Pitfalls in the measurement of the nocturnal blood pressure dip in adolescents with type 1 diabetes.

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Objective: To screen adolescents with type 1 diabetes using ambulatory blood pressure monitoring (ABPM) in order to: 1) test the hypothesis that using a preset sleep time results in an over-diagnosis of abnormal nocturnal dipping in systolic BP, 2) assess the reproducibility of an abnormal nocturnal systolic BP dip.

Research Design and Methods: Aim 1: ABPM was reviewed from 53 adolescent patients with type 1 diabetes. Nocturnal dip in systolic BP calculated by actual sleep time was compared with that from a preset sleep time. Aim 2: BPM was reviewed from 98 patients using actual reported sleep time. Reproducibility of nocturnal dip in systolic BP was assessed in a subset of non-dippers.

Results: 1. The actual mean decline in nocturnal systolic BP was 11.6 ± 4.7%, while the mean fall in nocturnal systolic BP calculated using the preset sleep time was 8.8 ± 4.9% (p<0.0001). 2. Sixty four percent had a normal nocturnal decline in systolic BP (14.9 ± 3.1 mmHg), while 36 percent had an abnormal dip (5.7 ± 2.8 mmHg). Repeat ABPM performed on 22 of the 35 non-dippers 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 BP. Repeating ABPM in non-dippers is essential to confirm this abnormality.
Elevated blood pressure (BP) is strongly associated with diabetic nephropathy. (1-3) However, in the pediatric population, patients with type 1 diabetes are rarely diagnosed with overt hypertension, as defined by blood pressure greater than or equal to the 95th percentile. Automated blood pressure readings in the office are often inaccurate, and single BP measurements, whether automated or manual, are often falsely elevated. (4,5) Mean BP ascertained by twenty-four hour ambulatory blood pressure monitoring (ABPM) has also been shown to better predict target organ damage when compared to isolated, intermittent clinic BP 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 twenty-four hour (ABPM) allows for the observation of circadian BP patterns by providing a profile of blood pressure over time. (7,9,10) This includes a normal decrease during sleep of both systolic and diastolic blood pressure by approximately 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 when compared to age and sex-matched control subjects. (9) Studies suggest that a loss of the nocturnal systolic BP dip may be a sensitive marker for incipient diabetic nephropathy. (11)

In some studies, preset sleep times 10:00 pm to 8:00 am are utilized for the interpretation of the ABPM data. (12); (13) We screened a random sample of our adolescent type 1 diabetes population with ABPM, and noted that when using the preset sleep time 10:00 pm to 8:00 am, while a normal nocturnal dip was suggested by visual inspection of the printed blood pressure graphs, the calculated nocturnal dip from the same graphs was frequently abnormal.

The first aim on 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 “non-dippers”. The second aim was to assess the reproducibility of loss of the nocturnal dip in systolic blood pressure.

RESEARCH DESIGN AND METHODS

Subjects: Aim 1: Subjects for this retrospective analysis were a random sample of 53 out of approximately 400 adolescents followed in our clinic with type 1 diabetes mellitus who had agreed to undergo ABPM. Approval for this analysis was obtained from the Institutional Review Board.

Ambulatory blood pressure monitoring: The SpaceLabs 90217 portable oscillometric recorder (SpaceLabs, Kaarst, Germany) was used with four different cuff sizes (12-20 cm, 17-26 cm, 24-32 cm, and 32-42 cm). The monitor was worn for twenty-four hours on a non-school day. The non-dominant arm was measured to ensure correct cuff size, and the patient reported the anticipated sleep/wake times prior to initializing the monitor. The blood pressure device was set up to record blood pressure every 20 minutes during the day, and every 40 minutes during the anticipated sleep period. Patients were instructed to avoid strenuous physical exertion during the study period. ABPM was performed in the absence of 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 preset sleep time of 10:00 pm to
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8:00 am. For the purpose of this study, non-dipping refers to an attenuated fall in systolic BP during the sleep period (less than 10%).

**Aim 2:** ABPM was analyzed from an additional 45 subjects. For the entire group, 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 non-dippers without major changes in diet, activity, or insulin regimen. These subjects were chosen based on 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 BP using the actual vs. preset sleep time, both paired t-test and Bland & Altman plot was performed. The 95% confidence interval (p<0.05) was considered statistically significant.

**RESULTS**

The initial group of 53 adolescents is shown in Table 1. Based on age, duration of diabetes and mean HbA1c, this group of adolescents was representative of our entire adolescent population with type 1 diabetes. Using the actual reported sleep time, the mean fall in nocturnal systolic blood pressure was 11.6 ± 4.7%. When the mean systolic nocturnal dip was instead measured using the preset sleep time, the mean fall in nighttime systolic blood pressure was 8.8 ± 4.9% (p<0.0001) (Figure 1). The Bland & Altman plot demonstrates an average discrepancy of 2.8% with relatively consistent variability across the graph (Figure 2). An example of one adolescent in whom the percent dip in nocturnal systolic BP calculated from the preset sleep time 10:00 pm to 8:00 am was abnormal (4%), while using the actual reported sleep time 2:00 am to 7:00 am identified a normal nocturnal dip (13.7%) is shown in Figure 3.

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%), while 35 patients (36%) had an abnormal dip (5.7 ± 2.8%).

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

**DISCUSSION**

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 suggests that nocturnal non-dipping may be a predictor that can be used to identify those at risk for nephropathy. Since the nocturnal dip is the difference between the mean daytime (period when ABP is higher) and nighttime (period when the ABP is lower), 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 night time 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 results in a nearly two-fold overestimation of the prevalence of non-dippers. In this cohort of adolescents with type 1 diabetes, using a preset sleep time of
10:00 pm to 8:00 am to interpret the 24 hour ABPM, 62% of the subjects were classified as non-dippers, while using the actual sleep time, 34% were classified as non-dippers (data not shown).

Although the mean reported bedtime in our subjects was 11:38 pm and mean wake time 8:31 am, there was wide range of bedtime and wake time, likely exacerbated by the fact that the study is 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 am to 6 am, and the daytime period as 8 am to 10 pm i.e. eliminating the period 6 am to 8 am and 10 pm to midnight.(9, 11, 16) This practice minimizes the potential pitfall in utilizing a preset bedtime, but is more labor intensive as the current Spacelab software does not allow times to be eliminated from the analysis. When we manually analyzed the nocturnal dip in our patient utilizing this method (i.e. defining the nighttime period as 12 am to 6 am, and the daytime period as 8 am to 10 pm), there was concordance (i.e. correct categorizing of the patients as dippers vs. non-dippers in 85 out of 98 (87%) of the subjects. However, in the remaining 13% or our subjects, there was discordance i.e. erroneously categorization of their dipping status (data not shown). This suggests that when 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 BP dipping, there is the question of general BP reproducibility. One of the limitations of this study is that we targeted apparent nocturnal non-dippers only. Ideally, a random sample of dippers should have been undertaken as well. However, previous larger studies have examined the general reproducibility of 24 hour ambulatory BP monitoring. Wang and colleagues examined over 600 healthy adolescents and young adults, and found good overall reproducibility over many years (18).

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 having analyzed the data from actual sleep times. However, of these putative non-dippers who had repeat ABPM performed, almost two-thirds were found to have normal nocturnal dipping. Thus, repeat ABPM reduced the prevalence of non-dipping from 36% to 13%. This suggests that finding a subnormal nocturnal dip in an adolescent with type 1 diabetes should be interpreted with caution and that a repeat 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 non-dipping. Similar to our findings, Wang and colleagues showed that nocturnal dipping was somewhat less reproducible than the measure of either day or night BP, despite having discarded data from day-night “transition hours” (18).

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

Based on our findings, caution should be exercised when interpreting nocturnal blood pressure profile with ABPM. When calculating the nocturnal dip with software that utilized the entire 24 hour 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.

**Figure Legends**

Figure 1. Comparison of nocturnal dip in systolic blood pressure calculated from actual sleep time vs. preset sleep time in 53 subjects with type 1 diabetes.

Figure 2. Bland & Altman Plot. Solid line represents the mean of differences between percent decline in nocturnal systolic BP calculated using actual vs. preset sleep time. The average discrepancy between the different sleep times is 2.8%, with relative consistent variability.

Figure 3. ABPM from an individual patient. Shaded area indicates sleep time.
A. Actual sleep time 2:00 am to 7:00 am. Mean daytime systolic BP 124 mmHg, mean nighttime systolic BP 107 mmHg, percent dip 13.7%.
B. Preset sleep time 10 pm to 8 am. Mean daytime systolic BP 122, mean nighttime systolic BP 117, percent dip 4%
REFERENCES

17. Eissa MA, Poffenbarger T, Portman RJ: Comparison of the actigraph versus patients' diary


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

<table>
<thead>
<tr>
<th>n</th>
<th>53 (27 male, 26 female)</th>
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<tr>
<td>Mean age</td>
<td>15.1 ± 2.2 years</td>
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<tr>
<td>Mean duration of diabetes</td>
<td>6.8 ± 4.2 years</td>
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<tr>
<td>Mean HbA1c</td>
<td>8.9 ± 1.8</td>
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<tr>
<td>Mean bedtime</td>
<td>11:38 pm ± 1.16 hours</td>
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<tr>
<td>Mean wake time</td>
<td>8:31 am ± 1.46 hours</td>
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<tr>
<td>Mean sleep time</td>
<td>8.8 ± 1.75 hours</td>
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Table 2. Characteristics of subjects investigated for risk factors associated with nocturnal non-dipping

<table>
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<td>Mean age</td>
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<tr>
<td>Mean duration of diabetes</td>
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<td>Mean BMI percentile</td>
<td>69.5 ± 24.2</td>
</tr>
<tr>
<td>Mean HbA1c</td>
<td>8.7 ± 1.7</td>
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Figure 1.
Figure 2:

![Graph showing the actual vs. preset percent decline in nocturnal systolic blood pressure. The graph includes a scatter plot with a horizontal line indicating the mean and dashed lines representing ±1.96 SD.](image)

Figure 3:

A. 

![Graph showing blood pressure (BP) and heart rate (HR) over time.](image)

B. 

![Graph showing blood pressure (BP) and heart rate (HR) over time.](image)