Ambulatory Blood Pressure, Microalbuminuria, and Autonomic Neuropathy in Adolescents With Type 1 Diabetes

ANTONY R. LAFFERTY, MB, CHB
GEORGE A. WERTHER, MD
CAROLINE F. CLARKE, DM

OBJECTIVE — To examine the relationship between 24-h blood pressure (BP) measurements, urinary albumin excretion rates, and autonomic neuropathy (AN) in adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS — A total of 31 patients with microalbuminuria (MA), 20 patients with intermittent MA (I-MA) and 11 patients with persistent MA (P-MA) were identified from the diabetes clinics at two major Australian tertiary care pediatric hospitals. Two control groups were used; one consisted of 19 age-, sex-, and diabetes duration–matched adolescents with normoalbuminuria (NA), and the other consisted of 46 age- and sex-matched nondiabetic control subjects. A medical history and physical examination were followed by a series of noninvasive tests of cardiovascular and pupillary autonomic function and then by 24-h ambulatory blood pressure monitoring (ABPM).

RESULTS — ABPM showed an incremental increase in all BP parameters from nondiabetic control subjects through subjects with NA. A parallel incremental increase in diurnal and nocturnal ambulatory heart rates was also evident. Subjects with MA had significantly reduced pupillary adaptation to darkness compared with nondiabetic subjects and subjects with NA. The above results paralleled an incremental increase in HbA1c levels in adolescents with type 1 diabetes from subjects with NA to subjects with P-MA.

CONCLUSIONS — Higher 24-h BP values and evidence of subclinical signs of AN are present before P-MA develops and may have important implications for timing the introduction of treatments designed to prevent or retard the microvascular complications of type 1 diabetes in adolescents.

From the Centre for Hormone Research (A.R.A.L., G.A.W.), Royal Children’s Hospital, Parkville; and the Department of Paediatrics (C.F.C.), Monash University, Clayton, Victoria, Australia.

Address correspondence and reprint requests to Antony R. Lafferty, MB, CHB, Department of Paediatrics, Monash Medical Centre, 246 Clayton Rd., Clayton, Victoria 3168, Australia. E-mail: laffertap@netscape.net.

Received for publication 2 July 1999 and accepted in revised form 9 December 1999.

Abbreviations: ABPM, ambulatory blood pressure monitoring; AER, albumin excretion rate; AN, autonomic neuropathy; ANOVA, analysis of variance; BP, blood pressure; CV, coefficient of variation; dBP, diastolic blood pressure; E/I ratio, heart rate response to deep breathing; dHR, postural change in heart rate; I-MA, intermittent microalbuminuria; MA, microalbuminuria; NA, normoalbuminuria; PD%, pupillary diameter percentage; P-MA, persistent microalbuminuria; dSBP, postural change in systolic blood pressure; SBP, systolic blood pressure; SDS, SD score.

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

The prevalence of microalbuminuria (MA) increases significantly with the onset of puberty in children with type 1 diabetes (1–3). Persistent MA (P-MA) is furthermore associated with the development of hypertension, which itself is a major risk factor for the progression of nephropathy (4,5). Treatment of hypertension has been shown to slow the progression of established diabetic nephropathy and may arrest or reverse its early stages (6). Ambulatory blood pressure monitoring (ABPM) is a better predictor of end organ damage than conventional blood pressure (BP) measurement (7) and can distinguish true hypertension from white coat hypertension, which may not need to be treated (8).

Autonomic neuropathy (AN) commonly coexists with established diabetic nephropathy (9,10), although the nature of the relationship between the two is still not fully established. Most of the previous studies that used ABPM to examine the relationships among BP, MA, and AN in type 1 diabetes have been performed in adults. Adult patients with P-MA have higher 24-h BP values and reduced diurnal BP variation (9,11–13) and also have a higher prevalence of subclinical AN than patients with normoalbuminuria (NA) and nondiabetic control subjects (12). Several studies have found similar abnormal ABPM findings in adolescents with type 1 diabetes (14–16), and two of these studies found that subjects with type 1 diabetes and NA had ABPM values that were intermediate between nondiabetic control subjects and patients with MA (14,16). These studies did not test for evidence of subclinical AN. Subclinical signs of cardiovascular (17–22) and pupillary (23–27) AN and peripheral neuropathy (28–30) can be demonstrated in adolescents with diabetes and correlate with poor glycemic control (31).

We hypothesized that BP may already be elevated in adolescents with diabetes and MA before MA becomes persistent and that this may be related to the development of subclinical signs of AN in these patients. The aim of this study was to examine the relationship between 24-h BP measurements, urinary albumin excretion rate (AER), and autonomic nerve function in a group of adolescents with type 1 diabetes who are at an early stage in the development of diabetes complications.
RESEARCH DESIGN AND METHODS — A total of 31 subjects with type 1 diabetes and varying stages of MA were identified and recruited from the diabetes clinics at the Royal Children's Hospital and Monash Medical Centre, Melbourne, Australia. These two institutions care for approximately 80% of the pediatric and adolescent patients with type 1 diabetes in the state of Victoria. Both have established comprehensive screening programs for the detection of early diabetes complications.

As part of this screening program, patients perform an overnight urine collection to test their AER every 1 to 2 years, depending on their age and duration of diabetes. Urinalysis is routinely performed to exclude infection. Collections are performed in the absence of intercurrent illness or acute deterioration in glycemic control. Patients are advised to avoid strenuous exercise on the day before they start the collection. Patients initially detected as having a urinary AER >20 µg/min are asked to perform three further urine collections at intervals of 3–6 months. This allows identification and categorization of patients having intermittent MA (I-MA) or persistent microalbuminuria (P-MA).

P-MA is defined as at least two of three AER values of 20–200 µg/min on at least two occasions during a 6-month period (32). I-MA is defined as one or more AER values of 20–200 µg/min on at least two occasions during a 6-month period but an insufficient number of elevated values to be classified with P-MA.

In the present study, each subject identified as having I-MA or P-MA was matched for age, sex, and diabetes duration with another subject with diabetes and NA. NA was defined as having no AER >10 µg/min on at least three collections. Subjects with established hypertension or those receiving antihypertensive therapy were excluded from the study. All subjects with type 1 diabetes were asked to invite a friend of the same age and sex to act as a nondiabetic control subject. This study was approved by the human research and ethics committees of both the Royal Children’s Hospital and Monash Medical Centre. All subjects and their parents gave their informed consent before the start of the study. Subjects were offered the option of being studied in their homes.

Information was obtained from each subject regarding risk factors for hypertension and included their medical history, family history, current medications (including oral contraceptives), and smoking habits. Height and weight were measured in all subjects. Height and weight SD scores (SDSs) were calculated for each subject to control for the influence of intergroup age and sex differences. Pubertal status was assessed either by the examiner or by self-assessment if the subject declined this part of the examination (33).

Urinary AER assay
Specimens were assayed by using an immunoturbidimetric method (Randox Laboratories, Crumlin, County Antrim, U.K.); coefficient of variation (CV) = 8.9% at 9 µg/min and 4.3% at 36 µg/min) at the Royal Children’s Hospital and an immunonephelometric technique (Beckman, Fullerton, CA; CV = 2.8% at 12.6 µg/min and 4.2% at 43 µg/min) at Monash Medical Centre. The two AER assays at the different institutions had a high degree of correlation (r = 0.94, P < 0.001). The mean AER for the last 12 months was calculated for each person with type 1 diabetes and was then log transformed. Results were expressed as the mean of the log-transformed AER values ± tolerance factor for each group. The antilog of this value was then calculated.

Mean HbA1c level
The mean HbA1c level in all subjects with diabetes was calculated from 4 years of readings assayed on the DCA 2000 (Bayer Diagnostics, Elkart, IN) in both institutions. The nondiabetic range is 3.7–6.0%.

Tests of autonomic functionality
All subjects underwent noninvasive tests of autonomic nervous function. Electrocardiogram leads were attached to each limb, and recordings for each test were made by using standard limb lead II. Details of the cardiovascular and pupillary reflex tests are as follows.

- Heart rate response to deep breathing (E:I ratio): the mean of the ratio of the maximum to minimum RR intervals for six vital capacity breaths during a period of 1 min (34) (CV = 4.9% [35]).
- Postural change in heart rate (ΔHR): the ratio of the maximum to minimum RR interval after standing from a supine rest (36,37) (CV = 9.8% [35]).
- Postural change in systolic BP (ΔsBP): the rise in sBP after standing from a supine rest measured with the Dinamap 1846SX (Criticon, Tampa, FL).
- Mean Valsalva ratio: the mean of three Valsalva ratios. Subjects were asked to perform three Valsalva maneuvers by exhaling for 10 s against 30–40 mmHg of fixed resistance. The ratio was calculated by dividing the mean of each maximum RR interval after completing the maneuver by the minimum RR interval during the maneuver (CV = 14.9% [35]).
- Daytime and nighttime heart rate: the mean 24-h daytime and nighttime heart rates were determined for each group from ABPM data.
- Pupillary diameter percentage (PD%): the ratio of the pupil diameter to the iris diameter expressed as a percentage was calculated from a photograph taken with a simple Polaroid (Cambridge, MA) pupillometer (38) (CV = 4.8% [35]). This has been shown to be an inexpensive alternative to the infrared pupillometer and has a high degree of agreement with the more expensive device.

Assessment of BP
Five automated BP readings were performed at 2-min intervals after a 5-min supine rest with the appropriately sized cuff by using the Dinamap 1846SX oscillometric BP monitor. This monitor was also used to determine the change in BP that occurred with changes in posture.

The 24-h ABPM was performed by using the Spacelabs 90207 (Redmond, WA) oscillometric ambulatory blood pressure monitor. The monitor was programmed to perform measurements at 20-min intervals during the day and at 60-min intervals during the night. The timing of the day/night transition was determined by the subjects’ intended bedtime and was confirmed by a diary that each subject completed. An appropriately sized BP cuff was fitted to the nondominant arm, and monitoring commenced after checking the accuracy of monitor readings against a mercury sphygmomanometer. Subjects were advised to avoid strenuous activity while wearing the monitor and were asked to keep a diary outlining their activity during this period. Hypertension was defined as an sBP and/or diastolic BP (dBP) of >95th percentile for the age and sex of the subject according to the Report of the Second Task Force on Blood Pressure Control in Children (39). All nondiabetic subjects who had hypertension according to this
definition were advised to visit their personal physicians for further assessment.

Statistical analysis
Statistical analysis was performed by using the Stata statistical package (College Station, TX). Analysis of variance (ANOVA) was used to determine the significance of differences between groups with Bonferroni post hoc analysis to determine which groups had the greatest differences. Multivariate analysis was used to examine the factors that were significantly influencing the observed differences. A P value < 0.05 was considered to be statistically significant.

RESULTS — Of the clinic patients identified as having I-MA or P-MA, 90% agreed to participate in the study. Subjects who did not participate were older, and most declined because of school commitments. A total of 40% of the subjects came to the hospital to be studied, and the remainder were studied in their homes. The four subject groups were comparable regarding age, sex, pubertal status, height, and weight, and the three groups with diabetes were comparable regarding diabetes duration (Table 1). Mean patient HbA1c values correlated with mean log AER (R² = 0.226, P < 0.001). An incremental increase occurred in the mean HbA1c level of subjects with type 1 diabetes from the group with NA through to the group with P-MA (P < 0.0001). The difference in HbA1c levels between subjects with NA and subjects with I-MA approached significance (P = 0.06).

The distribution of AER values was examined within and between each group with type 1 diabetes. Three distinct log AER means were evident with only minor overlap. The distribution of AER values in the group with I-MA was unimodal, which indicates that this group is distinct from both the NA and P-MA groups. Subjects with P-MA were three times as likely and subjects with I-MA were twice as likely to have a factor such as smoking or previous renal disease that predisposed them to hypertension than subjects with NA or nondiabetic subjects. No correlation was evident between BA status and the prevalence of parental hypertension. Table 2 illustrates the incremental rise in mean day and night heart rate was seen from the nondiabetic control group through to the patients with diabetes and P-MA. Both daytime and nighttime readings contributed to the intergroup differences.

As shown in Table 3, a similar incremental rise in mean day and night heart rate was seen from the nondiabetic control group through to the patients with diabetes and P-MA. PD% was lower in subjects with NA than in nondiabetic subjects and was lower still in the groups with MA. A highly significant difference was evident in PD% between subjects with I-MA and nondiabetic subjects. The differences between subjects with I-MA and NA, and between subjects with NA and P-MA did not reach statistical significance. However, this may be a reflection of the smaller size of the two groups with MA. ANOVA results for the remaining noninvasive tests of autonomic function failed to show significant differences between groups.

Multivariate analysis was performed to determine the influence of different variables on the BP and autonomic function test results. Factors that had the greatest influence on daytime and nighttime sBP included weight SDS (P < 0.005 for both) and sex (P < 0.05 for both). Subjects with higher weight SDSs had higher sBP values. At the same age, male patients have sBP values that average 3–4 mmHg higher than values of female patients. The even sex distribution in each group meant that sex did not significantly influence intergroup BP differences. Nocturnal sBP and dBP levels both correlated with mean HbA1c levels (P < 0.05 in both cases). Daytime dBP was related to log AER (P < 0.005), and a close relationship existed between log AER and

Table 1— Group characteristics

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Nondiabetic</th>
<th>NA</th>
<th>I-MA</th>
<th>P-MA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (F/M)</td>
<td>22/24</td>
<td>8/11</td>
<td>10/10</td>
<td>6/5</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>16.6 ± 1.7</td>
<td>16.6 ± 1.5</td>
<td>16.6 ± 1.9</td>
<td>17.0 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Tanner stage (2 or 3/4 or 5)</td>
<td>1/45</td>
<td>1/18</td>
<td>1/19</td>
<td>0/11</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>—</td>
<td>8.6 ± 3.1</td>
<td>10.5 ± 3.6</td>
<td>8.6 ± 2.1</td>
<td>NS</td>
</tr>
<tr>
<td>Weight SDS</td>
<td>0.49 ± 0.93</td>
<td>0.76 ± 0.89</td>
<td>0.47 ± 0.92</td>
<td>0.53 ± 1.26</td>
<td>NS</td>
</tr>
<tr>
<td>Height SDS</td>
<td>0.39 ± 1.03</td>
<td>0.32 ± 1.22</td>
<td>-0.10 ± 1.04</td>
<td>-0.12 ± 0.70</td>
<td>NS</td>
</tr>
<tr>
<td>BMI</td>
<td>22.7 ± 3.7</td>
<td>23.5 ± 2.7</td>
<td>23.3 ± 3.3</td>
<td>24.1 ± 5.2</td>
<td>NS</td>
</tr>
<tr>
<td>Mean HbA1c (%)</td>
<td>N/A</td>
<td>8.5 ± 1.0</td>
<td>9.5 ± 1.3</td>
<td>10.7 ± 2.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean log AER</td>
<td>N/A</td>
<td>0.6 ± 0.16</td>
<td>1.29 ± 0.20</td>
<td>1.64 ± 0.29</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AER (antilog)</td>
<td>N/A</td>
<td>4.29 ± 1.63</td>
<td>22.15 ± 15.06</td>
<td>54.85 ± 46.07</td>
<td>—</td>
</tr>
</tbody>
</table>

Data are n or means ± SD.

Table 2— Relationship of HbA1c to ambulatory blood pressure measurements

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Nondiabetic</th>
<th>NA</th>
<th>I-MA</th>
<th>P-MA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 24-h BP sBP</td>
<td>119.7 ± 8.3</td>
<td>122.4 ± 5.1</td>
<td>125.3 ± 8.9</td>
<td>128.1 ± 11.4*</td>
<td>0.009</td>
</tr>
<tr>
<td>Mean 24-h BP dBP</td>
<td>85.5 ± 7.0</td>
<td>87.7 ± 3.4</td>
<td>91.2 ± 6.1†</td>
<td>94.5 ± 7.2‡§</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Daytime BP sBP</td>
<td>68.2 ± 6.5</td>
<td>69.2 ± 3.5</td>
<td>72.7 ± 7.1</td>
<td></td>
<td>76.5 ± 7.3‡§</td>
</tr>
<tr>
<td>Daytime BP dBP</td>
<td>122.2 ± 8.5</td>
<td>124.8 ± 5.2</td>
<td>127.7 ± 9.4</td>
<td>130.4 ± 11.8*</td>
<td>0.012</td>
</tr>
<tr>
<td>Nighttime BP sBP</td>
<td>88.2 ± 6.4</td>
<td>89.6 ± 4.0</td>
<td>93.5 ± 6.6*</td>
<td>96.6 ± 7.9‡§</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nighttime BP dBP</td>
<td>70.7 ± 7.0</td>
<td>71.6 ± 4.3</td>
<td>75.4 ± 7.6</td>
<td>78.6 ± 7.7§</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Data are means ± SD by ANOVA. *P < 0.05 compared with nondiabetic subjects; †P < 0.01 compared with nondiabetic subjects; §P < 0.05 compared with subjects with NA; ||P = 0.054 compared with subjects with NA.
daytime sBP that approached statistical significance (P = 0.06). A highly significant association was evident between PD% and nocturnal dBP (P < 0.005), and the association between PD% and nocturnal sBP approached statistical significance (P = 0.07). Ambulatory heart rate was influenced by sex (P < 0.01). Regardless of MA status, female patients had mean heart rates that were 7 to 8 beats/min faster than that of male patients at all times of the day (P < 0.001).

**DISCUSSION** — This study has demonstrated two novel findings. The 24-h ABPM showed an increase in daytime and nighttime values for sBP, mean BP, and dBP in adolescents with diabetes and I-MA as well as for subjects with P-MA. In addition to this finding, subjects with I-MA also showed evidence of early signs of subclinical AN with reduced pupillary reaction to darkness compared with nondiabetic control subjects and subjects with NA and an incremental increase in heart rate compared with both control groups. The abnormalities of pupillary autonomic function were also seen in subjects with P-MA, but a statistically significant increase was evident in the ambulatory heart rate when compared with both control groups. Neither the BP differences nor the features of autonomic dysfunction have previously been described in adolescents with type 1 diabetes who have I-MA. Our further finding of a direct relationship between HbA1c level and log AER supports the notion of an increasing risk of nephropathy with progressive deterioration of glycemic control. The finding also confirms that I-MA is a distinct stage in the evolution of nephropathy and is not merely the result of an acute deterioration in glycemic control or exercise-induced MA.

Previous studies have demonstrated that, although few children and adolescents with P-MA have clinical hypertension, significant elevation of mean clinic sBP and dBP is present compared with healthy nondiabetic control subjects and subjects with NA (12,40). Adolescents with P-MA have significantly higher ABPM values during the day (12,15) and at night (15,41), although BP values remain within the normal range. This study confirmed this finding in subjects with P-MA but importantly also found that all BP parameters were higher in adolescents with I-MA than in subjects with NA and nondiabetic subjects and that the 24-h, daytime, and nighttime mean arterial BP and 24-h dBP were statistically significant when compared with nondiabetic control subjects. This finding is similar to that noted by Garg et al. (41), who found that all ABPM parameters were significantly higher in a group of adolescents with diabetes with mean AER values between 7.2 and 20 µg/min compared with subjects who had mean AER values of <7.2 µg/min. The same authors also previously demonstrated that the patients with AER values between 7.2 and 20 µg/min had significantly poorer glycemic control and were at significantly greater risk for developing P-MA than subjects with values of <7.2 µg/min (42). The authors did not look for evidence of autonomic dysfunction in this group. Viridis et al. (43) tracked clinic BP for 3 years in 106 children and adolescents with type 1 diabetes who were aged 2–16 years and determined that patients who subsequently developed MA initially had BP measurements in the upper quartile. The present study shows that subjects with diabetes and NA had higher, albeit clinically and statistically not significant, sBP, mean BP, and dBP measurements compared with the matched nondiabetic control subjects. This finding corresponds with other previously published studies in adolescents with type 1 diabetes (15,44). The results of our study and these previous studies suggest that, rather than using 20 µg/min as an AER threshold above which hypertension and nephropathy are more likely to develop, glycemic control is the major determinant of complication risk and that BP initially rises before consistent elevations in AER are detectable.

The nocturnal fall in BP remained intact in subjects with P-MA in this study, unlike the studies published by Sochett et al. (16) and Holl et al. (15), which found that subjects with diabetes and NA had higher BP values and reduced diurnal BP variation compared with nondiabetic control subjects and that this was more pronounced in subjects with MA. In the present study, daytime and nighttime sBP measurements increased in both subjects with I-MA and subjects with P-MA. Although the nocturnal sBP showed a greater increase, the normal nocturnal fall in BP was maintained in all groups so that no loss of diurnal variation was evident, which is similar to the findings of Khan et al. (14).

Although overt signs of autonomic dysfunction are rare during adolescence, the presence of subclinical cardiovascular (21,22,45–48) and pupillary (23,25,27) signs of autonomic dysfunction is well established. The ability of these signs to predict subsequent overt AN and their relationship to other microvascular diabetes complications is less clear. Clarke et al. (49) found that subjects with P-MA had significantly higher resting heart rates and impaired pupillary dilatation in darkness. In our study, the mean pupillary dilatation in darkness was significantly lower in groups with I-MA and P-MA than in both NA and nondiabetic control subjects. Madacy et al. (50) demonstrated a significant association between the loss of diurnal BP variation, nocturnal tachycardia, and other subclinical signs of AN in adolescents with type 1 diabetes. Loss of diurnal BP variation is more likely to be a later sign of autonomic dysfunction than pupillary dysfunction.

### Table 3—Relationship of HbA1c to tests of autonomic function

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Nondiabetic</th>
<th>NA</th>
<th>I-MA</th>
<th>P-MA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean HbA1c</td>
<td>—</td>
<td>8.5 ± 1.0</td>
<td>9.5 ± 1.3</td>
<td>10.7 ± 2.2</td>
<td>0.001</td>
</tr>
<tr>
<td>PD%</td>
<td>64.2 ± 5.3</td>
<td>61.7 ± 6.2</td>
<td>56.7 ± 9.3*</td>
<td>58.5 ± 5.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E:I ratio</td>
<td>1.47 ± 0.17</td>
<td>1.45 ± 0.19</td>
<td>1.40 ± 0.16</td>
<td>1.37 ± 0.26</td>
<td>0.29</td>
</tr>
<tr>
<td>Valsalva</td>
<td>1.81 ± 0.29</td>
<td>1.81 ± 0.38</td>
<td>1.94 ± 0.32</td>
<td>1.85 ± 0.44</td>
<td>0.50</td>
</tr>
<tr>
<td>ΔHR</td>
<td>1.59 ± 0.26</td>
<td>1.59 ± 0.26</td>
<td>1.50 ± 0.22</td>
<td>1.47 ± 0.29</td>
<td>0.34</td>
</tr>
<tr>
<td>ΔsBP (mmHg)</td>
<td>6.5 ± 9.6</td>
<td>5.1 ± 12.8</td>
<td>5.0 ± 9.4</td>
<td>−2.4 ± 12.6</td>
<td>0.11</td>
</tr>
<tr>
<td>Diurnal ΔsBP (mmHg)</td>
<td>12.9 ± 1.8</td>
<td>13.2 ± 2.9</td>
<td>12.8 ± 3.3</td>
<td>12.7 ± 3.8</td>
<td>0.90</td>
</tr>
<tr>
<td>Mean daytime heart rate</td>
<td>79.3 ± 10.7</td>
<td>80.5 ± 8.5</td>
<td>86.2 ±11.8</td>
<td>92.3 ± 14.8†</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Mean nighttime heart rate</td>
<td>67.7 ± 10.7</td>
<td>66.8 ± 6.8</td>
<td>73.5 ±12.5</td>
<td>77.9 ±10.1§†</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data are means ± SD, except for ΔsBP and diurnal ΔsBP, which are means ± 95% CIs. *P ≤ 0.001 compared with nondiabetic subjects; †P < 0.01 compared with nondiabetic subjects; §P < 0.01 compared with subjects with NA; ‡P < 0.01 compared with nondiabetic subjects.
and heart rate abnormalities, and thus was not present in our subjects. Loss of pupillary responsiveness may be a very early and sensitive sign of AN because it was present in the subjects with I-MA, although significant increases in heart rate were only apparent in subjects with P-MA.

The nature of the interaction among autonomic dysfunction, BP, and MA still requires further study. Poor glycemic control predisposes patients to the development of both MA and AN. However, as both complications develop, they likely may interact to accelerate the rate at which each progresses. Later in the evolution of these two complications, BP may be the common factor to both, given that impairment of diurnal BP variation (which appears to be the result of autonomic dysfunction) will result in an increase in the overall BP burden.

The results of this study may have important implications for the prevention of diabetic nephropathy. They provide further evidence that tight glycemic control is the single most effective means of preventing or limiting the progression of the chronic complications of type 1 diabetes. Recommendations from the adult literature advocate starting treatment with an ACE inhibitor before patients develop hypertension. Subjects with I-MA in the present study, in whom BP values were higher than for subjects in the NA and nondiabetic groups, may be at higher risk for developing P-MA and progressive nephropathy than subjects with NA, and the results of this study may thus have important implications for the timing of interventions that are aimed at preventing diabetic nephropathy. Couper et al. (51) studied a group of adolescents with borderline MA and I-MA and showed that, although the 25% who had higher BP levels and poorer glycemic control progressed to P-MA, a substantial proportion remained stable. Other studies in adolescents (52) and adults (53) with type 1 diabetes and MA have demonstrated a high rate of non-progression and even regression. In patients with I-MA, the coexistence of early AN, particularly AN detected by pupillometry, may be a means of identifying patients in whom MA is more likely to progress because of their potential risk of developing an increased BP burden. This may help to target patients at the earliest stage of nephropathy, in whom intervention with ACE inhibition or other therapies may be most appropriate.

In conclusion, this study has shown the coexistence of elevation of BP and subclinical AN in patients with very early stages of diabetic nephropathy. The study has important implications for identifying patients who are more likely to progress to overt nephropathy and for targeting therapy to prevent or minimize progression.

Acknowledgments — This research was supported by grants from Bristol-Myers Squibb and Novo Nordisk; and scholarships from the Australian Kidney Foundation and the University of Melbourne.

References

24. Karachaliou F, Karavanaki K, Greenwood R, Baum JD: Consistency of pupillary abnormality in children and adolescents with...