Prevalence of Circadian Variations and Spontaneous Variability of Cardiac Disorders and ECG Changes Suggestive of Myocardial Ischemia in Systemic Arterial Hypertension

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Background. Systemic hypertension is a well-known risk factor for coronary artery disease and sudden cardiac death. Recent interest focused on the presence of malignant ventricular arrhythmias (VA) and myocardial ischemia in hypertensive patients and provided a potential link for fatal tachyarrhythmic events.

Methods and Results. We studied 150 untreated normokalemic hypertensive patients (56±9 years; 56 women and 94 men) without manifest coronary artery disease to determine prevalence, severity, and interaction of VA and significant ST segment changes induced by daily activities. One third of the patients were randomized to 4 weeks of placebo and restudied for spontaneous variability of the two parameters. All patients were included in a 3-year follow-up study. VA were observed in 129 of 150 hypertensive patients (86%) and peaked in the early morning and late afternoon. Twenty-two patients (15%) had ventricular tachycardia; 20 patients (13%) had nonsustained ventricular tachycardia. Transient ST-segment depression observed in 47 patients (33%; mean incidence, 2.7±0.8 episodes/24 hr) showed a characteristic circadian variation similar to VA and were asymptomatic in 93% of the episodes. At the time of transient ST-segment depression, VA increased 4.6 times (p<0.01). After 4 weeks of placebo, marked variations in the incidence of VA (VA suppression rate >100%, or increase >400%) were observed in 29% of the patients, and in 60% of all patients repetitive VA were present in only one of the two Holter recordings. Day-and-night variations of VA and transient ST-segment changes were highly reproducible during the placebo period. After 3 years of follow-up, eight of 146 patients (5%) had suffered myocardial infarction, and five patients had died from cardiac events (three patients died from sudden cardiac death). Logistic regression analysis revealed left ventricular hypertrophy (relative risk, 6.1; p<0.01) and transient ST-segment abnormalities during daily activities (relative risk, 4.4; p<0.05) to be of independent prognostic significance to predict cardiac events during follow-up instead of repetitive VA (relative risk, 1.3; NS).

Conclusions. VA associated with a high spontaneous variability and predominantly asymptomatic transient ST-segment changes are common in hypertensives; the interaction of both risk factors may provide an important link for fatal VA. Antiarrhythmic therapy is not to be recommended in the majority of patients. Presence of left ventricular hypertrophy and transient ST-segment changes were the most powerful predictors of cardiac events during the follow-up. (Circulation 1992;85:1808–1815)

Key Words: hyper tension • ventricular arrhythmias • prognosis

Hypertensive heart disease is a major risk factor for the development of coronary artery disease and sudden cardiac death.1–5 Recent interest has focused on the presence of potentially malignant ventricular arrhythmias in patients with systemic hypertensive disease because sudden death is caused by ventricular fibrillation or rapid tachycardia in almost all monitored cases.6–9

In the presence of left ventricular (LV) hypertrophy, ventricular arrhythmias (VA) are common in treated or temporarily untreated patients.2,6,7 Recently, James et al.9 described a 26% prevalence of repetitive arrhythmias in untreated hypertensives; in that study, hypokalemia instead of LV hypertrophy was predictive for the presence of VA. This finding had also been discussed in the Multiple Risk Factor Intervention Trial (MRFIT) study10 and enhanced the debate on (drug-induced) hypokalemia as an important arrhythmogenic cofactor in hypertensive patients.11,12 Data on prevalence, spontaneous variability, and prognostic relevance of VA in untreated normokalemic hypertensives are missing.

An association between hypertensive disease and fatal arrhythmias has also been gathered from victims of
sudden cardiac death. In these patients, hypertensive disease or necropsy findings of LV hypertrophy were common. In addition, most of the studies also stressed the uncertain role of myocardial ischemia because of the high prevalence of ST segment depression in sudden cardiac death patients. However, myocardial ischemia as a potential link to sudden death is frequently not symptomatic in hypertensive patients. Recent use of stress testing in angiographically studied hypertensive patients indicates a high prevalence of asymptomatic myocardial ischemia. Similar data were obtained during daily activities by Holter recordings in another invasively controlled group of hypertensive patients and therefore raised the question of the prognostic impact and potential interaction with VA.

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In this prospective trial, 150 untreated and normokalemic hypertensive patients were studied to assess prevalence and interaction of VA and significant ST segment changes during 24-hour Holter recording. Spontaneous variability of both parameters was determined by re-studying a randomized subgroup of 50 patients after 4 weeks of placebo. For prognostic assessment, all patients were reassessed after 3 years of follow-up.

Methods

Patient Selection

From 1984 through 1986, 150 consecutive patients referred for antihypertensive treatment were enrolled in this study. There were 56 women and 94 men with a mean age of 56±9 years (range, 35–79 years). Informed consent was obtained from all patients.

Patients were included in the study if systolic and diastolic pressures were >160 and >95 mm Hg, respectively, on 3 consecutive days (three measurements per day separated by 10-minute intervals) after 15 minutes resting in the horizontal position. Presence of different ECG criteria of LV hypertrophy documented on surface ECG on day 3 are summarized in Table 1. Previous effective treatment of hypertension disqualified the patient from the study, and ineffective or untolerated treatment was stopped at least 1 week before assessment of the baseline criteria. Exclusion criteria included diagnostic evidence of symptomatic coronary artery disease or previous myocardial infarction based on history, surface ECG, and when suspected, exercise testing; hypertension caused by pheochromocytoma, aortic coarctation, etc.; patients with malignancies, pacemaker, atrial fibrillation, Wolff-Parkinson-White syndrome, valvular heart disease, heart failure (New York Heart Association class >II), second- and third-degree atrioventricular block; and patients with serum potassium levels less than 3.5 mmol/l. Concomitant medication with β-blocking agents, calcium channel–blocking agents, antiarrhythmic agents, potassium-depleting diuretics, and digitalis was not allowed.

Study Design

All patients (group A) underwent baseline examination including ECG, 24-hour Holter monitoring (analyzed time, >21 hours per patient), and repeated measurements of electrolyte plasma concentration. Blood pressure measurements were taken at the same time under standardized conditions (three consecutive measurements, separated by 10-minute intervals, after 15 minutes in horizontal position).

After baseline study, a subgroup of 50 of 150 patients (group B) were selected by randomization and treated with placebo twice a day for 4 weeks. In all other patients individual antihypertensive treatment was initiated, and the patients only were followed for prognostic reasons. All patients on placebo were restudied after 4 weeks of treatment, and at this time all baseline measurements were repeated.

Holter Recordings

All Holter recordings were performed using a two-channel bipolar recorder and analyzed semiautomatically after digitalization by a Cardiodata MK4 at the University of Freiburg. After careful preparation of the patient’s skin, electrodes were positioned to obtain leads CM2 and CM5 and tested for artifact elimination by changing body position. Patients were carefully instructed to closely report daily activities in a detailed diary and to mark symptoms such as palpitations or angina pectoris by pressing a button on the event marker of the Holter recorder.

### Table 1. Baseline Data in Group A (All Patients) and Group B (Patients Randomized to Placebo)

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>Group A (n=150)</th>
<th>Group B (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (men, women)</td>
<td>94 (6%)</td>
<td>33 (17%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56±9</td>
<td>55±10</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>75±6</td>
<td>74±6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170±9</td>
<td>169±11</td>
</tr>
<tr>
<td>Blood pressure (RR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic RR (mm Hg)</td>
<td>174±9</td>
<td>173±10</td>
</tr>
<tr>
<td>Diastolic RR (mm Hg)</td>
<td>97±6</td>
<td>96±7</td>
</tr>
<tr>
<td>Surface ECG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>6 (4%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sokolow-Lyon index</td>
<td>16 (11%)</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>Romhilt and Estes</td>
<td>14 (9%)</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Murphy, McLenachan</td>
<td>15 (10%)</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Casale</td>
<td>26 (17%)</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>Pathological ST changes</td>
<td>17 (12%)</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>24-Hour Holter ECG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single PVB (hour⁻¹)</td>
<td>129 (86%)</td>
<td>41 (82%)</td>
</tr>
<tr>
<td>PVB 0–10</td>
<td>63 (42%)</td>
<td>23 (46%)</td>
</tr>
<tr>
<td>PVB 10–100</td>
<td>48 (32%)</td>
<td>14 (28%)</td>
</tr>
<tr>
<td>PVB 100–1,000</td>
<td>27 (18%)</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>PVB &gt;1,000</td>
<td>12 (8%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Polymorphic PVB</td>
<td>115 (77%)</td>
<td>37 (74%)</td>
</tr>
<tr>
<td>Ventricular pairs/tachycardia</td>
<td>40 (27%)</td>
<td>13 (26%)</td>
</tr>
<tr>
<td>Episodes of ST depression</td>
<td>47 (33%)</td>
<td>14 (29%)</td>
</tr>
</tbody>
</table>

PVB, premature ventricular beats.

Differences between the two groups were not significant.

Data are given as number of patients or mean±SD.
All Holter analyses were made without knowledge of clinical data and follow-up of the patient and were not considered for any clinical decision concerning the diagnostic and therapeutic regimen. Exceptions were made only when a sustained tachyarrhythmia was documented, which was the case in one patient with atrial fibrillation. During Holter analysis, calibrated tapes were replayed under visual control at 60 times normal speed. ST segment analysis was based on trend recordings of the difference between a reference point within the PQ segment and a point 80 msec after the J point within the ST segment. The relative ST segment deviation and heart rate were averaged over periods of 8 seconds and continuously plotted on a strip-chart recorder. ST segment depressions resulted in negative shifts of the ST segment trend. QRS complexes different from the sinus beat morphology were excluded from analysis. Horizontal or downsloping episodes with ST segment depression of \( \geq 0.1 \) mV lasting for \( > 1 \) minute were considered significant, and each was recorded at a paper speed of 25 mm/second. In patients with electrocardiographic evidence of LV hypertrophy, only an additional amount of ST segment depression of \( \geq 0.15 \) mV lasting for \( > 1 \) minute was considered. Episodes of ST segment depression were analyzed for duration, maximal ST segment depression, and heart rate at the beginning of ST segment depression.

**Follow-up**

After 36 months from entry in the study, an attempt was made to contact all patients to determine survival. A questionnaire evaluated the continuation of antihypertensive treatment and the occurrence of nonfatal myocardial infarction and fatal events such as myocardial infarction, death, and (SCD, defined as death within 1 hour after occurrence of symptoms). In patients with fatal events, further information was collected from the relatives to better classify the event. The diagnosis of coronary artery disease was only considered when documented by invasive measurements or scintigraphic imaging.

**Statistical Analysis**

Data are expressed as mean±SD. Differences in group means were analyzed using the two-tailed unpaired \( t \) test. A \( \chi^2 \) square test was used to determine significance of symptomatic and asymptomatic ST segment depression detected by Holter monitoring. Results were considered to be significantly different when confidence limits exceeded 95% \( (p<0.05) \). Univariate analysis and Cox's proportional hazards model were used to determine prognostic significance of clinical variables.

**Results**

Of 150 hypertensive patients included in this study (group A), 129 patients (86%) exhibited VA, and 47 of 144 patients (33%) without bundle branch block had episodes of transient ST segment depression. The 50 patients randomized to 4 weeks of placebo (group B) were representative for the baseline study group concerning all clinical parameters listed in Table 1.

**Blood Pressure at Baseline and After 4 Weeks of Placebo**

At baseline, systolic blood pressure was \( 174\pm9 \) mm Hg and the diastolic value was \( 97\pm7 \) mm Hg. After placebo, systolic blood pressure was reduced by \( > 20 \) mm Hg in 15 patients (30%); an increase of \( > 20 \) mm Hg was observed in nine patients (18%). Mean systolic blood pressure decreased to \( 164\pm8 \) mm Hg \( (p<0.05) \), but the diastolic value was unchanged (96±6 mm Hg).

**ECG Findings at Baseline Registration and After Placebo Treatment**

At baseline, PQ interval was \( 165\pm36 \) msec (AV block I, two of 150 patients, 1%), QRS interval was \( 87\pm17 \) msec, and QT, interval was \( 399\pm3 \) msec. Presence of LV hypertrophy, left bundle branch block, and pathological ST segment changes are summarized in Table 1.

**Ventricular Arrhythmias During 24-Hour Holter Monitoring**

During baseline, 129 of 150 patients (86%) had VA, which were polymorphic in 115 patients (77%; Table 1 and Figure 1). In patients with ventricular pairs (22 patients, 15%) or salvos (20 patients, 13%), frequent episodes (more than five episodes per 24 hours) were rare (pairs, five patients, 3%; salvos, four patients, 3%). The incidence of ventricular pairs and salvos was not different when hypertensive patients \( \leq 55 \) years (24%), \( 55-65 \) years (27%), and \( > 65 \) years of age (29%) were considered. The longest episode lasted 12 beats and was polymorphic. The day-and-night variability of VA is given in Figure 2.

In the presence of a positive Sokolow-Lyon index, ventricular pairs and salvos (nine of 16 patients versus...
31 of 134 patients, \( p < 0.01 \) were more common (mean incidence of premature ventricular beats [PVB], 578±678 versus 402±1,194 PVB per 24 hours; ventricular pairs and salvos, 4.5±36 versus 3.1±54 episodes per 24 hours).

**ST Segment Depression During 24-Hour Holter Recording**

Of 144 hypertensive patients without bundle branch block, 47 patients (30%) had transient episodes of ST segment depression (mean incidence, 2.6±1.8 episodes per 24 hours; mean total duration, 15±14 minutes). Altogether, 111 of 120 episodes (93%) were asymptomatic, and 104 episodes (83%) were preceded by a heart rate increase (>10 beats per minute). Transient episodes of ST depression occurred with a characteristic day-and-night variability. Peak frequency of episodes was observed during the early morning and late afternoon hours, whereas episodes of ST segment changes were rare during the night (Figure 2).

A positive Sokolow-Lyon index was associated with a 2.8-fold higher prevalence of dynamic ST segment changes (13 of 16 patients, 81%; mean incidence of episodes, 3.4±3 per 24 hours; mean total duration, 19.2±6 minutes per 24 hours) compared with all other patients (29%, \( p < 0.01 \)). Forty-two of 44 episodes (95%) were asymptomatic.

**Prevalence and Spontaneous Variability of Ventricular Arrhythmias and ST Segment Depression After 4 Weeks of Placebo**

In the randomized patients, mean incidence of PVB at baseline (456±878) and after placebo were similar (479±945 PVB per 24 hours). However, PVBs were reduced by ~100% in five patients (12%) or increased by >400% in seven patients (14%). Three patients exhibited PVB only during the second Holter recording. Spontaneous VA variability is shown in Figure 3.

Ventricular pairs and salvos were present at baseline in 15 of 50 patients (30%) and in 13 of 50 patients (26%) after 4 weeks of placebo. However, of a total of 20 patients with ventricular pairs and salvos, 12 patients (60%) showed ventricular pairs or salvos in only one of the two Holter recordings. The mean incidence of these arrhythmias was similar before and after placebo (3.4 versus 3.7 episodes per 24 hours); absolute mean percentage of changes (percent decrease or increase) was 47±39%.

After 4 weeks of placebo, ST segment changes during daily activities were present in 13 of 14 patients who already suffered from this abnormality during baseline registration. Day-to-night variations were unchanged compared with baseline registration before placebo, despite marked variations in the number of episodes per patient (mean absolute percentage of increase or decrease: 64±14%).

**Interaction of Ventricular Arrhythmias and ST Segment Changes**

In hypertensives with ST segment depression, PVB were present in 46 of 47 patients (98%, NS), and ventricular pairs and salvos were present in 31 of 47 patients (66% versus 10% in all other patients, \( p < 0.001 \)). Total incidence of PVB was 601±588 PVB per 24 hours (versus 372±494 in all other patients, \( p < 0.05 \)) and the total incidence of ventricular pairs and salvos was 4.9±27 episodes per 24 hours (versus 2.9±49 episodes per 24 hours, \( p < 0.05 \)). During a total of 1,786 minutes of ST segment depression observed in all patients, 5,310 PVB (2.9 per minute) occurred compared with 5,149 minutes without ST segment depression and a total of 28,052 PVB (0.63 per minute, \( p < 0.01 \)). In 21 patients, polymorphic types of PVB occurred only during episodes of ST segment depression. The day-to-night variation of arrhythmias and ST segment depression were concordant (Figure 2).

The correlation of VA, Sokolow-Lyon index, and ST segment depression is illustrated in Figure 4. A positive relation \( (r=0.72) \) was present only in patients with ventricular pairs and salvos.

**Follow-up of Patients With Hypertensive Disease**

Data on 146 of 150 patients could be collected after 3 years of follow-up (Table 2). Eleven patients died: three
Total duration of TIE (sec/24-h-Holter)

**FIGURE 4. Scatterplot showing correlation between Sokolow-Lyon index and total duration of transient ischemia episodes (TIE) is given for patients with (●) and without (□) ventricular pairs and tachycardia.**

patients died from sudden cardiac death, one patient from myocardial infarction, one patient from heart failure, and six patients from unknown or noncardiac causes. All three patients with SCD had ventricular pairs and salvos and transient ST segment changes at baseline. Eight patients exhibited nonfatal myocardial infarction during this time, and coronary artery disease was diagnosed in 15 of 135 alive and responding patients (11%).

Univariate analysis showed that transient ST segment changes, as well as left ventricular hypertrophy and the presence of ventricular pairs and tachycardia during Holter monitoring were of prognostic relevance (Table 2). Cox's proportional hazards model considered LV hypertrophy (separate analysis for Sokolow-Lyon index and Casale index), arrhythmias of Lown class IV, transient ST segment depression, and systolic blood pressure >180 mm Hg for prognostic analysis. Of these variables, independent prognostic value for cardiac death or myocardial infarction was observed for episodes of transient ST segment depression (risk ratio, 4.4; p<0.05) and LV hypertrophy (Sokolow-Lyon index) (risk ratio, 6.1; p<0.01). The use of other ECG criteria for the diagnosis of LV hypertrophy did not increase the prognostic impact of this risk factor. During multivariate analysis, ventricular pairs and tachycardia were associated with a lower risk ratio (1.3), which may be due to a close relation of repetitive ventricular arrhythmias and episodes of transient ST segment depression (Spearman correlation coefficient, 0.58).

Of all surviving patients, 111 patients (82%) were still treated with antihypertensive medication (e.g., diuretics, 83 of 111 patients; β-blocking agents, 76; calcium channel--blocking agents, 41; angiotensin converting enzyme inhibitors, 35).

**Discussion**

The present study provides new insights into the prevalence and spontaneous variability of abnormal ECG findings in untreated normokalemic hypertensives. Ventricular pairs and salvos and predominantly asymptomatic transient ST segment changes suggestive

**TABLE 2. Cardiac Events in 140 Hypertensive Patients During 3-Year Observation Period**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Alive patients (n=127)</th>
<th>Nonfatal myocardial infarction (n=8)</th>
<th>Cardiac death (n=5)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (male, female)</td>
<td>96, 31</td>
<td>6, 2</td>
<td>3, 2</td>
<td>NS</td>
</tr>
<tr>
<td>Age (mean years)</td>
<td>55±9</td>
<td>59±3</td>
<td>63±5</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>173±10</td>
<td>180±9</td>
<td>184±7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>97±6</td>
<td>97±2</td>
<td>99±2</td>
<td>NS</td>
</tr>
<tr>
<td>ECG LVH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sokolow-Lyon*27</td>
<td>9</td>
<td>3</td>
<td>2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Casale*31</td>
<td>14</td>
<td>4</td>
<td>3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Abnormal ST changes</td>
<td>9</td>
<td>3</td>
<td>2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Holter data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single PVB (hour⁻¹)</td>
<td>109</td>
<td>7</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>PVB 10–100</td>
<td>40</td>
<td>3</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>PVB 100–1,000</td>
<td>21</td>
<td>2</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>PVB &gt;1,000</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Polymorphic PVB</td>
<td>100</td>
<td>7</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Ventricular pairs/tachycardia</td>
<td>28</td>
<td>4</td>
<td>4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Episodes of ST depression</td>
<td>32</td>
<td>6</td>
<td>4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ST depression+PVB</td>
<td>32</td>
<td>6</td>
<td>4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ST depression+repetitive PVB</td>
<td>20</td>
<td>3</td>
<td>4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

LVH, left ventricular hypertrophy; PVB, premature ventricular beats.

Six patients who died from unknown or noncardiac causes were excluded from analysis. Criteria for LVH are included in references.

* Alive patients versus all patients with myocardial infarction or cardiac death.

Data are given as number of patients or mean±SD.
of myocardial ischemia are common findings in one third of hypertensives and correlates with the presence of LV hypertrophy. A similar day-and-night variability and at least a temporal coincidence of VA and ST segment changes provide evidence of an important link to the increased risk of sudden cardiac death in hypertensives. Multivariate analysis shows LV hypertrophy and the presence of episodes of transient ST segment depression to be independent prognostic value for cardiac events during follow-up.

Prevalence and Clinical Importance of Ventricular Arrhythmias in Hypertensive Patients

It is well known that systemic hypertension, with and without the presence of LV hypertrophy, carries an increased risk of sudden tachyarrhythmic death.\(^1\)-\(^5\) The underlying mechanisms are still questioned, but ventricular pairs and salvos facilitated by arrhythmogenic cofactors (e.g., hypokalemia, myocardial ischemia) may play a dominant role. McLenahan et al\(^6\) reported an 8% prevalence of nonsustained ventricular tachycardia, increasing fourfold in the presence of LV hypertrophy. A study by Messerli et al\(^7\) also stressed the proarrhythmic effects of LV hypertrophy but included treated or only temporarily untreated patients and was characterized by a very low prevalence of arrhythmias in the control group. More recently, James et al\(^8\) studying untreated hypertensives, observed a 12% prevalence of patients with >500 PVB per 24 hours; 40% of patients had ventricular pairs and salvos. LV hypertrophy was proarrhythmic only in the setting of hypokalemia, which limits conclusions from the former two studies in which diuretics and hypokalemia were observed in nearly half of the patients. The crucial role of hypokalemia was also stressed by the Oslo study\(^9\) and the MR FIT trial,\(^10\) with both providing evidence of more frequent events of SCD in the subgroups of patients with potassium-depleting diuretic medication.

The present study was directed to a large group of untreated normokalemic hypertensives. Systemic hypertension was restrictively diagnosed by repetitive blood pressure measurements 1) to assess data in the early and uncomplicated state of hypertension, 2) not to rely on the ECG signs of LV hypertrophy, 3) because disorders of microcirculation are superior to LV hypertrophy for the induction of severe VA, and 4) because the Framingham study has gathered evidence that the clinical diagnosis of hypertension alone carries an increased risk of coronary artery disease and SCD.

VA were a common finding in >80% of hypertensive patients, 18% of patients suffered from >100 PVB per 24 hours, 8% exhibited >1,000 PVB per 24 hours, and 27% of patients had ventricular pairs or tachycardia. Although no normotensive control group was included in this study, the prevalence of frequent VA and ventricular pairs and salvos described in normal individuals with a mean age of 55–60 years is markedly lower.\(^35\)-\(^41\) Ventricular ectopies peaked during the early morning and late afternoon, which was well reproducible after 4 weeks of placebo. By contrast, the number of single and especially ventricular pairs and salvos showed marked variability. Therefore, 60% of patients exhibited ventricular pairs and salvos in only one of two Holter recordings, and 14% of patients showed a >400% increase in VA.\(^42\) There was a marked interindividual variability, poorly predictable by the number of VA at baseline. Therefore, the high spontaneous arrhythmia variability in hypertensive patients, the uncertainty about the interaction of class I agents and LV hypertrophy, or about the suppression criteria and, the overall benefit of conventional antiarrhythmic therapy, recently questioned in the Cardiac Arrhythmia Suppression Trial study,\(^43\) favor a very restrictive consideration of antiarrhythmic therapy and question the potential mechanisms involved in the genesis of (fatal) ventricular arrhythmias in the presence of hypertensive disease.

The mechanisms that may cause or facilitate VA are still under discussion: 1) at the cellular level: action potential prolongation associated with myocyte hypertrophy, decrease of conduction velocity, lower resting membrane potential, and, conversely, dispersion of refractoriness\(^44\)-\(^46\); 2) at the tissue level: diminished subendocardial coronary vascular reserve, and, under stress, subendocardial ischemia\(^47\),\(^48\) because of a long-term increase in myocardial oxygen demand that enhances differences in conduction velocity and recovery of excitability\(^49\) and facilitates the occurrence of VA\(^50\); 3) the reduced metabolic tolerance to ischemia\(^51\), lowering the fibrillation threshold; and 4) clinically, a close correlation between circadian blood pressure changes and the occurrence of ventricular arrhythmias.\(^52\) The latter three points stress the role of myocardial oxygen supply for the electrical instability of the hypertensive heart. Unfortunately, myocardial ischemia in hypertensive patients is frequently asymptomatic\(^23\) and, until recently, underestimated as to its incidence and prognostic relevance.\(^21\),\(^23\),\(^53\)

Prevalence and Severity of Symptomatic and Asymptomatic ST Segment Changes Suggestive of Myocardial Ischemia

Recent data utilizing exercise testing in angiographically studied hypertensives with and without overt coronary artery disease indicated a high prevalence of asymptomatic ST segment depression.\(^23\) Holter monitoring also showed that transient episodes of silent ST segment depression during daily activities were common in hypertensive patients with\(^23\) and without overt coronary artery disease.\(^24\)

In this study, one third of all 150 hypertensive patients had evidence of transient episodes of myocardial ischemia. As a typical finding, ST segment changes were preceded by heart rate increase in 88% of episodes. Most interestingly, 93% of the episodes were asymptomatic. Episodes of ST segment depression, once observed in a patient, were a well reproducible finding after 4 weeks of placebo and showed a characteristic day-and-night variation.

Interaction of Ventricular Arrhythmias and Myocardial Ischemia

This study shows that there is at least a close temporal relation between the occurrence of VA and episodes of transient ST segment depression. At the time when transient myocardial ischemia is evidenced by heart rate–related ST segment depression, the prevalence of VA increases by fourfold or fivefold. It still remains uncertain whether the two risk factors stimulate each
other or whether both VA and ST depression are covariate responses to an increased sympathetic drive. The prognostic impact of these observations becomes evident when we consider the well-known circadian rhythms of blood pressure and SCD.\textsuperscript{52,54} Blood pressure is highest and SCD most frequent during the early daytime, when hypertensive patients also suffer from an increase of ST segment depression and VA.

The fatal interaction of mostly asymptomatic myocardial ischemia and malignant VA, recently and controversially stressed in patients with known coronary artery disease,\textsuperscript{55,56} may therefore provide a potential link to the increased risk of coronary artery disease and sudden death in hypertensive patients.\textsuperscript{52} In this study, univariate analysis showed that frequently asymptomatic episodes of myocardial ischemia during daily activities, presence of LV hypertrophy, and presence of ventricular pairs and tachycardia were predictive for cardiac events during the follow-up. However, from a close interrelation of transient ST segment changes and repetitive VA, only transient ST segment changes and the presence of LV hypertrophy was shown to be of independent prognostic value. All three patients who died from SCD suffered from episodes of transient myocardial ischemia associated with the occurrence of VA. It would seem to be an important issue during the next years to early identify hypertensive patients who suffer from high risk of ischemic or arrhythmogenic complications. Presence of LV hypertrophy, transient episodes of myocardial ischemia, and the presence of ventricular pairs and salvos may help in early identification of these high-risk patients.

**Clinical Implications**

This study has several major implications for the diagnostic assessment and therapeutic regimen in patients with systemic hypertension. Single and repetitive VA are very common in untreated normokalemic hypertensives and show a characteristic day-and-night variation, similar to the circadian rhythm of SCV. However, with regard to the high spontaneous long-term variability, antiarrhythmic therapy in hypertensive patients should be used very restrictively. By contrast, from the interaction with VA and the independent prognostic value of transient episodes of frequently asymptomatic myocardial ischemia during daily activities, as well as from the worsened prognosis of hypertensive patients when coronary artery disease becomes manifest (myocardial infarction, etc.), ECG findings suggestive of transient myocardial ischemia should carefully be considered in this patient group. Hypertensive patients showing both risk factors or presenting with LV hypertrophy and evidence of myocardial ischemia during daily activities on 24-hour Holter recording appear to have the highest risk of fatal tachyarrhythmic events and should, therefore, be directed to consequent diagnostic and therapeutic interventions to cure or prevent myocardial ischemia instead of being treated with antiarrhythmics.

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