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Abnormal nocturnal blood pressure fall in normotensive adolescents with insulin-dependent diabetes is ameliorated following glycemic improvement

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Abstract

Lack of the physiological nocturnal fall in blood pressure (BP) has been found in diabetics and it seems to be related to the presence of diabetic complications. The present study examined the changes in the nocturnal BP pattern of 8 normotensive insulin-dependent diabetic adolescents without nephropathy following improvement in glycemic control induced by an 8-day program of adequate diet and exercise. The same number of age- and sex-matched control subjects were studied. During the first and eighth nights of the program, BP was obtained by ambulatory BP monitoring. After a 10-min rest, 3 BP and heart rate (HR) recordings were taken and the mean values were considered to represent their awake values. The monitor was programmed to cuff insufflation every 20 min from 10:00 p.m. to 7:00 a.m. The glycemic control of diabetics improved since glycemia (212.0 ± 91.5 to 140.2 ± 69.1 mg/dl, $P<0.03$), urine glucose (12.7 ± 11.8 to 8.6 ± 6.4 g/24 h, $P = 0.08$) and insulin dose (31.1 ± 7.7 to 16.1 ± 9.7 U/day, $P<0.01$) were reduced on the last day. The mean BP of control subjects markedly decreased during the sleeping hours of night 1 (92.3 ± 6.4 to 78.1 ± 5.0 mmHg, $P<0.001$) and night 8 (87.3 ± 6.7 to 76.9 ± 3.6 mmHg, $P<0.001$). Diabetic patients showed a slight decrease in mean BP during the first night. However, the fall in BP during the nocturnal period increased significantly on the eighth night. The average awake-sleep BP variation was significantly higher at the end of the study (4.2 *vs* 10.3%, $P<0.05$) and this ratio turned out to be similar to that found in the control group (10.3 *vs* 16.3%). HR variation also increased on the eighth night in the diabetics. Following the metabolic improvement obtained at the end of the period, the nocturnal BP variation of diabetics was close to the normal pattern. We suggest that amelioration of glycemic control may influence the awake-sleep BP and HR differences. This effect may be due at least in part to an attenuated insulin stimulation of sympathetic activity.

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- Insulin-dependent diabetes mellitus
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- Glycemic control

Introduction

The nocturnal decline in blood pressure (BP) and heart rate (HR) in healthy subjects is thought to be the result of dominating parasympathetic tone during sleep (1,2). Altered 24-h BP profiles have been found in adult diabetic patients which appear to be related to the presence of autonomic neuropathy (2,3). A decrease in nocturnal BP fall has also been observed in insulin-dependent diabetic patients with different degrees of diabetic nephropathy (4,5). It has been suggested that nephropathy *per se* was not responsible for the altered circadian pattern. On the other hand, the associated autonomic dysfunction has been implicated in these changes in BP profiles. In addition, autonomic neuropathy has been shown to play a pathogenetic role in the development of diabetic renal disease (6,7).

The lack of a nocturnal decline in BP during sleep is clinically significant and is associated with a greater prevalence of the development of hypertension, particularly in patients with diabetes mellitus (2,8). Besides being an important cardiovascular risk factor, hypertension represents a major determinant of the progression of diabetic nephropathy toward end-stage renal failure (9,10). Particularly, nocturnal hypertension may be important in terms of renal function deterioration (11). Data on BP monitoring in children and adolescents with insulin-dependent diabetes mellitus (IDDM) are limited and conflicting (12-14). Relatively elevated nocturnal BP was observed in a subgroup of normoalbuminuric diabetic children and was attributed to autonomic dysfunction (14). However, the role of glycemic control in these abnormalities of the 24-h BP profile could not be demonstrated. The present study examined the effects of glycemic control improvement achieved by a program of adequate diet and exercise on the nocturnal BP pattern of normotensive insulin-dependent diabetic adolescents without diabetic nephropathy.

Table 1 - Clinical characteristics of diabetic patients and control subjects.

Results are reported as mean ± SD. *P<0.02 *vs* control (unpaired Student *t*-test).

	Controls	Diabetics
N (male/female)	4/4	4/4
Age (years)	12.7 ± 1.1	12.8 ± 1.8
Weight (kg)	52.6 ± 7.4	42.6 ± 5.6*
Height (m)	1.57 ± 0.1	1.53 ± 0.1
Body mass index (kg/m²)	21.2 ± 0.4	18.6 ± 1.5*
Diabetes duration (years)	–	5.3 ± 2.2

Subjects and Methods

Eight adolescents with IDDM, aged 11-14 years, and eight age- and sex-matched healthy controls were studied (Table 1). Diabetic patients had no clinical symptom or sign of diabetic retinopathy or neuropathy. Microalbuminuria was ruled out by a qualitative colorimetric test using reagent tablets (Micro-Bumintest™ test kit for urinalysis, Ames, IA). None of the patients was taking any medication apart from insulin. Patients and controls were invited to participate in a summer camp where a program of twice daily exercise, including sports and aerobic gymnastics, was instituted. Patients received an appropriate diet for their diabetic condition (ADA recommendation), took NPH insulin twice a day and were supplemented with regular insulin according to capillary glycemia results. During the first and the eighth nights of the program, multiple BP measurements were carried out by oscillometric ambulatory BP monitoring (Space Labs 90202, Redmond, WA). Previous comparison with the reference auscultatory method showed strongly correlated values. Physical activities limited the BP monitoring during the daytime period. Using this technique, three initial BP recordings and HR

were taken between 9:30 to 10:00 p.m. at 5-min intervals after a 10-min rest in the sitting position. The mean value was considered to represent the BP and HR of the subjects in the awake condition. The monitor was then programmed to cuff insufflation every 20 min from 10:00 p.m. to 7:00 a.m. and a nurse observed the quality of sleep during the nights. None of the subjects woke up during the night and diabetic patients had no episode of hypoglycemia. In addition to glycemia monitoring, 24-h urinary glucose excretion was determined at the beginning and at the end of the program to assess metabolic control in the diabetic group. The initial and final insulin requirements of the diabetic patients were compared. Glucose concentration was determined by routine methods. Data are reported as means ± SD and the unpaired Student *t*-test was used to compare diabetic patients with control subjects. The paired Student *t*-test was used for comparisons within each group, regarding the values obtained during nights 1 and 8 and those recorded under the "sleep" and "awake" conditions. Correlation of the variations in BP and HR with insulin doses was tested using the Spearman correlation coefficient. A value of $P<0.05$ was considered significant. The study was approved by the Institutional Ethics Committee and informed consent was obtained from the parents of the children.

Results

Although age and sex matched, the control group was heavier and showed a higher body mass index than the diabetic one. The insulin requirement of diabetic patients was reduced from 31.1 ± 7.7 to 16.1 ± 9.7 U/day ($P<0.01$) to avoid recurrent episodes of hypoglycemia during the study period. Their fasting glycemia was significantly lower on the eighth morning compared to the first day of the program (212.0 ± 91.5 *vs* 140.2 ± 69.1 mg/dl, $P<0.03$). Also, the initial urine glucose excretion tended to fall during the period (12.7 ± 11.8 to 8.6 ± 6.4 g/24 h, $P = 0.08$). Significant differences in awake BP and HR values were found between the diabetic and control groups on both occasions, but not during sleep (Table 2). As expected, control subjects displayed a marked decrease in mean BP and HR during the sleeping hours of night 1 (92.3 ± 6.4 to 78.1 ± 5.0 mmHg, $P<0.001$) and night 8 (87.3 ± 6.7 to 76.9 ± 3.6 mmHg, $P<0.001$). On the other hand, diabetic patients showed a slight decrease in mean BP during the first night. However, the BP fall during the nocturnal period increased significantly during the eighth night (79.3 ± 4.3 to 72.8 ± 5.4 mmHg, $P<0.03$). This resulted in a higher awake-sleep BP variation at the end of the study as compared to the initial value (10.3% *vs* 4.2%, $P<0.05$) and this ratio turned out to be similar to that found for the control group (10.3% *vs* 16.3%, NS) (Figure 1, panel B). As far as HR variation is concerned, diabetic patients also showed a lower awake-sleep HR variation in comparison to normal subjects (8.3%

Table 2 - Average systolic, diastolic and mean blood pressure (BP), heart rate (HR) and "awake-sleep" variation (Δ) of mean blood pressure and heart rate (medians and range) in control and diabetic subjects during the first and eighth day of the exercise program.

Results are reported as means ± SD. *P<0.01, **P<0.001 diabetics *vs* controls; §P<0.01 night 8 *vs* night 1; †P<0.03, ‡P<0.001 sleep *vs* awake (paired Student *t*-test).

	Controls		Diabetics	
	Night 1	Night 8	Night 1	Night 8
Awake				
Systolic BP (mmHg)	122.0 ± 6.9	118.9 ± 7.6	107.2 ± 7.5*	107.2 ± 6.9*
Diastolic BP (mmHg)	77.4 ± 7.0	71.5 ± 7.4§	64.0 ± 6.0*	65.4 ± 4.9
Mean BP (mmHg)	92.3 ± 6.4	87.3 ± 6.7§	78.4 ± 6.4*	79.3 ± 4.3*
HR (bpm)	95.0 ± 8.0	78.8 ± 10.1§	84.2 ± 8.2*	76.5 ± 10.8§
Sleep				
Systolic BP (mmHg)	107.0 ± 5.4‡	104.1 ± 4.7‡	101.0 ± 7.4†	97.5 ± 7.3§†
Diastolic BP (mmHg)	58.3 ± 6.3‡	58.4 ± 4.3‡	59.0 ± 5.9‡	57.8 ± 5.3‡
Mean BP (mmHg)	78.1 ± 5.0‡	76.9 ± 3.6‡	75.4 ± 6.3	72.8 ± 5.4†
HR (bpm)	74.2 ± 8.0†	64.7 ± 10.1†	73.1 ± 9.8†	63.2 ± 7.6†
Awake-sleep BP Δ (%)	16.4 (8.0-19.1)	16.3 (5.7-19.1)	4.2** (1.0-11.6)	10.3§ (2.9-14.6)
Awake-sleep HR Δ (%)	20.3 (10.6-32.6)	16.9 (6.0-28.8)	8.3* (2.3-20.7)	13.9 (1.7-20.8)

vs 20.3%, P<0.01). Similarly to BP data, HR variation increased during the eighth night (8.3% to 13.9%, P = 0.05) when the difference between diabetic and normal subjects disappeared (13.9% *vs* 16.9%, respectively) (Figure 1, panel A). No correlation was detected between reductions in insulin doses and the awake-sleep BP or HR variations.

Discussion

Control subjects presented a significant decrease in BP and HR during sleeping hours on the two occasions when they were evaluated, when their awake-sleep variations were very close. Similar values of diurnal-nocturnal differences were obtained by other investigators studying healthy subjects in the same age range (14). Such decreases in BP and HR have been attributed to the dominating parasympathetic tone during the night (1). Although patients and subjects were age matched, the mean weight and BMI of the patients were smaller than the controls. Also, diabetic patients showed lower BP levels while awake but not statistically different from the normal subjects. We speculate that differences in baseline BP could be attributed at least in part to these different anthropometric parameters. In the former group the BP fall during sleep was slighter, particularly on the first day of the study, when the glycemic control was poor, requiring higher insulin doses. The hypertensive effect of long-term poor glycemic control in IDDM occurring before renal injury was previously reported (15). In addition to a primary effect of hyperglycemia, several lines of evidence pointed to a role of insulin in stimulating the sympathetic nervous system. Exogenous insulin administered with sufficient glucose to prevent hypoglycemia stimulates the sympathetic nervous system in rats (16) and humans (17), whereas insulin deficiency in hyperglycemic streptozotocin-induced diabetic rats is associated with diminished sympathetic activity (18). Since insulin is considered to be a potent stimulus of sympathetic activity, we speculate that the higher insulinemia present at the beginning of the study period might have prevented a normal nocturnal BP fall in the diabetic subjects. Following the metabolic improvement reached at the end of the study period, the awake-sleep BP variation in diabetics was close to the normal pattern. If any habituation to the BP monitor occurred on the second occasion, it should have been present in both groups of subjects. It is possible that the improved glycemic control, accompanied by a reduced plasma insulin concentration, contributed to the awake-sleep BP and HR differences. In fact, our group previously reported a hypotensive effect of glycemic control on BP levels in normotensive non-complicated diabetic adolescents (19). The significantly lower insulin doses required on the eighth day of this study program, which were associated with a better metabolic control, as evaluated by fasting glycemia and glucose excretion, could be interpreted as a reduced stimulus of the sympathetic nervous system. Since its inhibition is particularly important during the sleeping hours when the parasympathetic system should be dominant, our finding of lower nighttime BP levels is in agreement with this idea, which is also supported by the increased BP fall. Thus, we suggest a potential role for the improved glycemic control accompanied by lower plasma insulin concentrations in restoring the altered BP profile in unstable non-complicated diabetic subjects with IDDM, which occurs at least in part through reduced insu-

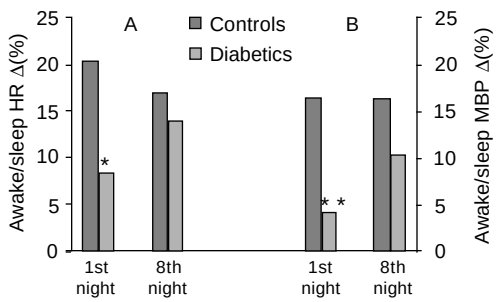

Figure 1 - Percent awake-sleep heart rate (HR) (panel A) and mean blood pressure (MBP) variations (panel B) in diabetic patients and control subjects during the first and eighth night of the study period. *P<0.01 and **P<0.001 *vs* controls (Wilcoxon test).

lin effects on sympathetic tone. However, a significant correlation between the awake-sleep BP variations and insulin requirement reductions could not be demonstrated in the present study. However, a direct effect of glucose on the sympathetic nervous system could not be excluded. In addition, exercise may also have contributed to a decrease in sympathetic tone and an increase BP fall in the diabetic patients after a period of regular physical activity. Actually, the hemodynamic changes observed in the control group should be attributed to exercise. It has been shown that the BP lowering effect induced by moderate regular exercise is accompanied by decreased peripheral resistance and noradrenaline concentration (20). No exercise-induced reductions in cardiovascular parameters were found in the diabetic group when awake but they occurred during the sleeping hours, when sympathetic inhibition seems to be especially important to guarantee a normal BP fall. On the other hand, long-term diabetic complications have been implicated in disturbed 24-h BP profiles. A diminished nocturnal BP fall was observed in diabetic patients with autonomic neuropathy and/or nephropathy (6,7,21). Based on clinical evaluation and on the short duration of diabetes, we believe that chronic diabetic complications may not have influenced our results.

Our findings support the hypothesis that the increased nocturnal BP fall at the end of the study period was related to glycemic control accompanied by decreased insulin requirements. The main determinant of the impaired nocturnal BP fall in IDDM before the onset of nephropathy may have been due to poor glycemic control. Since the use of the ambulatory BP recording technique has been suggested for early detection of hypertension in diabetic patients (22), this study pointed out a role for metabolic disturbances in BP changes. Besides the direct deleterious effect of hyperglycemia on the process of renal damage, long-term poor metabolic status through disturbances of BP homeostasis may also represent a pathogenetic mechanism in the development of diabetic nephropathy. This being the case, a better blood pressure profile induced by the lowest insulin doses necessary to maintain glycemic control would reduce the risk for diabetic renal disease. Whether or not the nocturnal behavior of BP in normotensive noncomplicated diabetic adolescents plays a significant pathophysiological role in the development of diabetic neuropathy and/or nephropathy is yet undetermined (23). Prospective studies on patients with a persistently blunted nocturnal BP fall are necessary to clarify its usefulness in identifying candidates for long-term diabetic complications.

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