Pitfalls in the Measurement of the Nocturnal Blood Pressure Dip in Adolescents with Type 1 Diabetes

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OBJECTIVE — The purpose of this study was to screen adolescents with type 1 diabetes using ambulatory blood pressure monitoring (ABPM) to *1*) test the hypothesis that using a preset sleep time results in an overdiagnosis of abnormal nocturnal dipping in systolic blood pressure and 2) assess the reproducibility of an abnormal nocturnal systolic blood pressure dip.

RESEARCH DESIGN AND METHODS — For aim 1, ABPM from 53 adolescent patients with type 1 diabetes was reviewed. Nocturnal dips in systolic blood pressure calculated by actual sleep time were compared with those from a preset sleep time. For aim 2, blood pressure monitoring from 98 patients using actual reported sleep time was reviewed. Reproducibility of the nocturnal dip in systolic blood pressure was assessed in a subset of "nondippers."

RESULTS — For aim 1, the actual mean ± SE decline in nocturnal systolic blood pressure was 11.6 ± 4.7%, whereas the mean decline in nocturnal systolic blood pressure calculated using the preset sleep time was 8.8 ± 4.9% ($P < 0.0001$). For aim 2, 64% of patients had a normal nocturnal decline in systolic blood pressure (14.9 ± 3.1% mmHg), whereas 36% had an abnormal dip (5.7 ± 2.8% mmHg). Repeat ABPM performed in 22 of the 35 nondippers revealed that only 36% had abnormal systolic dipping confirmed on the repeat ABPM.

CONCLUSIONS — The use of actual reported sleep time is required to accurately determine the nocturnal dip in systolic blood pressure. Repeating ABPM in nondippers is essential to confirm this abnormality.

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Elevated blood pressure is strongly associated with diabetic nephropathy (1–3). However, in the pediatric population, overt hypertension, as defined by blood pressure ≥95th percentile, is rarely diagnosed in patients with type 1 diabetes. Automated blood pressure readings in the office are often inaccurate, and single blood pressure measurements, whether automated or manual, are often falsely elevated (4,5). Mean blood pressure ascertained by 24-h ambulatory blood pressure monitoring (ABPM) has also been shown to better predict target organ damage than isolated, intermittent clinic blood pressure measurements in the adult population (6,7). The American Heart Association has recently presented recommendations for the use of ABPM in children and adolescents (8).

The use of 24-h ABPM allows observation of circadian blood pressure patterns by providing a profile of blood pressure over time (7,9,10). This pattern includes a normal decrease during sleep of both systolic and diastolic blood pressure by ~10% from daytime levels (7).

In many adolescents and young adults with type 1 diabetes who are normotensive by standard criteria, there is a blunted decline in nocturnal systolic blood pressure compared with that of age- and sex-matched control subjects (9). Studies suggest that a loss of the nocturnal systolic blood pressure dip may be a sensitive marker for incipient diabetic nephropathy (11).

In some studies, preset sleep times of 10:00 P.M.–8:00 A.M. are used for the interpretation of ABPM data (12,13). We screened a random sample of our adolescents who have type 1 diabetes with ABPM and noted that although a normal nocturnal dip was suggested by visual inspection of the printed blood pressure graphs with use of the preset sleep time of 10:00 P.M.–8:00 A.M., the calculated nocturnal dip from the same graphs was frequently abnormal.

The first aim of this study was to test the hypothesis that calculating the nocturnal systolic blood pressure dip in adolescent patients with type 1 diabetes using a preset sleep time results in an underestimate of the true nocturnal systolic blood pressure dip, thus potentially miscategorizing some individuals as "nondippers" (see below). The second aim was to assess the reproducibility of loss of the nocturnal dip in systolic blood pressure.

RESEARCH DESIGN AND METHODS

— For aim 1, subjects for this retrospective analysis were a random sample of 53 of ~400 adolescents with type 1 diabetes followed in our clinic who had agreed to undergo ABPM. Approval for this analysis was obtained from the institutional review board.

ABPM

A Spacelabs 90217 portable oscillometric recorder (Spacelabs, Kaarst, Germany) was used with four different cuff sizes (12–20, 17–26, 24–32, and 32–42 cm). The monitor was worn for 24 h on a nonschool day. The nondominant arm was measured to ensure correct cuff size, and the patient reported the anticipated sleep/wake times before initializing the monitor. The blood pressure device was set up to record blood pressure every 20 min during the day and every 40 min during the anticipated sleep period. Patients were instructed to avoid strenuous physical exertion during the study period. ABPM was performed in the absence of

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severe hypoglycemia, ketoacidosis, or acute infection. Upon returning the monitor, the patient reported actual sleep/wake times for interpretation of the data. The nocturnal dip in systolic blood pressure was then calculated based on actual sleep time and compared with that based on the preset sleep time of 10:00 P.M.–8:00 A.M. For the purpose of this study, nondipping refers to an attenuated fall in systolic blood pressure during the sleep period (<10%).

For aim 2, ABPM was analyzed from an additional 45 subjects. For the entire group, a nocturnal dip in systolic blood pressure was calculated from the actual reported sleep time.

After an interval of between 1 and 4 weeks, ABPM was repeated by the same method in 22 of the 35 subjects identified as nondippers, without major changes in diet, activity, or insulin regimen. These subjects were chosen on the basis of their availability for and cooperation with repeat ABPM testing. None of these subjects had microalbuminuria, and none had been treated with any antihypertensive medication. The nocturnal dip in systolic blood pressure was again measured using actual reported sleep time.

Statistical analysis

The statistical software MedCalc (version 9.6.4.0; MedCalc Software, Mariakerke, Belgium) was used for all data processing. To compare the percent dip in nocturnal systolic blood pressure using the actual versus preset sleep time, both a paired *t* test and Bland and Altman plot were performed. The 95% CI ($P < 0.05$) was considered statistically significant.

RESULTS — Characteristics of the initial group of 53 adolescents are shown in Table 1. On the basis of age, duration of diabetes, and mean A1C, this group of adolescents was representative of our entire adolescent population with type 1 diabetes. By using the actual reported sleep time, the mean ± SE fall in nocturnal systolic blood pressure was 11.6 ± 4.7%. When the mean systolic nocturnal dip was measured using the preset sleep time, the mean fall in nighttime systolic blood pressure was 8.8 ± 4.9% ($P < 0.0001$) (Fig. 1). The Brand and Altman plot demonstrates an average discrepancy of 2.8% with relatively consistent variability across the graph (Fig. 2). An example of one adolescent in whom the percent dip in nocturnal systolic blood pressure calculated from the preset sleep time of 10:00 P.M.–8:00 A.M. was abnormal (4%), whereas use of the actual reported sleep time of 2:00–7:00 A.M. identified a normal nocturnal dip (13.7%), is shown in Fig. 3.

Table 1—*Characteristics of subjects used for comparison of nocturnal dip comparing preset and actual sleep time*

n	53 (27 male, 26 female)
Age (years)	15.1 ± 2.2
Duration of diabetes (years)	6.8 ± 4.2
A1C (%)	8.9 ± 1.8
Bedtime	11:38 P.M. ± 1.16 h
Wake time	8:31 A.M. ± 1.46 h
Sleep time	8.8 ± 1.75 h

Data are means ± SE.

Characteristics of the entire group of 98 patients evaluated is shown in Table 2. Sixty-three (64%) had a normal nocturnal decline in systolic blood pressure (14.9 ± 3.1%), whereas 35 patients (36%) had an abnormal dip (5.7 ± 2.8%).

APBM was repeated in 22 of the 35 (63%) patients who had abnormal dipping. Fourteen of these 22 (64%) had normal nocturnal dipping upon repeat ABPM, whereas 8 of 22 (36%) had confirmed abnormal dipping.

CONCLUSIONS — Studies have shown that in patients with type 1 diabetes and incipient nephropathy, loss of the normal nighttime drop in systolic blood pressure may precede the development of microalbuminuria (9,11,13), which, in turn, if persistent, strongly predicts the development of clinical nephropathy (14,15). This result suggests that nocturnal nondipping may be a predictor that can be used to identify those at risk of nephropathy. Because the nocturnal dip is the difference between the mean daytime (period when ambulatory blood pressure is higher) and nighttime (period when the ambulatory blood pressure is lower) blood pressure, any inclusion of waking hours in the defined nighttime period will result in an increase in the mean nighttime blood pressure and thereby cause a reduction in the difference between the daytime and nighttime blood pressure.

Some studies have used a preset sleep time to interpret ABPM data (12,13). We have shown that calculating the nocturnal dip using preset sleep times should be interpreted with caution as this method re-

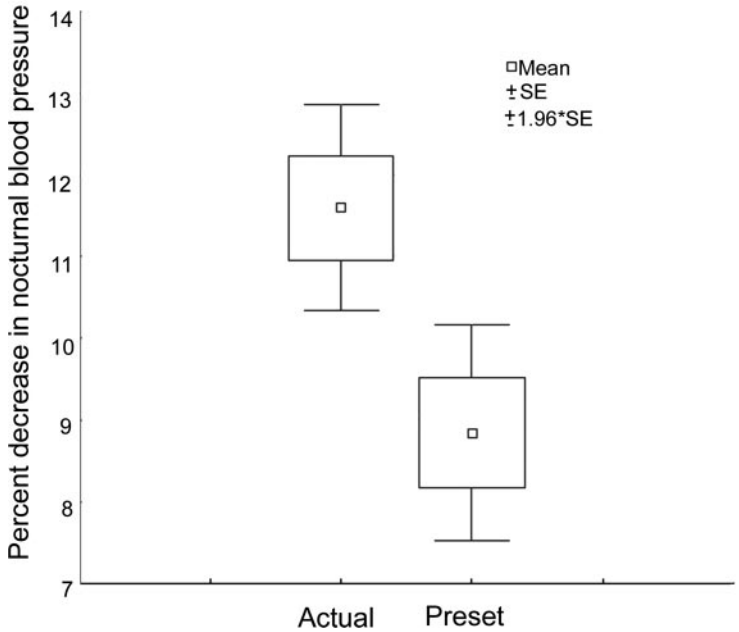

Figure 1—*Comparison of the percent nocturnal dip in systolic blood pressure calculated from actual sleep time versus that from preset sleep time in 53 subjects with type 1 diabetes.*

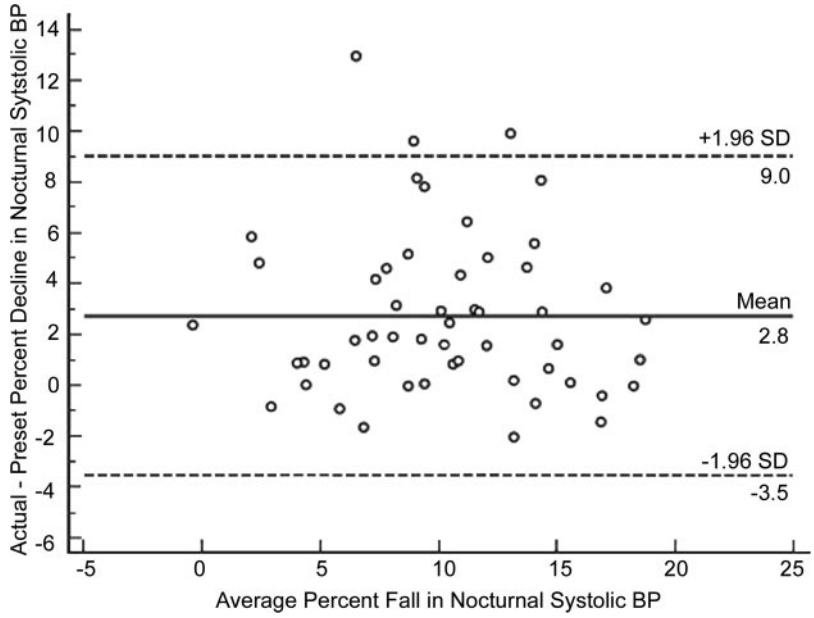

Figure 2—*Bland and Altman plot. Solid line represents the mean of differences between percent decline in nocturnal systolic blood pressure (BP) calculated using actual versus preset sleep time. The average discrepancy between the different sleep times is 2.8%, with relative consistent variability.*

sults in a nearly twofold overestimation of the prevalence of nondippers. In this cohort of adolescents with type 1 diabetes, when we used a preset sleep time of 10:00 P.M.–8:00 A.M. to interpret the 24-h ABPM, 62% of the subjects were classified as nondippers, whereas when we used the actual sleep time, 34% were classified as nondippers (data not shown). Although the mean reported bedtime in our subjects was 11:38 P.M. and mean wake time was 8:31 A.M., there was a wide range of bedtime and wake time, probably exacerbated by the fact that the study was done on a Friday (no school the next day).

Some investigators have attempted to minimize the potential error in calculating the nocturnal dip by defining the nighttime period as 12–6 A.M., and the daytime period as 8 A.M.–10 P.M., i.e., eliminating the period of 6–8 A.M. and 10 P.M. to midnight (9,11,16). This practice minimizes the potential pitfall of using a preset bedtime but is more labor intensive as the current SpaceLabs software does not allow times to be eliminated from the analysis. When we manually analyzed the nocturnal dip in our patient using this method (i.e., defining the nighttime period as 12–6 A.M. and the daytime period as 8 A.M.–10 P.M.), there was concordance (i.e., correct categorizing of the patients as dippers versus nondippers in 85 of 98 [87%] of the subjects. However, in the remaining 13% of our subjects, there was discordance, i.e., erroneous categorization of their dipping status (data not shown). This result suggests that when one is assessing the nocturnal dip in adolescents with type 1 diabetes, elimination of the "transition hours" is not sufficient, and actual reported sleep time should be used.

Admittedly, there is some inaccuracy in self-reported sleep times, and an even more precise method would be to determine sleep time using a device known as an actigraph to detect motion (17).

Beyond the issue of discerning actual sleep time to identify blood pressure dipping, there is the question of general blood pressure reproducibility. One of the limitations of this study is that we targeted apparent nocturnal nondippers only. Ideally, a random sample of dippers should have been undertaken as well. However, previous larger studies have examined the general reproducibility of 24-h ABPM. Wang et al. (18) examined >600 healthy adolescents and young adults and found good overall reproducibility over many years.

In our study, approximately one-third of the adolescents with type 1 diabetes were found to have an initial attenuated decline in nighttime systolic blood pressure on ABPM, despite use of data from actual sleep times for analysis. However, of these putative nondippers who had repeat ABPM performed, almost two-thirds were found to have normal nocturnal dipping. Thus, repeat ABPM reduced the prevalence of nondipping from 36 to 13%. This result suggests that finding a subnormal nocturnal dip in an adolescent with type 1 diabetes should be interpreted with caution and that a repeat

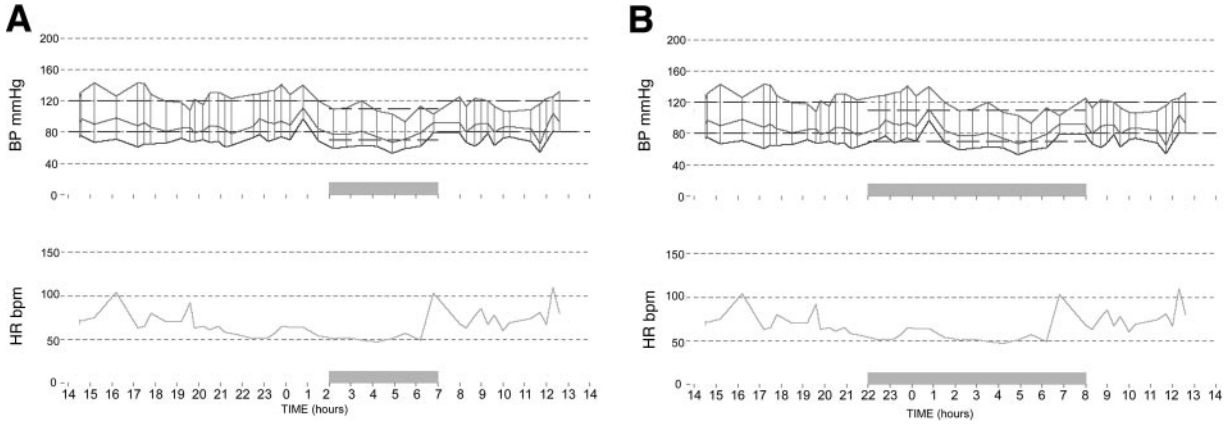

Figure 3—*ABPM from an individual patient. Shaded area indicates sleep time.* A*: Actual sleep time 2:00–7:00* A.M. *Mean daytime systolic blood pressure (BP) 124 mmHg; mean nighttime systolic blood pressure 107 mmHg; percent dip 13.7%.* B*: Preset sleep time 10* P.M.–8 A.M. *Mean daytime systolic blood pressure 122 mmHg; mean nighttime systolic blood pressure 117 mmHg; percent dip 4%.*

Table 2—*Characteristics of subjects investigated for risk factors associated with nocturnal nondipping*

n	98 (54 male, 44 female)
Age (years)	15.2 ± 2.2
Diabetes duration (years)	6.3 ± 3.8
BMI percentile	69.5 ± 24.2
A1C (%)	8.7 ± 1.7

Data are means ± SE.

ABPM is essential to confirm this abnormality. It is possible that the phenomenon of "regression to the mean" is partly responsible for the poor reproducibility of nondipping. Similar to our findings, Wang et al. showed that nocturnal dipping was somewhat less reproducible than the measure of either day or night blood pressure, despite having discarded data from day-night "transition hours" (18).

Although ABPM has not yet become routine in monitoring of adolescents with type 1 diabetes, it offers the ability to identify subjects with loss of the nocturnal dip and, therefore, an apparent increased risk for incipient diabetic nephropathy. It may be of interest in future studies to investigate treating persistent nondippers with renoprotective drugs before the development of overt proteinuria and hypertension. ACE inhibitors (19,20) would be a logical choice to investigate to determine whether *1*) they restore the normal circadian blood pressure pattern in nondippers and *2*) this therapy can prevent the development of microalbuminuria.

On the basis of our findings, caution should be exercised when one is interpreting the nocturnal blood pressure profile with ABPM. When the nocturnal dip is calculated with software that uses the entire 24-h period, it is important to use the actual reported sleep time rather than a preset sleep time for the analysis. In addition, it is essential to confirm abnormal nocturnal dipping by repeating the ABPM.

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