Circadian Rhythms of Blood Pressure After Liver Transplantation

Philippe van de Borne, Michel Gelin, Jean Van de Stadt, and Jean-Paul Degaute

Twenty-four-hour systolic blood pressure, diastolic blood pressure, and heart rate profiles were recorded in 17 liver-transplanted patients by noninvasive ambulatory monitoring and were analyzed with the periodogram method. These recordings were compared with those of control subjects matched for age, sex, and daytime ambulatory blood pressure. Abnormal blood pressure patterns were found in seven of the 17 patients, whereas the other 10 patients had circadian blood pressure profiles that were not different from those of control subjects. These two groups of liver-transplanted patients did not differ in age, sex, oral dose of cyclosporine, specific serum cyclosporine level, and proportion of patients receiving azathioprine and antihypertensive medications. In contrast, the daily oral dose of prednisolone was significantly higher ($p<0.001$) in the seven patients with abnormal circadian blood pressure patterns. Moreover, only the daily oral dose of prednisolone was inversely correlated with the magnitude of the nighttime systolic and diastolic blood pressure decrease ($r=−0.64$ and $r=−0.66$, $p<0.01$). In contrast to blood pressure, patients and control subjects had similar circadian heart rate variations. We conclude that exogenous glucocorticoid administration may have a dose-dependent effect on the nighttime blood pressure fall and may play an important role in the pathogenesis of the abnormal circadian blood pressure profiles observed in liver-transplanted patients. (Hypertension 1993;21:398–405)

**KEY WORDS** • circadian rhythm • blood pressure • heart rate • liver transplantation

**Methods**

**Subjects**

Liver-transplanted patients. Seventeen LTX patients (11 men, six women) aged 46±3 years (mean±SEM) were included in the study. All LTX patients were ambulatory outpatients and were studied at least 1 week after being discharged from the hospital. None suffered from diabetes mellitus. They were free of clinical or biological signs of rejection at the time of the study. All were physically active during the daytime, and all had a regular sleep-wake schedule. The indication for transplantation was posthepatic cirrhosis ($n=9$), alveolar echinococcosis ($n=1$), neoplasia ($n=2$), alcoholic cirrhosis ($n=3$), α-antitrypsin deficiency ($n=1$), and primary biliary cirrhosis ($n=1$).

Mean time after transplantation was 19±5 months (mean±SEM; range, 1–55 months). Immunosuppression consisted of a combination of cyclosporine and prednisolone. Nine patients were further immunosuppressed with azathioprine, and five patients received antihypertensive medications (captopril, lisinopril, nifedipine, indapamide, or bisoprolol). Before the ambulatory blood pressure recordings were started, the LTX patients underwent a routine physical examination including body weight measurements and serum chemistry. Determination of whole-blood cyclosporine levels was performed by a specific monoclonal radiolmmunoassay for the parent drug, which is unaffected by assay temperature or hematocrit and avoids the measurement of cyclosporine metabolites.

**Control subjects.** The control group consisted of 17 uncomplicated outpatients (11 men, six women; mean age±SEM, 49±3 years) referred to the hypertension

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clinic for a suspected diagnosis of high blood pressure. They were carefully matched to the LTX patients for sex, age, and daytime ambulatory BP values. All underwent a routine physical examination and routine serum chemistry. All were untreated, were physically active during the daytime, and had a regular sleep-wake schedule.

Protocol

The protocol was approved by the Ethics Committee of our institution. Informed consent was obtained from all patients. Ambulatory systolic BP (SBP), diastolic BP (DBP), and HR were recorded every 10 minutes for 25 hours in all individuals with a noninvasive ambulatory BP monitor (TM-2420, A&D Co. Ltd., Tokyo) yielding up to 150 consecutive measurements.

The cuff was placed on the nondominant arm (i.e., left arm for right-handed subjects and right arm for left-handed subjects), and all subjects were asked to keep their arm immobile during each cuff deflation. All kept a diary in which they carefully noted daytime activities, the time they went to bed, the quality of their sleep, and the time they woke up. The accuracy of our devices was checked in 74 subjects before the study was started by concomitant casual BP auscultations with a T device used and a calibrated mercury sphygmomanometer. The differences between the two concomitant measurements were $-2 \pm 5.6$ mm Hg (mean±SD) for SBP and $-2 \pm 7.6$ mm Hg (mean±SD) for DBP. Furthermore, the agreement of the SBP/DBP readings between the TM-2420 monitor and the mercury column determinations were, respectively, within 5 and 10 mm Hg for 79%/70% and for 95%/92% of the recordings (a result that could correspond to a B grade of the British Hypertension Society guidelines).

Statistical Analysis

For all ambulatory BP recordings, the first hour of measurement was not included in the analysis to eliminate possible artifacts related to the beginning of the experiment. All measurements corresponding to a pulse pressure of less than 15 mm Hg or which represented an isolated increase of more than 50% over the previous measurement were considered to be technical artifacts and were deleted from the data set. Deleted data points were replaced by linear interpolations between the previous and following measurements. The subject was not included in the study if, because of technical failure, 1 hour or more of recording was missing.

Great care was taken in the study protocol to ensure that the quality of the ambulatory BP recording was similar in the LTX patients and control subjects and that the percentage of invalid data (missing plus deleted data) was not different between LTX patients and control subjects (mean±SEM, $11 \pm 2\%$ versus $9 \pm 2\%$, respectively).

For each SBP, DBP, and HR profile, the 24-hour mean level was calculated as the mean of all measurements obtained during the 24-hour study period. The nighttime mean was defined as the mean of all measurements obtained from the time of going to bed to the time of awakening. The daytime mean was defined as the mean of all other measurements.

For each individual SBP, DBP, and HR profile, the overall 24-hour variation was quantified by building a best-fit curve based on periodogram calculations, a statistical methodology fully described elsewhere. This procedure provides a quantitative description of the long-term trends of the profiles independently of sporadic short-term variations. Briefly, the periodogram method consists of fitting a sum of sinusoid functions to the series of data and selecting those that contribute significantly to the observed variation. The components found significant with a minimum probability level of 95% are summed to build the best-fit curve. Because the method aims at describing slow-varying properties of the profile, only significant components with periods longer than 6 hours are retained for inclusion in the best-fit curve. As a consequence, the model underlying the method has a maximum of seven independent parameters, and the best-fit pattern can be unimodal, bimodal (Figure 1), or trimodal. The acrophases and nadirs are, respectively, the times of occurrence of maxima and minima in the best-fit curve. The amplitude of the best-fit curve is defined as 50% of the difference between its maximum and its minimum and may be expressed in absolute measurement units (i.e., millimeters of mercury or beats per minute; absolute amplitude) or as a percentage of the 24-hour mean level (relative amplitude). The level of an acrophase or nadir is defined as the level of the best-fit curve at the time of occurrence of the acrophase or nadir.

The value and timing of the major acrophase or major nadir correspond to those of the unique acrophase or nadir in the unimodal profiles. In the bimodal or trimodal profiles, the value and timing of the major acrophase or major nadir correspond to those of the highest acrophase or lowest nadir, or, if the acrophases or nadirs are of similar amplitude, to the mean of their values and timings.

An extensive quantitative analysis of the 24-hour BP and HR profiles in normal men demonstrated that the
normal circadian pattern was characterized by two
daytime acrophases and a major nighttime nadir.

Further statistical evaluation was done using paired
or unpaired two-tailed Student's t tests when appropri-
ate and χ² tests with Yates's correction.17

Differences in the characteristics of the circadian BP
and HR rhythms between subgroups of LTX patients
and control subjects were analyzed by analysis of vari-
ance (ANOVA). Pairwise contrasts were tested with the
Scheffé F test.18 Correlations were estimated with the
Pearson coefficient. Results were considered significant
at a value of p<0.05. All results are expressed as
mean±SEM.

Results

All individuals reported a normal day-night schedule
with usual daytime physical activities (walking, shop-
ing, social contacts), and no individuals complained of
poor sleep quality.

Blood Pressure

As a consequence of the matching procedure, the
daytime ambulatory SBP and DBP were similar in the
LTX patients and control subjects (SBP, 139±3 versus
136±3 mm Hg; DBP, 88±3 versus 88±2 mm Hg, re-
spectively). However, the nighttime SBP and DBP were
higher in the LTX patients than in the control subjects
(SBP, 134±5 versus 112±3 mm Hg, p<0.001; DBP,
81±3 versus 70±3 mm Hg, p<0.05), and consequently,
the day–night difference in SBP and DBP levels was
reduced in the LTX patients when compared with the
control subjects (SBP, 5±4 versus 24±2 mm Hg,
p<0.001; DBP, 8±3 versus 17±2 mm Hg, p<0.05) (see
top panels of Figure 2).

Based on the timings of the major SBP and DBP
acrophases and nadirs, periodogram analysis identified
two clear-cut nonoverlapping subgroups of 24-hour BP
profiles in the LTX patients (Tables 1 and 2, Figure 3).
All subjects in the first group (group A, n=10) had
normal timings of the major SBP and DBP acrophases
and nadirs, and all subjects in the second group (group
B, n=7) had inverted SBP and DBP profiles (major
daytime nadir and major nocturnal acrophase). As
shown by the ranges of the timings of the major SBP
and DBP acrophases and nadirs, the group A and B patients
consisted of two distinct subgroups of patients (Tables 1
and 2), and the major BP acrophases and nadirs oc-
curred, respectively, around 15:00 and 03:00 in both
LTX A patients and control subjects. In contrast, the
major BP acrophases and nadirs occurred, respectively,
around 03:30 and 16:30 in the LTX B patients.

The group A patients and control subjects presented
a nighttime decrease in SBP (p<0.001) and DBP
(p<0.001) (left panel of Figure 3 and top left panel of
Figure 2, respectively). In contrast, the group B patients
presented a nighttime increase in SBP (p<0.05) and a
slight, but not significant, increase in the nighttime DBP
(right panel of Figure 3). Furthermore, the group B
patients presented an increased nighttime pulse pres-

ANOVA failed to demonstrate any significant differ-
ences in the characteristics of the circadian BP varia-
TABLE 1. Quantitative Characteristics of 24-Hour Systolic Blood Pressure Variations in Control Subjects and in Group A and B Liver-Transplanted Patients

<table>
<thead>
<tr>
<th>Characteristics of SBP rhythms</th>
<th>Control (n=17)</th>
<th>LTX A (n=10)</th>
<th>LTX B (n=7)</th>
<th>ANOVA</th>
<th>Control/ LTX A</th>
<th>Control+ LTX A/LTX B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime mean level (mm Hg)</td>
<td>136±3</td>
<td>143±4</td>
<td>135±5</td>
<td>0.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nighttime mean level (mm Hg)</td>
<td>112±3</td>
<td>127±5</td>
<td>145±9</td>
<td>0.0002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplitude</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute (mm Hg)</td>
<td>19±2</td>
<td>15±2</td>
<td>14±2</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (%)</td>
<td>15±1</td>
<td>11±2</td>
<td>10±1</td>
<td>0.093</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major acrophase clock time</td>
<td>15:20±00:14</td>
<td>14:10±00:37</td>
<td>03:28±01:22</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Value of major acrophase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute (mm Hg)</td>
<td>142±3</td>
<td>148±4</td>
<td>153±8</td>
<td>0.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (%)</td>
<td>111±1</td>
<td>110±2</td>
<td>111±2</td>
<td>0.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major nadir clock time</td>
<td>03:42±00:15</td>
<td>02:21±00:37</td>
<td>15:49±02:00</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Value of major nadir</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute (mm Hg)</td>
<td>107±3</td>
<td>121±5</td>
<td>125±6</td>
<td>0.014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (%)</td>
<td>84±2</td>
<td>89±2</td>
<td>91±1</td>
<td>0.023</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime pulse pressure (mm Hg)</td>
<td>49±2</td>
<td>51±3</td>
<td>52±5</td>
<td>0.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nighttime pulse pressure (mm Hg)</td>
<td>42±2</td>
<td>49±4</td>
<td>60±8</td>
<td>0.0059</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; LTX, liver-transplanted patients; ANOVA, analysis of variance; NS, pairwise contrast not significant at p<0.05.

TABLE 2. Quantitative Characteristics of 24-Hour Diastolic Blood Pressure Variations in Control Subjects and in Group A and B Liver-Transplanted Patients

<table>
<thead>
<tr>
<th>Characteristics of DBP rhythms</th>
<th>Control (n=17)</th>
<th>LTX A (n=10)</th>
<th>LTX B (n=7)</th>
<th>ANOVA</th>
<th>Control/ LTX A</th>
<th>Control+ LTX A/LTX B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime mean level (mm Hg)</td>
<td>88±2</td>
<td>92±4</td>
<td>83±2</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nighttime mean level (mm Hg)</td>
<td>70±3</td>
<td>78±5</td>
<td>85±3</td>
<td>0.037</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplitude</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute (mm Hg)</td>
<td>13±1</td>
<td>12±2</td>
<td>7±3</td>
<td>0.092</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent of mean</td>
<td>16±1</td>
<td>15±3</td>
<td>9±3</td>
<td>0.084</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major acrophase clock time</td>
<td>14:56±00:18</td>
<td>14:06±00:34</td>
<td>03:45±02:43</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>11:50-16:50</td>
<td>10:30-16:10</td>
<td>22:20-08:40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Value of major acrophase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute (mm Hg)</td>
<td>92±3</td>
<td>97±5</td>
<td>95±4</td>
<td>0.59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent of mean</td>
<td>113±1</td>
<td>113±2</td>
<td>115±3</td>
<td>0.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major nadir clock time</td>
<td>03:11±00:20</td>
<td>02:03±00:26</td>
<td>16:20±02:39</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>23:50-05:10</td>
<td>23:20-03:10</td>
<td>09:20-20:40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Value of major nadir</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute (mm Hg)</td>
<td>67±3</td>
<td>72±6</td>
<td>71±2</td>
<td>0.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent of mean</td>
<td>82±2</td>
<td>82±3</td>
<td>85±2</td>
<td>0.76</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DBP, diastolic blood pressure; LTX, liver-transplanted patients; ANOVA, analysis of variance; NS, pairwise contrast not significant at p<0.05.

As shown in Table 3, the group A and group B patients did not differ significantly in age, sex, oral dose of cyclosporine, whole-blood specific serum cyclosporine, proportion of patients receiving antihypertensive medications, proportion of patients receiving azathioprine, and renal function. The difference in the time elapsed since the most recent illness in the two groups of patients (i.e., surgical intervention or, if more recent, time elapsed since the last rejection episode) just failed to reach significance (LTX A, 22±6 months; LTX B, 5±3 months; p=0.06). In contrast, the daily oral dose of prednisolone was 0.14±0.02 mg/kg body wt in the group A patients and 0.28±0.03 mg/kg body wt in the group B patients (p<0.001).

The differences between daytime and nighttime SBP and DBP were inversely correlated with the daily oral dose of prednisolone in the 17 LTX patients (SBP, r=-0.64; DBP, r=-0.66; p<0.01; Figure 4). These...
correlations remained significant when the analysis was restricted to the patients receiving no antihypertensive therapy (SBP, \( r = -0.66; \) DBP, \( r = -0.60; \) \( p < 0.05, n = 12 \)).

No correlations were found between oral dose of cyclosporine, whole-blood specific cyclosporine level, oral dose of azathioprine, time elapsed since the most recent illness, and the magnitude of the nighttime decrease in SBP and DBP in the LTX patients.

**Heart Rate**

The LTX patients and control subjects had similar daytime HR values (81±3 versus 78±2 beats per minute, respectively) and nighttime HR values (69±3 versus 66±2 beats per minute, respectively) (bottom panels of Figure 2). No differences were found between the LTX patients and control subjects when daytime and nighttime HR variability was expressed in terms of variation coefficient (VC LTX/control, 13.5±2% versus 12.7±1% [daytime]; VC LTX/control, 9.8±1% versus 9.6±1% [nighttime]).

Furthermore, ANOVA did not reveal any significant differences in the characteristics of the circadian HR rhythm between LTX A patients, LTX B patients, and control subjects (Table 4). The mean daytime and nighttime HR levels were not different. The nighttime decrease in HR (LTX A, 11±4 beats per minute; LTX B, 15±4 beats per minute; control, 13±1 beats per minute; ANOVA: \( p = 0.73 \)) and even the daytime (VC LTX A, 15.2±3%; VC LTX B, 11.1±2%; VC control, 13±1%; ANOVA: \( p = 0.33 \)) and nighttime (VC LTX A, 9.6±0.8%; VC LTX B, 9.8±0.9%; VC control, 9.7±1.6%; ANOVA: \( p = 0.99 \)) HR variability as estimated by the coefficient of variation did not differ.

**Discussion**

In this study, the quantitative characteristics of the 24-hour BP and HR profiles of 17 LTX patients were compared with those observed in 17 control subjects matched for age, sex, and daytime ambulatory BP. To our knowledge, circadian BP and HR profiles have not been previously investigated in LTX patients. The analysis revealed that almost 40% of these patients showed a paradoxical nighttime increase in SBP and DBP.

Some methodological issues about our data deserve discussion. First, to improve the quality of matching for daytime BP, the LTX patients and control subjects were matched for daytime ambulatory BP instead of isolated casual BP readings. Second, although the evaluation of the accuracy of the Takeda recorder has given conflicting results,\(^{19-21}\) the reliability checks of our recorders produced similar results of good accuracy as those reported by White et al\(^{20}\) and Clark et al.\(^{21}\) Moreover, the comparative analysis presented in this study is primarily based on characteristics of the long-term trends of the profiles, which are independent of absolute BP values (i.e., relative amplitude, timings of nadirs and acrophases). Third, in this study, as in the study of Reeves et al,\(^{3}\) antihypertensive medications were not withdrawn for ethical reasons. It is noteworthy that previous studies have consistently shown that various antihypertensive treatments do not significantly affect the major relative characteristics of the 24-hour BP profiles.\(^{2}\) Furthermore, the conclusions of our study hold when LTX patients receiving antihypertensive

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**TABLE 3. Group A and B Liver-Transplanted Patient Characteristics**

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>LTX A (n=10)</th>
<th>LTX B (n=7)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44±3</td>
<td>50±4</td>
<td>0.23</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>6/4</td>
<td>5/2</td>
<td>0.98*</td>
</tr>
<tr>
<td>Number of patients receiving:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive medications</td>
<td>3</td>
<td>2</td>
<td>0.63*</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>3</td>
<td>6</td>
<td>0.077*</td>
</tr>
<tr>
<td>Oral dose of cyclosporine (mg/kg body wt)</td>
<td>3.4±0.4</td>
<td>3.5±0.5</td>
<td>0.86</td>
</tr>
<tr>
<td>Whole-blood specific cyclosporine (ng/mL)</td>
<td>150±3</td>
<td>126±22</td>
<td>0.35</td>
</tr>
<tr>
<td>Oral dose of prednisolone (mg/kg body wt)</td>
<td>0.14±0.02</td>
<td>0.28±0.03</td>
<td>0.0007</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.3±0.1</td>
<td>1.4±0.1</td>
<td>0.48</td>
</tr>
</tbody>
</table>

LTX, liver-transplanted patient.\(^*\)\(^2\) test; otherwise, Student's \( t \) test.
medications are excluded. Fourth, because it is well known that in continuously recumbent subjects the nighttime BP fall is reduced in amplitude,22-23 none of the LTX patients was investigated shortly after transplantation, and no BP recording was performed in the hospital setting.

Blunted or even inverted 24-hour BP profiles have been reported in cardiac-transplanted patients,3,4 and these authors suggested that the force-fed pump characteristics of the denervated heart together with salt and water retention induced by cyclosporine therapy might contribute to the abnormal BP profiles presented by these patients.

In contrast, the new finding of our study is the presence of abnormal BP profiles in organ-transplanted patients without surgically denervated hearts and with normal circadian HR variations. Although all transplanted patients were ambulatory outpatients with a normal day-night schedule, a clear-cut difference in the circadian BP profiles could be evidenced, allowing for the identification of two distinct subgroups of patients that differed only by the daily oral prednisolone intake. Furthermore, similar results were found when correlation analysis was performed on the whole patient group, suggesting that exogeneous glucocorticoid administration plays an important role in the pathogenesis of the abnormal BP profiles presented by these patients. These findings support those of Imai et al,7-8 who reported abnormal BP profiles and normal HR profiles in patients with Cushing's syndrome7 and in subjects treated with exogeneous glucocorticoids.8 However, in this latter study, the glucocorticoid dose was higher than in our LTX patients, and this may explain the failure to demonstrate a dose-dependent effect of exogeneous

TABLE 4. Quantitative Characteristics of 24-Hour Heart Rate Variations in Control Subjects and in Group A and B Liver-Transplanted Patients

<table>
<thead>
<tr>
<th>Characteristics of HR rhythms</th>
<th>Control (n=17)</th>
<th>LTX A (n=10)</th>
<th>LTX B (n=7)</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime mean level (bpm)</td>
<td>78±2</td>
<td>79±3</td>
<td>84±5</td>
<td>0.45</td>
</tr>
<tr>
<td>Nighttime mean level (bpm)</td>
<td>66±2</td>
<td>68±3</td>
<td>69±5</td>
<td>0.68</td>
</tr>
<tr>
<td>Amplitude</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute (bpm)</td>
<td>13±1</td>
<td>13±1</td>
<td>13±1</td>
<td>0.99</td>
</tr>
<tr>
<td>Percent of mean</td>
<td>17±1</td>
<td>17±2</td>
<td>16±2</td>
<td>0.90</td>
</tr>
<tr>
<td>Major acrophase clock time</td>
<td>15:29±00:22</td>
<td>14:14±01:41</td>
<td>12:44±01:02</td>
<td>0.19</td>
</tr>
<tr>
<td>Value of major acrophase</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute (bpm)</td>
<td>82±2</td>
<td>85±3</td>
<td>90±4</td>
<td>0.18</td>
</tr>
<tr>
<td>Percent of mean</td>
<td>112±1</td>
<td>114±1</td>
<td>114±2</td>
<td>0.45</td>
</tr>
<tr>
<td>Major nadir clock time</td>
<td>03:49±00:17</td>
<td>03:04±01:20</td>
<td>02:00±01:18</td>
<td>0.37</td>
</tr>
<tr>
<td>Value of major nadir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute (bpm)</td>
<td>60±2</td>
<td>61±2</td>
<td>66±5</td>
<td>0.36</td>
</tr>
<tr>
<td>Percent of mean</td>
<td>82±1</td>
<td>82±2</td>
<td>83±3</td>
<td>0.92</td>
</tr>
</tbody>
</table>

HR, heart rate; LTX, liver-transplanted patients; ANOVA, analysis of variance; bpm, beats per minute.

FIGURE 4. Scatterplots show daily oral prednisolone intake (in milligrams per kilogram body weight [BW]) in 17 liver-transplanted patients versus the difference between daytime and nighttime systolic (SBP) (left panel) and diastolic (DBP) (right panel) blood pressure levels.
glucocorticoid administration on the circadian BP variations. In contrast, our study clearly indicates that the magnitude of the nocturnal SBP and DBP decrease is correlated with the oral prednisolone intake.

However, we cannot exclude the fact that additional factors may have been involved in causing the alterations in the blood pressure profiles. In particular, variable levels of daytime physical activities and of sleep quality, which were not directly assessed in this study, could theoretically alter the BP profiles. The difference in the time elapsed since the most recent illness in the two groups of LTX patients just failed to reach the level of statistical significance. However, the clinical relevance of this finding is doubtful, because there is no reason to believe that rehabilitation would not be sufficient after a mean recovery period of 5 months, and, accordingly, the time elapsed since the most recent illness did not correlate with the magnitude of the nighttime BP fall. Moreover, the diaries of the patients, the similar daytime and nighttime HR levels and variability, and also the similar nighttime decrease in HR suggest that the physical activities were the same in the different groups of patients and that the patients without nocturnal BP decline were not poorer sleepers. Furthermore, if environmental stimuli and changes in physical activity are minimized, there is still a fall in BP of approximately 20% during sleep. Hence, a reduced level of physical activity cannot explain per se the increase in the nighttime BP observed in the group B patients. On the other hand, interactive effects of glucocorticoids, cyclosporine, and azathioprine could also be involved in the loss of the normal circadian variations of BP. However, the absence of a dose-response effect of cyclosporine and azathioprine suggests that they are not the primary cause of the alterations.

Furthermore, if exogenous glucocorticoids are known to reverse or eliminate the circadian BP variations, and although hypertension in transplanted patients is mainly cyclosporine related, it has never been clearly demonstrated that hypertension affects 24-hour BP profiles. We have recently reported that normal circadian BP profiles reappeared in patients with long-term heart transplants and that glucocorticoid administration contributed to the abnormal BP profiles observed shortly after transplantation. To differentiate between the specific effects of the different immunosuppressive regimens on the nighttime BP decrease, we have performed a multiple regression analysis using the oral dose of cyclosporine, prednisolone, and azathioprine (in milligrams per kilogram of body weight) as independent variables and the nighttime SBP and DBP decrease as dependent variables. In this multiple regression analysis, the previously published cardiac-transplanted patients and the LTX patients were included, resulting in a group of 43 patients who were all treated with cyclosporine, prednisolone, and azathioprine. The following equation was obtained for SBP: magnitude of the nighttime SBP fall = 22.6 + (2.2 cyclosporine dose) – (82.5 prednisolone dose) – (4.0 azathioprine dose). The effect of prednisolone was significant at p < 0.0001 but was not significant for cyclosporine (p = 0.21) and for azathioprine (p = 0.41). Concerning DBP, the following equation was obtained: magnitude of the nighttime DBP fall = 19.4 – (0.05 cyclosporine dose) – (33.5 prednisolone dose) – (4.9 azathioprine dose). The effect of prednisolone was significant at p = 0.009 but was not significant for cyclosporine (p = 0.96) and azathioprine (p = 0.13). Hence, the effect of prednisolone on the nighttime BP fall was 38 times greater for SBP and 670 times greater for DBP than the effect of cyclosporine, which was not significant.

The present report of abnormal circadian BP rhythm in LTX patients has potentially important clinical implications, because both daytime and nighttime ambulatory BP levels are predictive of cardiac organ damage and performing only daytime BP measurements in organ-transplanted patients may result in an underestimation of the severity of their hypertension. Moreover, increased pulse pressure, which was found during the nighttime in the high glucocorticoid–treated patients, is associated with increased cardiac mass and is an independent risk factor of cardiovascular mortality.

In conclusion, we report abnormal circadian BP rhythms but normal circadian HR rhythms in LTX patients. Exogenous glucocorticoid administration appears to play an important role in the pathogenesis of these abnormal BP profiles. Extended longitudinal studies will be necessary to further delineate the role of glucocorticoids in controlling the 24-hour BP profile.

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