Dokkyo Journal of Medical Sciences
35(3) : 161～168, 2008

Originals

Association Between Nerve Conduction Velocity and Clinical Parameters Related to Diabetic Complications in Patients with Type 2 Diabetes

Kohzo Takebayashi, Mariko Suetsugu, Yoshimasa Aso, Toshihiko Inukai

Department of Internal Medicine, Dokkyo Medical University Koshigaya Hospital, Koshigaya, Japan

SUMMARY

The main purpose of the study was to investigate the association of median motor nerve conduction velocity (MCV) and sural sensory nerve conduction velocity (SCV) with parameters related to diabetic complications in patients with type 2 diabetes. A total of 263 patients hospitalized for glycemic control from 1999 to 2006 who underwent single or multiple nerve conduction velocity tests (at least a right median MCV test) were enrolled in the study retrospectively. Right median MCV showed a significant negative correlation with age and diabetic duration, and was also significantly negatively correlated with systolic blood pressure (SBP) and log urinary albumin excretion (UAE). Right median MCV showed strong positive correlations with left median MCV and right median SCV, and significant but relatively mild positive correlations with right peroneal MCV and right sural SCV. In multiple regression analysis, only SBP and diabetic duration showed a significant association with right median MCV. Although right sural SCV showed significant negative correlations with SBP and log UAE, the correlations were relatively weak compared with those for right median MCV. Of 215 patients who underwent complete sural SCV measurements, right and left sural SCV were detected in 159 (74%) and 163 patients (76%), respectively. In conclusion, these results suggest that median MCV is more closely associated with markers related to diabetic complications such as SBP or UAE, compared with sural SCV, but that sural SCV is more sensitive than median MCV for detection of diabetic neuropathy.

Key Words : Diabetic neuropathy, nerve conduction velocity, type 2 diabetes

INTRODUCTION

Among diabetic miocroangiopathies including neuropathy, retinopathy and nephropathy, neuropathy generally develops at a relatively early stage after onset of diabetes[1]. Progression of diabetic neuropathy may result in sudden death from cardiac autonomic neuropathy[2～4] or require amputation of the lower extremities due to impairment of the peripheral autonomic and sensory nerves, and therefore early and accurate diagnosis of diabetic neuropathy is important in patients with diabetes. Subjective symptoms such as pain and numbness of the foot is helpful in diagnosis, but these symptoms weaken because of hypoesthesia with severe progression of neuropathy[1] and objective tests are required for accurate diagnosis. Measurement of nerve conduction velocity is a reliable and recommended test for diabetic neuropathy because of its high sensitivity and reproducibility[5], although this

Received April 24, 2008 ; accepted May 30, 2008
Reprint requests to : Kohzo Takebayashi MD.
Department of Internal Medicine, Dokkyo Medical University Koshigaya Hospital, 2-1-50, Minami-Koshigaya, Koshigaya, 343-8555, Japan

method requires a lengthy measurement time and is somewhat invasive due to the pain caused by electrical stimulation.

Factors such as age, diabetic duration, glycemic control, blood pressure and circulating lipid concentrations appear to influence nerve conduction velocity in patients with type 2 diabetes, and these patients also frequently develop hypertension or hyperlipidemia. However, the factors that are most important in the decrease of nerve conduction velocity in patients with type 2 diabetes have not been established clearly. Based on this background, the main purpose of the current study was to investigate the association of median motor nerve conduction velocity (MCV) and sural sensory nerve conduction velocity (SCV) with parameters related to diabetic complications in patients with type 2 diabetes. We also explored correlations of median MCV with median SCV, peroneal MCV and sural SCV, and examined the correlation between median MCV on both sides.

PATIENTS AND METHODS

Patients

The study included 263 patients admitted to our hospital for glycemic control from 1999 to 2006 who underwent single or multiple nerve conduction velocity tests (at least a test of right median nerve conduction velocity). These patients were enrolled in the study retrospectively based on our previous studies[6~8]. Exclusion of specific patients was not performed, but several patients were enrolled redundantly among these studies and data from the latest study were used for these patients. The clinical characteristics and laboratory data for the 263 patients are shown in Table 1.

Table 1 Clinical characteristics and laboratory data of the type 2 diabetic subjects

		Diabetic subjects
No. (male/female)		263 (146/117)
Age (years old)		59.4 ± 11.6
Duration of diabetes (years)		11.4 ± 8.9
FPG (mg/dL)		156.7 ± 65.3
HbA_{1C} (%)		9.6 ± 2.2
BMI (kg/m^2)		24.3 ± 4.4
Right Median MCV (m/s)		50.7 ± 4.9
Left Median MCV (m/s) (n = 214)		50.9 ± 4.8
Right Median SCV (m/s) (n = 237)		47.0 ± 7.5
Left Median SCV (m/s) (n = 198)		47.8 ± 7.7
Right Peroneal MCV (m/s) (n = 188)		41.5 ± 5.3
Left Peroneal MCV (m/s) (n = 191)		41.1 ± 5.6
Right Sural SCV (m/s) (n = 159)		42.2 ± 5.7
Left Sural SCV (m/s) (n = 163)		42.3 ± 6.3
Therapy (n)	Diet	10
	OHA	113
	Insulin	140
Anti-hypertensive drugs (+/−)		176/87
Retinopathy (n)	NDR	131
	SDR	52
	PDR	80
*Diabetic neuropathy (+/−)		45/67

FPG : fasting plasma glucose, HbA_{1c} : hemoglobin A_{1c}, BMI : body mass index, MCV : motor nerve conduction velocity, SCV : sensory conduction nerve velocity, OHA : oral hypoglycemic agents, NDR : no diabetic retinopathy, SDR : simple diabetic retinopathy, PDR : proliferative diabetic retinopathy

* : Diabetic neuropathy was evaluated only in 112 in the entire 263 patients. It was defined that the patients had diabetic neuropathy when the patients showed both "absent ATR" and "subjective symptoms assessed by pain or numbness of foot".

Methods

All tests were performed during hospitalization. Venous blood samples for biochemical tests were collected in the morning before breakfast after an overnight fast of at least 10 hours.

Measurement of MCV and SCV : MCV and SCV were measured in a supine position in a quiet room maintained at a temperature of about 25℃. Median and peroneal MCV on both sides were determined at the elbow and wrist, and at the popliteal fossa and inside of the ankle, respectively. SCV was determined in the median and sural nerves on both sides. For measurement of MCV, supramaximal stimuli were applied to the wrist and elbow or popliteal fossa and inside of the ankle, and the compound muscle action potential was measured with surface electrodes attached to the palm (for median MCV) or lateral portion of the sole of the foot (for peroneal MCV). MCV was calculated from the motor nerve conduction time, which is the difference between the proximal and distal latencies divided by the distance from the elbow to the wrist (for median MCV) or from the popliteal fossa to the inside of the ankle (for peroneal MCV). For SCV, a

surface electrode was attached to the wrist (for median SCV) or lateral malleolus of the ankle (for sural SCV), and supramaximal stimuli were applied to the index (second) finger (for median SCV) or to a 15-cm region proximal to the active electrode (for sural SCV). SCV was calculated from the conduction time divided by the distance.

Measurement of the systolic blood pressure response to standing (ΔSBP) : ΔSBP was measured as the fall in systolic blood pressure when the subject arose from a supine to a standing position. Specifically, blood pressure was measured several times in the afternoon, always more than 2 h after meals and after each subject had maintained a supine position at rest for more than 10 min[9]. Then the subject stood up slowly and blood pressure was measured again. The difference between the standing SBP and the final supine SBP was defined as ΔSBP, with a negative number indicating a decrease in blood pressure on standing.

Achilles tendon reflex (ATR) : The ATR was classified as "normal", "weak" and "absent" based on the degree of the reflex, which was assessed subjectively by doctors.

Determination of the coefficient of variation of the RR interval (CV_{RR}) : CV_{RR} was chosen for assessment of heart rate variability. Electrocardiographic (ECG) RR intervals were measured from 100 consecutive cardiac cycles recorded mostly in the morning. During recording, all subjects were at rest in a supine position and were instructed to maintain a respiratory rate above 9 breaths/min to decrease the effect of respiratory sinus arrhythmia. CV_{RR} was calculated using the formula : CV_{RR} = (standard deviation of RR/mean RR) × 100. Patients with arrythmia were excluded from CV_{RR} analysis.

Plasma glucose, HbA_{1C}, and serum lipid concentrations : Fasting plasma glucose was evaluated by an automated glucose oxidase method (Glucose Auto Stat GA1160 ; Arkray, Kyoto, Japan). HbA_{1C} was measured by high-performance lipid chromatography (HPLC ; Hi-auto A_{1C}, HA8150 ; Arkray). This method only detects HbA_{1C} and the normal range is 4.3% to 5.8%. Serum total, low-density and high-density lipoprotein cholesterol (TC, LDL-C, and HDL-C) and serum triglyceride (TG) concentrations were measured enzymatically.

Blood pressure : Blood pressure was measured using a mercury sphygmomanometer in the morning at rest.

Urinary albumin excretion (UAE) : UAE was measured once during the hospital stay by enzyme immunoassay in a 24-hr urine specimen maintained at 4℃. Albumin values were corrected for the urinary creatinine concentration. Creatinine clearance (Ccr) was also assessed using a 24-hr urine specimen.

Assessment of diabetic retinopathy : Diabetic retinopathy was assessed by each patient's ophthalmologist in our hospital according to the Davis classification : [10] no diabetic retinopathy (NDR), simple diabetic retinopathy (SDR) or proliferative diabetic retinopathy (PDR).

Assessment of subjective symptoms of diabetic neuropathy : These symptoms were evaluated by pain or numbness of foot, based on each patient's declaration ("normal", "mild", and "severe").

Ethical considerations : All subjects gave informed consent to inclusion in the study. The study was performed according to the guidelines in the Declaration of Helsinki.

Statistical methods : All data are presented as means ± standard deviation (SD). The significance of correlations between two variables was determined by simple regression analysis. UAE values were $\log_{10}$-transformed because of their skewed distribution. Comparisons between two groups were made using an unpaired *t* test. For multiple comparisons, significances of individual differences were assessed using a Bonferroni test. Multiple regression analysis with right median MCV as the dependent variable was performed in 256 patients ; the tested independent variables were age, BMI, duration of diabetes, SBP, diastolic blood pressure (DBP), FPG, HbA_{1C}, TC and TG. No combination with a strong correlation ($R > 0.9$) was found among these variables. A P value < 0.05 was accepted as indicating statistical significance.

RESULTS

Correlations between right median MCV or right sural SCV with various parameters in type 2 diabetic patients are shown in Table 2, and the results of multiple regression analysis of factors associated with right median MCV are summarized in Table 3. Right median MCV was detected in all 263 patients in the study

Table 2 Correlation between right median MCV or right sural SCV and various factors in type 2 diabetic patients

Variant	(n) Right Median MCV		(n) Right Sural SCV	
Age (years)	(263) r = − 0.1334	P = 0.0306*	(159) r = 0.0054	P = 0.9464
BMI (kg/m^2)	(263) r = 0.0362	P = 0.5584	(159) r = 0.0198	P = 0.8044
Duration (years)	(263) r = − 0.2186	P = 0.0004*	(159) r = − 0.1351	P = 0.0896
FPG (mg/dL)	(263) r = − 0.1030	P = 0.0955	(159) r = 0.2068	P = 0.0088*
HbA_{1C} (%)	(263) r = 0.0193	P = 0.7550	(159) r = 0.0815	P = 0.3074
SBP (mmHg)	(263) r = − 0.3024	P < 0.0001*	(159) r = − 0.1695	P = 0.0327*
DBP (mmHg)	(263) r = − 0.0880	P = 0.1547	(159) r = − 0.1773	P = 0.0254*
TC (mg/dL)	(259) r = − 0.1025	P = 0.0999	(158) r = − 0.0357	P = 0.6558
TG (mg/dL)	(256) r = − 0.0532	P = 0.3966	(155) r = − 0.0836	P = 0.3012
HDL-C (mg/dL)	(208) r = − 0.1366	P = 0.0492*	(155) r = − 0.0110	P = 0.8920
LDL-C (mg/dL)	(208) r = 0.0138	P = 0.8433	(155) r = 0.0150	P = 0.8530
U-CPR (pg/mL)	(136) r = 0.1233	P = 0.1526	(65) r = 0.1397	P = 0.2671
log_{10}UAE (mg/g.Cr)	(249) r = − 0.3890	P < 0.0001*	(150) r = − 0.2147	P = 0.0083*
CV_{RR} (%)	(249) r = 0.2237	P = 0.0004*	(148) r = 0.0079	P = 0.9235
ΔSBP (mmHg)	(158) r = 0.4195	P < 0.0001	(73) r = 0.2690	P = 0.0213*
Median MCV (Left) (m/s)	(214) r = 0.8742	P < 0.0001*	(158) r = 0.4460	P < 0.0001
Median SCV (m/s)	(237) r = 0.6129	P < 0.0001*	(152) r = 0.2524	P = 0.1050
Peroneal (MCV) (m/s)	(188) r = 0.4025	P < 0.0001*	(150) r = 0.5629	P < 0.0001*
Sural SCV (m/s)	(159) r = 0.4025	P < 0.0001*	—	—

r : Pearson's correlation coefficient, P : P value, P < 0.05 are defined as statistical significance. (n) : the number of patients

BMI : body mass index, FPG : fasting plasma glucose, HbA_{1c} : hemoglobin $A_{1c,}$ SBP : systolic blood pressure, DBP : diastolic blood pressure, TC : total cholesterol, TG : triglyceride, HDL-C : high density lipoprotein cholesterol, LDL-C : low density lipoprotein cholesterol, UAE : urinary albumin excretion, $CV_{R\text{-}R}$: coefficient of variation of RR intervals, ΔSBP : systolic blood pressure response to standing

Table 3 Multiple regression analysis with right Median MCV in 256 patients with type 2 diabetes

Independent variable	β	F	P
Age (year)	− 0.0345	0.2491	0.6182
BMI (kg/m^2)	0.0125	0.0390	0.8434
Duration (year)	− 0.1338	3.9103	0.0491*
SBP (mm Hg)	− 0.3047	15.7635	< 0.0001*
DBP (mm Hg)	0.0528	0.5255	0.4692
FPG (mg/dL)	− 0.1156	3.3179	0.0697
HbA_{1C} (%)	− 0.0268	0.1538	0.6953
TC (mg/dL)	− 0.0632	0.8757	0.3503
TG (mg/dL)	− 0.0355	0.2604	0.6103
(R^2 for the model : 14.7 %)			

β : standardized regression coefficient, F : F value, P : P value, R^2 : coefficient of determination.

BMI : body mass index, SBP : systolic blood pressure, DBP : diastolic blood pressure, FPG : fasting plasma glucose, HbA_{1c} : hemoglobin A_{1c}, TC : total cholesterol, TG : triglyceride

and showed significant negative correlations with age, diabetic duration and HDL-C. Right median MCV was also significantly negatively correlated with SBP and log UAE (Fig. 1A, B) and significantly positive correlated with CV_{RR} and ΔSBP.

Right median MCV showed strong positive correlations with left median MCV and right median SCV (Fig. 2A, B) and a significant but relatively mild positive correlation with right peroneal MCV and right sural SCV (Fig. 2C). In multiple regression analysis with right median MCV as the dependent variable, only SBP (P < 0.0001) and diabetic duration (P = 0.0491) showed a significant association. In contrast, right sural SCV showed significant positive correlations with ΔSBP, and significant negative correlations with SBP, DBP and log UAE. Of 215 patients who underwent complete sural SCV measurements, right and left sural SCV were detected in 159 (74 %) and 163

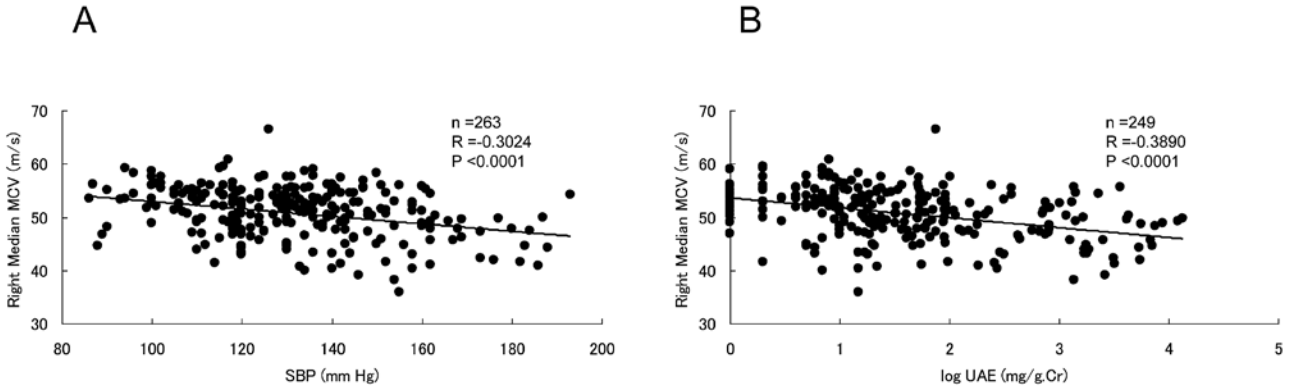

Fig. 1 The correlation between right median MCV and SBP (A) or log UAE (B)

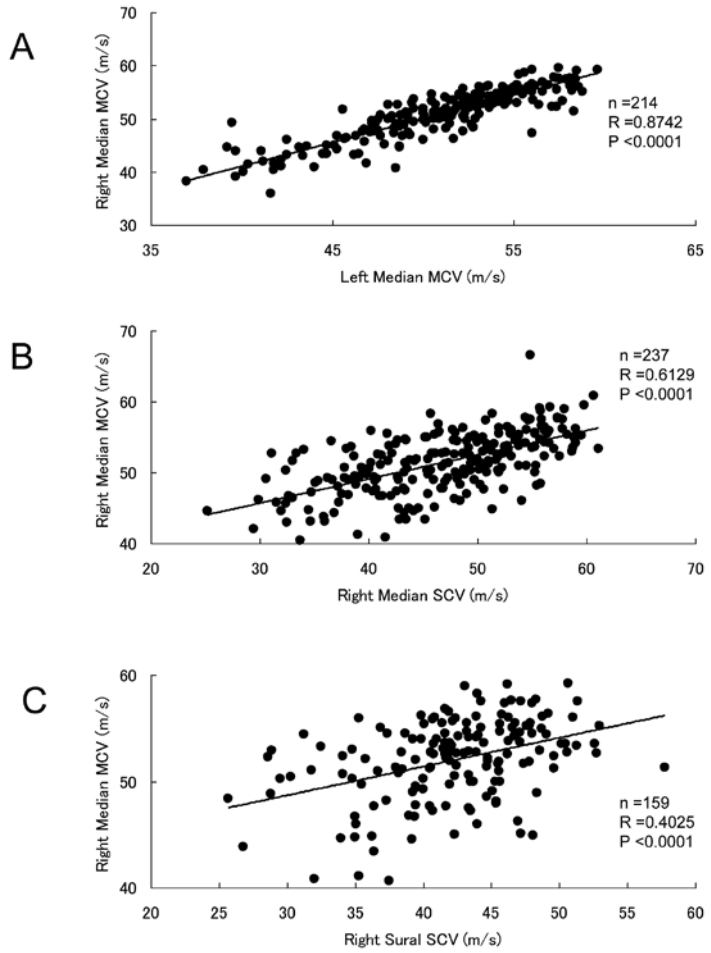

Fig. 2 The correlation between right median MCV and left median MCV (A), right median SCV (B) and right sural SCV (C)

patients (76%), respectively.

There were no-gender related differences in right median MCV, but significant decrease in right sural SCV in men's patients was obtained (41.3 ± 5.5 for men vs. 43.7 ± 5.7 m/s for women, P = 0.008).

Regarding retinopathy in the 263 patients, the right median nerve MCV was 52.3 ± 4.3 m/s in NDR patients, 50.7 ± 5.1 m/s in SDR patients, and 48.1 ± 4.7 m/s in PDR patients. MCV differed significantly between NDR and SDR (P = 0.0030), NDR and PDR (P < 0.0001), and SDR and PDR (P = 0.0022) patients (Fig. 3). The right median MCVs in patients treated

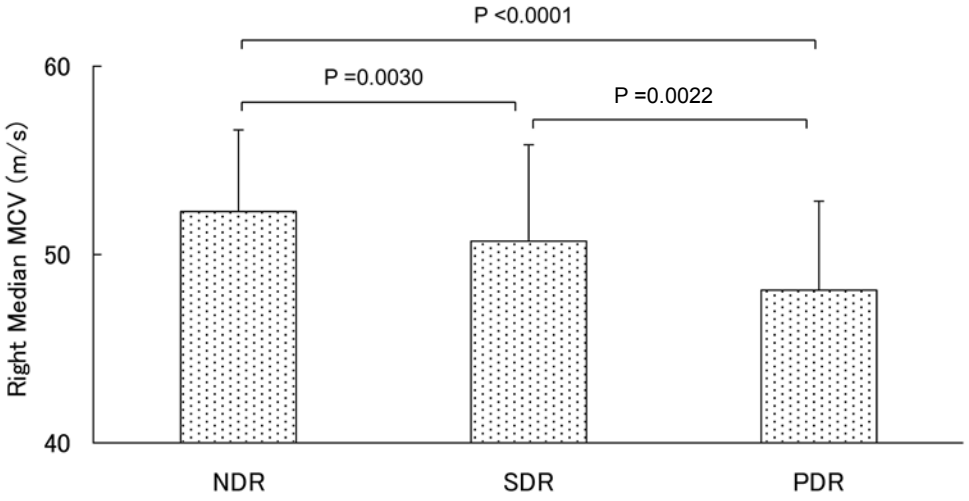

Fig. 3 The differnce in right median MCV among the NDR, SDR, and PDR patients

with diet alone (n = 10), in those treated with an oral hypoglycemic agent (OHA) (n = 113), and in those treated with insulin (n = 140) were 51.7 ± 4.3, 51.9 ± 4.2, and 49.7 ± 5.3 m/s, respectively ; a significant difference was detected only between patients treated with an OHA and those treated with insulin (P = 0.0003). The right median MCV differed significantly in patients who did (n = 87) and did not (n = 176) receive antihypertensive drugs (49.8 ± 4.8 and 51.1 ± 4.9 m/s, respectively ; P = 0.0345).

In patients who underwent right median MCV measurement, ATR were evaluated only in 112 patients. The number of patients with normal, weak, absent ATR was respectively 58, 30 and 24 ; no significant difference in right median MCV was obtained among these patients' groups. Regarding subjective symptoms, in these 112 patients, the number of patients assigned to "normal", "mild", and "severe" was respectively 61, 31, and 20. Significant difference in right median MCV was detected only between patients with normal and mild symptoms (P = 0.0308).

DISCUSSION

In the current study, median and peroneal MCV and median and sural SCV were all close to the lower limits described for healthy subjects[11]. These findings appear to be reasonable, since diabetes often causes diabetic neuropathy as a microangiopathy[1]. MCV showed significant negative correlations with age and diabetic duration, and the particularly strong correlation with diabetic duration is consistent with the importance of diabetic duration as a cause of diabetic neuropathy. Contrary to our expectation, median MCV did not correlate with fasting plasma glucose (FPG) or HbA_{1c}, which suggests that diabetic neuropathy is not always closely associated with short-term diabetic control. Notably, we found a significant negative correlation between median MCV and SBP, and SBP had the strongest association with median MCV as a dependent variable in multiple regression analysis. In previous studies we have also found significant associations of SBP with CV_{RR}[12] and QTc[13], which mainly reflect autonomic nervous function. Therefore, our current and previous studies suggest that SBP closely influences diabetic neuropathy. Although these results are based on cross-sectional observation, we speculate that long-term control of blood pressure may be more important for inhibition of progression of diabetic neuropathy, and that continuous treatment for hypertension may be important in prevention of progression of this complication. A further prospective study is needed to examine this hypothesis.

It is well known that hyperlipidemia (or dyslipidemia) is closely associated with diabetic macroangiopathy based on atherosclerosis. In fact, in the CARDS study, LDL-C-lowering therapy with atorvastatin in patients with type 2 diabetes with mild hyperlipidemia dramatically reduced cardiovascular events[14], suggesting that glycemic control and circulating LDL-C levels are very important in progression of diabetic macroangiopathy. However, in the current study, median MCV did not correlate with circulating

lipids levels, including TC, TG and LDL-C ; only HDL-C showed a weak negative correlation with median MCV. This suggests that circulating lipids levels are not strongly associated with diabetic neuropathy as reflected by median MCV. Furthermore, no correlation was observed between median MCV and BMI, suggesting that MCV is also unaffected by the degree of obesity. Taken together, our results show that median MCV is closely associated with SBP and diabetic duration but not with FPG, HbA_{1c}, lipids levels and BMI. Therefore, control of blood pressure and long-term (but not short-term) glycemic control may be especially important for inhibition of progression of diabetic neuropathy.

In the current study, we also investigated the association of median MCV with retinopathy and nephropathy. Median MCV was significantly lower in PDR patients compared with NDR or SDR patients, and there was also a significant negative correlation between median MCV and log UAE, which reflects the degree of diabetic nephropathy. These results indicate that progression of diabetic neuropathy proceeds in parallel with that of diabetic retinopathy and nephropathy, suggesting that it is important to evaluate retinopathy and nephropathy routinely in patients with a relatively low MCV.

Sural SCV is known to be an especially sensitive parameter in nerve conduction velocity tests[15], and in the current study sural SCV was detected in only about 75 % of patients with detectable MCV. Sural SCV was also closely correlated with variables related to diabetic complications, such as SBP and log UAE, but the correlations were relatively weak compared with those for median MCV. In addition, sural SCV did not correlate with age and diabetic duration, which were both significantly associated with median MCV. These results suggest that median MCV is more suitable than sural SCV as a standard marker in nerve conduction velocity tests. Furthermore, median MCV is generally easier to measure compared to sural SCV, which also supports the use of median MCV as a standard marker. Right median MCV was closely correlated with left MCV, and this suggests that measurement on one side only may be appropriate if patients do not have apparent organic lesions such as carpal tunnel syndrome, which can influence nerve conduction velocity. Furthermore, right median MCV and right median SCV were also closely correlated, and this suggests that measurement of median SCV may not always be needed in follow-up. Determination of sural SCV is important in the initial assessment of diabetic neuropathy, since measurement of sural SCV is more sensitive than measurement of median SCV.

Based on the above results, we recommend that measurements of median MCV (which has a close correlation with markers related to diabetic complications) and sural SCV (which has high sensitivity as a test for diabetic neuropathy) on both sides should be performed in an initial assessment of diabetic neuropathy. Measurement of median MCV on one side only may be sufficient in subsequent follow-up to reduce the invasiveness of the tests.

In the current study, MCV and SCV were not investigated in age-matched healthy subjects, and the study was performed retrospectively based on data in previous studies, although without exclusion of specific patients. Furthermore, we could not evaluate SNAP amplitude in sural nerve or F wave minimum latency, which are important parameters for accurate diagnosis of neuropathy (15). These were major limitations of the current study.

CONCLUSION

The study showed that median MCV is significantly negatively correlated with age, diabetic duration, SBP, and log UAE, but not correlated with FPG, HbA_{1c}, or circulating lipid concentrations. Sural SCV was also significantly negatively correlated with SBP and log UAE, but the correlation was weak compared with those for median MCV. Sural SCV was not detectable in many patients who had a detectable median MCV. There were close positive correlations between right and left median MCV, and between right median MCV and right median SCV. Taken together, these results suggest that median MCV is more closely associated with markers related to diabetic complications, compared with sural SCV, but that sural SCV is more sensitive than median MCV for detection of diabetic nephropathy.

REFERENCES

1) Suzuki Y, Matsuoka K. : Early detection for diabetic

neuropathy. Nippon Rinsho, **56**(supplement) : 848-854, 1997.
2) Ewing DJ, Campbell IW, Clarke BF. : The national history of diabetics autonomic neuropathy. QJM, **49** : 95-108, 1980.
3) Sampson MJ, Wilson S, Karagiannis P, et al : Progression of diabetic autonomic neuropathy over a decade in insulin-dependent diabetes. QJM, **75** : 635-646, 1990.
4) Billman G, Schwarts PJ, Stone HL. : Barometer reflex control of heart rate : a predictor of sudden death. Circulation, **85** : 164-171, 1992.
5) Dyck PJ, Karness JL, O'Brien PC, et al : The Rochester diabetic neuropathy study ; Reassessment of tests and criteria for diagnosis and staged severity. Neurology, **42** : 1164-1170, 1992.
6) Takebayashi K, Aso Y, Sugita R, et al : Clinical usefulness of corrected QT intervals in diabetic autonomic neuropathy in patients with type 2 diabetes. Diabetes Metab, **28** : 127-132, 2002.
7) Matsutomo R, Takebayashi K, Aso Y. : Assessment of peripheral neuropathy using measurement of the current perception threshold with the neurometer in patients with type 2 diabetes mellitus. J Int Med Res, **33** : 442-453, 2005.
8) Takebayashi K, Suetsugu M, Wakabayashi S, et al : Retinol binding protein-4 levels and clinical features of type 2 diabetes patients. J Clin Endocrinol Metab, **92** : 2712-2719, 2007.
9) Lipsitz LA. : Orthostatic hypotension in the elderly. N Engl J Med, **321** : 952-957, 1989.
10) Davis MD. : Vitreous contraction in proliferative diabetic retinopathy. Arch Ophthalmol, **74** : 741-751, 1965.
11) Sano T, Sakamoto N. : Sensory perception test and nerve conduction study in diabetes mellitus. Nippon Rinsho, **56**(supplement) : 463-468, 1997.
12) Takebayashi K, Matsutomo R, Matsumoto S, et al : Relationships between heart rate variability and urinary albumin excretion in patients with type 2 diabetes. Am J Med Sci, **331** : 72-78, 2006.
13) Takebayashi K, Aso Y, Matsutomo R, et al : Association between the corrected QT intervals and combined intimal-medial thickness of the carotid artery in patients with type 2 diabetes. Metabolism, **53** : 1152-1157, 2004.
14) Colhoun HM, Betteridge DJ, Durrington PN, et al : Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS) : multiple randomized placebo-controlled trial. Lancet, **364** : 685-696, 2004.
15) Kamiya T, Kuroiwa Y. : Electrophysiology in diabetic neurological complications. Nippon Rinsho, **56**(supplement) : 855-862, 1997.