Nondipping and Its Relation to Glomerulopathy and Hyperfiltration in Adolescents With Type 1 Diabetes

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OBJECTIVE — To determine whether there is a relation between dipping/nondipping status and end-organ damage (measured as renal glomerulopathy) and long-term renal function in order to predict the development of nephropathy in normoalbuminuric patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Analysis of renal biopsy and ambulatory blood pressure measurements was done in relation to renal function tests performed during a 10-year period. Forty unselected patients (16 girls), with a mean age of 17.7 years and a mean duration of 10.7 years, were studied. The renal biopsies were examined by electron microscopy. Ambulatory blood pressure was monitored (Space Labs 90 207). Systolic nondippers were defined as a <7%, diastolic nondippers as a <14%, and mean arterial blood pressure (MAP) nondippers as a <12% fall in blood pressure during the night. Renal function was evaluated every other year by clearances of inulin (glomerular filtration rate [GFR]) and para-amino hippurate (effective renal plasma flow [ERPF]), and filtration fraction (GFR/ERPF) was calculated. Overnight urinary albumin excretion rate and long-term mean HbA_{1c} were measured.

RESULTS — MAP (27% of the patients) and diastolic nondippers (12%) had a significantly thicker basement membrane; larger mesangial matrix volume fraction; and higher long-term GFR, nighttime heart rate, and mean HbA_{1c} than dippers.

CONCLUSIONS — Nondipping status was related to more renal morphological changes and long-term hyperfiltration in normoalbuminuric adolescents and young adults, despite a short duration of type 1 diabetes. Nondipping status may be an early predictor of later nephropathy.

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Nephropathy is a threatening complication of type 1 diabetes that leads to renal failure in many patients (1,2). It seems important to find those at risk of developing nephropathy as soon as possible to prevent or postpone renal damage (3). A matter of interest is the relation between hypertension and nephropathy in the early stages of type 1 diabetes. Nighttime hypertension seems to be related to target-organ damage (4–7). Measurements of ambulatory blood pressure give information not only about the level of daytime and nighttime blood pressure but also about the diurnal variation in blood pressure during regular activities. O'Brien, Sheridan, and O'Malley (8) pointed out the significance of nighttime dippers and nondippers, and the methodological aspects have been discussed in the literature (9,10). The nondipping pattern and its relation to the target-organ damage has recently been discussed (6,10).

The present study gives new information on the relations between dipping/nondipping blood pressure status, long-term renal function, and glomerular changes in normoalbuminuric subjects with type 1 diabetes.

RESEARCH DESIGN AND METHODS

— In our pediatric clinic at Huddinge University Hospital, all patients >12 years of age with diabetes for >5 years, who were soon to undergo their regularly performed renal function test, were asked to take part in a kidney biopsy study. Of 61 patients, 45 participated while 16 declined or wanted to have the biopsy done later. Of these 45 patients, 41 had had 24-h ambulatory blood pressure measurements; 1 was excluded because of no nighttime values. Therefore, the findings in 40 patients are presented. The day- and nighttime blood pressure values and their relation to morphological data have been described elsewhere (11). Some data on 31 of these 40 patients, who had undergone at least three investigations of their renal function, have been reported (12). The 16 patients who did not participate, and the 4 with no ambulatory blood pressure measurements, had renal function, casual blood pressure, albuminuria, and metabolic control values similar to those who agreed to participate.

The investigations were performed during a 3-day period. On the first day, a renal function test was done and overnight urine collected to determine the albumin excretion rate. On the second day, a renal biopsy was taken. After the biopsy, the patients were kept supine for 24 h and pulse rate and blood pressure were determined at regular intervals. Some patients developed microscopic hematuria, and in 7 of 40 (18%), subcapsular hematomas were found on ultrasound on the day after the biopsy, although no clinical complications occurred apart from slight pain in the muscles overlying the biopsy site. The

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Abbreviations: BMT, basement membrane thickness; ERPF, effective renal plasma flow; GFR, glomerular filtration rate; MAP, mean arterial blood pressure; UAE, urinary albumin excretion rate.

study was approved by the ethics committee of Karolinska Institutet at Huddinge University Hospital and performed after informed consent had been obtained from the patients and their parents.

Blood pressure

The casual blood pressure was measured in the right arm, after the patients had rested for 30 min, with an Omron digital blood pressure monitor (Model Hem-700C; Boehringer Mannheim, Scandinavia AB, Bromma, Sweden) and taken before the renal function test on the first day of the study.

Ambulatory blood pressure was recorded for 24 h with portable automatic Space Labs 90 207 equipment (Space Labs, Wokingham, U.K.). The monitor was programmed for cuff insufflations every 20 min between 7:00 A.M. and 10:00 P.M. and every 30 min from 10:00 P.M. to 7:00 A.M. The technique is described elsewhere (13–15). In 23 patients, the recordings were started at ~12:00 P.M. on the day after the kidney biopsy, when the patients were discharged from the hospital. In 17 patients, these were done within 10 months (mean 6) of the kidney biopsy. The patients were told to live as usual but to avoid sports. Day- and nighttime blood pressures and heart rates were based on standardized daytime (8:00 A.M. to 8:00 P.M.) and nighttime (12:00 A.M. to 6:00 A.M.) values, using the method of Soergel et al. (16). The time intervals were corrected in six patients, for whom reported routines for sleeping differed from the standardized time periods. All patients had a median of 94% (range 71–100) successful readings (38 of 40 had >80% successful readings).

Their mean arterial blood pressure (MAP) was calculated as the diastolic blood pressure plus one-third of the difference between the systolic and diastolic blood pressures. The day- and nighttime systolic and diastolic blood pressures, MAPs, and heart rates were calculated using ABP PC Direct/Base Station Interface 90 219. We compared our blood pressure and heart rate (personal communication) measurements with those of Soergel et al. (16), which were based on 1,141 healthy children and adolescents aged 5–21 years.

The percentage nighttime fall in blood pressure (the "dipping") was calculated as: (daytime blood pressure – nighttime blood pressure) × 100/daytime blood pressure (16,17). Soergel et al. (16) found systolic and diastolic falls in blood pressure of 13 ± 6 and 23 ± 9% (means ± SD), respectively, during the night in control subjects. In the present study, nondippers were defined as those with a percent fall in blood pressure of less than the mean minus 1 SD (i.e., <7% for systolic blood pressure and <14% for diastolic blood pressure), whereas dippers were defined as those with a fall in blood pressure during the night that exceeded these values. We defined the MAP nondippers as those with a percentage fall <12%.

Renal function tests

Renal function was evaluated every second or third year after the onset of diabetes. The glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were determined by the clearances of inulin and para-amino hippurate during water diuresis with a standard clearance technique (12,18). In the morning before the start of the renal function test, the patients were given their ordinary insulin dose and then breakfast. The GFR and ERPF values were corrected for body surface area. Filtration fraction was calculated as GFR/ERPF.

The mean GFR, ERPF, and filtration fraction of all previous renal function tests were calculated in every patient except one, in whom only one function test had been performed. Renal function was compared with that of 59 healthy children and young adults 3.5–25.9 years of age (median 13.2) who had been evaluated in our Pediatric Nephrology Unit. The age range of the control subjects resembles that of these patients during the entire follow-up period.

Urine samples

Timed overnight-collected urine was analyzed for albumin by an automated immuno-nephelometric method (Behring Nephelometer Analyzer; Behringwerken AG, Marburg, Germany), and the urinary albumin excretion rate (UAE) was determined. UAE was measured in 33 patients.

Metabolic control

We have determined total HbA_1 with ion exchange chromatography since 1980, using Isolab's Fast Hemoglobin Test System (Quik-Step Fast Hemoglobin Test System; Isolab, Akron, OH) (reference values 5.5–8.5%) and HbA_{1c} with the fast-protein liquid chromatography method between 1986 and 1988 (Fast Protein Liquid Chromatography; Pharmacia, Uppsala, Sweden [19]) (reference values 3.4–5.0%). Since 1988, we used the high-performance liquid chromatography method (Variant; Bio Rad Laboratories, Hercules, CA) (reference values 3.4–5.0%). To compare glycemic control over time, HbA_1 data were converted to HbA_{1c} using the equation $HbA_1 = 1.13 \times HbA_{1c} + 0.85$. In our laboratory, the correlation coefficient between the two methods is 0.957.

Since 1980, we have checked the HbA_1 or HbA_{1c} values in each patient three to four times a year. We calculated the mean HbA_{1c} for each year and the mean of all years as a measure of long-term metabolic control. Actual HbA_{1c} was taken at the day of the renal function test. Our HbA_{1c} values are 1.1% lower than those of the Diabetes Control and Complication Trial reference lab (20).

Renal biopsy

The biopsies were taken during ultrasound guidance (Acuson, Mountain View, CA) using an automatic biopsy device (Biopty Bard Urological, Covington, GA) and a 16-gauge needle (Manan Medical Products, Northbrook, IL) (12). They were fixed in 4% paraformaldehyde in phosphate buffer. Small tissue blocks for electron microscopy were postfixed in 2% glutaraldehyde and 4% paraformaldehyde in phosphate buffer and embedded in Polybed 812. Ultra-thin sections were stained with uranyl acetate and lead citrate. Every biopsy was examined by a single nephropathologist (G.A.J.) at Karolinska Institutet without knowledge of the patient's history.

Electron microscopic quantitation

The sampling of the glomerular profiles taken for ultra-thin sectioning was performed as described elsewhere (12). Four to five glomeruli were analyzed from each biopsy. Seven to 19 electron micrographs, covering ~40% of the area of each glomerular profile, were sampled in a systematic random manner by moving the specimen stage of the electron microscope (Philips 420; Phillips, Eindhoven, Netherlands) between predetermined points. The micrographs were analyzed at a magnification of about ×10,000 that was corrected using a grating grid (EF Fullan) (28,800 lines/inch). Glomerular

profiles representing less than seven sampled areas were excluded. The reference space, here called "glomerulus," was defined as a minimal convex polygon enclosing the glomerular tuft (i.e., tuft plus urinary space entrapped in the polygon) (21). The definition of the mesangium and its demarcation from the peripheral capillary wall was used as in the study by Østerby and Gundersen (21). All the estimated relative structural quantities were expressed in relation to the reference space given above.

Mesangial V_v(mes/glom) and mesangial matrix V_v(matrix/glom) volume fractions per glomerulus were estimated by point counting using a superimposed lattice square grid with points 30 mm apart. Total points hitting the mesangial areas and the mesangial matrix substance were divided by the total points hitting the reference space. Mesangial matrix was defined as all extracellular material in the mesangial areas.

Using the same square lattice grid as above, the intersections (I) with the epithelial aspect of the basement membrane of the peripheral capillary walls were counted and the surface density of the peripheral capillary walls [S_v(pcap/glom)] was calculated as $S_v(\text{pcap/glom}) = 2 \times I/[P \times (2d/\text{mag})]$ (μm^{-1}) and the number of their related filtration slits (Q), the length density of filtration slits [L_V(slit pore/glom)], was estimated as $L_V(\text{slit pore/glom}) = 2 \times Q/(P \times [d^2/\text{mag}^2])$ (μm^{-2}) (P, total points in the reference space; d, distance between each point of the grid; and mag, final magnification). The mean foot process width was estimated as the ratio of S_V(pcap/glom) and L_V(slit pore/glom) (nm). The basement membrane thickness (BMT) (nm) was estimated by using the orthogonal intercept method of Jensen, Gundersen, and Østerby (22). None of our patients had any occluded glomeruli.

Statistical analyses

The Shapiro-Wilk's *W* test for normality was used. Mean HbA_{1c}, UAE, and heart rate were not normally distributed and are given as median (min–max). UAE are $\log_{10}$ transformed for calculations. The Student's *t* test was used to compare two groups, dippers and nondippers, when equal variances and approximately normal distribution (mean ± SD) were present. If the distribution was skewed, we used the Mann-Whitney *U* test (median [min–max]). Fisher's exact test was used to compare the distribution of sex and of smoking habits in both groups.

Pearson regression analysis was done with the least square method, and *r* is given. Multiple regression analysis was performed by the least square method, and adjusted r^2 was used to adjust for the number of X-factors used. A test performed to determine whether the residuals were normally distributed did not show any trend toward a predicted value. A *P* value <0.05 was considered significant. The statistical program of JMP version 4.0.5 was used.

RESULTS — The patients were aged 17.7 ± 2.9 years and had had diabetes for 10.7 ± 3.3 years. Their age at onset was 7.0 ± 3.7 years and BMI 22.3 ± 2.7 kg/m^2. Of the patients, 18% had an insulin pump and the rest had one to two injections three to five times per day. The insulin dose was 0.95 ± 0.19 IU/kg. The HbA_{1c} at biopsy was 7.7% (5.4–14.8) and long-term mean HbA_{1c} 7.9% (6.8–10.9). One patient had asymptomatic bacteriuria. Twenty-five percent were smokers, and 71% were in Tanner stage 5 (adult sexual maturity). One patient had well-controlled hypothyroidism. Their casual blood pressure was 122 ± 12/74 ± 10 mmHg. No patient was on antihypertensive treatment. All patients were Caucasian.

Blood pressure and heart rate dipping

Daytime ambulatory blood pressure was 129 ± 8/77 ± 6 mmHg and nighttime 113 ± 9/60 ± 7 mmHg. The heart rate was 86 bpm (range 65–108) during the day and 63 bpm (49–94) throughout the night. The systolic decline during the night was 12 ± 5% (mean ± SD), the diastolic decline was 22 ± 7%, and the heart rate dipping was 23 ± 10%. The MAP decline was 16 ± 6%. We found no significant differences between boys and girls. Positive correlations were found between systolic dipping and diastolic dipping ($r = 0.78$, $P < 0.001$) and between heart rate dipping and MAP dipping ($r = 0.36$, $P = 0.022$).

Morphology

The mean BMT, V_V(mes/glom), and V_V(matrix/glom) were 510 ± 109 nm, 19.3 ± 3.1%, and 10.7 ± 2.1%, respectively. S_V(pcap/glom), L_V(slit pore/glom), and foot process width were 0.146 ± 0.019 μm^{-1}, 0.354 ± 0.058 μm^{-2}, and 414 ± 36 nm, respectively.

Renal function

The number of renal function tests performed in each patient, except one, was two to seven (median four). The mean previous GFR and filtration fraction before biopsy were significantly (<0.001) higher in the patients with diabetes than in 59 healthy control subjects (137 ± 19 vs. 117 ± 10 ml · min^{-1} · 1.73 m^{-2} and 22.2 ± 2.5 vs. 19.2 ± 2.6%), while the mean previous ERPF did not differ from that of the control subjects (628 ± 81 vs. 622 ± 97 ml · min^{-1} · 1.73 m^{-2}).

The mean previous filtration fraction showed a significant correlation with the BMT ($r = 0.33$, $P = 0.036$), V_V(mes/glom) ($r = 0.44$, $P = 0.0053$), and V_V(matrix/glom) ($r = 0.52$, $P = 0.0007$) and the mean previous ERPF with V_V(matrix/glom) ($r = -0.38$, $P = 0.019$), while we found no correlations between mean previous GFR and morphology.

Dippers and nondippers: findings concerning clinical data, metabolic control, blood pressure, heart rate, renal function, and morphology

Table 1 shows data on clinical findings, blood pressure, heart rate, kidney function, and renal morphological changes of the patients when divided into dippers and nondippers. Seventeen percent of the patients were systolic, 12% diastolic, and 27% MAP nondippers. Body height, age at onset, and smoking habits were similar in the two groups. All nondipper groups had a higher long-term GFR, blood pressure, and heart rate at night than the dipper groups. Diastolic and MAP nondippers had more renal morphological changes and worse metabolic control than dippers.

There are overlaps between the dipper and nondipper groups concerning the renal functional and morphological parameters in Table 1. In the MAP nondipper group, we found 8 of 10 patients with mean previous GFR >2 SD of control subjects (hyperfiltration), 7 of 11 with BMT above mean (>510 nm) in our patients with diabetes, and 7 of 11 with V_V(matrix/glom) above mean (>10.7%). In the *MAP* dipper group, we found 12 of 29 patients with hyperfiltration, 9 of 29 with BMT >510 nm, and 11 of 29 with V_V(matrix/glom) >10.7%.

In multiple regression analyses, we

Table 1—*Data on clinical findings, blood pressure, heart rate, kidney function, and renal morphological changes of dippers and nondippers*

	Systolic blood pressure		Diastolic blood pressure		MAP	
	Dippers ≥7%	Nondippers <7%	Dippers ≥14%	Nondippers <14%	Dippers ≥12%	Nondippers <12%
n	33	7	35	5	29	11
Female sex [*n* (%)]	13 (39)	3 (43)	13 (37)	3 (60)	11 (38)	5 (45)
P	1.00		0.37		0.73	
Duration (years)	10.6 ± 3.5	11.2 ± 2.6	10.7 ± 3.4	10.7 ± 2.7	10.7 ± 3.7	10.6 ± 2.2
P	0.66		0.98		0.93	
Age (years)	17.7 ± 3.1	17.7 ± 2.2	17.7 ± 2.9	17.7 ± 3.2	17.7 ± 3.1	17.7 ± 2.6
P	0.97		0.99		0.96	
Mean HbA_{1c} (%)	7.9 (6.8–10.9)	8.3 (7.3–10.8)	7.9 (6.8–10.9)	9.5 (7.7–10.8)	7.8 (6.8–10.9)	8.6 (7.3–10.8)
P	0.32		0.055		0.037	
UAE (μg/min)	6 (2–64), *n* = 27	7 (3–30), *n* = 6	5 (2–64), *n* = 30	9 (2–17), *n* = 3	6 (2–64), *n* = 24	4 (2–30), *n* = 9
P	0.96		0.97		0.30	
Daytime blood pressure (mmHg)	128 ± 9/77 ± 6	130 ± 8/75 ± 5	128 ± 9/77 ± 6	131 ± 5/76 ± 6	128 ± 9/77 ± 6	130 ± 7/76 ± 5
P	0.63/0.48		0.46/0.68		0.52/0.78	
Nighttime blood pressure (mmHg)	111 ± 8/59 ± 6	124 ± 8/66 ± 6	112 ± 9/59 ± 6	123 ± 7/68 ± 7	110 ± 8/57 ± 5	122 ± 7/66 ± 5
P	0.006/0.0006		0.016/0.003		0.0001/0.0001	
Daytime heart rate (bpm)	86 (66–104)	88 (65–108)	84 (65–105)	95 (81–108)	86 (66–104)	88 (65–108)
P	0.56		0.082		0.50	
Nighttime heart rate (bpm)	61 (49–94)	66 (66–89)	62 (49–87)	85 (66–94)	61 (49–87)	66 (56–94)
P	0.044		0.003		0.008	
Previous GFR ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$)	134 ± 17, *n* = 32	153 ± 19	135 ± 18	158 ± 13, *n* = 4	132 ± 18	151 ± 17, *n* = 10
P	0.011		0.018		0.006	
Previous ERPF ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$)	623 ± 83, *n* = 32	648 ± 75	622 ± 82	677 ± 63, *n* = 4	621 ± 86	648 ± 65, *n* = 10
P	0.47		0.20		0.37	
Previous filtration fraction (%)	21.8 ± 2.3, *n* = 32	23.8 ± 2.9	22.0 ± 2.6	23.5 ± 0.8, *n* = 4	21.7 ± 2.4	23.5 ± 2.5, *n* = 10
P	0.058		0.27		0.054	
BMT (nm)	498 ± 91	564 ± 169	492 ± 92	636 ± 147	485 ± 85	574 ± 141
P	0.15		0.004		0.020	
V_v(mes/glom) (%)	19.1 ± 2.8	20.4 ± 4.1	18.8 ± 2.6	23.0 ± 3.8	18.7 ± 2.7	21.0 ± 3.4
P	0.33		0.003		0.028	
V_v(matrix/glom) (%)	10.5 ± 1.9	11.3 ± 3.0	10.3 ± 1.7	13.1 ± 3.0	10.2 ± 1.8	11.9 ± 2.5
P	0.38		0.004		0.020	
S_v(pcap/glom) (μm^{-1})	0.147 ± 0.019	0.138 ± 0.019	0.148 ± 0.018	0.133 ± 0.023	0.147 ± 0.019	0.144 ± 0.019
P	0.23		0.097		0.66	
L_v(slit pore/glom) (μm^{-2})	0.358 ± 0.057, *n* = 32	0.334 ± 0.063	0.361 ± 0.056, *n* = 34	0.300 ± 0.047	0.357 ± 0.059, *n* = 28	0.345 ± 0.059
P	0.34		0.025		0.57	
Foot process width (nm)	414 ± 37, *n* = 32	416 ± 34	410 ± 37, *n* = 34	441 ± 9	412 ± 39, *n* = 28	419 ± 30
P	0.86		0.074		0.59	

Data are means ± SD.

found that the regression lines for dippers and nondippers were significantly different with morphological changes as dependent variables and renal function or metabolic control as independent variables. V_V(matrix/glom) was related to mean HbA_{1c} in the MAP nondipper group ($r = 0.74$, $P = 0.009$) but not in the dipper group ($r = 0.21$, $P = 0.14$). The foot process width was directly related to mean previous GFR in the MAP nondipper group ($r = 0.65$, $P = 0.042$) but reversly related to mean previous GFR in the dipper group ($r = -0.39$, $P = 0.042$). With regard to the BMT or V_V(mes/glom) versus renal function or metabolic control, the regression lines for MAP dippers and nondippers were not significantly different. Moreover, when adjusting for HbA_{1c} values, the differences between the diastolic dippers and nondippers concerning the BMT, V_V(mes/glom), or V_V(matrix/glom) stayed significant ($P = 0.050$, $P = 0.020$, and $P = 0.039$, respectively), whereas the differences between the MAP dippers and nondippers did not reach significance ($P = 0.17$, $P = 0.12$, and $P = 0.12$, respectively). We found no influence of metabolic control on the differences between the dipping groups in S_V(pcap/glom), L_V(slit pore/glom), or foot process width.

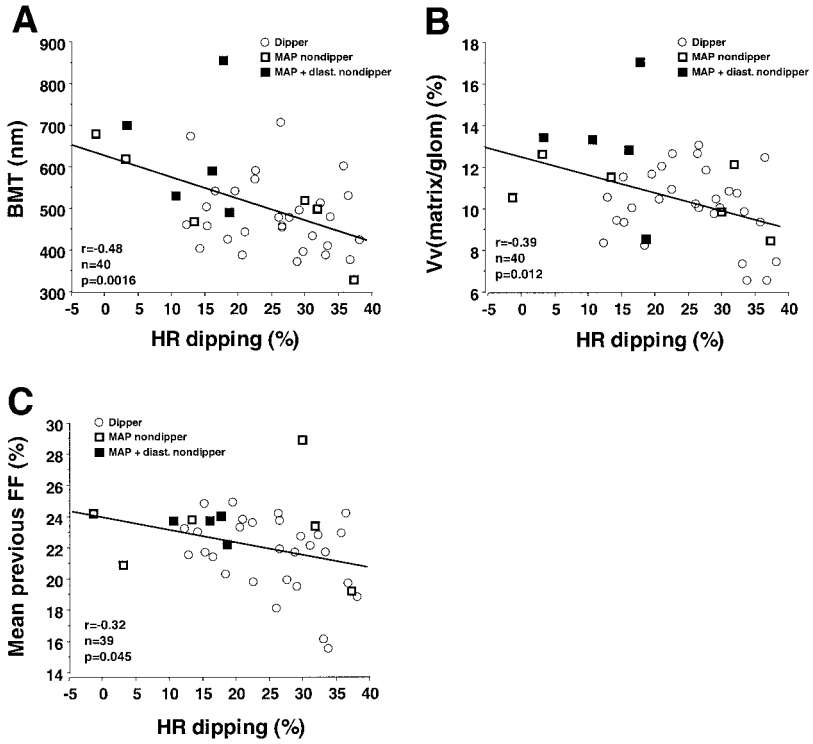

Figure 1—*Heart rate dipping in relation to BMT* (A)*, V_V(matrix/glom)* (B)*, and mean previous filtration fraction* (C)*.*

Correlations with dipping

In single correlations, the heart rate dipping was related to the BMT (Fig. 1*A*), V_V(mes/glom) ($n = 40$, $r = -0.34$, $P = 0.032$), V_V(matrix/glom) (Fig. 1*B*), and mean previous filtration fraction (Fig. 1*C*). The MAP dipping correlated with the BMT ($n = 40$, $r = -0.32$, $P = 0.046$). No correlations were found between the systolic or diastolic dipping and the morphological parameters, kidney function, diabetes duration, or mean HbA_{1c}.

UAE

The UAE was 6 μg/min (range 2–64) on the day before the biopsy, but none of the patients had persistent microalbuminuria, defined as UAE >15 μg/min in two of three urine samples. We found no differences in the systolic, diastolic, MAP, and heart rate nocturnal decline between the patients with microalbuminuria (>15 μg/min, $n = 7$) and those without ($n = 26$) at the time of the renal biopsy.

CONCLUSIONS — In the present study, we have shown, for the first time, that nighttime blood pressure dipping has a direct relation to target-organ damage, i.e., glomerulopathy changes. It has previously been reported that nondipping (23,24) is related to indirect signs of target-organ damage, i.e., albuminuria. Poulsen et al. (25) studied 40 initially normotensive and normoalbuminuric type 1 diabetic patients during 3 years and observed that those patients who developed microalbuminuria had less initial diastolic dipping. It was also found that nocturnal diastolic nondipping showed a positive correlation to diastolic cardiac dysfunction (26). The absence of a drop in nocturnal blood pressure has been associated with an increase in the mortality rate of adult patients with diabetes and overt nephropathy (27).

It is not known whether the reduction in the nocturnal dip or the increase in blood pressure at night is responsible for the target organ damage or if it is the same thing. One study shows that the reduction in the nocturnal dip precedes the increase in day- and nighttime blood pressure (28). They found no increase in ambulatory systolic and diastolic blood pressure, although diastolic dipping at night decreased significantly ($P < 0.03$) in 117 children and teenagers with type 1 diabetes during at least 4 years of follow-up. We have previously presented the relations between renal morphological changes and day and night ambulatory blood pressure values (11). If a multiple regression analysis is performed, there is a stronger relation between the BMT and nighttime MAP than to MAP dipping. On the other hand, there is a stronger relation between the mesangial volumes to MAP dipping than to the nighttime MAP.

Some authors have shown less systolic and diastolic dipping in normoalbuminuric teenagers and young adults with type 1 diabetes than in control subjects (28,29). In our patients, the dipping at night in the entire group was within normal limits, which accords with the findings of some authors (30–32). No sex differences were found in contrast to one author (28) who noted that diastolic dipping was significantly less in male patients than in females with type 1 diabetes. As in another study (16), we found a strong correlation between systolic and diastolic blood pressure dipping.

The elevated mean previous filtration fraction found in our patients may reflect

a long-term increase in intraglomerular pressure that might damage the glomeruli in the long term (33–35) with increased BMT and augmented mesangial areas. One reason for the increase in intraglomerular pressure has been thought to be autonomic neuropathy (36,37). Less variability in heart rate during deep breathing, due to autonomic dysfunction, seems to be related to heart rate dipping (38). The correlation between heart rate dipping and blood pressure dipping in our patients has also been reported by others (7,16,24). This may indicate that autonomic neuropathy is a factor of importance for the reduced dipping at night. In a stepwise regression analysis, an "autonomic score" was reported to be the variable of main importance for the day-night difference in blood pressure in patients with type 1 diabetes (39). This accords with our findings concerning the relationship between heart rate dipping and mean previous filtration fraction and between heart rate dipping and BMT, V_V(mes/glom), and V_V(matrix/glom), which suggests that autonomic neuropathy may play a role in the development of diabetic glomerulopathy. The relation between the V_V(matrix/glom) to heart rate dipping and mean previous filtration fraction is of particular interest because mesangial volume is believed to be the most specific early change in diabetic glomerulopathy (40).

The hyperfiltration noted in our patients agrees with other studies (41,42) and has been discussed in more detail in a previous report (12). In the present article, we found long-term hyperfiltration in systolic, diastolic, and MAP nondippers. Glomerular hyperfiltration has been reported to be associated with a blunted reduction in diastolic blood pressure at night and an expansion of extracellular fluid volume in normotensive and normoalbuminuric type 1 diabetes patients (43). They propose that a redistribution of extracellular volume in a recumbent position during the night could transiently increase the blood volume and explain the abnormalities in the diurnal pattern of the blood pressure (43). It has been suggested that early hyperfiltration may contribute to glomerular damage in diabetic nephropathy (44). This has been confirmed by a longitudinal study in which an initial increase in GFR predicts diabetic nephropathy independently of metabolic control, even in normoalbuminuric diabetic adolescents (45).

In conclusion, to detect nondippers early in the course of diabetes, it seems important to distinguish between systolic, diastolic, and MAP dipping at night. We have shown that despite a short duration of type 1 diabetes, the diastolic and MAP nondipping status is related to a thicker basement membrane and a larger mesangial matrix volume fraction per glomerulus in adolescents and young adults. Consequently, the nondipping status seems to be an early predictor of later nephropathy. Moreover, an increase in heart rate at night, possibly due to autonomic neuropathy, long-term hyperfiltration, and worse metabolic control, is found more frequently in the nondipping group. The only way to find the nondippers is by 24-h ambulatory blood pressure measurements in order to detect patients at risk of developing end-stage nephropathy in the normoalbuminuric phase.

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