Targeting Nocturnal Hypertension in Type 2 Diabetes Mellitus

Niklas Blach Rossen, Søren Tang Knudsen, Jesper Fleischer, Anne-Mette Hvas, Eva Ebbehøj, Per Løgstrup Poulsen, Klavs Würgler Hansen

Abstract—Several studies in different populations have suggested that nighttime blood pressure (BP) is a stronger predictor of cardiovascular events than daytime BP. Consequently, treatment strategies to target nighttime BP have come into focus. The aim of the present study was to investigate the effect of change of administration time of antihypertensive drugs. We included 41 patients with type 2 diabetes mellitus and nocturnal hypertension (nighttime systolic BP ≥120 mmHg) in an open-label, crossover study. Patients were randomized to 8 weeks of either morning or bedtime administration of all of the individual’s once-daily antihypertensive drugs, followed by 8 weeks of switched dosing regimen. Bedtime administration of antihypertensive drugs resulted in a significant reduction in nighttime (7.5 mmHg; P<0.001) and 24-hour (3.1 mmHg; P=0.014) systolic BP, with a nonsignificant reduction in daytime (1.3 mmHg; P=0.336) systolic BP. We did not find morning BP urge to be different between dosing regimens. Levels of C-reactive protein were significantly lower with bedtime administration, which may indicate an effect on low-grade inflammation. We found no difference in urinary albumin excretion, regardless of albuminuria status. Urinary sodium/creatinine was significantly increased and urinary osmolality significantly reduced with bedtime administration, which can be interpreted as increased nocturnal natriuresis. In patients with type 2 diabetes mellitus and nocturnal hypertension, administration of once-daily antihypertensive drugs at bedtime may be favorable. The increased nocturnal natriuresis may reflect increased effect of bedtime-administered thiazides and renin–angiotensin system inhibitors, suggesting a potential mechanism of the observed effects on BP with chronotherapeutic intervention. (Hypertension. 2014;64:1080-1087.) ● Online Data Supplement

Key Words: blood pressure monitoring, ambulatory ▪ chronotherapy ▪ diabetes mellitus, type 2 ▪ hypertension

During the past decades, several studies in different populations have suggested that nighttime blood pressure (BP) is a stronger predictor of cardiovascular (CV) events than daytime BP.1-5 Indeed, a recent meta-analysis concluded that nighttime BP is superior to daytime BP in predicting CV events and total mortality in both patients and general populations.6 Consequently, treatment strategies to target nighttime BP have come into focus.

Bedtime administration (BA) of different classes of antihypertensive drugs has been shown to reduce nighttime BP, although results are not unequivocal.7 Moreover, a recent prospective study concluded that BA of ≥1 antihypertensive drugs resulted in a significantly lower relative risk of total events and major CV events.8 Consequently, the American Diabetes Association now recommends administering ≥1 antihypertensive drugs at bedtime.9

Diabetes mellitus is a condition in which CV risk is markedly increased.10 The predictive role of nighttime BP has also been established in patients with diabetes mellitus.11 Nocturnal hypertension is more frequent in diabetic compared with that in nondiabetic patients, in part, because of autonomic dysfunction. Only a few studies have investigated the effect of BA of antihypertensive drugs in diabetes mellitus,11,12 and these studies applied BA irrespective of the level of nighttime BP.

Hence, it was our aim to conduct a randomized crossover study on the effect of change of administration time of once-daily antihypertensive drugs in a population of patients with type 2 diabetes mellitus and nocturnal hypertension, defined as nighttime systolic BP (SBP) ≥120 mm Hg. Our primary end point was changes in ambulatory BP parameters, with specific focus on nighttime BP.

Methods

The study was approved by the Central Denmark Region Committees on Health Research Ethics and the Danish Data Protection Agency. All patients provided informed consent. The study was registered at ClinicalTrials.gov with ID NCT01158625.

Study Population

Inclusion criteria included (1) type 2 diabetes mellitus, (2) antihypertensive treatment including ≥1 once-daily renin–angiotensin system inhibitors, (3) ambulatory monitoring for at least 1 week before randomization, (4) nighttime BP ≥120 mm Hg for at least 1 month before randomization, and (5) nighttime hypertension defined as nighttime SBP ≥120 mm Hg and nighttime diastolic BP ≥75 mm Hg. Exclusion criteria were secondary hypertension, requirement for treatment with antihypertensive drugs for less than 1 month, overt peripheral vascular disease, renal insufficiency, significant renal stones, and use of interferon alpha.

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From the Department of Medicine, Silkeborg Regional Hospital, Silkeborg, Denmark (N.B.R., K.W.H.); and Department of Endocrinology and Internal Medicine (N.B.R., S.T.K., E.E., P.L.P.), Medical Research Laboratory (J.F.), and Department of Clinical Biochemistry (A.-M.H.), Aarhus University Hospital, Aarhus, Denmark.

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Correspondence to Niklas Blach Rossen, Department of Medicine, Silkeborg Regional Hospital, Falkevej, DK-8600 Silkeborg, Denmark. E-mail nikklas. rosen@rm.dk

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inhibitor, (3) all once-daily antihypertensive drugs administered in the morning, (4) antihypertensive treatment unaltered for 8 weeks, (5) nighttime SBP ≥120 mm Hg, and (6) daytime SBP fulfilling the following criteria: (1) ≤130 mm Hg and minimum 1 antihypertensive drug, (2) 131 to 135 mm Hg and minimum 2 antihypertensive drugs, (3) 136 to 140 mm Hg and minimum 3 antihypertensive drugs, or (4) 141 to 150 mm Hg and minimum 4 antihypertensive drugs. For all inclusion, exclusion, and withdrawal criteria see online-only Data Supplement.

Sample size calculation was based on a standard deviation of differences of nighttime SBP of 7.5 mm Hg and a minimal relevant difference in nighttime SBP of 3.5 mm Hg. α was set to 5% and power to 80%. Under these assumptions sample size was calculated to 40 patients.

Patients were recruited from the outpatient clinics of endocrinology at Silkeborg Regional Hospital and Aarhus University Hospital, Denmark, from October 2010 to November 2012. Approximately 700 medical records and ambulatory blood pressure monitoring (ABPM) reports were evaluated. Just <200 patients fulfilled preliminary inclusion criteria and were invited to participate. A total of 99 patients accepted participation and underwent qualifying ABPM. All inclusion criteria were met by 45 patients. Four patients were withdrawn from the study because of the development of atrial fibrillation (2 patients), third-degree atrioventricular block, and severe hyponatremia (based on undisclosed alcohol abuse). Thus, 41 patients completed the study.

**Study Design**

We conducted an open-label crossover study. Patients were randomized to 8 weeks of either morning administration (MA) or BA of all of the individual’s once-daily antihypertensive drugs, followed by 8 weeks of switched dosing regimen. Throughout the study, the antihypertensive treatment per se was unchanged. At baseline and after each of the two 8-week periods, patients underwent ABPM and measurements of office BP, arterial stiffness and autonomic dysfunction, and blood and urine sampling were performed. All physical examinations were conducted in the morning by the same investigator (N.B.R.). A graphical presentation of the study design is available in Figure S1 in the online-only Data Supplement.

**BP Measurement and ABP Data**

After assuring correct cuff size by measurement of arm circumference, we checked for interarm BP difference with Microlife WatchBP Office (Microlife AG Swiss Corporation, Widnau, Switzerland), averaging 3 consecutive measurements. If the difference in SBP was >20 mm Hg (1 patient), we used the arm with the highest BP for office BP measurements and ABPM, otherwise the nondominant arm was used. Office BP was measured 4 times, reporting the average of the 3 latter. For both office BP measurement and ABPM, we applied Spacelabs 90217 monitor and used Spacelabs Report Management System 92506, version 3.0.0.9 (Spacelabs Healthcare, Issaquah, WA). The ABPM monitors were programmed to measure every 20 minutes, day and night. Patients were instructed to note time of going to bed in the evening and getting up in the morning. If hourly averages were missing for >2 hours during daytime or 1 hour during nighttime, the ABPM was repeated (4 cases of 123 expected ABPMs). For each patient, repeated ABPM was performed on days of similar activity level (work/day off).

The applied Spacelabs Report Management System determines the daytime, nighttime, and 24-hour BP by calculation of the average of the hourly averages in the respective periods. We defined the nighttime period as starting at the full hour after the patient went to bed until the last full hour of sleep. Thus, for a patient going to bed at 10:37 pm and getting up at 6:22 am, the nighttime period was registered as 11:00 PM to 6:00 AM (7 hours). However, for the determination of the morning BP surge, we manually calculated the hourly averages from the exact time of getting up in the morning. Thus, the preawakening morning BP surge was calculated as the average of the 2 hourly averages after getting up minus the average of the 2 hourly averages before getting up. The sleep-trough morning BP surge was calculated as the average of the 2 hourly averages after getting up minus the nadir-average. The nadir-average was defined as the average of the 3 BP readings centered on the lowest nighttime BP (ie, the lowest BP reading and the readings immediately before and after).

**Arterial Stiffness and Central Hemodynamics**

We performed measurements of arterial stiffness and central BPs with the TensioClinic Arteriograph TL1 with TensioClinic software version 1.10.1.11 (TensioMed Ltd, Budapest, Hungary). Patients were instructed not to drink coffee or smoke within 3 hours of examination nor to drink alcohol within 10 hours of examination. Measurements were done after 10 minutes of rest in the supine position.

**Blood and Urine Analyses**

Blood samples were drawn after 30 minutes of rest in the supine position. Standard blood samples (creatinine, HbA1c, cholesterol, etc) were analyzed immediately, whereas parameters of the renin–angiotensin–aldosterone system, markers of endothelial dysfunction (E-selectin, intercellular adhesion molecule [ICAM]) and inflammation (C-reactive protein, fibrinogen), arginine vasopressin, and atrial natriuretic peptide were analyzed in batches. Patients collected urine samples morning and evening for 3 days before visits at baseline and at the end of each of the two 8-week periods. Urinary albumin, creatinine, and sodium were analyzed continuously. Data on morning and bedtime urinary albumin and creatinine are available, whereas we only have data on morning urinary sodium, potassium, and osmolality.

**CV Autonomic Neuropathy**

Using the Vagus device (Medicus Engineering, Aarhus, Denmark), diagnosis of CV autonomic neuropathy (CAN) was based on measurements of heart rate variability during 3 CV reflex tests: (1) response to active standing, (2) expiration:inspiration ratio, and (3) the Valsalva maneuver. Following the criteria set forth by the Toronto Consensus Panel on Diabetic Neuropathy, results were interpreted as follows: all tests normal, no CAN; 1 test abnormal, early CAN; and 2 to 3 tests abnormal, manifest CAN. Diagnosis of CAN required ≥2 valid tests. All tests were evaluated according to the age-dependent cut-off levels.

**Compliance and Tolerability**

To enhance the level of compliance, we administered all antihypertensive drugs in segmented pill containers, clearly indicating MA and BA. Patients were instructed to leave missed dosages in the container. If >10% of dosages were missed, the criteria of compliance were not met. Patients were instructed to record time of ingestion of antihypertensive drugs and number of nighttime toilet visits as well as any discomfort or adverse effects.

**Statistical Analyses**

Assumptions of normal distributions were tested by histograms and QQ-plots. Data are presented as mean±SD or median(range) for skewed data. In case of retransformed logarithmic data, geometric mean (95% confidence interval) is presented. Statistical analyses were performed for differences between MA and BA of antihypertensive drugs. Differences between MA and BA were assessed by paired t test. A 2-tailed P value of <0.05 was considered statistically significant. We tested for and excluded period and group effect. StataIC 11.2 (StataCorp LP, TX) was used for data analyses.

**Results**

**Baseline Characteristics**

Baseline characteristics are presented in Table 1 and described in the online-only Data Supplement.

**BP, Arterial Stiffness, and Central Hemodynamics**

BA of antihypertensive drugs resulted in a significant reduction in nighttime and 24-hour SBP, with a nonsignificant reduction in daytime SBP (Figure 1; Table 2). The same pattern of significant reduction in nighttime and 24-hour BP and nonsignificant reduction in daytime BP was found for diastolic BP, pulse pressure, and mean arterial pressure (Table 2). Nighttime heart rate was nonsignificantly reduced...
with BA. We found no difference in office SBP and diastolic BP. Subgroup analyses showed consistent effects on nighttime BP with BA (Figure 2).

The difference in nighttime SBP between dosing regimens was unrelated to the SBP night/day ratio both in the group of patients considered as a whole and within the subgroup of nondippers.

Figure 3 illustrates the BP curves with MA and BA, based on the hourly averages and fixed at the last and the first hour awake.

The preawakening and sleep-through morning BP surge did not differ between dosing regimens (Table 3). The reduced number of patients (n=27) is explained by the fact that some patients removed the ABPM monitor shortly after awakening.

When accepting only to have data from the first hour after getting up (n=35) morning BP surge still did not differ between regimens (data not shown).

We found no difference in pulse wave velocity or central SBP between MA and BA (pulse wave velocity [m/s]: 8.75±0.90 versus 9.00±0.97; P=0.055 and central SBP [mm Hg]: 128.12±15.73 versus 128.06±17.84; P=0.980).

**Blood and Urine Analyses**

Renin tended to be increased and C-reactive protein was significantly reduced with BA. None of the other blood analyses showed significant changes between dosing regimens (Table 4).

Urinary albumin/creatinine did not differ between MA and BA, neither for the morning nor for the bedtime samples. Moreover, subgroup analysis of patients with microalbuminuria (urinary albumin/creatinine >30 mg/g) and macroalbuminuria (urinary albumin/creatinine >300 mg/g) did not reveal any differences (Table 4).

We found no difference in pulse wave velocity or central SBP between MA and BA (pulse wave velocity [m/s]: 8.75±0.90 versus 9.00±0.97; P=0.055 and central SBP [mm Hg]: 128.12±15.73 versus 128.06±17.84; P=0.980).

**Sleep Duration and Time of Drug Intake, Nocturia, Compliance, and Tolerability**

Duration of sleep did not differ between dosing regimens (MA, 7 hours 41 minutes; BA, 7 hours 50 minutes; P=0.326).
Time from getting up in the morning to drug intake was 25 minutes (range, 5–130 minutes) with MA, whereas time from drug intake and going to bed in the evening was 20 minutes (range, 5–165 minutes). The frequency of nocturia did not differ between MA and BA (MA, 1.02±1.13; BA, 1.15±1.24; P=0.303). All patients met the criteria of compliance. We did not register more discomfort or adverse effects with BA.

### Discussion

We have demonstrated for the first time that BA of all once-daily antihypertensive drugs reduces not only nighttime BP but also 24-hour BP, in patients with type 2 diabetes mellitus and nocturnal hypertension. Previous studies have found the same effect on nighttime BP, but not 24-hour BP, and no studies have specifically targeted nocturnal hypertension but applied BA irrespective of nighttime BP level.

Tofé Povedano et al.11 conducted a crossover study with 40 patients with type 2 diabetes mellitus and newly diagnosed hypertension. Patients were randomized to 8 weeks of 40 mg olmesartan in the morning or at bedtime, followed by 8 weeks at switched administration time. BA resulted in a significant reduction in nighttime SBP, with nonsignificant increase in daytime SBP and decrease in 24-hour BP.

In a subgroup of the Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares (MAPEC) study,12 Hermida et al. investigated whether, compared with MA, bedtime treatment with ≥1 antihypertensive drugs exerted better BP control and CV risk reduction in 448 hypertensive patients with type 2 diabetes mellitus. BA of ≥1 antihypertensive drugs resulted in a significant reduction in nighttime BP, with nonsignificant reduction in daytime and 48-hour BP.

Thus, the effects of BA on nighttime BP between studies are comparable. However, substantial differences are present. In the present study, we also found a significant reduction in 24-hour BP with BA. Moreover, all patients in our study were known hypertensives and we changed the time of administration of all once-daily antihypertensive drugs (median, n=3). In the study by Tofé Povedano et al.,11 patients were newly diagnosed hypertensive patients and receiving only 1 antihypertensive drug. On request,12 Hermida et al. stated that all patients could be considered newly diagnosed and the percentages of patients ingesting 1, 2, or ≥3 at bedtime were 56.5, 25.0, and 18.5, respectively. The mean number of antihypertensive

### Table 2. Blood Pressure Results With Morning and Bedtime Administration of Once-Daily Antihypertensive Drugs

<table>
<thead>
<tr>
<th>Blood Pressure Parameter</th>
<th>n</th>
<th>MA</th>
<th>BA</th>
<th>Difference (MA–BA)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic BP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nighttime</td>
<td>41</td>
<td>125.3±10.2</td>
<td>117.8±10.7</td>
<td>7.5 (4.3 to 10.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Daytime</td>
<td>41</td>
<td>134.2±9.8</td>
<td>133.0±12.1</td>
<td>1.3 (−1.4 to 4.0)</td>
<td>0.336</td>
</tr>
<tr>
<td>24 hours</td>
<td>41</td>
<td>131.7±8.7</td>
<td>128.7±10.9</td>
<td>3.1 (0.7 to 5.5)</td>
<td>0.014</td>
</tr>
<tr>
<td><strong>Diastolic BP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nighttime</td>
<td>41</td>
<td>68.9±9.7</td>
<td>65.2±8.3</td>
<td>3.7 (1.7 to 5.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Daytime</td>
<td>41</td>
<td>76.7±7.9</td>
<td>76.1±6.8</td>
<td>0.6 (−0.9 to 2.1)</td>
<td>0.421</td>
</tr>
<tr>
<td>24 hours</td>
<td>41</td>
<td>74.5±8.0</td>
<td>73.1±6.7</td>
<td>1.4 (0.02 to 2.9)</td>
<td>0.047</td>
</tr>
<tr>
<td><strong>Pulse pressure</strong></td>
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</tr>
<tr>
<td>Nighttime</td>
<td>41</td>
<td>56.4±9.0</td>
<td>52.6±9.4</td>
<td>3.7 (1.9 to 5.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Daytime</td>
<td>41</td>
<td>57.6±9.3</td>
<td>56.9±11.2</td>
<td>0.7 (−0.8 to 2.2)</td>
<td>0.371</td>
</tr>
<tr>
<td>24 hours</td>
<td>41</td>
<td>57.2±8.6</td>
<td>55.6±10.4</td>
<td>1.6 (0.2 to 3.0)</td>
<td>0.023</td>
</tr>
<tr>
<td><strong>Mean arterial pressure</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Nighttime</td>
<td>41</td>
<td>88.5±8.3</td>
<td>83.6±7.5</td>
<td>4.9 (2.6 to 7.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Daytime</td>
<td>41</td>
<td>95.8±6.6</td>
<td>95.0±6.5</td>
<td>0.8 (−0.9 to 2.5)</td>
<td>0.337</td>
</tr>
<tr>
<td>24 hours</td>
<td>41</td>
<td>93.7±6.5</td>
<td>91.9±6.0</td>
<td>1.9 (0.3 to 3.5)</td>
<td>0.022</td>
</tr>
<tr>
<td><strong>Heart rate</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Nighttime</td>
<td>41</td>
<td>70.2±10.2</td>
<td>68.9±9.3</td>
<td>1.3 (−0.4 to 3.0)</td>
<td>0.123</td>
</tr>
<tr>
<td>Daytime</td>
<td>41</td>
<td>76.8±11.3</td>
<td>76.7±10.4</td>
<td>0.2 (−1.6 to 1.9)</td>
<td>0.845</td>
</tr>
<tr>
<td>24 hours</td>
<td>41</td>
<td>75.1±10.6</td>
<td>74.4±9.7</td>
<td>0.6 (−0.9 to 2.1)</td>
<td>0.420</td>
</tr>
<tr>
<td><strong>Office BP</strong></td>
<td></td>
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</tr>
<tr>
<td>Systolic BP</td>
<td>41</td>
<td>136.6±16.5</td>
<td>132.8±14.8</td>
<td>3.8 (−1.4 to 9.0)</td>
<td>0.149</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>41</td>
<td>76.7±11.7</td>
<td>76.0±8.7</td>
<td>0.6 (−2.5 to 3.8)</td>
<td>0.687</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>41</td>
<td>60.0±12.6</td>
<td>56.8±12.9</td>
<td>3.1 (0.1 to 6.2)</td>
<td>0.044</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>41</td>
<td>97.1±11.3</td>
<td>95.0±8.8</td>
<td>2.1 (−1.3 to 5.6)</td>
<td>0.224</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD or mean (95% confidence interval). All BPs are in mmHg and heart rate is in bpm. BA indicates bedtime administration; BP, blood pressure; and MA, morning administration.
drugs in the bedtime group was 2.4±1.2. Thus, most antihypertensive drugs in the bedtime group were taken in the morning. We speculate that the effect on 24-hour BP found in our study may be explained by the larger number of antihypertensive drugs administered at bedtime.

A recurring discussion is on the importance of the morning BP surge. Several studies have found an association between a larger morning BP surge and CV events, primarily stroke.\(^{13,14,19}\) In contrary, Verdecchia et al\(^{20}\) recently found that a blunted morning BP surge was an independent predictor of CV events, whereas an excessive morning BP surge was not. We did not find morning BP surge to be different between dosing regimens (Table 3). Compared with MA, preawake SBP was lower with BA, but also rose to a lower level in the first awake hours, leaving morning BP surge essentially unchanged. Thus, considerations on potentially harmful effects of BA on morning BP surge are not supported by our data.

C-reactive protein and fibrinogen are well-established risk factors of CV disease.\(^{21,22}\) Both markers have been associated with nondipping,\(^{23,24}\) and elevated levels of C-reactive protein.
have been demonstrated in subjects with nocturnal hypertension.25 Fibrinogen was shown to be significantly reduced with BA of valsartan.26 To our knowledge, no studies have examined the effects of BA on C-reactive protein. We found C-reactive protein to be significantly reduced with BA, whereas no difference was seen for fibrinogen. We have no explanation for the differing results. However, the perspectives of reduced low-grade inflammation with BA of antihypertensive drugs are intriguing and our findings merit further investigation.

Microalbuminuria is established as a strong and independent predictor of CV events.27 Antihypertensive treatment is known to reduce urinary albumin excretion, with renin–angiotensin system inhibitors being the most effective treatment modality.28 In patients with type 2 diabetes mellitus, studies have demonstrated an association between nighttime SBP and urinary albumin excretion, both in the normo- and microalbuminuric ranges.29–31 Interestingly, BA of antihypertensive drugs has been shown to reduce urinary albumin excretion.26,32 Despite significant reduction in nighttime and 24-hour BP with BA, we found no significant reduction in urinary albumin/creatinine, regardless of albuminuria status. We speculate that the low number of patients with micro/macroalbuminuria

### Table 3. Preawakening and Sleep-Through Morning Blood Pressure Surge With Morning and Bedtime Administration of Once-Daily Antihypertensive Drugs

<table>
<thead>
<tr>
<th>Morning Surge Type</th>
<th>n</th>
<th>Nadir-Average</th>
<th>Average 120–0</th>
<th>Average 0–120</th>
<th>MBPS</th>
<th>Difference (MA−BA)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preawakening</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA</td>
<td>27</td>
<td></td>
<td>129.7±12.2</td>
<td>139.2±13.4</td>
<td>9.6±15.6</td>
<td>−3.2 (−7.7 to 1.3)</td>
<td>0.156</td>
</tr>
<tr>
<td>BA</td>
<td>27</td>
<td></td>
<td>118.7±12.2</td>
<td>131.4±15.1</td>
<td>12.8±12.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep-through</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA</td>
<td>27</td>
<td>117.4±12.4</td>
<td></td>
<td>139.2±13.4</td>
<td>21.8±17.4</td>
<td>−0.9 (−6.4 to 4.7)</td>
<td>0.754</td>
</tr>
<tr>
<td>BA</td>
<td>27</td>
<td>108.7±11.3</td>
<td></td>
<td>131.4±15.1</td>
<td>22.7±14.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All BPs are systolic values (mmHg), expressed as mean±SD or mean (95% confidence interval). Nadir-average is defined as the average of the 3 BP readings centered on the lowest nighttime BP. Average 120–0 denotes the average BP of the 2 hours before getting up and 0–120, the average BP of the 2 hours after getting up. BA indicates bedtime administration; BP, blood pressure; MA, morning administration; and MBPS, morning blood pressure surge.

### Table 4. Blood and Urine Results With Morning and Bedtime Administration of Once-Daily Antihypertensive Drugs

<table>
<thead>
<tr>
<th>Biochemical Parameter</th>
<th>n</th>
<th>Morning Administration</th>
<th>Bedtime Administration</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renin, pg/mL</td>
<td>41</td>
<td>28.8 (18.9–43.8)*</td>
<td>40.1 (25.8–62.4)*</td>
<td>0.061</td>
</tr>
<tr>
<td>Angiotensin II, pg/mL</td>
<td>41</td>
<td>9.1 (5.9–14.0)*</td>
<td>10.3 (6.4–16.4)*</td>
<td>0.352</td>
</tr>
<tr>
<td>Aldosterone, pg/mL</td>
<td>41</td>
<td>74.2±65.9</td>
<td>85.6±87.8</td>
<td>0.168</td>
</tr>
<tr>
<td>Arginine vasopressin, pg/mL</td>
<td>41</td>
<td>0.8 (0.6–1.1)*</td>
<td>0.7 (0.5–1.0)*</td>
<td>0.339</td>
</tr>
<tr>
<td>Atrial natriuretic peptide, pg/mL</td>
<td>39</td>
<td>173.3 (140.7–213.5)*</td>
<td>152.6 (124.3–187.3)*</td>
<td>0.123</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>40</td>
<td>1.5 (1.1–2.2)*</td>
<td>1.2 (0.8–1.7)*</td>
<td>0.017</td>
</tr>
<tr>
<td>Fibrinogen, μmol/L</td>
<td>39</td>
<td>10.4±2.4</td>
<td>10.1±2.2</td>
<td>0.153</td>
</tr>
<tr>
<td>E-selectin, ng/mL</td>
<td>41</td>
<td>44.2±20.1</td>
<td>43.7±18.1</td>
<td>0.806</td>
</tr>
<tr>
<td>ICAM, ng/mL</td>
<td>41</td>
<td>218.9±64.4</td>
<td>212.6±65.1</td>
<td>0.154</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>41</td>
<td>85.7±18.9</td>
<td>86.7±20.4</td>
<td>0.406</td>
</tr>
<tr>
<td>eGFR</td>
<td>41</td>
<td>76.8±21.2</td>
<td>75.5±19.8</td>
<td>0.312</td>
</tr>
<tr>
<td>Morning u-alb/creat, mg/g</td>
<td>40</td>
<td>18.5 (11.1–30.7)*</td>
<td>18.2 (11.5–29.0)*</td>
<td>0.852</td>
</tr>
<tr>
<td>Bedtime u-alb/creat, mg/g</td>
<td>40</td>
<td>22.3 (13.2–37.9)*</td>
<td>23.6 (13.7–40.8)*</td>
<td>0.496</td>
</tr>
<tr>
<td>Morning u-alb/creat, mg/g (micro+macroalbuminuria)</td>
<td>14</td>
<td>104.7 (58.8–186.4)*</td>
<td>90.2 (52.9–153.9)*</td>
<td>0.169</td>
</tr>
<tr>
<td>Bedtime u-alb/creat, mg/g (micro+macroalbuminuria)</td>
<td>14</td>
<td>133.5 (78.9–225.7)*</td>
<td>135.3 (73.3–249.8)*</td>
<td>0.940</td>
</tr>
<tr>
<td>Urinary creatinine, mmol/L</td>
<td>41</td>
<td>8.2±3.1</td>
<td>6.6±2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary sodium, mmol/L</td>
<td>41</td>
<td>103.6±41.4</td>
<td>111.1±42.2</td>
<td>0.109</td>
</tr>
<tr>
<td>Urinary sodium/creatinine</td>
<td>41</td>
<td>14.3±6.7</td>
<td>18.8±6.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary potassium, mmol/L</td>
<td>41</td>
<td>35.3±19.4</td>
<td>35.2±16.3</td>
<td>0.979</td>
</tr>
<tr>
<td>Urinary potassium/creatinine</td>
<td>41</td>
<td>4.5±2.1</td>
<td>5.5±2.2</td>
<td>0.013</td>
</tr>
<tr>
<td>Urinary osmolality, mosmol/kg</td>
<td>41</td>
<td>563.5±191.8</td>
<td>509.4±172.2</td>
<td>0.031</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD. eGFR indicates estimated glomerular filtration rate; ICAM, intercellular adhesion molecule; and u-alb/creat, urinary albumin/creatinine.

*Values are expressed as geometric mean (95% confidence interval).
may explain the lack of reduction in urinary albumin excretion. Moreover, the relatively short interventional period of 8 weeks may be important.

The mechanism for the BP effects with chronotherapeutic intervention remains unclear, but changes in pharmacokinetics and pharmacodynamics are pivotal.

We found a significant increase in urinary sodium/creatinine and a reduction in urinary osmolality with BA, which can be interpreted as increased nocturnal natriuresis. This, in combination with the reduced BP during nighttime and early daytime hours, may explain the trend toward increased renin. We speculate that our findings reflect increased effect of bedtime-administered thiazides and renin–angiotensin system inhibitors, suggesting a potential mechanistic explanation of the BP effects with chronotherapeutic intervention.

Currently, BP limits in diabetes mellitus are debated, in part, because of renewed focus on the J-curve. The recently published 2013 European Society of Hypertension/European Society of Cardiology Guidelines for the management of arterial hypertension suggest a new BP target for patients with diabetes mellitus of 140/85 mm Hg, rather than 130/80 mm Hg.

In this context, our intervention of reducing nighttime BP, the time where BP usually is lowest, calls for discussion from a safety point of view. First, it should be emphasized that the mentioned BP target is related to office BP. Ambulatory BP limits for patients with diabetes mellitus are not established. Second, the definition of nocturnal hypertension (SBP >120 mm Hg) is conservative. Previously, a nighttime SBP <115 mm Hg was recommended as optimal. In the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) study (8% of participants with diabetes mellitus), a nighttime SBP <120 mm Hg corresponded to the 10-year CV risk of an office SBP <140 mm Hg, and a nighttime SBP <110 mm Hg corresponded to the risk of office SBP <130 mm Hg. Moreover, a recent study in high-risk patients with type 2 diabetes mellitus reported significantly more CV events for an achieved nighttime SBP ≥120 mm Hg compared with nighttime SBP <110 mm Hg. Interestingly, from the data of the MAPEC study, lower CV risk was found with the progressive reduction in achieved asleep SBP, irrespective of administration time of antihypertensive drugs. Thus, for both dosing regimens CV risk was lowest in patients with achieved asleep SBP <103 mm Hg and significantly higher when >115 mm Hg. No major CV event was registered in patients of either dosing regimen with an achieved asleep SBP <103 mm Hg.

In our study, 2 patients achieved a nighttime SBP <100 mm Hg with BA. In clinical practice, it is recommended to evaluate the effect of change of administration time by performing a new ABPM, thereby allowing for modification of antihypertensive treatment if necessary.

Our study has several strengths. We investigated a daily clinical challenge, nocturnal hypertension, by conducting a randomized crossover study. We ensured that nocturnal hypertension was not a consequence of insufficient antihypertensive treatment by applying specific criteria for daytime BP. In a real life setting, we accepted all classes of antihypertensive drugs, and the time of administration of all of the individual patient’s once-daily antihypertensive drugs was changed. The use of segmented pill containers enhanced compliance and yielded the opportunity to monitor adherence. We meticulously registered time of going to bed in the evening and getting up in the morning as well as time of ingestion of antihypertensive drugs. Finally, the number of nighttime toilet visits was also noted.

Limitations include lack of blinding. However, being a clinical study, accepting all classes of antihypertensive drugs, it was not feasible to use placebo. Moreover, we primarily had biochemical data from morning samples. Samples taken at bedtime could potentially provide important information, especially on levels of renin and urinary sodium.

**Perspectives**

In this study of 41 patients with type 2 diabetes mellitus, we found a significant reduction in both nighttime and, importantly, 24-hour BP with BA of once-daily antihypertensive drugs. To our knowledge, this is the first study to target nocturnal hypertension, thus addressing a specific nighttime BP level at which the intervention can be applied. Despite reduced nighttime BP, BA did not result in increased morning BP surge. Levels of C-reactive protein were significantly lower with BA, which may indicate an effect on low-grade inflammation. Interestingly, the reduced nighttime BP with BA was associated with increased nocturnal natriuresis, suggesting a potential mechanism of the observed effects on BP. In patients with type 2 diabetes mellitus and nocturnal hypertension, administration of once-daily antihypertensive drugs at bedtime may be favorable.

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**Disclosures**

J. Fleischer holds stock in Medicus Engineering. The other authors report no conflicts.

**References**


Novelty and Significance

What Is New?

This is the first study to target nocturnal hypertension, thus addressing a specific nighttime blood pressure (BP) level at which chronotherapeutic intervention can be applied.

What Is Relevant?

We found a significant reduction in both nighttime and 24-hour BP with bedtime administration of once-daily antihypertensive drugs. The latter finding is novel. Moreover, we found an increased nocturnal natriuresis with bedtime administration, suggesting a potential mechanism of the observed effects on BP.

Summary

In this study of 41 patients with type 2 diabetes mellitus and nighttime systolic BP ≥120 mm Hg, we found a significant reduction in both nighttime and, importantly, 24-hour BP with bedtime administration of once-daily antihypertensive drugs. In patients with type 2 diabetes mellitus and nocturnal hypertension, administration of once-daily antihypertensive drugs at bedtime may be favorable.
Targeting Nocturnal Hypertension in Type 2 Diabetes Mellitus
Niklas Blach Rossen, Søren Tang Knudsen, Jesper Fleischer, Anne-Mette Hvas, Eva Ebbehøj, Per Løgstrup Poulsen and Klavs Würgler Hansen

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Running title
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Authors
Niklas Blach Rossen, Søren Tang Knudsen, Jesper Fleischer, Anne-Mette Hvas, Eva Ebbehøj, Per Løgstrup Poulsen, Klavs Würgler Hansen

Corresponding author
Niklas Blach Rossen
Department of Endocrinology and Internal Medicine
Aarhus University Hospital
Tage-Hansens Gade
DK-8000 Aarhus
Denmark
Telephone: +45 78467575
Fax: +45 78462072
E-mail: niklas.rossen@rm.dk
Inclusion, exclusion and withdrawal criteria

Inclusion criteria were (1) type 2 diabetes, (2) age between 30 and 75 years, (3) antihypertensive treatment including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers or direct renin-inhibitors, (4) antihypertensive treatment including at least 1 once-daily drug, (5) all once-daily antihypertensive drugs administered in the morning, (6) antihypertensive treatment unaltered for 8 weeks, (7) nighttime SBP ≥120 mmHg, and (8) daytime SBP fulfilling the following criteria: (a) ≤130 mmHg and minimum one antihypertensive drug, (b) 131-135 mmHg and minimum two antihypertensive drugs, (c) 136-140 mmHg and minimum three antihypertensive drugs, or (d) 141-150 mmHg and minimum four antihypertensive drugs. Type 2 diabetes was defined as (1) diabetes diagnosed at age ≥30 years, (2) no need for insulin within first year of diagnosis, and (3) no episodes of ketoacidosis.

Exclusion criteria were (1) myocardial infarction (MI), stroke or transient cerebral ischemia within 6 months, (2) atrial fibrillation or flutter, (3) known heart failure with EF <45%, (4) drugs with potential impact on BP including nitroglycerin, adrenergic alpha-antagonists (for lower urinary tract symptoms in males), non-steroidal anti-inflammatory drugs or glucocorticoids, or (5) inability to accept ABPM.

Included patients were withdrawn if any of the following occurred: (1) MI, unstable angina pectoris, stroke, transient cerebral ischemia or heart failure, (2) atrial fibrillation or flutter, (3) rise in creatinine >30%, (4) daytime SBP >160 mmHg, (5) any condition, which affected the ability to complete the study.
Figure S1. Graphical presentation of the study

-8 weeks 0 8 weeks 16 weeks

- Confirmation of preliminary inclusion criteria
- Verification of antihypertensive therapy
- ABPM
  Measurement of arterial stiffness and CAN
  Blood and urine sampling
Baseline characteristics

The study population was characterized by a predominance of men and the median age was 65 years. Median diabetes duration was 13 years, glycemic regulation acceptable and lipid levels below recommendations. The majority of patients were normoalbuminuric, with no prior history of ischemic heart disease, stroke, transient cerebral ischemia or peripheral arterial disease. More than half (58.5%) had signs of CAN. All patients were receiving pharmacological antidiabetic treatment and most were in lipid lowering and antithrombotic treatment.

The median number of once-daily antihypertensive drugs was 3 (range 1-6). The number of patients on 1, 2, 3, 4, 5, and 6 once-daily antihypertensive drugs was 1, 13, 12, 9, 5, and 1, respectively.

The median number of all antihypertensive drugs (including twice-daily drugs) was 3 (range 1-6). The number of patients on 1, 2, 3, 4, 5, and 6 antihypertensive drugs was 1, 13, 10, 7, 9, and 1, respectively.