Circadian Blood Pressure During the Early Course of Type 1 Diabetes

Analysis of 1,011 ambulatory blood pressure recordings in 354 adolescents and young adults

REINHARD W. HOLL, MD
MLADEN PAVLOVIC, MD
EBERHARD HEINZE, MD
ANGELIKA THON, MD

OBJECTIVE — Little information is available on the early course of hypertension in type 1 diabetes. The aim of our study, therefore, was to document circadian blood pressure profiles in patients with a diabetes duration of up to 20 years and relate daytime and nighttime blood pressure to duration of diabetes, BMI, insulin therapy, and HbA_{1c}.

RESEARCH DESIGN AND METHODS — Ambulatory profiles of 24-h blood pressure were recorded in 354 pediatric patients with type 1 diabetes (age 14.6 ± 4.2 years, duration of diabetes 5.6 ± 5.0 years, follow-up for up to 9 years). A total of 1,011 profiles were available for analysis from patients not receiving antihypertensive medication.

RESULTS — Although daytime mean systolic pressure was significantly elevated in diabetic subjects (+3.1 mmHg; $P < 0.0001$), daytime diastolic pressure was not different from from the height- and sex-adjusted normal range (+0.1 mmHg, NS). In contrast, both systolic and diastolic nighttime values were clearly elevated (+7.2 and +4.2 mmHg; $P < 0.0001$), and nocturnal dipping was reduced ($P < 0.0001$). Systolic blood pressure was related to overweight in all patients, while diastolic blood pressure was related to metabolic control in young adults. Blood pressure variability was significantly lower in girls compared with boys ($P < 0.01$). During follow-up, no increase of blood pressure was noted; however, diastolic nocturnal dipping decreased significantly ($P < 0.03$). Mean daytime blood pressure was significantly related to office blood pressure ($r = +0.54$ for systolic and $r = +0.40$ for diastolic pressure); however, hypertension was confirmed by ambulatory blood pressure measurement in only 32% of patients with elevated office blood pressure.

CONCLUSIONS — During the early course of type 1 diabetes, daytime blood pressure is higher compared with that of healthy control subjects. The elevation of nocturnal values is even more pronounced and nocturnal dipping is reduced. The frequency of white-coat hypertension is high among adolescents with diabetes, and ambulatory blood pressure monitoring avoids unnecessary antihypertensive treatment.

Diabetes Care 22:1151–1157, 1999

Elevated blood pressure has repeatedly been shown to represent a risk factor for the early development of nephropathy (1–3). Reliable detection of mild hypertension, however, is hampered by the "white-coat" effect (4,5). This phenomenon is found in 20–30% of hypertensive adults, but is even more prevalent in adolescents, where up to 70% of patients with elevated office blood pressure display normal 24-h blood pressure profiles (6). In a previous study in adolescents with diabetes, we confirmed this high incidence of white-coat hypertension in pediatric patients (7).

Twenty-four–hour ambulatory blood pressure measurement (ABPM) has been used as an investigative tool in adult patients with diabetes, focusing primarily on the relationship to urinary albumin excretion as an early sign of diabetic nephropathy (8,9). For pediatric diabetology, only small patient groups have been studied with this technique (10,11). In contrast to older patients, where hypertension may be a consequence of early diabetic nephropathy, studying young patients with a shorter duration of diabetes (up to 2 decades) may help to clarify whether the prevalence of primary hypertension is increased in diabetic patients and whether there is a relationship to the duration of diabetes early on. While office blood pressure measurements are always taken during daytime, automatic 24-h blood pressure recording allows the investigation of nocturnal blood pressure values and the circadian rhythm or "nocturnal dipping" of blood pressure.

The aim of this study is to answer the following questions:

1. Are blood pressure measurements using objective ABPM elevated in adolescent and young adult patients with type 1 diabetes?
2. Which anthropometric or metabolic factors are relevant for blood pressure in this group of patients?
3. Are nocturnal dipping of blood pressure or blood pressure variability affected by sex, age, duration of diabetes, insulin dose, or metabolic control?

RESEARCH DESIGN AND METHODS

— The SpaceLabs 90207 ABP-monitor (SpaceLabs, Kaarst, Germany) was used with three different cuff sizes (upper arm circumferences 13–20, 17–26, and 24–32 cm). Blood pressure was recorded automatically every 20 min during daytime (0800 to 2200) and every 40 min at night. ABPM was performed on days with normal physical activity and

From the Department of Pediatrics, University of Ulm, Ulm, Germany.
Address correspondence and reprint requests to Priv-Doz. Dr. Reinhard W. Holl, Department of Pediatrics, University of Gießen, Feulgenstr. 12, D-35385 Gießen, Germany. E-mail: reinhard.w.holl@paediat.med.uni-giessen.de.
Received for publication 14 October 1998 and accepted in revised form 5 April 1999.
Abbreviations: ABPM, ambulatory blood pressure measurement.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Patient characteristics for the entire group of 354 subjects, as well as separately for male and female subjects*

	All patients	Males	Females	*P* value
n	354	167	187	—
Age (years)	14.6 ± 4.2	15.2 ± 4.4	14.2 ± 3.9	0.03
Duration of diabetes (years)	5.6 ± 5.0	6.1 ± 5.3	5.3 ± 4.8	NS
z score				
Height	0.29 ± 1.1	0.23 ± 1.1	0.35 ± 1.1	NS
Weight	0.95 ± 1.2	1.00 ± 1.2	0.89 ± 1.2	NS
BMI	1.05 ± 1.1	1.16 ± 1.1	0.95 ± 1.2	0.02
HbA_{1c}	7.3 ± 1.6	7.2 ± 1.4	7.5 ± 1.8	NS
Daily dose of insulin/kg	0.78 ± 0.27	0.75 ± 0.27	0.8 ± 0.28	NS
Injections/day	2.8 ± 1.2	2.7 ± 1.2	2.9 ± 1.2	NS

Data are means ± SD. *P* values refer to Wilcoxon test for between-sex comparison.

absence of acute infections, ketoacidosis, or severe hypoglycemic episodes (defined as the requirement of help by another person). A large multicenter study on 1,141 healthy children and adolescents provided normative material for height- and sex-dependent analysis of 24-h blood pressure (12). As recommended by the authors of this article, blood pressure was assessed based on height rather than chronological age of the patient. To compare diabetic children with nondiabetic control subjects, the difference between the individual blood pressure measurement in the diabetic subject and the 50th percentile according to height and sex in the reference group was calculated for daytime and nighttime systolic and diastolic blood pressures. Nocturnal systolic and diastolic dipping were calculated as (mean daytime pressure − mean nighttime pressure)/mean daytime pressure × 100 (%).

Yearly ABPM recordings were performed in all diabetic patients aged >10 years. All patients or their parents gave informed consent. A total of 354 subjects with type 1 diabetes were studied (167 males, 187 females). The average age at the initial recording was 14.6 ± 4.2 years (mean ± SD; range 7.2–30.9); the duration of diabetes was 5.6 ± 5.0 years (0–21). Anthropometric data are summarized in Table 1. Out of a total of 1,051 ABPM profiles, 40 were excluded because the patients were taking antihypertensive medication for hypertension or microalbuminuria at the time of the recording. A total of 1,011 ABPM profiles were available, collected between October 1989 and August 1997. Up to nine recordings were available per patient; 250, 178, and 117 patients had two, three, and four consecutive recordings, respectively. Analysis of mean daytime and nighttime pressure, sex comparison and relation to overweight, insulin therapy, and metabolic control was based on the first ABPM measurement in each of the 354 patients. As subgroups, adolescents (age <16 years) and young adults (age ≥16 years) were analyzed separately. For the longitudinal follow-up, 117 patients who had completed at least four consecutive recordings were evaluated. For the relationship between ABPM and office blood pressure, all 1,011 profiles were included.

All patients were treated with a free mixture of regular and NPH insulin; 19% of patients were on two injections per day, 41% on three, and 40% on four injections. Repeated daily blood glucose measurements and self-adjustment of insulin dose were encouraged irrespective of age. All patients as well as their parents participated in a structured education program at diagnosis as well as every 2–3 years thereafter. Patients were seen in our diabetes outpatient department on average every 3.1 months.

HbA_{1c} was measured by high-performance liquid chromatography (Microcolumn System; Pharmacia, Freiburg, Germany) every 3 months. The normal range for this method, based on 93 healthy control subjects, is 3.5–5.7%, which falls 0.5% lower than the Diabetes Control and Complications Trial reference lab (13). Until 1991, ion exchange chromatography was applied for measurement of HbA_{1c} (normal range: 3.3–5.3%) (14). These values were mathematically adjusted to the current assay using the SD-score method (15). To reflect long-term metabolic control, the median of all HbA_{1c} measurements during the year prior to ABPM was calculated.

All relevant data from diabetic patients are stored in a computer database system developed under the auspices of the German Secretary of Health at our institution; this system is now widely used throughout Germany (16). This program was compiled with the Foxpro for Windows compiler (Microsoft, Seattle, WA); relevant data were extracted from the database using the dBase V software (Borland, Scotts Valley, CA). Age, height, weight, diabetes duration, daily dose of insulin, number of insulin injections per day, and the median HbA_{1c} concentration during the year prior to the ABPM recording (excluding values measured at diagnosis) were investigated. To analyze height, weight, and BMI independently of age and sex, the respective *z* scores were calculated based on the Zurich longitudinal growth data (17).

Using the SAS software package (SAS Institute, Cary, NC), Student's *t* test and analysis of variance were applied for normally distributed data, Kolmogorov test to demonstrate normal distribution, and Wilcoxon/Kruskal-Wallis test for non-normally distributed data, in addition to Pearson's coefficient of correlation and multiple regression analysis with Wald statistics. Significance was assumed for *P* values <0.05. Data are given as means ± SD in the text and as means ± SEM in the figures.

RESULTS — Figure 1 relates the mean daytime and nighttime blood pressures from the first ABPM recording in 354 patients to height, in comparison with published data from 1,141 control subjects. To quantitatively compare systolic and diastolic daytime and nighttime pressure recordings in diabetic subjects with normal control subjects, the difference between the respective value in each patient and the expected value according to height and sex was evaluated. The mean systolic blood pressure during daytime in patients was 3.1 ± 7.5 mmHg above the expected value (mean ± SD; $P < 0.0001$, Wilcoxon's signed-rank test), while the mean daytime diastolic pressure fell 0.1 ± 6.1 mmHg below the reference (NS) (Fig. 2). In contrast, both systolic and diastolic mean pressures during nighttime were elevated (+7.2 ± 7.9 mmHg for nocturnal systolic and +4.2 ± 6.5 mmHg for nocturnal diastolic pressure; $P < 0.0001$, Wilcoxon). Nocturnal dipping was significantly reduced: systolic dipping, 10.1 ± 5.0% compared with 13% in control subjects; diastolic dipping, 18.2 ± 7.3% vs. 23% in control subjects ($P < 0.0001$, Wilcoxon). Results in young adults (age ≥16 years) did not differ from those in adolescents (age <16 years).

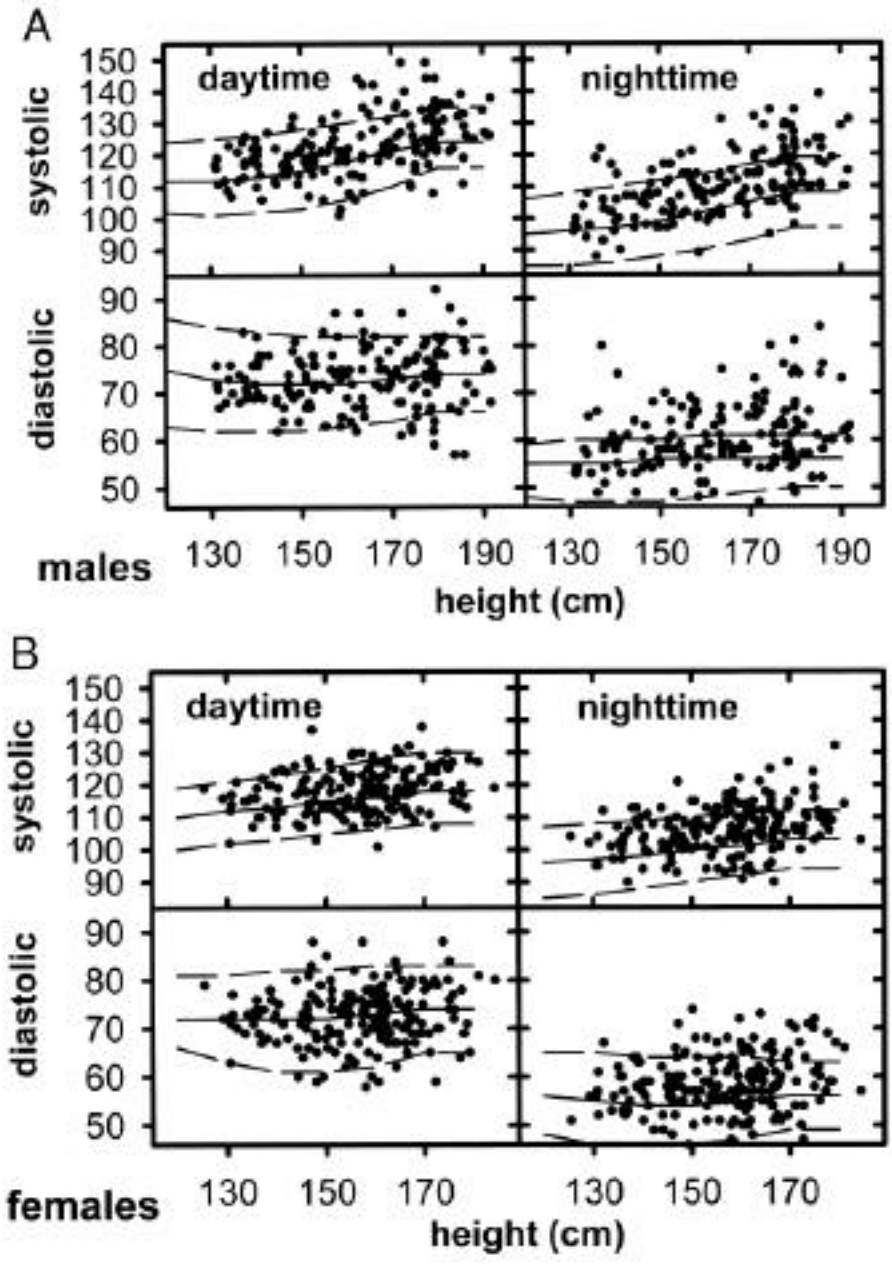

Figure 1—*Mean systolic and diastolic blood pressure during daytime and nighttime related to height in 354 patients with type 1 diabetes. The 10th, 50th, and 90th percentiles taken from a multicenter study in healthy control children (13) are displayed as dashed lines. A: Boys* (n = *167); B: girls* (n = *187).*

For the analysis of sex differences, again the first ABPM recording in each patient was used. Of the patients, 167 were male, 187 female. Male patients were slightly older and slightly more overweight compared with female patients (Table 1). Compared with their respective control subjects adjusted for height and sex, no significant sex differences were present between diabetic boys and girls for systolic and diastolic pressure during daytime and nighttime (Wilcoxon's rank-sum test). However, diastolic dipping was significantly reduced in male patients compared with female patients (16.9 ± 7.8% compared with 19.3 ± 6.6%; $P < 0.01$, Wilcoxon) (Fig. 2). No sex difference was present for systolic dipping.

Overweight was significantly related to systolic blood pressure in young patients with diabetes. The z score for BMI (+1.05 ± 1.1 at the initial measurement) was significantly correlated with blood pressure excess for systolic pressure during daytime ($r = +0.15$, $P < 0.006$) and during nighttime ($r = +0.16$, $P < 0.002$). No significant relationship to overweight was present for diastolic blood pressure. Using simple correlation analysis, diabetes duration was related to daytime and nighttime systolic and diastolic blood pressure in type 1 diabetes ($r = +0.25$–0.30, $P < 0.0001$). Long-term metabolic control was evaluated by the median of all HbA_{1c} measurements in a patient during the year before ABPM recording. In the 354 patients studied, long-term metabolic control was inversely related to mean daytime systolic ($r = -0.17$, $P < 0.002$) and nighttime systolic pressure ($r = -0.14$, $P < 0.01$). In addition, the daily dose of insulin per kilogram of body weight was related to blood pressure. The closest correlations with insulin dose were found for mean daytime systolic ($r = +0.19$, $P < 0.0005$) and diastolic ($r = +0.18$, $P < 0.001$) pressures. If patients were stratified according to the number of daily insulin injections, analysis of variance revealed significantly higher blood pressure in patients on more injections (daytime systolic pressure: $P < 0.05$; daytime diastolic and nighttime systolic pressures: $P < 0.01$; nighttime diastolic pressure: $P < 0.005$).

Many of the anthropometric and metabolic factors studied are interrelated. Therefore, multiple linear regression analysis was applied, using standardized BMI, duration of diabetes, metabolic control, daily dose of insulin, and injection frequency as independent parameters and standardizing for age and sex. As dependent parameters, daytime and nighttime systolic and diastolic pressure as well as systolic and diastolic nocturnal dipping were used. The results, separately for adolescent and for young adult patients, are summarized in Table 2. F statistics for the whole model and Wald statistics for the contribution of individual parameters are provided. Overweight is the most relevant factor for systolic blood pressure during daytime or nighttime in young adults. In addition, duration of diabetes affects diastolic pressure in the adolescent group and metabolic control is related to diastolic pressure in adults. Neither diabetes duration, metabolic control, insulin dose, nor BMI affected systolic or diastolic dipping.

Blood pressure variability, reflected by the standard deviation of individual measurements around the mean pressure in the

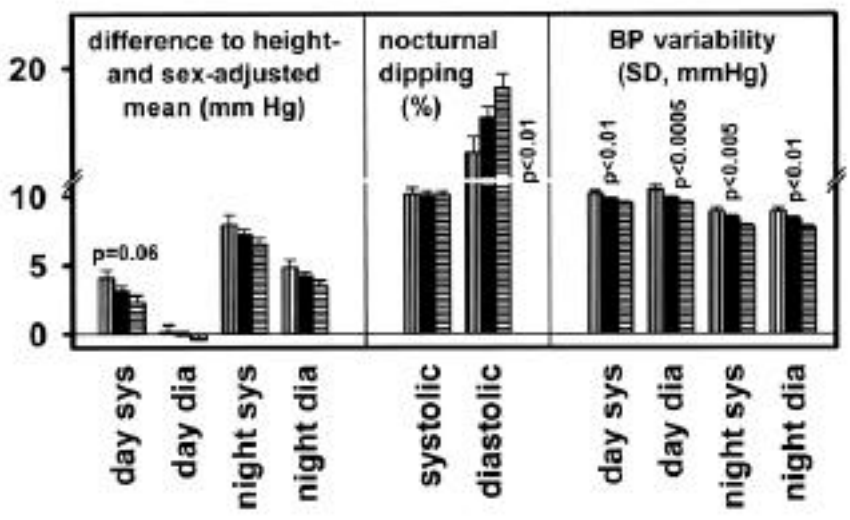

Figure 2—*Relevant indices of 24-h blood pressure profiles in 354 pediatric patients with diabetes. Data are means ± SEM of the first measurement in each patient for all patients (■), boys (*n* = *167*) (▥), and girls (*n* = *187*) (▤). Significant differences between sexes are indicated by* P *values; for statistical comparison to the reference population, see* RESULTS. *BP variability, blood pressure variability for the daytime and nighttime systolic and diastolic recordings.*

patient for the respective period, might also be relevant for diabetes. Variability was significantly reduced in female subjects compared to males for systolic and diastolic daytime and nighttime pressures (daytime systolic, $P < 0.01$; daytime diastolic, $P < 0.0005$; nighttime systolic, $P < 0.005$; and nighttime diastolic, $P < 0.01$ [Wilcoxon's signed-rank test]) (Fig. 2). Using multiple regression analysis and Wald statistics, male sex and overweight were significantly and positively associated with the variability of systolic and diastolic blood pressure during day and night. In addition, age and insulin dose affected nighttime systolic and diastolic blood pressure variability.

Prospective yearly follow-up measurements of ABPM for at least 4 years were available in 117 patients. As depicted in Fig. 3, the difference between patients' blood pressure and the height- and sex-adjusted mean in the reference population did not increase over time for either parameter. Nocturnal dipping did not change during follow-up for systolic pressure (9.9% on the 1st measurement, 9.6% on the 4th measurement); however, diastolic dipping significantly and steadily decreased from the 1st measurement (17.9%) to the 4th measurement (15.2%; $P < 0.03$). Blood pressure variability did not change over the observation period (daytime or nighttime, systolic or diastolic).

For all 1,011 measurements available, daytime mean systolic and diastolic blood pressures were related to the office blood pressure measurement taken during the visit to the outpatient clinic. A highly significant correlation was present ($r = +0.54$ for systolic and $r = +0.40$ for diastolic pressure; $P < 0.0001$, Pearson). However, regression analysis revealed that the regression line was significantly different from the line of identity. The equations relating the mean daytime systolic or diastolic pressure ($RR_{sys\text{-}mean}$ or $RR_{dia\text{-}mean}$) to office blood pressure recording ($RR_{sys\text{-}o}$ or $RR_{dia\text{-}o}$) were

$$RR_{sys\text{-}mean} = 0.299 \times RR_{sys\text{-}o} + 83.6$$

and

$$RR_{dia\text{-}mean} = 0.276 \times RR_{dia\text{-}o} + 53.1$$

Table 2—*Multiple linear regression analysis relating indices of 24-h blood pressure monitoring to diabetes duration, insulin dose, metabolic control (median HbA_{1c} during the year before ABPM), and standardized BMI*

	Diabetes duration	Insulin dose	Metabolic control	*z* score for BMI	*F* statistics
Adolescent patients (<16 years of age) (*n* = 252)					
Daytime blood pressure					
Systolic	0.21 (NS)	4.10 ($P < 0.03$)	–0.11 (NS)	0.63 ($P = 0.1$)	3.86 ($P < 0.002$)
Diastolic	0.38 ($P < 0.001$)	2.69 ($P = 0.07$)	0.09 (NS)	0.33 (NS)	4.73 ($P < 0.0001$)
Nighttime blood pressure					
Systolic	0.21 (NS)	3.96 (NS)	–0.08 (NS)	1.19 ($P < 0.004$)	3.62 ($P < 0.002$)
Diastolic	0.41 ($P < 0.001$)	0.27 (NS)	0.07 (NS)	0.24 (NS)	3.68 ($P < 0.002$)
Young adult patients (≥16 years of age) (*n* = 193)					
Daytime blood pressure					
Systolic	–0.12 (NS)	4.87 ($P = 0.09$)	0.29 (NS)	1.66 ($P < 0.003$)	3.17 ($P < 0.003$)
Diastolic	0.08 (NS)	2.05 (NS)	0.7 ($P < 0.0001$)	0.19 (NS)	5.64 ($P < 0.0001$)
Nighttime blood pressure					
Systolic	–0.15 (NS)	3.02 (NS)	0.07 (NS)	1.41 ($P < 0.01$)	1.92 ($P = 0.08$)
Diastolic	0.00 (NS)	3.38 (NS)	0.45 ($P < 0.006$)	0.09 (NS)	2.79 ($P < 0.02$)

Adolescent and young adult patients are analyzed separately, using the first ABPM recording of each patient in the respective age-group. Data are corrected for age and sex. The estimate for the contribution of each parameter, together with the respective *P* value as derived by Wald statistics in parentheses, are given for each model. The last column shows the *F* statistics and the *P* values for the entire model.

for systolic and diastolic pressure, respectively. No significant differences between male and female subjects were present.

The classification as normotensive or hypertensive in 1,011 ABPM recordings was compared with the office blood pressure measurement taken at the clinic visit. Based on the criteria published by the Second Task Force on Hypertension in Childhood (18), office systolic blood pressure was classified as elevated (>95th percentile for age and sex) in 257 measurements (25.4%). ABPM confirmed hypertension in 83 out of 257 (32%), while 174 ABPM recordings were classified as normal (daytime mean systolic pressure below the 95th percentile based on 1,141 healthy control subjects [12]). The probability of white-coat hypertension in the presence of an elevated systolic office blood pressure measurement is therefore 68%. Diastolic office blood pressure was elevated in only 14 out of 1,011 recordings (1.4%); in 13 out of these 14 measurements (93%), the corresponding daytime mean diastolic pressure in ABPM fell below the 95th percentile.

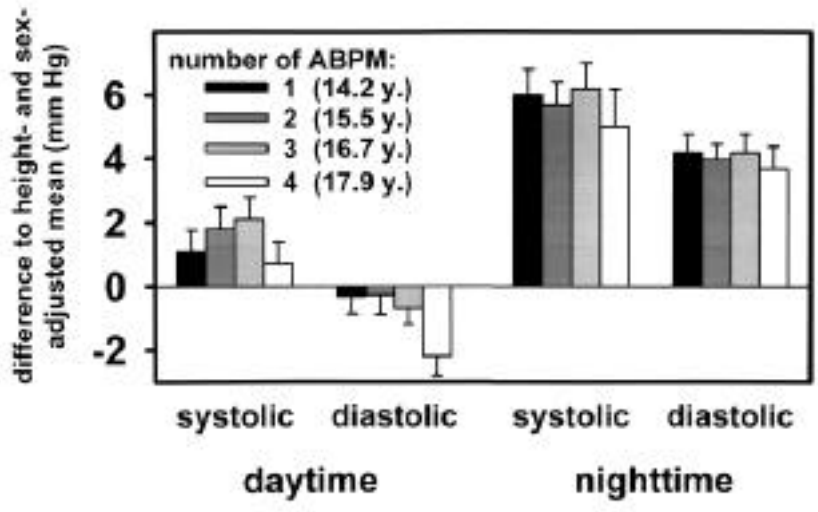

Figure 3—*Mean difference of 24-h blood pressure parameters in diabetic patients from the respective normal values based on height and sex during a prospective follow-up for 4 years in 117 pediatric patients. The mean chronological age at the time of each measurement is indicated in parentheses. Bars represent means ± SEM. No significant changes during the follow-up period were noted for systolic or diastolic blood pressure during daytime and nighttime.*

CONCLUSIONS — Hypertension is clearly more prevalent in adult patients with longstanding diabetes (19), and even more so in the subgroup with diabetic nephropathy (20). Two conflicting hypotheses for hypertension in diabetic subjects have been proposed: secondary hypertension might be the consequence of diabetic nephropathy, or alternatively, the presence of hypertension in a diabetic patient might promote the onset of renal changes with a subsequent further increase in blood pressure. To address this question, it is relevant to study the prevalence of hypertension in young patients with a relatively short duration of diabetes. In our large sample of adolescent and young adult patients, daytime systolic pressure was slightly elevated compared with healthy control subjects, while daytime diastolic pressure was normal in diabetic subjects. Daytime blood pressure did not increase further during the 4-year-follow-up period, and in the multiple linear regression analysis, diabetes duration had an influence only on diastolic pressure in adolescents, but not in adults with diabetes. Even if an elevation of systolic daytime blood pressure of 3.1 mmHg is significant due to the large number of subjects studied, on clinical grounds this elevation is small. Our finding—that the prevalence of hypertension is not dramatically increased in young patients with a short duration of the disease—is confirmed by a study comparing blood pressure in young diabetic patients with their nondiabetic siblings (21).

Nocturnal systolic and diastolic pressures were significantly higher in patients compared to published normal ranges, and the nocturnal dipping was reduced. Similar data were reported in a small study of 28 diabetic children without albuminuria (11). Two explanations are possible. First, reduced nocturnal blood pressure fall is indicative of secondary (renal) hypertension, as circadian blood pressure variability is usually absent in patients with secondary hypertension (22). In adults, circadian variation was only moderately disturbed in microalbuminuric patients, while a marked reduction of nocturnal blood pressure fall was present in patients with advanced diabetic nephropathy (8,20,23). However, a second possible explanation is that reduced nocturnal dipping may also be a sign of early diabetic neuropathy (24). We have previously demonstrated that asymptomatic cardiac neuropathy is present in children and adolescents even with a short duration of diabetes, closely related to long-term metabolic control (25). Metabolic control had a significant influence on both daytime as well as nighttime diastolic pressure in young adults in our study.

Our data revealed a relationship between overweight and systolic hypertension. Interestingly, this relation is much stronger for adolescents and young adults than for older subjects (26). As a group, adolescents with diabetes were found to be overweight in several studies (27,28), a factor that is likely to explain, at least in part, elevated systolic daytime and nighttime blood pressure. The finding that insulin dose is positively related to some indices of 24-h blood pressure may be explained by sodium retention, as the daily injected insulin dose has been shown to dose-dependently increase the total exchangeable sodium pool in isotope studies (29). Hyperinsulinism in essential hypertension has repeatedly been demonstrated both in pediatric and adult patients (30,31), and insulin concentrations in diabetic patients are clearly elevated in peripheral blood due to the unphysiologic application of insulin into the subcutaneous tissue instead of the physiological release into the portal circulation.

Blood pressure variability has been proposed as a further parameter derived from 24-h blood pressure profiles; however, the clinical relevance is still debated (19). In patients aged >55 years, daytime systolic blood pressure variability has been shown to be a strong predictor of early carotid atherosclerosis (32). In this context, it is interesting for the interpretation of this finding that overweight was positively correlated to blood pressure variability in our study.

White-coat hypertension is defined as an elevated office blood pressure measurement that is not confirmed by home blood pressure measurement or by ABPM. The frequency of white-coat hypertension is especially high during adolescence: in the age-group 14–18 years, 70% of subjects with elevated casual blood pressure measurements display normal 24-h pressure profiles (6). This figure corresponds well with the 68% of elevated office systolic blood pressure recordings subsequently classified as white-coat hypertension according to ABPM in our study on young patients with diabetes. Therefore, suspected hypertension in pediatric patients with diabetes has to be confirmed by ABPM before medical therapy is initiated. There is general agreement that patients with white-coat hypertension do not need antihypertensive therapy (33). However, this patient group needs careful follow-up; according to one report, 60 out of 81 patients with this condition (74%) developed ambulatory hypertension during the following 5 to 6 years (34).

ABPM has shown to be feasible and reliable not only in adults, but also in children and adolescents (35). While this method has been widely used in adult diabetic patients, so far only small studies in pediatric patients with diabetes have been published (9,11). The importance of ABPM is underlined by the relatively low correlation with office blood pressure and by the "regression toward the mean" that has previously been described in nondiabetic normotensive pediatric subjects (36,37) and confirmed for patients with diabetes in the present study. Subjects with elevated office blood pressure tend to have lower values on ABPM, while patients with low casual blood pressure readings display higher mean daytime values, resulting in a significant tilting of the regression line (38).

In conclusion, our data indicate that slightly higher blood pressure in young patients with diabetes is related to overweight, insulin dose, and metabolic control. Elevated nocturnal blood pressure and reduced "dipping" might reflect subclinical autonomic neuropathy. ABPM provides a valuable tool to detect patients with white-coat hypertension and avoid unnecessary antihypertensive therapy.

Acknowledgments — We are grateful for financial support from the State Government of Baden-Württemberg, Stuttgart, Germany (Landesschwerpunkt Spätkomplikationen bei Diabetes Mellitus), the Federal Ministry of Health, Bonn, Germany (Modellprogramm zur Verbesserung der Versorgung chronisch Kranker), the Dr.-Karl-Wilder-Stiftung of the German life insurance companies, as well as grants from the German Diabetes Association and the NovoNordisk Pharma, Mainz, Germany.

Excellent technical support was provided by H. Nebenführ, R. Völk, and U. Weinstein. Statistical advice was provided by J. Rosenbauer, Düsseldorf, Germany.

This study was presented in part at the 56th Annual Meeting of the American Diabetes Association, San Francisco, CA, 8–11 June 1996.

References

1. Barzilay J, Warram JH, Bak M, Laffel LMB, Canessa M, Krolewski AS: Predisposition to hypertension: risk factor for nephropathy and hypertension in IDDM. *Kidney Int* 41:723–730, 1992
2. Christlieb AR, Warram JH, Krolewski AS, Busick EJ, Gauda OP, Asmal AC, Soeldner JS, Bradley RF: Hypertension: the major risk factor in juvenile-onset insulin-dependent diabetics. *Diabetes* 30:90–96, 1981
3. Hostetter TH: Diabetic nephropathy, metabolic versus hemodynamic considerations. *Diabetes Care* 15:1205–1215, 1992
4. Julius S, Mejia A, Jones K, Krause L, Schork N, van de Ven C, Johnson E, Petrin J, Sekkarie MA, Kjeldsen SE: "White-coat" versus "sustained" borderline hypertension in Tecumseh, Michigan. *Hypertension* 16:617–623, 1990
5. Julius S, Jamerson K, Gudbrandsson T, Schork N: White coat hypertension: a follow-up. *Clin Exp Hypertens* A14:45–53, 1992
6. Waeber G, Waeber B, Nussberger J, Brunner HR: Ambulatory blood pressure monitoring in adolescent untreated hypertensive patients. *Clin Exp Hypertens* A8:611–614, 1986
7. Holl RW, Rehm R, Walker P, Heinze E: 24-Stunden-Blutdruckmessung bei Kindern und Jugendlichen mit Diabetes mellitus Typ I: Beziehung zu Diabetesdauer, Übergewicht und Urinalbuminausscheidung. *Zeitschrift für Kardiologie* 81 (Suppl. 2):25–27, 1992
8. Hansen KW, Pedersen MM, Marshall SM, Christiansen JS, Mogensen CE: Circadian variation of blood pressure in patients with diabetic nephropathy. *Diabetologia* 35: 1074–1079, 1992
9. Moore WV, Donaldson DL, Chonko AM, Ideus P, Wiegmann TB: Ambulatory blood pressure in type 1 diabetes mellitus. *Diabetes* 41:1035–1041, 1992
10. Wiegmann TB, Herron KG, Chonko AM, Macdougall ML, Moore WY: Recognition of hypertension and abnormal blood pressure burden with ambulatory blood pressure recordings in type 1 diabetes mellitus. *Diabetes* 39:1556–1560, 1990
11. Madacsy L, Yasar A, Tulassay T, Körner A, Kelemen J, Hobor M, Miltenyi M: Relative nocturnal hypertension in children with IDDM. *Acta Paediatr* 83:414–417, 1994
12. Soergel M, Kirschstein M, Busch C, Danne T, Gellermann J, Holl RW, Krull F, Reichert H, Reusz GS, Rascher W: Twenty-four hour ambulatory blood pressure values in healthy children and adolescents: a multicenter trial including 1141 subjects. *J Pediatr* 130:178–184, 1997
13. Kullberg CE, Bergström A, Dinesen B, Larsson L, Little RR, Goldstein DE, Arnqvist HJ: Comparisons of studies on diabetic complications hampered by differences in GHb measurements. *Diabetes Care* 19:726–729, 1996
14. Friedmann SH, Humbert JR: A simple microchromatographic column for determination of hemoglobins A_{1a+b} and A_{1c}. *Hemoglobin* 3:411–428, 1979
15. Heinze E, Vetter U, Thon A, Kohne E: Is there a "risk-free" haemoglobin A1 concentration in type I diabetics? *Deutsch Med Wschr* 108:1632–1634, 1983
16. Holl RW, Grabert M, Schweiggert F, Heinze E: A computer program for prospective documentation of pediatric patients with type I diabetes mellitus. *Diabetes und Stoffwechsel* 3:232–238, 1993
17. Prader A, Largo RH, Molinari L, Issler C: Physical growth of Swiss children from birth to 20 years of age. *Helvetica Paediatrica Acta* 52:1–125, 1989
18. Task Force on Blood Pressure Control in Children: Report of the Second Task Force. *Pediatrics* 79:1–25, 1987
19. Norgaard K, Feldt-Rasmussen B, Borch-Johnsen K, Saelan H, Deckert T: Prevalence of hypertension in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 33:407–410, 1990
20. Torffvit O, Agardh CD: Day and night variation in ambulatory blood pressure in type 1 diabetes mellitus with nephropahty and autonomic neuropathy. *J Int Med* 233:131–137, 1993
21. Tarn AC, Drury PL: Blood pressure in children, adolescents and young adults with type I (insulin-dependent) diabetes. *Diabetologia* 29:275–281, 1986
22. Middeke M, Schrader J: Nocturnal blood pressure in normotensive subjects and those with white coat, primary, and secondary hypertension. *BMJ* 308:630–632, 1994
23. Poulsen PL, Hansen KW, Mogensen CE: Ambulatory blood pressure in the transition from normo- to microalbuminuria. *Diabetes* 43:1248–1253, 1994
24. Monteagudo PT, Nobrega JC, Cezarini PR, Ferreira SRG, Kohlmann O, Ribeiro AB, Zanella MT: Altered blood pressure profile, autonomic neuropathy and nephropathy in insulin-dependent diabetic patients. *Eur J Endocrinol* 135:683–688, 1996

25. Holder M, Holl RW, Barth J, Hecker W, Heinze E, Leichter HE, Teller W: Influence of long-term glycemic control on the development of cardiac autonomic neuropathy in pediatric patients with type 1 diabetes. *Diabetes Care* 20:1042–1043, 1997
26. Chen Y, Rennie DC, Reeder BA: Age-related association between body mass index and blood pressure: the Humboldt Study. *Int J Obesity* 19:825–831, 1995
27. Thon A, Heinze E, Feilen KD, Holl RW, Schmidt H, Koletzko S, Wendel U, Nothjunge J: Development of height and weight in children with diabetes mellitus: report on two prospective multicentre studies. *Eur J Pediatr* 151:258–262, 1992
28. Holl RW, Heinze E, Seifert M, Grabert M, Teller WM: Longitudinal analysis of somatic development in paediatric patients with IDDM: genetic influences on height and weight. *Diabetologia* 37:925–929, 1994
29. Norgaard K, Feldt-Rasmussen B: Sodium retention and insulin treatment in insulin-dependent diabetes mellitus. *Acta Diabetol* 31:19–25, 1994
30. Rocchini AP, Key J, Bondie D, Chico R, Moorehead C, Katch V, Martin M: The effect of weight loss on the sensitivity of blood pressure to sodium in obese adolescents. *N Engl J Med* 321:580–585, 1989
31. Lender D, Arauz-Pacheco C, Adams-Huet B, Raskin P: Essential hypertension is associated with decreased insulin clearance and insulin resistance. *Hypertension* 29:111–114, 1997
32. Sander D, Klingelhöfer J: Diurnal systolic blood pressure variability is the strongest predictor of early carotid atherosclerosis. *Neurology* 47:500–507, 1996
33. Pickering TG, James GD: Ambulatory blood pressure and prognosis. *J Hypertens* 12 (Suppl. 8):S29–S33, 1994
34. Bidlingmeyer I, Burnier M, Bidlingmeyer M, Waeber B, Brunner HR: Isolated office hypertension: a prehypertensive state? *J Hypertens* 14:327–332, 1996
35. Harshfield GA, Alpert BS, Pulliam DA, Somes GW, Wilson DK: Ambulatory blood pressure recordings in children and adolescents. *Pediatrics* 94:180–184, 1994
36. Nishibata K, Nagashima M, Tsuji A, Hasegawa S, Nagai N, Goto M, Hayashi H: Comparison of casual blood pressure and twenty-four-hour ambulatory blood pressure in high school students. *J Pediatr* 127:34–39, 1995
37. Lurbe E, Redon J, Liao Y, Tacons J, Cooper RS, Alvarez V: Ambulatory blood pressure monitoring in normotensive children. *J Hypertens* 12:1417–1423, 1994
38. Holl RW, Heinze E, Neumann R, Traub P, Teller WM: 24-hour blood pressure monitoring in pediatrics: results in healthy children compared to patients with primary or secondary hypertension, as well as diabetes mellitus type I. *Mschr Kinderheilkd* 142:272–278, 1994