina pectoris was considered to have ischemic heart disease (IHD). For evaluation of cerebrovascular disease, a transient ischemic attack (TIA) was diagnosed in patients with focal neurologic symptoms that subsided within 24 hours and no responsible lesion on computed tomography (CT) or magnetic resonance imaging (MRI) of the brain. A cerebral infarction was diagnosed in patients with a history of focal neurologic symptoms and a corresponding infarct lesion on CT or MRI of the brain. Any patient diagnosed with IHD or cerebrovascular disease was considered to have cardiovascular disease.

PWV was measured with patients in the supine position after 15 min of bed rest using a pulse-wave velocimeter (model PWV-200, Fukuda Denshi, Tokyo). The PWV values were standardized for a diastolic pressure of 80 mmHg. PWV was measured for five consecutive pulses and average values were used for analysis.

Follow-up evaluations were performed up to 31 August 1999 in patients in whom PWV was measured (mean follow-up period, 1,144.0 ± 572.3 days). Each patient was followed up in the outpatient clinic, including biochemical blood studies, chest x-rays, and ECGs every 6 months. Patients with any abnormal symptoms, signs, laboratory studies, x-rays, or ECGs received further detailed evaluation. The development of IHD based on the previously mentioned diagnostic criteria or the occurrence of sudden death was regarded as a "coronary event". The development of a TIA or cerebral infarction based on the previously mentioned criteria was regarded as a "cerebrovascular event". The development of either a coronary event or cerebrovascular event was considered to be a "cardiovascular event".

Information was also obtained for patients no longer receiving medical care at our clinic. We contacted the physician directly after obtaining patient consent to inquire about the presence or absence of any cardiovascular event. If the new physician was not known, we contacted the patient by telephone to inquire about their status. For patients who died or those with cardiovascular event, we attempted to directly contact the current attending physician.

Information about 46 patients was obtained in the above manner. No information could be obtained for 8 patients; these patients were considered dropouts from the study. Follow-up observation was discontinued in 19 patients. The reason was death in 18 patients (cancer, n=8; pneumonia, n=6; subarachnoid hemorrhage, n=2; asphyxia, n=2). One patient had been placed on hemodialysis.

All of the data were entered into a computerized database and analyzed using SPSS (Statistical Package Version 10.0; SPSS Inc, Chicago, Illinois USA). The data in this report are expressed as mean ± SD. Categorical variables were compared by Chi-square analysis (Yates' correction used if necessary). Continuous variables were compared by Student's *t* test. The event rates were compared by Kaplan-Meier analysis (log-rank test). Logistic regression and a Cox proportional hazard model were used for multivariate analysis. For multivariate analysis, 3 sets of explanatory variables were used, including age, tobacco lifelong dose, the presence of diabetes mellitus, gender (ie, male sex), systolic blood pressure, uric acid, total cholesterol, triglyceride, and H group (model 1); diastolic blood pressure instead of systolic blood pressure (model 2); and hypertension instead of systolic blood pressure (model 3).

Results

Cross-Sectional Study at Baseline

Fig. 1 shows the prevalence of cardiovascular disease, IHD, and cerebrovascular disease for subgroups of patients with different PWV values stratified in 1 m/sec increments. The prevalence of cardiovascular disease and IHD increased gradually with higher PWV values ($p<0.021$, $p<0.022$, respectively). The prevalence of cerebrovascular disease was generally 20% or less in patients with a PWV of less than 10 m/sec and 30% or higher in patients with a PWV exceeding 10 m/sec. However, there was no statistically significant difference. Based on the above results, the patients were divided into two groups using 10 m/sec as the cutoff value. Patients with a PWV of less than 10 m/sec were classified as the L (low) group, and patients with a PWV of 10 m/sec or greater were classified as the H (high) group.

Table 1 shows the baseline characteristics of patients in the L group and H group. The H group patients were significantly older than the L group patients. The prevalence of hypertension, cardiovascular disease, IHD, and cerebrovascular disease were also significantly higher in the H group. All patients with cerebrovascular disease had lacunar infarcts. Systolic blood pressure and uric acid were significantly

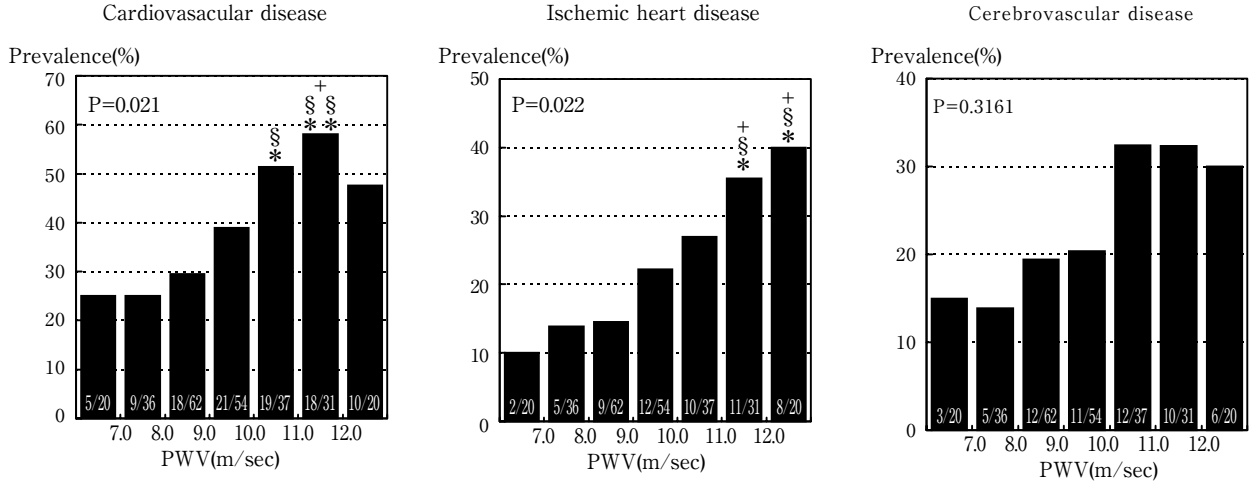

Fig. 1 Prevalence of the presentation of cardiovascular disease (left panel), ischemic heart disease (middle panel), and cerebrovascular disease (right panel) as a function of pulse wave velocity + $p<0.1$ vs −7.0 m/sec group, § $p<0.05$, §§ $p<0.01$ vs 7.0～8.0 m/sec group, *$p<0.05$, **$p<0.01$ vs 8.0～9.0 m/sec group using Chi-square analysis.

Table 1 Characteristics of the 260 study participants

Characteristic	L-Group	H-Group	P-Value
Number of cases (male/female)	171 (85/86)	89 (49/40)	
Age	65.1 ± 11.1	72.3 ± 8.9	0.001
Body mass index (kg/m^2)	22.4 ± 3.4	22.6 ± 3.9	0.620
Diabetes	88 (51.5%)	41 (46.1%)	0.435
Hypertension	81 (47.4%)	61 (68.5%)	0.002
Cardiovascular disease	53 (31.0%)	47 (52.8%)	0.001
Ischemic heart disease	28 (16.4%)	29 (32.6%)	0.004
Angina pectoris	21 (12.3%)	18 (20.2%)	0.101
Myocardial infarction	8 (4.7%)	15 (16.9%)	0.002
Cerebrovascular disease	31 (18.1%)	28 (31.5%)	0.019
Transient ischemic attack	4 (2.3%)	3 (3.4%)	0.694
Cerebral infarction (lacunar infarction)	28 (16.4%)	27 (30.3%)	0.011
Tobacco lifelong dose (pack-years)	22.5 ± 30.7	29.5 ± 42.5	0.173
Blood pressure (mmHg)			
Systolic	140.2 ± 18.6	145.5 ± 21.0	0.038
Diastolic	800 ± 11.9	77.6 ± 13.0	0.143
Total cholesterol (mg/d*l*)	206.8 ± 39.7	198.5 ± 36.5	0.103
Triglyceride (mg/d*l*)	129.1 ± 78.6	120.8 ± 50.5	0.365
Uric Acid (mg/d*l*)	5.1 ± 1.3	5.5 ± 1.3	0.032
Creatinine (mg/d*l*)	1.02 ± 0.65	1.04 ± 0.38	0.801
Fasting Plasma Glucose (mg/d*l*)	132.5 ± 51.4	123.8 ± 42.0	0.181

* Plus-minus value are mean ± SD.

higher in the H group than in the L group.

Table 2 shows the results of logistic regression analyses using the "model 1" factors. Analysis using the prevalence of cardiovascular disease as the dependent variable showed "age" and "H group" to be independent variables. When the prevalence of IHD or cerebrovascular disease was used as the dependent variable, only "age" was an independent variable. When analyses were performed using the "model 2" factors, the results were the same as with the "model 1" factors. Analyses using the "model 3" factors with cardiovascular disease, IHD, or cerebrovascular disease as the dependent variables each showed "age" as the only independent variable.

Longitudinal Follow-up Study

During study follow-up, coronary events occurred in 21 patients, including angina pectoris in 4 patients, myocardial infarction in 16 patients, and sudden death in 1 patient. Cerebrovascular events occurred in 9 patients; all these events were cerebral infarctions, including 2 patients who died as a result of cerebral infarction.

Fig. 2 depicts the event-free rates in the L group and H group patients. The cardiovascular event rate and cerebrovascular event rate were significantly higher in the H group than in the L group. The coronary event rate in the H group tended to be higher than in the L group, but the difference was not statistically significant.

Table 3 shows the results of analyses using a Cox proportional hazard model with "model 1" factors. Analyses using the cardiovascular event or coronary event as the dependent variable showed "age" to be the only independent variable. When the cerebrovascular event was used as the dependent variable, "uric acid" and "H group" were independent variables. Analyses with "model 2" and "model 3" factors showed results similar to those using the "model 1" factors.

Discussion

In the present study, we stratified the measured PWV values in 1 m/sec increments in order to compare the rates of cardiovascular disease, IHD, and cerebrovascular disease. The prevalence of each of these disorders tended to be higher when the PWV was 10 m/sec and higher. We therefore divided the

Table 2 Logistic regression analysis of the presence of cardiovascular disease, ischemic heart disease, and cerebrovascular disease

Cardiovascular disease

Variable	β Coefficient	Standard Error	Odds Ratio	P Value	95%CI
Male sex	− 0.333	0.339	0.717	0.327	0.369—1.394
Age	0.057	0.016	1.058	0.000	1.026—1.092
Tobacco lifelong dose	0.000	0.000	1.000	0.101	1.000—1.001
Diabetes Mellitus	− 0.240	0.313	0.787	0.443	0.426—1.453
Systolic blood pressure	− 0.003	0.007	0.997	0.703	0.983—1.012
Total cholesterol	− 0.001	0.004	0.999	0.840	0.991—1.007
Triglyceride	0.003	0.002	1.003	0.217	0.999—1.007
Uric acid	− 0.150	0.116	0.860	0.196	0.685—1.081
H-Group	0.609	0.302	1.838	0.044	1.017—3.324

Ischemic heart disease

Variable	β Coefficient	Standard Error	Odds Ratio	P Value	95%CI
Male sex	− 0.134	0.384	0.875	0.728	0.412—1.857
Age	0.047	0.018	1.049	0.009	1.012—1.087
Tobacco lifelong dose	0.000	0.000	1.000	0.242	1.000—1.001
Diabetes Mellitus	0.261	0.360	1.298	0.469	0.641—2.628
Systolic blood pressure	− 0.010	0.009	0.990	0.223	0.973—1.006
Total cholesterol	− 0.003	0.005	0.997	0.550	0.988—1.006
Triglyceride	0.001	0.002	1.001	0.755	0.996—1.006
Uric acid	− 0.020	0.134	0.980	0.882	0.755—1.274
H-Group	0.635	0.340	1.888	0.061	0.970—3.674

Cerebrovascular disease

Variable	β Coefficient	Standard Error	Odds Ratio	P Value	95%CI
Male sex	− 0.478	0.389	0.645	0.261	0.301—1.384
Age	0.071	0.019	1.074	0.000	1.034—1.114
Tobacco lifelong dose	0.000	0.000	1.000	0.726	1.000—1.001
Diabetes Mellitus	− 0.355	0.364	0.701	0.330	0.344—1.432
Systolic blood pressure	− 0.002	0.008	0.998	0.834	0.982—1.015
Total cholesterol	0.000	0.005	1.000	0.956	0.991—1.009
Triglyceride	0.004	0.002	1.004	0.123	0.999—1.008
Uric acid	− 0.101	0.135	0.904	0.454	0.694—1.177
H-Group	0.396	0.340	1.485	0.243	0.764—2.892

patients into two groups based on the PWV, using a cutoff value of 10 m/sec, to compare the two groups. Blacher et al.[1] reported a higher cardiovascular disease prevalence in patients with a PWV of 13 m/sec or greater. As in our study, Blacher et al.[1] also measured PWV between the common carotid and femoral arteries. However, the apparatus they used was different, and the distribution of measured values and mean values were higher than those that we observed. The results of our measurements were in general agreement with other studies in Japanese patients using similar equipment[4, 10, 11].

In our study we used multivariate analysis to examine the significance of PWV in relation to cardiovascular disease. Age is a common independent variable for the prevalence of cardiovascular disease, IHD, and cerebrovascular disease. The "H group" is an independent risk factor only for cardiovascular disease. Lehman et al.[12] reported elevated PWV values in patients with cerebral infarction and relation between number of cardiovascular risk factors/events and PWV[5]. Blacher et al.[1] and Eldon et al.[5] reported a correlation between cerebrovascular/transient ischemic event and PWV. Lehmann[13] reported a correlation between PWV and not only cardiovascular event but also carotid atherosclerosis. Blacher et al.[1] also

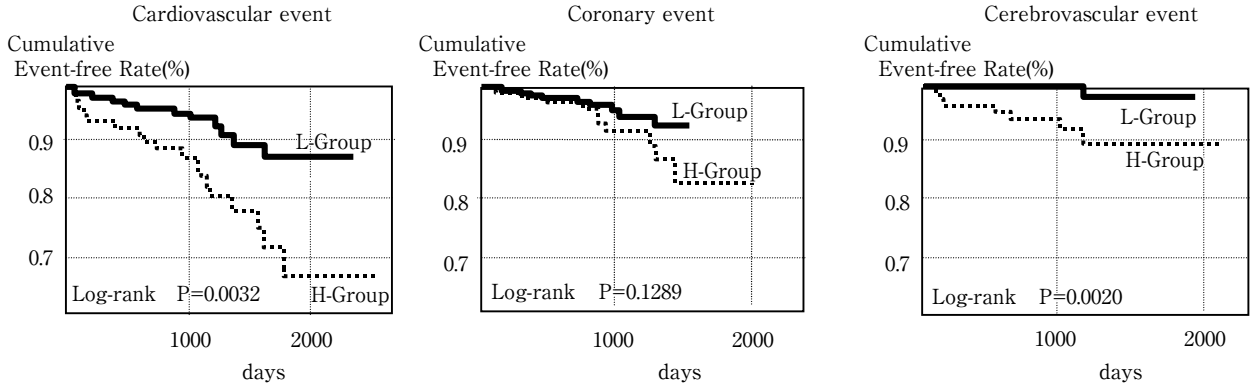

Fig. 2 Kaplan-Meier analysis of the time to a definite cardiovascular event (left panel), coronary event (middle panel), and cerebrovascular event (right panel), according to pulse wave velocity group during follow-up period.

Table 3 Cox proportional hazards models to the cardiovascular event, coronary event, and cerebrovascular event

Cardiovascular event

Variable	β Coefficient	Standard Error	Relative Risk	P Value	95%CI
Male sex	− 0.517	0.470	0.602	0.279	0.240—1.510
Age	0.060	0.024	1.062	0.014	1.012—1.114
Tobacco lifelong dose	0.000	0.000	1.000	0.635	1.000—1.001
Diabetes Mellitus	0.186	0.444	1.204	0.676	0.504—2.876
Systolic blood pressure	0.003	0.010	1.003	0.754	0.983—1.024
Total cholesterol	− 0.003	0.005	0.997	0.622	0.987—1.008
Triglyceride	− 0.003	0.004	0.997	0.450	0.988—1.005
Uric acid	0.000	0.176	1.000	0.998	0.709—1.411
H-Group	0.706	0.413	2.025	0.087	0.902—4.550

Coronary event

Variable	β Coefficient	Standard Error	Relative Risk	P Value	95%CI
Male sex	− 0.464	0.536	0.629	0.386	0.220—1.797
Age	0.080	0.029	1.083	0.006	1.023—1.147
Tobacco lifelong dose	0.000	0.000	1.000	0.875	0.999—1.001
Diabetes Mellitus	0.355	0.514	1.427	0.489	0.521—3.905
Systolic blood pressure	0.006	0.013	1.006	0.627	0.982—1.031
Total cholesterol	− 0.001	0.006	0.999	0.818	0.986—1.011
Triglyceride	− 0.005	0.005	0.995	0.315	0.984—1.005
Uric acid	0.249	0.203	1.283	0.221	0.861—1.911
H-Group	0.068	0.479	1.071	0.887	0.419—2.736

Cerebrovascular event

Variable	β Coefficient	Standard Error	Relative Risk	P Value	95%CI
Male sex	− 1.294	1.063	0.274	0.223	0.034—2.200
Age	0.010	0.043	1.010	0.823	0.927—1.100
Tobacco lifelong dose	0.000	0.000	1.000	0.480	0.999—1.001
Diabetes Mellitus	− 0.270	0.902	0.763	0.765	0.130—4.475
Systolic blood pressure	− 0.009	0.019	0.991	0.625	0.954—1.029
Total cholesterol	− 0.004	0.012	0.996	0.705	0.973—1.019
Triglyceride	0.002	0.007	1.002	0.828	0.988—1.015
Uric acid	− 0.763	0.362	0.446	0.035	0.229—0.949
H-Group	3.003	1.181	20.149	0.011	1.992—203.864

revealed a correlation between cardiovascular disease and PWV. However, there have also been conflicting reports. Ohmori et al.[4] found no association between PWV and cardiovascular disease. Megnien et al.[14] noted no relationship between PWV and coronary artery calcification or atherosclerotic changes in other vessels. Ouchi et al.[11] using multivariate analysis showed no correlation between PWV and findings on coronary angiography. This discrepancy may be attributable to various factors. One is the variation in ages among study patients. Measured PWV values are known to be significantly affected by age. Another is that previous studies have been conducted as cross-sectional studies; thus, patients with severe cardiovascular disease may not have been included. Therefore, we believed that a longitudinal follow-up study was necessary to address these issues.

This follow-up evaluation results did show significantly higher cardiovascular event and cerebrovascular event rates in patients with a high PWV. Multivariate analyses with respect to the cardiovascular event and coronary event showed "age" to be the only independent explanatory variable. However, for the cerebrovascular event,"uric acid" and "high PWV" were independent variables. Our findings suggest that a high PWV value might be useful in predicting the development of cerebral infarction. A high PWV was not an independent risk factor for development of a coronary event in the follow-up study. The number of years of follow-up in the L group was relatively short. This in part may have contributed to the absence of a statistically significant difference in coronary event rates between the low and high PWV groups

The stage in the process of atherosclerosis at which PWV increases still remains unclear based on the results in this study. Lacolly et al.[15]reported no association between PWV and nitric oxide. On the other hand, Nishiwaki et al.[16] described a correlation between PWV and plasminogen activator inhibitor (PAI-1) and thrombin antithrombin III complex (TAT). Based on information in these reports, PWV may not be related to very early atherosclerotic changes such as endothelial cell damage, but PWV probably begins to increase relatively early during the progression of atherosclerosis[17]. This is in agreement with findings in an animal study in which an increase in PWV occurred earlier than macroscopic atherosclerotic changes[18].

In conclusion, the findings in our study suggest that measurement of PWV is clinically useful means in predicting the development of cerebral infarction.

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(Received, February 6, 2001)
(Accepted, May 17, 2001)