**Abstract**—The aim of our study was to assess the effects of lacidipine, a long-acting calcium antagonist, on 24-hour average blood pressure, blood pressure variability, and baroreflex sensitivity. In 10 mildly to moderately hypertensive patients with type II diabetes mellitus (aged 18 to 65 years), 24-hour ambulatory blood pressure was continuously monitored noninvasively (Portapres device) after a 3-week pretreatment with placebo and a subsequent 4-week once daily lacidipine (4 mg) or placebo treatment (double-blind crossover design). Systolic blood pressure, diastolic blood pressure, and heart rate means were computed each hour for 24 hours (day and night) at the end of each treatment period. Similar assessments were also made for blood pressure and heart rate variability (standard deviation and variation coefficient) and for 24-hour baroreflex sensitivity, which was quantified (1) in the time domain by the slope of the spontaneous sequences characterized by progressive increases or reductions of systolic blood pressure and RR interval and (2) in the frequency domain by the squared ratio of RR interval and systolic blood pressure spectral power at 0.1 and 0.5 Hz over the 24 hours. Compared with placebo, lacidipine reduced the 24-hour, daytime, and nighttime systolic and diastolic blood pressure ($P<0.05$) with no significant change in heart rate. It also reduced 24-hour, daytime, and nighttime standard deviation ($-19.6\%$, $-14.4\%$, and $-24.0\%$, respectively; $P<0.05$) and their variation coefficient. The 24-hour average slope of all sequences ($7.7\pm1.7$ ms/mm Hg) seen during placebo was significantly increased by lacidipine ($8.7\pm1.8$ ms/mm Hg, $P<0.01$), with a significant increase being obtained also for the 24-hour average $\alpha$ coefficient at 0.1 Hz (from $5.7\pm1.5$ to $6.4\pm1.3$ ms/mm Hg, $P<0.01$). Thus, in diabetic hypertensive patients, lacidipine reduced not only 24-hour blood pressure means but also blood pressure variability. This reduction was accompanied by an improvement of baroreflex sensitivity. Computer analysis of beat-to-beat 24-hour noninvasive blood pressure monitoring may offer valuable information about the effects of antihypertensive drugs on hemodynamic and autonomic parameters in daily life. *(Hypertension. 2000;36:622-628.)*

**Key Words:** blood pressure monitoring, ambulatory calcium antagonists hypertension, essential diabetes mellitus baroreflex

**S**everal studies have shown that the organ damage of hypertension is more closely associated with 24-hour average blood pressure (BP) than with the BP obtained in the clinical environment.1,2 They have also shown that in addition to 24-hour average BP, organ damage bears a significant association with 24-hour BP standard deviation (SD), ie, with BP variability (BPV).2–4 This implies that antihypertensive treatment should aim at reducing not only ambulatory mean BP values but also ambulatory BP fluctuations. However, these fluctuations cannot be easily measured in an accurate fashion by available noninvasive techniques, because the intermittent BP sampling, which characterizes commonly used 24-hour automatic ambulatory BP monitoring devices, misses most fast BP changes, thereby providing data of limited accuracy and significance in assessing BPV.5 The above problem can be overcome by beat-to-beat monitoring, which until recently was possible only through intra-arterial recording of BP. However, this approach is difficult to apply in clinical practice because of its invasiveness, particularly when, as requested by studies on antihypertensive treatment, BP recordings have to be performed not just once but both before and during treatment.

An alternative noninvasive approach to continuous BP monitoring has been recently made available (Portapres device).6 We used the Portapres technique to determine the ability of lacidipine, a long-acting dihydropyridine calcium antagonist,7 to reduce 24-hour mean BP and its BPV. We studied diabetic hypertensive patients, because in these patients autonomic dysfunction is a frequent complication, which may contribute to an increased BPV. Despite the limitations above, the effect of lacidipine on BPV may provide valuable information about the vasodilator properties of this drug.


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evidence that a pronounced BP reduction by treatment is particularly beneficial in hypertensives with diabetes, the information on the possibility of also reducing BPV is limited. We estimated baroreflex function throughout the day and night because BRS is an important determinant of the magnitude of BP fluctuations in daily life.

Methods

Subjects

The present study was performed in 10 mildly to moderately hypertensive outpatients (7 men and 3 women) with type II diabetes mellitus. Although the duration of diabetes and hypertension is always difficult to assess precisely, both conditions had been present in these patients for at least a few years. The selection criteria were (1) grade 1 to 2 essential hypertension (diastolic BP [DBP] ≥90 and ≤110 mm Hg, systolic BP [SBP] ≥160 and ≤200 mm Hg without complications), (2) age ≥18 and ≤65 years, (3) type II diabetes mellitus, and (4) body mass index ≤30 kg/m² for men and ≤20 kg/m² for women. Patients were excluded from the study if they had any major disease besides diabetes and/or clinical manifestations of cardiac or vascular disease. Microalbuminuria was present in 50% of the patients, who had, on the other hand, no significant retinopathy (grade III and IV of the Keith-Wagener classification) or neuropathy. All patients had received oral antidiabetic and antihypertensive drugs, but antihypertensive treatment was withdrawn 3 weeks before the administration of lacidipine or placebo (see below). The demographic and blood chemistry data of the patients recruited for the present study are shown in Table 1. Fasting plasma glucose levels were, on average, within normal limits, whereas glycated hemoglobin was slightly abnormal in most patients. All subjects gave their informed consent to the study. The study protocol was approved by the local ethics committee.

Ambulatory BP and Heart Rate Monitoring

Beat-to-beat BP was monitored noninvasively through the Portapres model 2 device (TNO-TPD, Biomedical Instrumentation), which is based on the arterial volume clamp method of Peñaz (Wesseling et al^10). It measures BP through 2 small cuffs wrapped around the middle and ring fingers of one hand; the fingers are used alternatively at 30-minute intervals to avoid the discomfort associated with prolonged measurements from one finger only. The Portapres device also includes a system capable of automatically correcting for changes (with a 2-second time constant) in finger BP induced by modifications in the hydrostatic height difference between the heart and the instrumented finger that are due to hand displacements during the activities of daily life. These changes are further minimized by instructing the subjects to refrain from unnecessary movements of the equipped arm and hand. The height-corrected finger BP and the hydrostatic height signal are all stored on a flash memory device. The cuff pressures were automatically converted into real-time arterial BP readings by means of the arterial volume clamp method of Peñaz (Wesseling et al^10). The cuff pressures were automatically converted into real-time arterial BP readings by means of the arterial volume clamp method of Peñaz (Wesseling et al^10).

![Figure 1. Twenty-four–hour profiles of SBP (top), DBP (middle), and HR (bottom) for 10 hypertensive diabetic patients. Data are shown as mean ± SEM hourly values. ○ indicates placebo data; ●, lacidipine data.]
memory card. The microprocessor, the electronic pump, the memory card, and the battery package are all included in a soft belt bound to the patient’s waist. Although analysis of finger BP tracings leads to some overestimation of SBP variability, compared with data obtained invasively from more proximal arteries, such an overestimation is constant with time and at different BP levels, and it does not affect comparisons between recordings performed at different periods with or without antihypertensive treatment.

**Protocol**
The present study was performed in a single center and had a double-blind, placebo-controlled, randomized crossover design. All patients were subjected to a careful clinical history and physical examination. The eligible patients first entered a single-blind 3-week run-in period with placebo, followed by either lacidipine (4 mg) or placebo once daily for 4 weeks. The treatment was then switched for another 4 weeks. BP was measured in the sitting position with a mercury sphygmomanometer, and heart rate (HR) was measured from the radial pulse for 30 seconds. Each patient was given an appropriate number of placebo tablets to cover the whole run-in period (21 ± 2 days) and thereafter was visited a second time to obtain a blood sample (for measurement of fasting serum glucose plus collection of routine biochemical and hematological data) and a urine sample (for urinalysis). Patients were hospitalized in the...
morni...ng and instrumented with the Portapres device (see below), which began its recording around noon, after the administration of lacidipine or placebo. This procedure was repeated at the end of the run-in period and at the end of the first and second 4-week treatment periods. During the 24-hour Portapres recordings, patients were free to move within the hospital area, attending to their usual activities. Some activities were standardized more strictly; eg, the patients were asked to be in bed for the medical visit, the afternoon siesta, and at night (from 10:00 PM to 7:00 AM) and to have meals at the regular hospital times.

### Data Analysis

The 24-hour Portapres recording was analyzed offline, with the analog signals sampled at 168-Hz real time and analog-to-digital conversion carried out with a 0.25 mm Hg resolution by dedicated software (FAST package, TNO-TPD, Biomedical Instrumentation). SBP and DBP values were derived from each single pulse wave. HR was computed from consecutive pulse waves. BP and HR data were visually scanned and edited for artifacts by an interactive procedure. Editing included the recorded segments containing the automatic calibration signal, which were removed from the tracings. In each subject, mean±SD values for SBP, DBP, and HR were computed for each half hour of the recording and then averaged over the entire 24 hours, daily (from 7:00 AM to 10:00 PM), and nightly (from 10:00 PM to 7:00 AM) and for each hourly subperiod. The SD and the variation coefficient (VC) of the mean values (SD divided by the mean multiplied by 100) were taken, respectively, as measures of absolute and normalized short-term variability of the signals.

BRS was assessed by time-domain and frequency-domain methods for the evaluation of spontaneous baroreflex control of HR; these methods have been validated and described in detail previously. Both these methods are based on the computerized analysis of spontaneous fluctuations in SBP and of the associated reflex fluctuations in pulse interval (PI, the reciprocal of HR), with no need of any external intervention on the patient. Briefly, the time-domain method consisted of computer scanning of the SBP tracing to identify sequences of ≥4 consecutive beats characterized by (1) a progressive increase in SBP and a linearly related increase in PI (+PI/ SBP) (correlation coefficient, r=0.85) or (2) a progressive reduction in SBP and linearly related decrease in PI (−PI/ SBP) (r=0.85). The combined number of the +PI/ SBP and −PI/ SBP sequences was calculated for the entire 24 hours, the day and night subperiods, and each hour of the recording. The slope of the regression line between PI and SBP values within each sequence was taken as an index of BRS and averaged over the 24 hours, the day and night subperiods, and each recording hour.

The frequency-domain measure of BRS was obtained from stationary SBP and PI signal segments of 512 beats characterized by a coherence value >0.5 between SBP and PI spectral powers in the frequency ranges from 0.04 to 0.15 Hz (midfrequency [MF]) and from 0.16 to 0.5 Hz (high frequency [HF]), by calculating for these segments the squared ratios between PI and SBP powers. These were called the MF and HF α coefficients and taken as indices of BRS in the frequency domain. As with the sequence method, for each subject, average values for the MF and HF α coefficients were computed for the whole 24-hour period, daily, and nightly and for each recording hour.

### Statistical Analysis

From individual averages, we obtained means for the group that were statistically analyzed in 3 different ways: (1) by comparing the 2 placebo periods to determine whether there was any effect of time per se on BP and HR; (2) after the evidence that this was not the case (see Results), by comparing the average of the 2 placebo periods with the treatment period; and (3) by comparing the treatment period separately with either placebo period, with special emphasis on the second period (ie, after randomization) to eliminate from the treatment effect whatever small and insignificant time-treatment interaction might have occurred. Comparison between placebo and lacidipine data were made by both the Student t test for paired observations and by ANOVA for repeated measurements. Given the nonnormal distribution of SD values, the statistical significance of data obtained for lacidipine and placebo was assessed by the Wilcoxon signed rank test. A value of P<0.05 was taken as the level of statistical significance. The ±SEM values in the Figures refer to the between-subject standard error of the mean.

### Results

The 24-hour averages of the SBP, DBP, and HR values obtained for the 10 diabetic hypertensive patients in the present study were not significantly different for the 2 placebo periods, ie, the one before and the one after randomization. As shown in Figure 1, the 24-hour BP profiles (average of the 2 placebo periods) shared a marked between-hour variability in daytime SBP and DBP, with some BP reduction at night with respect to daytime values. SBP and DBP for lacidipine displayed a similar 24-hour profile, but values were in most instances lower than those seen during the placebo period. Twenty-four hour, daytime, and nighttime SBP and DBP values were all significantly less for lacidipine than for placebo (Figure 2). HR also showed some reduction for nighttime compared with daytime values, but these values were not significantly and consistently different for placebo and lacidipine (Figures 1 and 2). Figure 3 shows the variability data. For placebo (average of 2 placebo periods), the SD was greater for SBP than for DBP. For 24-hour, daytime, and nighttime placebo data, the SD values for SBP were similar, and the SD values for DBP were similar. This was also the case for lacidipine, which was characterized, however, by significantly lower SD values for SBP, although not for DBP, throughout. The VC for SBP was also always slightly lower for lacidipine than for placebo. On the other hand, SD and VC

### Table 2. Comparison Between Data Obtained for Lacidipine and During Second Placebo Period

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Lacidipine</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP average, mm Hg</td>
<td>146.0</td>
<td>138.1</td>
<td>0.05</td>
</tr>
<tr>
<td>SBP SD, mm Hg</td>
<td>23.0</td>
<td>16.0</td>
<td>0.05</td>
</tr>
<tr>
<td>DBP average, mm Hg</td>
<td>76.5</td>
<td>69.9</td>
<td>0.05</td>
</tr>
<tr>
<td>DBP SD, mm Hg</td>
<td>12.3</td>
<td>11.5</td>
<td>NS</td>
</tr>
<tr>
<td>HR average, bpm</td>
<td>72.9</td>
<td>71.2</td>
<td>NS</td>
</tr>
<tr>
<td>HR SD, bpm</td>
<td>11.1</td>
<td>12.1</td>
<td>NS</td>
</tr>
<tr>
<td>Daytime values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP average, mm Hg</td>
<td>151.4</td>
<td>146.4</td>
<td>0.05</td>
</tr>
<tr>
<td>SBP SD, mm Hg</td>
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<td>17.9</td>
<td>0.05</td>
</tr>
<tr>
<td>DBP average, mm Hg</td>
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<td>74.2</td>
<td>0.05</td>
</tr>
<tr>
<td>DBP SD, mm Hg</td>
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<td>10.5</td>
<td>NS</td>
</tr>
<tr>
<td>HR average, bpm</td>
<td>75.1</td>
<td>72.1</td>
<td>NS</td>
</tr>
<tr>
<td>HR SD, bpm</td>
<td>12.1</td>
<td>10.3</td>
<td>NS</td>
</tr>
<tr>
<td>Nighttime values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP average, mm Hg</td>
<td>136.1</td>
<td>132.2</td>
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<tr>
<td>SBP SD, mm Hg</td>
<td>23.0</td>
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<tr>
<td>DBP average, mm Hg</td>
<td>74.4</td>
<td>66.4</td>
<td>0.05</td>
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<tr>
<td>DBP SD, mm Hg</td>
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<td>12.1</td>
<td>NS</td>
</tr>
<tr>
<td>HR average, bpm</td>
<td>68.4</td>
<td>65.8</td>
<td>NS</td>
</tr>
<tr>
<td>HR SD, bpm</td>
<td>8.9</td>
<td>11.5</td>
<td>0.05</td>
</tr>
</tbody>
</table>
values for HR were similar for the 2 conditions, with the exception of the nighttime values, for which both were significantly greater for lacidipine than for placebo. The lower ambulatory BP mean values and variability for lacidipine than for placebo were also apparent when comparisons were made between the active treatment and the second placebo period (ie, the placebo period after randomization) (Table 2). Figure 4 shows the baroreflex data obtained by the time-domain and frequency-domain analysis of the 24-hour SBP and PI signals. The number of PI/SBP sequences identified over the 24 hours was significantly greater for lacidipine than for placebo (average of 2 periods) and so was the average 24-hour regression coefficient (or slope) of the sequences (Figure 4, top panels). The number of segments showing a high coherence between PI and SBP powers was similar for the 2 conditions, both in the MF and in the HF band. The \( \alpha \) coefficient of the HF band was similar for placebo and lacidipine, whereas the \( \alpha \) coefficient of the MF band was greater for lacidipine than for placebo. The increases in the slope of the PI/SBP sequences and in the \( \alpha \) coefficient of the MF band for lacidipine were more evident during the nighttime (Figure 5).

Discussion
In the present study, the ability of lacidipine at the once-a-day dose of 4 mg to lower 24-hour BP in hypertensive patients with type II diabetes was investigated by means of a technique that allows beat-to-beat noninvasive ambulatory BP monitoring to be obtained. The results show that (1) SBP and DBP values were significantly less for lacidipine than for placebo throughout the 24 hours, (2) the BP reduction was accompanied by a reduction in 24-hour SBP SD and VC, and (3) the above 2 effects were associated with no tachycardia. Thus, we can conclude that in hypertensive patients with diabetes, once-a-day lacidipine effectively lowers daytime and nighttime BP. We can also conclude that this reduction is not accompanied by an increase in HR, as is sometimes seen with a vasodilator, also belonging to the dihydropyridine class. We can finally conclude that SBP variability in diabetic hypertensive individuals is also reduced by this drug. Given
the association between BP variability and hypertension-related organ damage,\(^2\)–\(^4\) this reduction may be regarded as an additional potential benefit of this type of treatment.

The present study was not designed for and therefore cannot explain the mechanisms responsible for the reduction in BP variability induced by lacidipine in diabetic hypertensive patients. However, it is tempting to relate this effect to the increase in BRS induced by the drug, because previous studies have shown that the magnitude of hourly BP fluctuations is inversely related to the hourly BRS.\(^9\),\(^16\) We can speculate that the enhancing effect of lacidipine on BRS takes place because this drug (because of its high lipophilicity\(^7\)) acts on the structures that centrally integrate the baroreflex arch, as has been suggested in relation to the enhancing effect on the baroreflex of agents with a more clearly documented central influence, such as \(\beta\)-blockers and rilmenidine.\(^17\),\(^18\)

However, it is also possible that lacidipine increases large-artery distensibility through the relaxation of contracted (and thus stiffer) vascular muscles,\(^19\) thereby increasing the baroreceptor responsiveness to sudden BP changes. Finally, it is possible that to some extent the increased arterial distensibility is brought about by the reduction in BP per se, because large-artery distensibility is related to BP in an inverse curvilinear fashion.\(^19\)

In previous studies, 24-hour ambulatory BP profiles of untreated and treated patients with diabetic hypertension were obtained through automatic devices that sample BP only intermittently. However, intermittent sampling does not reliably record BP variations, which can be particularly pronounced in diabetics. In this context, our beat-to-beat ambulatory BP results provide 2 sets of novel data of some interest: (1) Patients with diabetic hypertension can indeed be characterized by increased values of hourly BP SDs and between-hour average BP differences, ie, by an increase in 24-hour BP variability that, compared with the SD found in patients with essential hypertension on beat-to-beat BP monitoring,\(^20\) may amount to >50% (+66.6% and +50.1% SD for SBP and DBP, respectively). (2) In patients with diabetic hypertension with no clinical evidence of autonomic dysfunction (see inclusion criteria) compared with patients with essential hypertension, the magnitude of nocturnal hypotension may already be somewhat blunted. In particular, there may be a clear-cut blunting of the marked reductions in BPV and HRV that normally occur at night (≈50%) but occurred to a much lesser extent in our patients. This supports previous evidence that alterations in autonomic cardiovascular modulation can occur before disclosure by traditional laboratory tests.\(^21\) That diabetic patients may have an autonomic impairment earlier than is commonly believed is further supported by the observation that in our patients the number and the slope of events in which HR was modulated by the baroreflex were, over the 24 hours, less than those observed in healthy subjects,\(^11\) indicating an early dysfunction of spontaneous reflex cardiac control.

Because no other studies have been performed on the effects of antihypertensive treatment on the beat-to-beat ambulatory BP of diabetic patients, the effects of lacidipine shown in the present study cannot be compared with those of other agents. However, this will be made possible in the future if the important advantages of the Portapres technique over both automatic BP (ie, beat-to-beat recording) and intra-arterial monitoring (ie, lack of invasiveness) make this approach more widely used in clinical pharmacological studies and in studies addressing the effect of antihypertensive drugs on the mechanisms involved in cardiovascular regulation.

References


Figure 5. Twenty-four-hour BRS profile. Data are shown as mean±SEM hourly values of sequence slope (slopes of \(\pm PI/\pm SBP\) and \(-PI/-SBP\) sequences are pooled, top) and \(\alpha\) coefficient for spectral powers \(<0.1\) Hz (MF, bottom) in a representative subject. ○ indicates placebo data; ●, lacidipine data. \(^*\)P<0.05 for difference between placebo and lacidipine.


Lacidipine and Blood Pressure Variability in Diabetic Hypertensive Patients
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