Circadian Blood Pressure Changes and Left Ventricular Hypertrophy in Essential Hypertension

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The effects of circadian blood pressure (BP) changes on the echocardiographic parameters of left ventricular (LV) hypertrophy were investigated in 235 consecutive subjects (137 untreated hypertensive patients with essential hypertension and 98 healthy normotensive subjects) who underwent 24-hour noninvasive ambulatory blood pressure monitoring (ABPM) and cross-sectional and M-mode echocardiography. In the hypertensive group, LV mass index correlated with nighttime (8:00 PM to 6:00 AM) systolic (r=0.51) and diastolic (r=0.35) blood pressure more closely than with daytime (6:00 AM to 8:00 PM) systolic (r=0.38) and diastolic (r=0.20) BP, or with casual systolic (r=0.33) and diastolic (r=0.27) BP. Hypertensive patients were divided into two groups by presence (group 1) and absence (group 2) of a reduction of both systolic and diastolic BP during the night by an average of more than 10% of the daytime pressure. Casual BP, ambulatory daytime systolic and diastolic BP, sex, body surface area, duration of hypertension, prevalence of diabetes, quantity of sleep during monitoring, funduscopic changes, and serum creatinine did not differ between the two groups. LV mass index, after adjustment for the age, the sex, the height, and the daytime BP differences between the two groups (analysis of covariance) was 82.4 g/m² in the normotensive patient group, 83.5 g/m² in hypertensive patients of group 1 and 98.3 g/m² in hypertensive patients of group 2 (normotensive patients vs. group 1, p=NS; group 1 vs. group 2, p=0.002). The other echocardiographic parameters of LV anatomy (i.e., interventricular septum and posterior wall thickness, relative wall thickness, cross-sectional area) differed between the groups as did LV mass index. A statistically significant inverse correlation was found between LV mass index and percentage of nocturnal reduction of daytime ambulatory systolic (r=−0.34; p<0.001) and diastolic (r=−0.30; p=0.001) BP. These findings suggest that in unselected hypertensive patients, an ambulatory BP decline from day to night is associated with a lower LV muscle mass. In these patients, a nocturnal reduction of systolic and diastolic BP by more than 10% of daytime values could delay or prevent the development of cardiac LV hypertrophy. (Circulation 1990;81:528–536)

Left ventricular hypertrophy (LVH) detected by electrocardiography (ECG) is an important predictor of cardiovascular morbidity and mortality.

In the Framingham study about 45% of all cardiovascular deaths were preceded by left ventricular hypertrophy detected by electrocardiography (ECG-LVH), and the 5-year mortality rate in men with ECG-LVH was about 35%, as compared with 10–15% in the absence of ECG-LVH.1–3 LVH is a usual consequence of arterial hypertension, and it has been shown to appear within 12 years in about 50% of patients with systolic blood pressure (BP) above 180 mm Hg.2

Compared with ECG, echocardiography shows a higher sensitivity and an equally high specificity for the diagnosis of LVH.4 Echocardiography allows quantitation of LV muscle mass and provides values reasonably near to those found at necropsy.4–7 ECG allowed detection of LVH in no more than 38% of hypertensive patients with echocardiographic LVH.8

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Some findings suggest that echocardiographic LVH could be an independent predictor of cardiovascular morbidity and mortality. The weak relation of casual BP to echocardiographic LVH becomes closer by using 24-hour BP averages obtained with noninvasive or intraarterial ambulatory blood pressure monitoring (ABPM).

Daytime BP, particularly that recorded during recurring stressful situations, seems to be more closely related to LVH than nighttime BP, but in other studies, both awake and sleep BP correlated equally well with LV muscle mass, or nighttime BP showed a better relation to LV muscle mass than did daytime BP.

ABPM shows that, in hypertensive patients, daytime BP usually decreases during night. The degree and duration of nocturnal BP and wall stress reduction could, thus, influence development of cardiovascular changes in hypertensive patients but such hypothesis has never been specifically investigated.

Consequently, the present study was designed to examine the relation of BP decline from day to night to the echocardiographic parameters of LV anatomy in a large population of unselected hypertensive patients and healthy normotensive subjects undergoing 24-hour noninvasive ABPM.

**Methods**

**Patient Population**

One-hundred thirty-seven patients with essential hypertension (47% female) and 98 healthy normotensive subjects (49% female) were studied. They were consecutively chosen from patients with documented essential hypertension and healthy normotensive subjects examined in our laboratory and meeting all the following criteria: 1) no antihypertensive drugs from at least 4 weeks, 2) good quality of echocardiographic tracings, 3) agreement within 5 mm Hg between ambulatory BP recording unit and mercury sphygmomanometer in at least three consecutive measurements taken simultaneously on the same arm, 4) absence of clinical, ECG, or echocardiographic evidence of coronary artery disease, valvular disease (Doppler echocardiography), or renal disease. Seven patients with mitral valve prolapse and mild (grade 1) mitral regurgitation were included.

Hypertensive patients were identified in a rather restricted rural area of 6,500 inhabitants by a group of general practitioners who referred all the subjects with supine diastolic BP of 90 mm Hg or higher to our hypertension clinic.

To be admitted to the study, supine diastolic BP had to be 90 mm Hg or higher in at least three visits at 1-week intervals, and all the four aforementioned criteria had to be fulfilled.

Healthy normotensive patients were voluntary subjects chosen among medical students, hospital staff, and other subjects examined for clinical check-up and found healthy.

**Experimental Procedures**

**Blood pressure measurements.** Clinic BP was measured after 10 minutes of supine rest by using a Hawksley Random Zero manometer (phase 1 and 5) (Hawksley and Sons, Ltd., Lancig, West Sussex, England). Ambulatory BP was recorded by using the fully automatic unit ICR 5200 system (Spacelabs, Redmond, Washington) that, in our laboratory, showed a correlation of 0.97 with both systolic and diastolic pressures measured simultaneously on the same arm (by a Y connector) with a mercury sphygmomanometer. Others have reported a similar correlation using the same unit.

The reading, editing, and analysis of data provided by the unit was done by the ABP5600 interface (Spacelabs, Redmond, Washington) installed on an IBM/XT personal computer. Systolic readings greater than 260 or less than 70 mm Hg, diastolic readings greater than 150 or less than 40 mm Hg, and pulse pressure readings greater than 150 or less than 20 mm Hg were automatically discarded. The unit was set to take readings automatically every 15 minutes throughout the 24 hours. Overall, there were 107.4 (SD, 12) BP readings per patient, with 89.5 (SD, 11) readings per patient fulfilling the editing criteria. Error percentage was 15.9% (SD, 12).

**Echocardiographic Methods**

M-Mode echocardiograms were performed under cross-sectional control, with the patient in partial left decubitus position, using an ATL Ultramark 8 system (Advanced Technology Laboratories, Bellevue, Washington) with an ATL 3.00 MHz mechanical transducer. LV measurements were made at end-diastole and end-systole according to the recommendations of the American Society of Echocardiography (ASE).

LV mass was calculated using the following equation, based on necropsy validation studies: LV mass = 0.80(ASE-cube LV mass) + 0.6 g, where ASE-cube LV mass = 1.04* [{(IVSd + LVIDD + PWd) − LVIDD}^3 − LVIDD^3] g; IVSd is interventricular septal thickness at end-diastole, LVIDd is left ventricular internal dimension at end-diastole, and PWd is posterior wall thickness at end diastole.

All echocardiographic examinations were performed by the same experienced sonographer. Reading of echocardiographic tracings was made in random order by two investigators who had no knowledge of patients’ BPs and other clinical data.

Both investigators marked locations on stop frames on the screen of the ATL Ultrasound System, and the mean values from at least five measurements for each parameter for observer were computed. Only frames with optimal visualization of LV interfaces and showing simultaneous visualization of interventricular septal thickness (IVS), posterior wall thickness (PW), and left ventricular internal dimension (LVID) throughout the whole cardiac cycle were considered for reading.
Forty-three subjects, most of whom were affected by long-term obstructive lung disease or obesity, were excluded from the study because of unsatisfactory echocardiographic tracings. Forty-two treated patients with complicated or severe hypertension were not investigated because it would have been unethical to discontinue therapy.

Relative wall thickness (RWT)$^{22}$ and cross-sectional area (CSA)$^{23}$ were calculated as previously described. Fractional shortening (FS) was calculated according to the formula: $FS(\%) = \frac{\{LVIDd-LVIDs\}}{LVIDd} \times 100$.

**Nocturnal Blood Pressure Behavior**

Study subjects were divided into two groups by the presence (group 1) or absence (group 2) of significant nocturnal BP reduction, defined as daytime (6:00 AM to 8:00 PM) systolic and diastolic BP averages decreasing by more than 10% during night (8:00 PM to 6:00 AM).

**Statistical Analysis**

All data were handled and stored by using the DBASE III software, and analyzed by using the BMDP package$^{24}$ (1985 version) installed on an IBM AT/3 personal computer. One-way analysis of variance (ANOVA) and nonparametric tests were used to compare the groups in their demographic, blood pressure, and heart rate findings. Analysis of covariance (ANCOVA) (age, sex, height, and daytime ambulatory systolic and diastolic BP acting as simultaneous covariates) was used to compare the normotensive group, the hypertensive subgroup with, and the hypertensive subgroup without nocturnal BP fall in the echocardiographic parameters ($p$ values less than 0.05 were considered statistically significant).

**Results**

The main characteristics of the study population, including the statistical significance of differences between hypertensives and normotensives, are reported in Table 1. Hypertensive patients and normotensive controls did not differ for age, height, weight, sex prevalence, and body surface area. The heart rate, both casual and ambulatory, was slightly higher in the hypertensive group. Prevalence of LVH, defined as LV mass index above 120 g/m$^2$, was 14.6% in the hypertensive groups.

**Reproducibility of Ambulatory Blood Pressure**

Figure 1 shows the hourly ambulatory BP profile on the two recording sessions in a subgroup of 32 hypertensive patients who repeated ABPM within 3–5 days in the absence of therapy. Average 24-hour systolic/diastolic BP values were 164.4/97.9 mm Hg (SD, 19/7) on the first session, and 158.2/95.8 mm Hg (SD, 19/8) on the second session (all, $p=NS$). A statistically significant difference ($p<0.05$) between the two sessions was found only from hours 1:30 to 2:30 PM in the
hourly averages of systolic BP, the values recorded on the second occasion being slightly lower.

**Relation of Blood Pressure to Left Ventricular Hypertrophy**

As shown in Table 2, nighttime systolic BP showed the best correlations with LV mass (r=0.54), LV mass index (r=0.51), RWT (r=0.38), CSA (r=0.57), and CSAI (r=0.51) in the hypertensive group. Overall, in the hypertensive population, the relations between the echocardiographic indexes of LVH and BP values were slightly closer with the nighttime values, and progressively weaker with the daytime and casual values.

**Table 2. Relation of Casual and Ambulatory Blood Pressure to Left Ventricular Mass, Left Ventricular Mass Index, Relative Wall Thickness, Cross-sectional Area, and Cross-sectional Area Index**

<table>
<thead>
<tr>
<th></th>
<th>All subjects (n=235)</th>
<th>Normotensive patients (n=98)</th>
<th>Hypertensive patients (n=137)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LVM</td>
<td>LVMI</td>
<td>RWT</td>
</tr>
<tr>
<td>Casual SBP</td>
<td>0.34*</td>
<td>0.38*</td>
<td>0.26*</td>
</tr>
<tr>
<td>Casual DBP</td>
<td>0.32*</td>
<td>0.29*</td>
<td>0.24*</td>
</tr>
<tr>
<td>Average 24-hr SBP</td>
<td>0.51*</td>
<td>0.48*</td>
<td>0.38*</td>
</tr>
<tr>
<td>Average 24-hr DBP</td>
<td>0.41*</td>
<td>0.36*</td>
<td>0.30*</td>
</tr>
<tr>
<td>Daytime SBP</td>
<td>0.43*</td>
<td>0.40*</td>
<td>0.31*</td>
</tr>
<tr>
<td>Daytime DBP</td>
<td>0.33*</td>
<td>0.28*</td>
<td>0.23*</td>
</tr>
<tr>
<td>Nighttime SBP</td>
<td>0.50*</td>
<td>0.47*</td>
<td>0.38*</td>
</tr>
<tr>
<td>Nighttime DBP</td>
<td>0.41*</td>
<td>0.37*</td>
<td>0.30*</td>
</tr>
</tbody>
</table>

Daytime is 6:00 AM to 8:00 PM; night time is 8:00 PM to 6:00 AM.
LVM, left ventricular mass; LVMI, left ventricular mass index; RWT, relative wall thickness; CSA, cross sectional area; CSAT, cross sectional area index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

*p<0.01; †p<0.05.
nal BP decline but the differences from the other group were not statistically significant.

No fundoscopic changes, focal or generalized narrowing of the retinal arteries, or retinal haemorrhages and exudates were found, respectively, in 48, 26, and eight hypertensive patients with, and in 34, 15, and six patients without significant nocturnal BP reduction ($\chi^2=0.32, p=NS$).

In comparison with the usual sleeping habits, there were no changes in the duration of sleep, or a reduction up to 2 hours, or of 2–4 hours, or of more than 4 hours in 36, 13, 26, and seven patients with,
between the three groups. None of the differences between normotensive and hypertensive patients with nocturnal BP reduction by more than 10% yielded statistical significance. In contrast, all differences between the two groups of hypertensive patients were statistically significant. FS and LV end-diastolic diameter did not differ among the three groups. Adjusted values of LV mass index in the three groups are also depicted in Figure 3. A score of five or more by Romhilt-Estes criteria was found in 46% of patients with echocardiographic LVH.

An inverse relation was found (all, \( p<0.01 \)) in the hypertensive group between percentage of nocturnal decline of systolic BP and LV mass \(( r=-0.35 \), LV mass index \(( r=-0.34 \), RWT \(( r=-0.29 \), CSA \(( r=-0.37 \), CSA index \(( r=-0.34 \), IVSd \(( r=-0.30 \), PWD \(( r=-0.38 \).

In the hypertensive group, there was also an inverse relation (all, \( p<0.01 \)) between percentage of nocturnal decline of diastolic BP and LV mass \(( r=-0.32 \), LV mass index \(( r=-0.30 \), RWT \(( r=-0.22 \), CSA \(( r=-0.31 \), CSA index \(( r=-0.27 \), IVSd \(( r=-0.22 \), PWD \(( r=-0.32 \).

None of the relations between percentage of nocturnal decline of systolic or diastolic BP and echocardiographic measures of LV anatomy was statistically significant in the normotensive group.

### Discussion

In agreement with previous investigations, \(^{12-14}\) our findings confirm that ambulatory BP is more closely related to LV muscle mass than is casual BP. The most important finding, however, of this study was the inverse relation between nocturnal BP decline and LV muscle mass in a large population of unselected and untreated patients with essential hypertension.

#### Table 5. Correlations Between Casual or Ambulatory Blood Pressure (24-Hour, Daytime, and Nighttime) and Left Ventricular Mass Index in Hypertensive Patients

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Reference</th>
<th>Rowlands et al(^{14}) (( n=50 )</th>
<th>Devereux et al(^{13}) (( n=100 )</th>
<th>Drayer et al(^{12}) (( n=12 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casual blood pressure</td>
<td></td>
<td>0.45*</td>
<td>0.24†</td>
<td>0.55</td>
</tr>
<tr>
<td>Systolic</td>
<td></td>
<td>0.46*</td>
<td>0.20†</td>
<td>0.10</td>
</tr>
<tr>
<td>Diastolic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambulatory blood pressure</td>
<td></td>
<td>0.60*</td>
<td>0.38*</td>
<td>0.81*</td>
</tr>
<tr>
<td>Average 24-hr systolic</td>
<td></td>
<td>0.35*</td>
<td>0.31*</td>
<td>0.56</td>
</tr>
<tr>
<td>Daytime systolic</td>
<td></td>
<td>0.57*</td>
<td>…</td>
<td>0.82*</td>
</tr>
<tr>
<td>Daytime diastolic</td>
<td></td>
<td>0.41*</td>
<td>…</td>
<td>0.49</td>
</tr>
<tr>
<td>Nighttime systolic</td>
<td></td>
<td>0.56*</td>
<td>0.10</td>
<td>0.70†</td>
</tr>
<tr>
<td>Nighttime diastolic</td>
<td></td>
<td>0.49*</td>
<td>0.24†</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Devereux et al\(^{13}\) \(( n=100 \) is mixed population of 81 hypertensive and 19 normotensive patients. Rowlands et al\(^{14}\) \(( n=50 \) gives daytime systolic and ambulatory blood pressure reported as awake blood pressure. Rowlands et al\(^{14}\) \(( n=50 \) and Devereux et al\(^{13}\) \(( n=100 \) gives nighttime systolic and diastolic ambulatory blood pressure reported as sleep blood pressure. Devereux et al\(^{13}\) \(( n=100 \) gives daytime systolic and diastolic ambulatory blood pressure separately reported for clinic, work, and home blood pressure. Drayer et al\(^{12}\) \(( n=12 \) gives daytime systolic and diastolic ambulatory blood pressure reported as blood pressure averages from 6 AM to 8 PM. Drayer et al\(^{12}\) \(( n=12 \) gives nighttime systolic and diastolic ambulatory blood pressure reported as blood pressure averages from 8 PM to 6 AM.

\( p<0.01; \) \( \dagger p<0.05. \)
Relation of Blood Pressure to Left Ventricular Mass

Table 5 shows the correlation coefficients between LV mass index and casual or ambulatory BP in the three main investigations comparable with our own. In the study by Rowlands et al\textsuperscript{14} who performed intra-arterial BP monitoring in 50 patients with mild to moderate hypertension, the relations of casual and ambulatory BP to LV mass index were similar as in this study (see Table 2).

In the study by Devereux et al\textsuperscript{13} the correlation coefficients between casual or ambulatory BP and LV mass index were generally lower, and in that by Drayer et al\textsuperscript{12} generally higher than our values. As we could not differentiate between work, clinic, and home ambulatory BP measurements, our findings about the inverse relation of nocturnal BP decline to LV muscle mass do not rule out the possibility that daytime BP during stress can be an independent determinant of LVH development in hypertensive patients.

Prevalence of Left Ventricular Hypertrophy in Essential Hypertension

Our prevalence figure (14.6\%) is comparable with that reported by Hammond et al\textsuperscript{28} who studied an unselected group of hypertensive patients drawn from an employed population (prevalence of LVH approximating 12\% in borderline hypertension and 20\% in sustained hypertension). In another study done in 93 patients with mild-to-moderate hypertension, prevalence of LVH was 16\%.\textsuperscript{29}

Prevalence of echocardiographic LVH was higher in other studies,\textsuperscript{11,13,30} presumably done on more selected hypertensive populations. In the study by Hammond et al\textsuperscript{28} as well as in our own, several treated patients (about 30\% of the study population) with complicated or severe hypertension and, presumably, a higher prevalence of LVH,\textsuperscript{2,3} could not be included in the study, it being unethical to discontinue antihypertensive therapy.

These findings suggest that the prevalence of LVH in essential hypertension is strongly influenced by the recruiting criteria of the study population, and implicate that prevalence figures in different studies might not always be comparable.

Relation of Daytime and Nighttime Blood Pressure to Left Ventricular Hypertrophy

Both in the study by Devereux et al\textsuperscript{13} and in that by Drayer et al\textsuperscript{12} daytime BP showed a generally closer relation to LV mass than did nighttime BP. In the study by Rowlands et al\textsuperscript{14} awake BP and sleep BP correlated equally well with LV mass, whereas in another study performed on a mixed population of hypertensive and normotensive patients, sleep BP showed a closer relation to LV mass than did awake BP.\textsuperscript{15} Therefore, the available data do not allow to draw definite conclusions about the possible predominance of daytime or nighttime BP on LVH development in hypertensive patients.

A constant finding in this and other studies\textsuperscript{12-15} is the generally closer relation of systolic over diastolic BP to the degree of hypertrophy, another evidence that wall stress, which is mostly related to systolic BP, is a key factor influencing LVH development.

In our normotensive population, the relation of ambulatory BP to the echocardiographic parameters of LV anatomy was slightly closer using daytime values, whereas in the hypertensive population, it was closer with nighttime values. We referred to nighttime BP, and not to sleep BP, because in our experience, sleep can be interrupted by cuff inflation and accompanying noise. Thus, one cannot be confident that all indirect BP measurements over a given nocturnal period have been really obtained during sleep.

As shown with intra-arterial\textsuperscript{16} and noninvasive\textsuperscript{31} monitoring, ambulatory BP decreases during night by an average of 20\% of the waking values. Individual profiles, however, can diverge widely with some patients showing greater nocturnal changes associated with normal BP values even for several hours and some others showing negligible changes.\textsuperscript{16} To our knowledge, the possibility that nocturnal BP reduction might tend to outweigh the effect of daytime hypertension on LV hypertrophic response to increased afterload has never been investigated.

In one study,\textsuperscript{32} intra-arterial BP variation from day to night in 23 untreated hypertensive patients was apparently similar in the presence versus absence of LVH.\textsuperscript{32} An inspection to individual data of such study, however, shows that BP decreased by less than 10\% from day to night in one of six patients with LVH, against one of 17 patients without LVH. Another study\textsuperscript{33} with intra-arterial BP monitoring reported no difference in the diurnal rhythm of BP in patients with and without LVH.

In another study,\textsuperscript{13} with noninvasive monitoring, BP reduction from day to night was similar in the presence versus absence of LVH. In a recent preliminary report, Lang et al\textsuperscript{24} have shown increased values of LV mass in 20 patients diagnosed as having both diurnal and nocturnal hypertension, in comparison with values in 10 patients with only daytime hypertension. In our study, patients with and without nighttime BP reduction by more than 10\% of daytime values slightly differed for age, but not for other variables that might have independently influenced LV muscle mass, such as sex, height, weight, body surface area, duration of hypertension, renal function, prevalence of diabetes mellitus, and fundoscopic changes. Also, casual BP and ambulatory BP during the day did not differ significantly between the groups, however, both being slightly higher in the group with a smaller nocturnal BP decline.

Therefore, only nighttime ambulatory BP disclosed a very evident differentiation between the two hypertensive groups. All the echocardiographic indexes of LVH, after adjustment for age differences, sex differences, height differences, and daytime systolic and diastolic BP differences, were increased in the group
of hypertensive patients with a smaller nocturnal BP decline, and the prevalence of LVH was increased in this latter group.

Thus, the differences in LV muscle mass between the groups appeared to be mostly explained by the different nocturnal BP decline. The inverse relation between percentage of nocturnal reduction of systolic and diastolic BP and degree of LVH gives further support to this point.

Conclusions

The prognostic and therapeutic implications of the changes in blood pressure from day to night are still unknown. It has been suggested that hypertensive patients losing nocturnal BP reduction as detected with noninvasive monitoring might be at higher risk of stroke.35

The findings of this study support the concept that the duration of exposure to increased levels of BP and wall stress over the 24 hours can play an important role in the pathogenesis of LVH in unscreened patients with arterial hypertension. In these patients, a nocturnal reduction of systolic and diastolic BP by more than 10% of daytime values can exert the beneficial effect of delaying or preventing development of cardiac LVH.

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**KEY WORDS** • echocardiography • ambulatory blood pressure monitoring • hypertension • left ventricular hypertrophy
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