A Prognostic Role of Mean 24-h Pulse Pressure Level for Cardiovascular Events in Type 2 Diabetic Subjects Under 60 Years of Age

SHIGERU NAKANO, MD
KAZUNORI KONISHI, MD
KEISUKE FURUYA, MD
KEIGO UEHARA, MD
MAKOTO NISHIZAWA, MD
ATSUSHI NAKAGAWA, MD
TOSHIKAZU KIGOSHI, MD
KENZO UCHIDA, MD

OBJECTIVE — To assess the prognostic role of ambulatory 24-h pulse pressure (PP) on various vascular events in relatively young type 2 diabetic subjects under 60 years of age.

RESEARCH DESIGN AND METHODS — In this prospective study, 237 type 2 diabetic subjects without any history of vascular complications were analyzed. After excluding 9 dropout subjects, 228 subjects (mean age, 46 years; 69% men; mean follow-up period, 100 months) entered the study.

RESULTS — Distribution of 24-h PP for all subjects showed left skewed data, indicating that there may be a diabetic subgroup that had a wide PP. Therefore, further analysis was performed by stratifying the diabetic subjects by quartile of 24-h PP. Outcomes for the widest quartile (n = 58; cut point = 53.3 mmHg) was then compared with those from the other narrower quartiles (n = 170). In the diabetic subjects with a wide PP, cardiovascular events occurred more frequently than those in the diabetic subjects with a narrow one (20.7 vs. 4.1%; $P < 0.001$), resulting in the significant difference in the cumulative incidence of cardiovascular events ($P < 0.001$, log-rank test), but not cerebrovascular events, between the two subgroups. The Cox model revealed that a wide 24-h PP at baseline independently predicted subsequent cardiovascular events but not cerebrovascular events. By contrast, only duration of diabetes was the risk factor for cerebrovascular events.

CONCLUSIONS — This study showed that a wide 24-h PP is predictive for cardiovascular events in relatively young diabetic subjects.

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There is now increasing evidence that wide pulse pressure (PP), which is an indicator of large arterial stiffness, is an independent predictor for cardiovascular disease in elderly subjects with essential hypertension (1,2). A prognostic role for PP has been extended to an unselected general population, including relatively young aged (3,4) and normotensive subjects (5). Furthermore, the Atherosclerosis Risk in Communities study (6) and the Hoorn study (7) demonstrated that type 2 diabetic subjects have stiffer arteries than individuals with normal glucose tolerance, which was confirmed using ambulatory 24-h monitoring of PP by van Dijk et al. (8). Recently, Domanski et al. (9) and Miyagi et al. (10) pointed out that a cardiovascular risk in subjects with a wide PP increased with the presence of diabetes. On the other hand, previous studies suggest that in subjects with essential hypertension, ambulatory PP not only correlates with organ damage (11) but also independently predicts cardiovascular events more precisely than clinic PP does (12,13). However, there is little information concerning PP of relatively young type 2 diabetic subjects, and the predictive value of ambulatory 24-h PP among these subjects has not been previously reported.

The aim of this present study was to assess a prognostic role of ambulatory 24-h PP on various vascular events in type 2 diabetic subjects <60 years of age.

RESEARCH DESIGN AND METHODS

— The blood pressure (BP) monitoring program recruited 392 consecutive subjects with type 2 diabetes (249 men and 143 women, aged between 17 and 88 years) who were initially admitted to our hospital from December 1988 to June 1998 and then followed in our outpatient clinic (14,15). In this study, 237 type 2 diabetic subjects under 60 years of age, who were defined as those without any history of vascular complications based on atherosclerosis, were subanalyzed. The study protocol and analytical methods have been described previously (14,15). After excluding nine dropout subjects (four cancer, one pneumonia, one traffic accident, one suicide, and two unknown), 228 subjects (46 ± 11 years of age [mean ± SD]; 69% men) entered the study. The mean follow-up period was 100 ± 44 months (range 3–168).

Statistical analysis

Data are presented as means ± SD. Because all data for the comparison of group means were almost normally distributed,

From the Department of Internal Medicine, Division of Endocrinology and Metabolism, Kanazawa Medical University, Uchinada, Ishikawa, Japan.

Address correspondence and reprint requests to Dr. Shigeru Nakano, Division of Endocrinology, Department of Internal Medicine, Kanazawa Medical University, 1-1 Daigaku, Uchinada, Ishikawa 920-0293, Japan. E-mail: nakano-s@kanazawa-med.ac.jp.

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Abbreviations: BP, blood pressure; dBP, diastolic BP; PP, pulse pressure; sBP, systolic BP.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

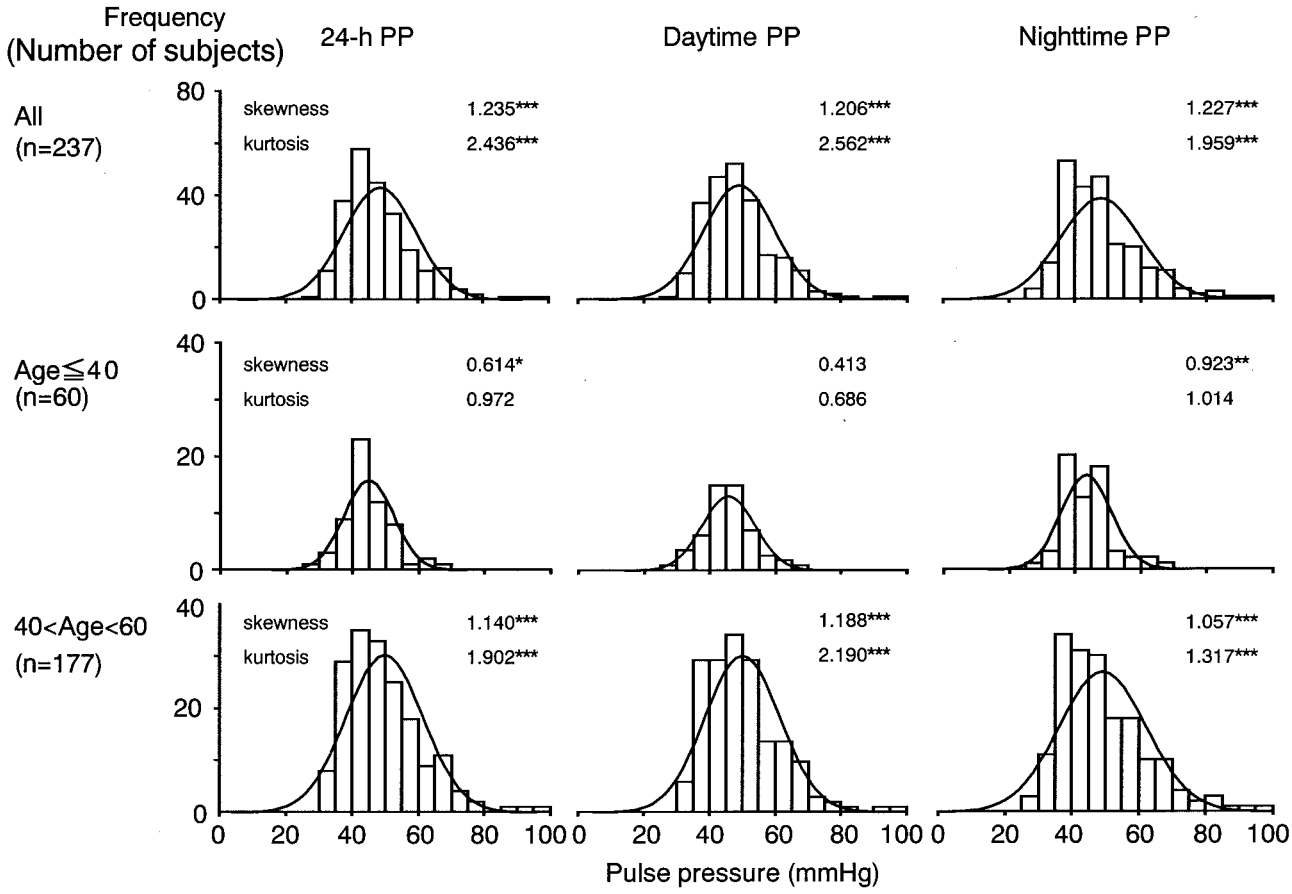

Figure 1—*Histograms of the distribution of mean 24-h, daytime, and nighttime PPs divided by 5 mmHg each. Skewness and kurtosis were examined for normality. On each histogram, a theoretical normal distribution curve was superimposed.*

ANOVA was applied, except for serum triglyceride, for which variables were log-transformed to approximate normality. When testing the number of subjects in groups, the χ^2 test was used. Histograms divided by 5 mmHg each were depicted to evaluate the distribution of mean 24-h, daytime, and nighttime PPs, and skewness and kurtosis were examined for normality. On each histogram, a theoretical normal distribution curve was superimposed. An association between ambulatory PP and age was determined using Pearson's correlation analysis. The rates of occurrences of cardiovascular, cerebrovascular, and all events were expressed in cases per 1, 000 patient-years in diabetic subgroups divided by quartile of the distribution of mean 24-h PPs. Cumulative incidence of cardiovascular, cerebrovascular, and all events were estimated using the Kaplan-Meier product-limit method and compared using the log-rank test, and relative risks between two diabetic subgroups were calculated using the Cox-Mantel test. The effects of prognostic factors on occurrences of various vascular events were evaluated by the Cox proportional-hazards model. In this analysis, dummy variables were used for hypertension (absent or present), and the other measured data were treated as continuous variables. Relative risks and their 95% CIs in the Cox's model were calculated as previously described (14). The statistical significance was defined as a two-tailed P value <0.05. Multivariate models were used to adjust for potential confounding factors at $P < 0.05$ in the comparison of baseline characteristics.

RESULTS

Distribution of ambulatory PP in the diabetic subjects

In Fig. 1, histograms of mean 24-h, daytime, and nighttime PP were depicted with a theoretical normal distribution curve. Distribution of PP in any time periods for all subjects (Fig. 1, upper panels) was positively skewed, meaning that there might be a diabetic subgroup that had a wide PP. When diabetic subjects were divided into two subgroups (young subjects [≤40 years of age] and middle-aged subjects [between 41 and 59 years of age]), all histograms of 24 h, daytime, and nighttime tended to be similar to those for all subjects. Further analysis was therefore performed by stratifying the diabetic subjects by quartile of the distribution of mean 24-h PP. The cut points for quartiles of mean 24-h PP were 41.0, 46.3, and 53.3 mmHg. Then the widest quartile of diabetic subjects ($n = 58$) was compared with the other narrower quartiles ($n = 170$).

Clinical characteristics of the two diabetic subgroups at entry

In the diabetic subjects with a wide PP, age was older, the prevalence of hypertensive subjects was higher, duration of diabetes was longer, and serum levels of creatinine, total cholesterol, and lipid ra-

Table 1—*Clinical characteristics of diabetic subjects with narrow and wide PP*

	Diabetic subjects		
	With a narrow PP	With a wide PP	*P*
n	170	58	
Follow-up period (months)	107 ± 41	79 ± 46	<0.001
Age (years)	45 ± 11	51 ± 8	<0.001
Sex (M/F)	115/55	43/15	NS
BMI (kg/m^2)	24.4 ± 4.6	24.2 ± 4.1	NS
Hypertensive subjects (%)	16	78	<0.001
Current smokers (%)	36	43	NS
Duration of diabetes (years)	6.1 ± 5.8	8.3 ± 6.5	0.015
HbA_{1c} (%)	9.4 ± 2.5	8.6 ± 2.2	NS
Insulin use (%)	23	33	NS
Serum creatinine (μmol/l)	70.7 ± 23.0	89.3 ± 42.4	0.003
Serum total cholesterol (mmol/l)	5.04 ± 1.19	5.48 ± 1.45	0.043
Serum triglyceride (mmol/l)*	2.13 ± 0.28	2.18 ± 0.22	NS
Lipid ratio (total/HDL cholesterol)	5.11 ± 2.04	6.15 ± 2.40	<0.01
sBP (mmHg)			
24 h	115 ± 12	143 ± 16	<0.001
Daytime	117 ± 13	144 ± 16	<0.001
Nighttime	110 ± 13	141 ± 19	<0.001
dBP (mmHg)			
24 h	72 ± 9	80 ± 11	<0.001
Daytime	73 ± 10	81 ± 12	<0.001
Nighttime	68 ± 9	78 ± 12	<0.001
PP (mmHg)			
24 h	43 ± 5	63 ± 9	<0.001
Daytime	44 ± 6	63 ± 9	<0.001
Nighttime	42 ± 6	63 ± 11	<0.001
Pulse rate (bpm)			
24 h	72 ± 9	72 ± 11	NS
Daytime	76 ± 9	75 ± 11	NS
Nighttime	64 ± 10	65 ± 12	NS
Nocturnal fall in sBP (mmHg)	−7 ± 9	−3 ± 12	<0.05
Nondipper (%)	64	67	NS

Data are means ± SD, unless otherwise indicated. *This variable was log transformed.

tio were higher than in individuals with a narrow PP. There was however no difference in sex, BMI, HbA_{1c}, serum triglyceride, or prevalence of insulin use and current smokers between the two groups (Table 1).

Moreover, Table 1 shows the comparison of mean 24-h, daytime, and nighttime levels of systolic BP (sBP), diastolic BP (dBP), PP, and pulse rate in diabetic subjects with a narrow PP or a wide PP. Mean levels of not only PP and sBP, but also sBP, in any time periods were consistently higher in diabetic subjects with a wide PP than in those with a narrow PP. Furthermore, mean 24-h PP levels for all subjects were significantly correlated with age ($r = 0.257$, $P < 0.001$). Pulse rate levels were similar, even in the nighttime, between the two groups. Although the prevalence of nondippers in the two diabetic subgroups was similar, nocturnal fall in sBP was significantly smaller in diabetic subjects with a wide PP than in those with a narrow PP.

Comparison of various vascular events in the two diabetic subgroups

Various vascular events that occurred during the follow-up period were summarized in Table 2. Prevalence of cardiovascular and all events were significantly higher in diabetic subjects with a wide PP than those with a narrow PP ($P < 0.001$ for each), whereas there was no difference in the prevalence of cerebrovascular events between the two groups. Moreover, cardiovascular events, but not cerebrovascular events, seemed to be more fatal in diabetic subjects with a wide PP than in those with a narrow PP.

Rates of occurrences of various vascular events in diabetic subjects divided by quartiles of mean 24-h PP and age stratification were illustrated in Fig. 2. In spite of age stratification, cardiovascular and all events were more frequent in the highest quartile than the other quartiles.

The Kaplan-Meier analysis of cumulative incidence of various vascular events in diabetic subjects with narrow and wide PPs revealed that there was a significant difference in cardiovascular and all events between the two groups ($P < 0.001$ for each, log-rank test). Relative risks for these events were 25.3 and 5.0, respectively ($P < 0.001$ for each, Cox-Mantel test). However, there was no statistical difference in cumulative incidences of cerebrovascular events between the two subgroups.

Factors predicting various vascular events

In the Cox proportional-hazards model, the adjusted relative risks for all factors listed are shown in Table 3. Although mean 24-h sBP (model 1) and dBP (model 2) were independent predictors for both cardiovascular and all events, mean 24-h PP was a better predictor than sBP and dBP. In model 3, mean 24-h PP as well as presence of hypertension and lipid ratio exhibited a statistically significant adjusted relative risk for cardiovascular events ($P < 0.05$ for each), whereas only duration of diabetes exhibited risk for cerebrovascular events ($P < 0.01$). Furthermore, duration of diabetes, lipid ratio, nocturnal fall in sBP, and mean 24-h PP exhibited a significant adjusted relative risk for all events ($P < 0.05$ for each).

CONCLUSIONS — In this prospective study of diabetic subjects under 60 years of age, we clearly demonstrated that a wide 24-h PP at baseline was a better predictor than sBP and dBP and independently predicted subsequent cardiovascular and all events but not cerebrovascular events. By contrast, only the duration of diabetes was the risk factor for cerebrovascular events.

Atherosclerotic changes are generally more pronounced in type 2 diabetic subjects compared with those with a normal glucose tolerance (6,7). Mean 24-h PP of relatively young diabetic subjects in this

Table 2—*Summary of various vascular events observed during the follow-up*

	Diabetic subjects					
	With a narrow PP			With a wide PP		
	Fatal	Nonfatal	Total	Fatal	Nonfatal	Total
Cerebrovascular events			14 (8.2%)			6 (10.3%)
Infarction	2	8		1	3	
Hemorrhage	2	2		1	1	
Cardiovascular events			7 (4.1%)			12 (20.7%)*
Angina pectoris	—	2		—	4	
Cardiac infarction	—	—		2	2	
Cardiac failure	1	3		2	—	
Sudden cardiac death	1	—		2	—	
Other events			24 (14.1%)			13 (22.4%)
Introduced hemodialysis	—	14		—	11	
Severe retinal lesion	—	8		—	—	
Gangrene	—	2		—	1	
Massive nasal bleeding	—	—		—	1	
All events	6	39	45 (26.5%)	8	23	31 (53.4%)*

*$P < 0.001$ vs. the diabetic subjects with a narrow PP.

study was significantly correlated with age. Therefore, when a wide 24-h PP appears, even in young diabetic subjects, it may be indicative of large artery stiffness and thereby may be an early marker of vascular disease, especially cardiovascular events. However, histograms of distribution of mean 24-h PP showed that there was a diabetic subgroup in which 24-h PPs were wider than those thought to already have wide PPs. Thus, it is clinically important to detect and manage such a diabetic subgroup to prevent vascular events.

Many investigators have reported that nephropathy (microalbuminuria and gross proteinuria) in type 2 diabetic subjects is related to the occurrence of cardiovascular events (16,17), and even in nondiabetic subjects (18), microalbuminuria is a cardiovascular disease risk factor. Riu et al. (19) recently confirmed this relationship based on the observation that mean urinary albumin excretion during follow-up was closely associated with occurrences of cardiovascular disease in type 2 diabetic subjects. Mattock et al. (20), however, demonstrated that although microalbuminuria predicted incident clinical coronary heart disease in men with type 2 diabetes, preexisting coronary heart disease was also a risk factor for microalbuminuria in such subjects, suggesting that both factors were not causally related but rather resulted from common determinants. Thus, the causal relationship between nephropathy and cardiovascular events in type 2 diabetic subjects is not clear, but it may be clinically undoubting that type 2 diabetic subjects with nephropathy are at high risk for cardiovascular disease, suggesting that management for PP as well as sBP and dBP focused on arterial stiffness is required, even in relatively young diabetic subjects.

In the previous reports dealing with middle-aged subjects with essential hypertension (3–5), sBP increased progressively from the lower to the higher PP group, whereas dBP was significantly lower in the subgroups with the higher PP. In contrast to those findings, our data showed that sBP and dBP as well as PP in the diabetic subjects with a wide PP were consistently higher than those with a narrow PP (Table 1). Therefore, it seems that this difference could not be explained merely by age-related progression of stiffening in large arteries. Knudsen et al. (21) demonstrated that ambulatory daytime and nighttime sBP but also dBP values, when grouped according to severity of each microvascular and macrovascular complication, were consistently higher in type 2 diabetic subjects with advanced microvascular and macrovascular complications than those without them, accompanying a widening of the PPs as well as blunted diurnal BP variations. Taken together, underlying mechanisms for widening PP in relatively young diabetic

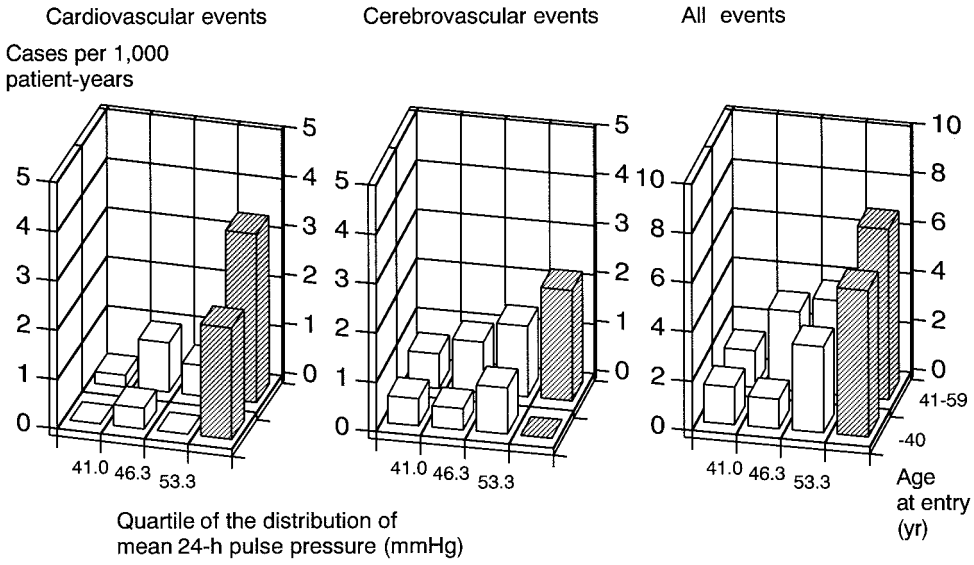

Figure 2—*The rates of occurrences of cardiovascular, cerebrovascular, and all events expressed in cases per 1, 000 patient-years in diabetic subgroups divided by quartile of the distribution of mean 24-h PPs and by age at entry (≥40 and 41–59 years).*

Table 3—*Adjusted relative risks for cardiovascular, cerebrovascular, and all events in the diabetic subjects*

	Events		
	Cardiovascular	Cerebrovascular	All
Model 1			
Age	1.04 (0.98–1.11)	1.06 (0.99–1.12)*	1.01 (0.99–1.04)
24-h sBP	1.04 (1.00–1.08)*	1.03 (0.99–1.08)	1.03 (1.01–1.05)*
24-h PP	1.04 (1.00–1.10)*	0.99 (0.92–1.06)	1.03 (1.00–1.06)*
Model 2			
Age	1.04 (0.98–1.11)	1.06 (1.00–1.13)*	1.01 (0.99–1.04)
24-h dBP	1.04 (1.00–1.08)*	1.03 (0.99–1.08)	1.03 (1.01–1.05)†
24-h PP	1.08 (1.04–1.12)‡	1.02 (0.97–1.07)	1.05 (1.03–1.08)‡
Model 3			
Age	1.03 (0.96–1.10)	1.01 (0.95–1.08)	0.98 (0.95–1.01)
Hypertension	4.02 (1.03–15.67)*	1.92 (0.57–6.42)	1.56 (0.86–2.86)
Duration of diabetes	1.01 (0.95–1.13)	1.11 (1.04–1.20)†	1.09 (1.05–1.13)†
Serum creatinine	0.32 (0.04–2.32)	1.05 (0.24–4.63)	1.76 (0.92–3.35)
Lipid ratio	1.35 (1.04–1.75)	1.19 (0.94–1.51)	1.18 (1.06–1.31)†
Nocturnal fall in sBP	0.99 (0.94–1.04)	1.04 (0.99–1.10)	1.03 (1.00–1.06)*
24-h PP	1.07 (1.02–1.12)*	1.00 (0.95–1.06)	1.04 (1.01–1.07)†

Data are relative risks (95% CI). Lipid ratio = serum total/HDL cholesterol. *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$.

subjects may differ from those in subjects with essential hypertension. Although diabetes-specific atherosclerotic changes are not known, it is feasible that widening of PP with increases in both sBP and dBP in the diabetic subjects may be involved in hemodynamic alterations associated with the development of microvascular complications. In fact, in this study, duration of diabetes was longer, and serum creatinine level was higher at baseline in diabetic subjects with a wide PP compared with individuals with a narrow PP. In addition, duration of diabetes was an independent predictor for cerebrovascular and all events. Another possibility is the blunted nocturnal fall in sBP or nondipper status, which was pronounced at baseline in the diabetic subjects with a wide PP compared with those with a narrow PP. Accordingly, altered diurnal pattern of BP may contribute to not only the progression of microvascular complications but also to the stiffening of large arteries. Finally, autonomic dysfunction causing altered vascular reactivity may be associated with the worse outcomes, although at least cardiac sympathovagal imbalance was not largely different at baseline between the two subgroups.

In this study, the cut point for mean 24-h PP between the diabetic subjects with a wide PP and a narrow PP was 53.3 mmHg, which was closely equal to the observations of Verdecchia et al. (12). They showed that both total and fatal cardiovascular event risks in untreated subjects with uncomplicated essential hypertension (mean age 51.7 years) were highest in the top tertile, who had a mean 24-h PP value wider than 53 mmHg, while the cut point of 65 mmHg for office PP was shown. Thus, this finding suggests that the ambulatory 24-h PP value is a clinically useful predictor for cardiovascular risk, even in a hemodynamically different population.

The main limitation of our study is the lack of information on the degree of BP and glycemic control during the follow-up periods in all participants and on the effect of antihypertensive drugs on BP level, pattern, and protection from organ damage in the long term. However, we made every effort to obtain excellent BP and glycemic control in each individual during the whole follow-up period by using a standard treatment.

In conclusion, this study showed that a wide 24-h PP is predictive of cardiovascular events in the relatively young and low-disease risk group, suggesting that this measure can be used as an additional tool in assisting risk stratification of young diabetic subjects, where other conventional risk factors are not helpful. Further studies are needed to establish the strategies of pharmacological and nonpharmacological management for type 2 diabetic subjects with a high cardiovascular disease risk.

References

1. Franklin SS, Gustin IVW, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D: Hemodynamic patterns of age-related changes in blood pressure: the Framingham Heart Study. *Circulation* 96:308–315, 1997
2. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D: Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study. *Circulation* 100:354–360, 1999
3. Benetos A, Safar M, Rundnichi A, Smulyan H, Richard JL, Ducimetiere P, Guize L: Pulse pressure: a predictor of long-term cardiovascular mortality in a French male population. *Hypertension* 30:1410–1415, 1997
4. Benetos A, Rudnichi A, Safar M, Guize L: Pulse pressure and cardiovascular mortality in normotensive and hypertensive subjects. *Hypertension* 32:560–564, 1998
5. Fang J, Madhavan S, Alderman MH: Pulse pressure: a predictor of cardiovascular mortality among normotensive subjects. *Blood Pressure* 9:260–266, 2000
6. Saloman V, Riley W, Kark JD, Nardo C, Folsom AR: Non-insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with atrial stiffness indexes: the ARIC Study. *Circulation* 91:1432–1443, 1995
7. Schram MT, Henry RMA, van Dijk RAJM, Kostense PJ, Dekker JM, Nijpels G, Heine RJ, Bouter LM, Westerhof N, Stehouwer CDA: Increased central artery stiffness in impaired glucose metabolism and type 2 diabetes: the Hoorn Study. *Hypertension* 43:176–181, 2004
8. van Dijk RAJM, van Ittersum FJ, Westerhof N, van Dongen EM, Kamp O, Stehouwer CDA: Determinants of brachial artery mean 24-h pulse pressure in individuals with type II diabetes mellitus and untreated mild hypertension. *Clin Sci* 102: 177–186, 2002
9. Domanski M, Norman J, Wolz M, Michell G, Pfeffer M: Cardiovascular risk assessment using pulse pressure in the First National Health and Nutrition Examination Survey (NHANES I). *Hypertension* 38: 793–797, 2001
10. Miyagi T, Muratani H, Kimura Y, Fukiyama K, Kawano Y, Fujii J, Abe K, Kuwajima I, Ishii M, Shiomi T, Mikami H, Ibayashi S, Omae T: Increase in pulse pressure relates to diabetes mellitus and low HDL cholesterol, but not to hyperlipidemia in hypertensive patients aged 50 years or older. *Hypertens Res* 25:335–341, 2002

11. Khatter RS, Acharya DU, Kinsey C, Senior R, Lahiri A: Longitudinal association of ambulatory pulse pressure with left ventricular mass and vascular hypertrophy in essential hypertension. *J Hypertens* 15: 737–743, 1997
12. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Pede S, Porcellati C: Ambulatory pulse pressure: a potent predictor of total cardiovascular risk in hypertension. *Hypertension* 32:983–988, 1998
13. Staessen JA, Thijs L, O'Brien ET, Bulpitt CJ, de Leeuw PW, Fagard RH, Nachev C, Palatini C, Parati G, Tuomilehto J, Webster J, Safar ME, for the Syst-Eur Trial Investigators: Ambulatory pulse pressure as predictor of outcome in older patients with systolic hypertension. *Am J Hypertens* 15:835–843, 2002
14. Nakano S, Fukuda M, Hotta F, Ito T, Ishii T, Kitazawa M, Nishizawa M, Kigoshi T, Uchida K: Reversed circadian blood pressure rhythm is associated with occurrences of both fatal and nonfatal vascular events in NIDDM subjects. *Diabetes* 47: 1501–1506, 1998
15. Nakano S, Ito T, Furuya K, Tsuda S, Konishi K, Nishizawa M, Nakagawa A, Kigoshi T, Uchida K: Ambulatory blood pressure level rather than dipper/nondipper status predicts vasculae events in type 2 diabetic sybjects. *Hypertens Res* 27:647–656, 2004
16. Macleod JM, Lutale J, Marshall SM: Albumin excretion and vascular deaths in NIDDM. *Diabetologia* 38:610–616, 1995
17. Valmodrid CT, Klein R, Moss SE, Klein BEK: The risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in persons with older-onset diabetes mellitus. *Arch Intern Med* 160:1093–1100, 2000
18. Damsgaard EM, Frøland A, Jørgensen OD, Mogensen CE: Prognostic value of urine albumin excretion rate and other risk factors in elderly diabetic patients and non-diabetic control subjects surviving the first 5 years after assessment. *Diabetologia* 36:1030–1036, 1993
19. Riu FR, Vert IS, Martin AL, Gonzalez RR, Sala AS: A prospective study of cardiovascular disease in patients with type 2 diabetes 6.3 years of follow-up. *J Diabetes Complications* 17:235–242, 2003
20. Mattock MB, Barnes DJ, Viberti G, Keen H, Burt D, Hughes JM, Fitzgerald AP, Sandhu B, Jackson PG: Microalbuminuria and coronary heart disease in NIDDM: an incidence study. *Diabetes* 47:1786–1792, 1998
21. Knudsen ST, Poulsen PL, Hansen KW, Ebbehøj E, Bek T, Mogensen CE: Pulse pressure and diurnal blood pressure variation: association with micro- and macrovascular complications in type 2 diabetes. *Am J Hypertens* 15:244–250, 2002