A relationship exists between blood pressure and cardiovascular morbidity and mortality. Recent data suggest that the variability of blood pressure is also related to hypertensive target organ damage. We studied the relationship of ambulatory daytime and night-time and supine beat-to-beat Finapres blood pressure variability to left ventricular mass index (LVMI) and urinary albumin excretion (albumin/creatinine ratio: ACR) in 33 hypertensive patients, untreated for more than 3 months. In a multiple stepwise regression model the strongest relationship with the LVMI existed for night-time systolic pressure (R = 0.46, multiple regression coefficient: 0.90 ± 0.26 P < .01) and daytime diastolic blood pressure variability (multiple R increased to 0.60, multiple regression coefficient 3.16 ± 1.18, P < .05). Log ACR had the strongest relationship to ambulatory systolic daytime pressure (R = 0.40, multiple regression coefficient 0.0093 ± 0.0040, P < .05) and the variability of diastolic Finapres blood pressure (multiple R increased to 0.52, multiple regression coefficient 0.081 ± 0.0036, P < .05). Both ambulatory and steady state blood pressure variability are related to early hypertensive target organ damage. This relationship exists independent of the height of blood pressure. Am J Hypertens 1996;9:455-460.

**KEY WORDS:**
Ambulatory blood pressure, Finapres, left ventricular mass index, urinary albumin excretion, target organ damage, hypertension, blood pressure variability.

Numerous epidemiological studies have shown that blood pressure is positively related to cardiovascular morbidity and mortality. Although the relationship between blood pressure and the incidence of morbid events is consistent and highly significant, absolute risk for patients with mild to moderate hypertension is low and difficult to predict.1 This may in part be explained by the fact that blood pressure is in itself highly variable, incidental clinic measurements of blood pressure can therefore not be very representative for the strain put on the circulation during long-term blood pressure elevation.2-4 The fact that ambulatory blood pressure is indeed more closely related to target organ damage than office blood pressure certainly points to the more important burden put on the circulation by a persistently elevated blood pressure.5

However, recent cross-sectional studies in ambulatory subjects have shown that there may also be a relationship between blood pressure variability and the severity of hypertensive target organ damage, independent of the height of pressure.6-8 Variations in blood pressure during ambulatory monitoring are pri-
primarily caused by physical and mental stimuli. Also, variations in beat-to-beat blood pressure exist in steady state circumstances. Animal experiments have shown that beat-to-beat blood pressure variations may induce metabolic changes in the vascular wall, suggesting that they have a pathophysiological role in the development of cardiovascular injury.

We studied the relationship of both ambulatory and steady state beat-to-beat blood pressure variability with left ventricular mass and urinary albumin excretion, which are considered to provide information about early cardiovascular damage. So far, other studies on the relationship of blood pressure variability and target organ damage studied patients with relatively advanced cardiovascular damage.

**METHODS**

**Patients** We studied 33 patients consecutively referred to our clinic with suspected hypertension. Patients were aged on average 41 years (range 26 to 59), mean weight was 74 kg (range 45 to 115), 17 patients were male. All patients were untreated for at least 3 months. Secondary hypertension was excluded by routine procedures. Subjects with renal disease, macroalbuminuria (more than 300 mg/24 h) or diabetes mellitus were excluded. Patients with other signs of advanced target organ damage such as left ventricular hypertrophy on the ECG, a history of myocardial ischemia or infarction, stroke or peripheral vascular disease were not included. Informed consent was obtained from each patient.

**Measurements** *Ambulatory Blood Pressure* Noninvasive ambulatory blood pressure (ABP) was measured with the Oxford Medilog device (Oxford Medical, Abingdon, Oxfordshire, England). Blood pressure was measured for 24 h starting between 9 and 10 AM. Patients engaged in their normal daily activities, and slept at home. The device was programmed to measure blood pressure every 15 min during the day and every 30 min during the night.

*Steady State Blood Pressure* Noninvasive beat-to-beat finger blood pressure was measured with a TNO Finapres model 5741 during 20 min quiet rest in the supine position. These measurements took place immediately after the ABP recording, between 11 and 12 AM in a quiet room with an ambient temperature between 22 and 24°C. Beat-to-beat blood pressure data were transferred to a personal computer and on line analog-to-digital converted with 100 Hz.

*Urinary Albumin Excretion* Patients collected their urine for 24 h on the day of the ambulatory blood pressure measurement. Urinary albumin excretion was determined by a nephelometric method and expressed as the albumin/creatinine ratio (ACR).

**Echocardiography** On the day following the ambulatory blood pressure monitoring M-mode echocardiography was performed using a Hewlett-Packard model 77020 echocardiographic system (Andover, MA). Measurements were made according to the Penn Convention protocol to measure left ventricular mass, which was calculated by the formula according to Devereux and expressed as left ventricular mass index (LVMI).

**Blood Pressure Data Analysis** Ambulatory blood pressure measurements which were considered erroneous were deleted as reported elsewhere. Individual daytime and nighttime averages for systolic and diastolic pressure and the within person standard deviations (SD) of daytime pressure were determined as indices of variability. Nighttime SD was not used in the analysis as the nightly measurement frequency was not sufficient for a reliable estimate of blood pressure variability. The day–night difference in blood pressure was also calculated, and the number of nondippers (defined as subjects with a nightly drop in both systolic and diastolic pressure of less than 10% of the daytime average) was determined.

The beat-to-beat finger arterial blood pressure was analyzed by a signal analysis program after analog-to-digital conversion to determine actual systolic and diastolic pressure for each beat. Individual standard deviations for all beats of systolic and diastolic pressure were calculated for the 20-min supine period as measures of steady state beat-to-beat blood pressure variability. Before the calculation of the SD of Finapres blood pressure a correction for linear trends was performed by the least squares method.

**Statistics** Statistical analysis was performed with Biomedical Programs (BMDP) statistical software (University of California, Los Angeles, CA). Univariate correlations between the two measures of target organ damage on the one hand and the level and variability of blood pressure and age on the other hand were calculated. To determine the independent relationships of the height and the variability of blood pressure to the LVMI and the log ACR a stepwise multiple regression analysis was performed with forward and backward stepping. Standardized regression coefficients are also given to eliminate the effect of scale on the various coefficients in the same regression equation. As the distribution of the ACR was skewed to the higher values, a logarithmic transformation was performed on the ACR.

**RESULTS** A satisfactory ambulatory blood pressure registration was obtained in all 33 patients with each having no more than 10% failed readings. Average daytime systolic/diastolic blood pressure was 142/96 mm Hg (range 178 to 109/111 to 70 mm Hg). Average nighttime blood pressure was 120/78 mm Hg (range 143...
to 95/94 to 57 mm Hg). In eight of the 33 patients averaged diastolic daytime blood pressure was below 90 mm Hg. Averages and ranges of parameters which were used in the stepwise regression model are listed in Table 1. Systolic blood pressure dropped during nighttime on average 22 mm Hg (range -42 to 8 mm Hg), diastolic blood pressure dropped on average 18 mm Hg (range -31 to -2 mm Hg). In four patients nightly systolic and diastolic pressure dropped less than 10% of the daytime average. Average Finapres supine blood pressure was 143 / 77 mm Hg (range 175 to 108/101 to 51 mm Hg).

The average left ventricular mass index was 11.5 g/m² (range 67 to 153 g/m²). Left ventricular hypertrophy (LVH), according to the normal values provided by Devereux, was present in 12 patients. Urinary albumin excretion was on average 21 mg/24 h (range 4 to 112 mg/24 h), average ACR was 1.78 mg/mmol (range 0.29 to 9.73 mg/mmol). In four patients urinary albumin excretion exceeded 30 mg/24 h.

The correlations of the independent variables to LVMI and log ACR are listed in Table 2. For LVMI ambulatory nighttime systolic blood pressure and the SD of daytime diastolic blood pressure could be included in the multiple regression equation (Figure 1, Table 3). The multiple R was 0.60 and the variance ratio of the complete regression equation for the LVMI was 8.59 (P < 0.05). Both nighttime systolic pressure and the SD of daytime diastolic pressure were significantly related to the LVMI and thus contributed separately to the effectiveness of the overall regression.

For log ACR ambulatory systolic daytime blood pressure and the SD of supine beat-to-beat diastolic blood pressure could be included in the multiple regression equation (Figure 1, Table 3). The multiple R was 0.52 and the variance ratio of the complete regression equation for the log ACR was 5.48 (P < 0.05). Both variables were significantly and thus independently related to the log ACR.

**DISCUSSION**

Literature shows that ambulatory measured daytime blood pressure is a better predictor for hypertensive morbidity than casual measurements in the office. The results of this study indicate that a relationship between variability of blood pressure and target organ damage may exist independent of the level of pressure. Several other studies also showed an independent relationship between the severity of hypertensive target organ damage and daytime ambulatory blood pressure variability. Two studies in smaller patient groups failed to demonstrate a relationship between LVH and ambulatory blood pressure variability. However, patients in these last studies were treated before they were studied, and their medication was discontinued only several weeks prior. To avoid the possible confounding effect of previous treatment, we decided to study only patients who had never received antihypertensive treatment or who had not been treated for at least 3 months. Moreover, one of the studies that failed to demonstrate an association between blood pressure variability and target organ damage, assessed blood pressure variability not separately for day and night but for the complete 24 h. This is recognized to limit the applicability of the use of the SD as a measure of ambulatory blood pressure variability.

As variability and level of pressure are also correlated, this could cause a cross-correlation of variability to organ damage dependent on the level of pressure. However only a part of the blood pressure vari-
ability can be explained by the level of pressure, and it has been shown that level and variability of blood pressure can change independently of each other.26 The extent of blood pressure variability is for a large part depending on the ability of the baroreflex to buffer these variations and a decrease in baroreflex sensitivity may increase blood pressure variability.27 It has been shown that the baroreflex sensitivity is decreased in hypertensive patients,28 which helps to explain why in these patients blood pressure variability may be related to target organ damage, independently of the level of pressure.

Apart from its relationship with the level of blood pressure the development of LVH may be related to peaks in blood pressure during daily life. Our data showed a correlation of the LVMl to the variability of daytime diastolic pressure and it has been shown that blood pressure measured under stressful situations appears to be more closely related to LVH than basal blood pressure.29 Additional evidence is provided by the fact that in other studies a relationship between post exercise blood pressure and blood pressure load to LVH was found.30,31 However, it has also been suggested that especially the nighttime blood pressure level, and a decreased day-night difference, is associated with LVH.23 The importance of nighttime blood pressure for LVH was supported by our data (Table 2). To explain this apparent conflict between the relevance of nighttime blood pressure and daytime variations in blood pressure, it has been suggested that in studies which attributed greater importance to the nightly blood pressure, a substantial proportion of subjects did not show a nightly decrease in blood pressure.32 However, this was not supported by our results as only four of the 35 patients (12%) were classified as nondippers.

Care should be taken in interpreting our results, as we studied a relatively small number of patients, and our study (as with most other studies in this field) had a cross-sectional design, for reason of which we could not follow the development of target organ damage in relation to blood pressure variability. Moreover, one has to take into account that the identification of various factors as being independently associated with target organ damage does not necessarily imply causality. Increased blood pressure variability may well be the cause of target organ damage.

### Table 3. Regression Coefficients

<table>
<thead>
<tr>
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<th>RC</th>
<th>Standardized RC</th>
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<tbody>
<tr>
<td>LVMI</td>
<td></td>
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</tr>
<tr>
<td>Nighttime SBP</td>
<td>0.90 ± 0.26*</td>
<td>0.50</td>
</tr>
<tr>
<td>SD daytime DBP</td>
<td>3.16 ± 1.18*</td>
<td>0.39</td>
</tr>
<tr>
<td>log ACR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime SBP</td>
<td>0.0093 ± 0.0040*</td>
<td>0.37</td>
</tr>
<tr>
<td>SD supine- to- to-beat DBP</td>
<td>0.081 ± 0.016*</td>
<td>0.32</td>
</tr>
</tbody>
</table>

RC, regression coefficient; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation.

Regression coefficients and standardized regression coefficients of the parameters included in the multiple regression equations.

*P < .05, †P < .01.
but it may also be its consequence: the present study cannot provide an answer to this controversial issue. However, the patients in the present study were selected on the condition that they had no advanced hypertensive cardiovascular damage: the fact that we found a relationship between blood pressure variability and two markers of early target organ damage suggests that blood pressure variability may have at least some causal relationship to hypertensive organ damage.

It has been hypothesized that the fatiguing effects of the cyclic stress of each pressure wave cause fractures in the load bearing fibers of the arterial wall. This may cause a remodelling of the vessel and contribute to the process of arteriosclerosis with aging. If the cyclic stress of each pulse wave is amplified by an increase in both blood pressure level and variability, it is conceivable that this could lead to an increased rate of arteriosclerosis. However, such views are as yet purely hypothetical. Moreover, in our patients a significant correlation with target organ damage was only found for diastolic and not for systolic variability, while systolic pressure generally, and also in our patients (Table 1), shows a higher variability. Data from literature also indicates that, compared to systolic pressure, the variations in diastolic pressure are closer, or at least comparable, related to hypertensive target organ damage.

We recorded ambulatory blood pressure by noninvasive intermittent measurements. It has been shown that, compared to intraarterial monitoring, this technique is sufficiently accurate and precise. But for determination of blood pressure variability the intermittent method cannot of course fully substitute beat-to-beat monitoring. However, given a measurement interval between 5 and 15 min, it yields sufficiently reliable results. When the measurement interval is increased, the level of blood pressure is still determined accurately and precisely, but the assessment of blood pressure variability progressively deteriorates. In our group of subjects nighttime blood pressure was measured with intervals of 30 min, and therefore nighttime blood pressure variability was not included in the analysis. So far, only one study which showed a relation between blood pressure variability and target organ damage has been performed by ambulatory beat-to-beat intraarterial monitoring. Obviously, the necessity for arterial cannulation, a procedure which carries a certain risk, remains an obstacle.

In conclusion, in this cross-sectional study we found a significant relationship of blood pressure variability to early hypertensive target organ damage independent of the level of blood pressure. Ambulatory daytime diastolic blood pressure variability correlated to left ventricular mass. Steady state supine beat-to-beat diastolic blood pressure variability correlated to urinary albumin excretion. It is suggested that beat-to-beat variations might primarily damage the vascular tree, while longer-term variability mainly puts a strain on the left ventricle. These results undoubtedly call for further research.

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REFERENCES


