# Prevalence and Circadian Variations of ST-Segment Depression and Its Concomitant Blood Pressure Changes in Asymptomatic Systemic Hypertension

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Coronary artery disease is a major complication of hypertension; one of its manifestations is silent ischemia. The aim of this study was to assess the prevalence and circadian distribution of ST-segment depression together with concomitant blood pressure (BP) and heart rate variations. One hundred patients (male:female ratio 1:1) with a mean age (± SD) of 51 ± 8 years underwent ambulatory monitoring using the combined AMP 5600 monitor which simultaneously records a continuous Holter electrocardiogram and intermittent noninvasive BP measurements at 15-minute intervals, with extra measurements triggered by detection of a horizontal or downsloping ST depression (>1 mm and >60 seconds). Cardiovascular risk factors were fully evaluated in all patients; accurate and reliable echocardiogram enabled left ventricular mass index to be calculated in 52 patients. Twenty-three patients (15 men and 8 women) experienced a total of 72 episodes of ST depression. Duration of such episodes (mean ± SD) was 132 ± 65 seconds and amplitude was 1.51 ± 0.55 mm. Circadian distribution showed 2 peaks: on awakening and in the late afternoon periods. The mean ambulatory BP load was greater in the patients with than without ST-segment depression for both systolic and diastolic BP (135 ± 14 vs 129 ± 15 and 84 ± 8 vs 79 ± 10 mm Hg, respectively; $p < 0.01$). Plasma glucose (5.83 ± 0.70 vs 5.46 ± 0.71 mmol/L; $p = 0.04$) and self-rated work-related stress levels (22% vs 13% ; $p = 0.03$) were also higher in patients with ST-segment depression. There were no significant differences between groups for clinical parameters, left ventricular mass index, and other cardiovascular risk factors. During ST depression episodes, systolic BP increased by 9 ± 15 mm Hg, diastolic BP by 7 ± 11 mm Hg, and heart rate by 5 ± 17 beats/min. Thus, 24-hour Holter electrocardiographic monitoring showed ST depression episodes in 23 of 100 hypertensive patients (23%); ambulatory BP load was greater in these patients. BP variations, and mainly its elevation, may trigger such episodes of ST-segment depression.

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Several studies have shown that the prevalence of ST-segment depression episodes was higher in hypertensive subjects during the electrocardiogram at rest, exercise testing, or Holter monitoring compared with normotensive subjects,[1–3] and that they occur mainly in the morning.[4,5] Investigations used to elucidate the pathophysiology of this condition include electrocardiographic analysis combined with exercise testing, myocardial scintigraphy, coronary angiography, and assessment of other cardiac and circulatory hemodynamic and neurohormonal parameters.[1,3,6–8] From these studies, dysregulation of coronary blood flow and reserve has been found even in asymptomatic hypertensive patients with apparently normal coronary arteries, with or without left ventricular hypertrophy.[9–11] However, although several studies have shown that systolic BP and heart rate are the main factors triggering ischemia in overt coronary artery disease,[12,13] to our knowledge, few studies have analyzed those parameters (i.e., mainly heart rate and mean BP) in untreated[4,5,14] or treated[15] hypertensive patients. In none of those studies was BP measured specifically during episodes of ST-segment depression. The aim of the present study was: (1) to determine the prevalence of ST-segment depression in asymptomatic untreated patients with mild to moderate hypertension, and (2) to describe the circadian variation of BP and heart rate and assess BP and heart rate changes during episodes of ST-segment depression.

## METHODS

**Patients:** One hundred fourteen male or female outpatients (aged 40 to 75 years) with untreated mild to moderate essential hypertension and no clinical evidence of coronary artery disease were preselected by several cardiologists. Patients returned to the clinic a few days later to be screened for etiologic and risk factors as described elsewhere,[16] and patients with serum potassium levels within the normal range were fitted with an ambulatory BP and Holter electrocardiographic monitor between 0830 and 1000. They were also asked to evaluate their own physical, intellectual, family, and business stress using the self-rated stress scale shown in Table I. All patients gave informed consent and the study was approved by the Broussais Hospital Ethics Committee.

**Casual blood pressure determination:** BP and heart rate were measured on 3 occasions: at the preselection visit, before fitting the ambulatory monitor, and at the

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day of hospital workup. Measurements were obtained in triplicate at 2-minute intervals after 10-minutes rest in the supine position, and in duplicate after standing for 2 minutes using a mercury sphygmomanometer with an appropriate cuff circumference (systolic and diastolic BP, Korotkoff phases I and V, respectively). The means of the triplicate supine values recorded before fitting the monitor were used for statistical analysis.

**Ambulatory blood pressure and Holter electrocardiogram:** Ambulatory BP and Holter monitoring were performed over 24 hours using the combined AMP 5600 microrecorder (Advanced Medical Products), which has been shown to be reliable, specific, and sensitive for the electrocardiographic signal according to AAMI guidelines, and accurate for BP measurements by comparison with the intraarterial method. This monitor allows Holter recording with continual analysis of the ST-segment, and intermittent, fully automatic, programmable BP measurements, recordings at 15-minute intervals, and an extra BP measurement triggered by the onset of ST-segment depression (defined as 1 mm amplitude for a duration of 60 seconds occurring 80 ms after the J point). The electrocardiographic signal was recorded from leads CM2 and CM5; the entire electrocardiogram was read by an observer, and all ST-segment depression episodes were printed out for manual checking (Figure 1). Use of the 24-hour Holter electrocardiogram to study ST-segment depression in hypertensive patients has been evaluated in several reports, and its reproducibility after 4 weeks of placebo has been demonstrated by Zehender,[5] Trenkwalder,[14] Tzivoni[17] and co-workers. The quality of BP data was systematically checked against a hard copy of the Korotkoff sounds recorded during cuff deflation (Figure 1); data were expressed by their mean values over the entire 24 hours, and during the day (0700 to 2200) and night (2200 to 0700). During ST depression episodes, heart rate was determined at the onset of the episode from the continuous electrocardiographic signal recording; BP measurements were obtained 60 seconds

**TABLE 1** Comparison of Clinical Characteristics and Cardiovascular Risk Factors Between Patients With and Without ST-Segment Depression

| | Patients With ST-Segment Depression (n = 23) | Patients Without ST-Segment Depression (n = 77) |
|---|---|---|
| Sex | | |
| Men | 15 | 35 |
| Women | 8 | 42 |
| Age (yr) | 51 ± 8 | 50 ± 8 |
| Weight (kg) | 72 ± 15 | 69 ± 13 |
| Height (cm) | 167 ± 8 | 167 ± 8 |
| Duration of hypertension (mo) | 23 ± 60 | 33 ± 67 |
| Smoker | 6 (26) | 22 (29) |
| Alcohol | 9 (39) | 27 (35) |
| Blood glucose (mmol/L) | 5.83 ± 0.70 | 5.46 ± 0.71* |
| Total cholesterol (mmol/L) | 6.16 ± 0.9 | 6.05 ± 1.06 |
| Types of stress | | |
| None | 15 (65) | 58 (75) |
| Physical | 2 (9) | 0 (0) |
| Intellectual | 0 (0) | 0 (0) |
| Family | 1 (4) | 9 (12) |
| Business | 5 (22) | 10 (13)* |
| Left ventricular mass index ($g/m^2$) | 122 ± 37 | 111 ± 34 |

*p <0.05.
Values are expressed as mean ± 1 SD or number (%).

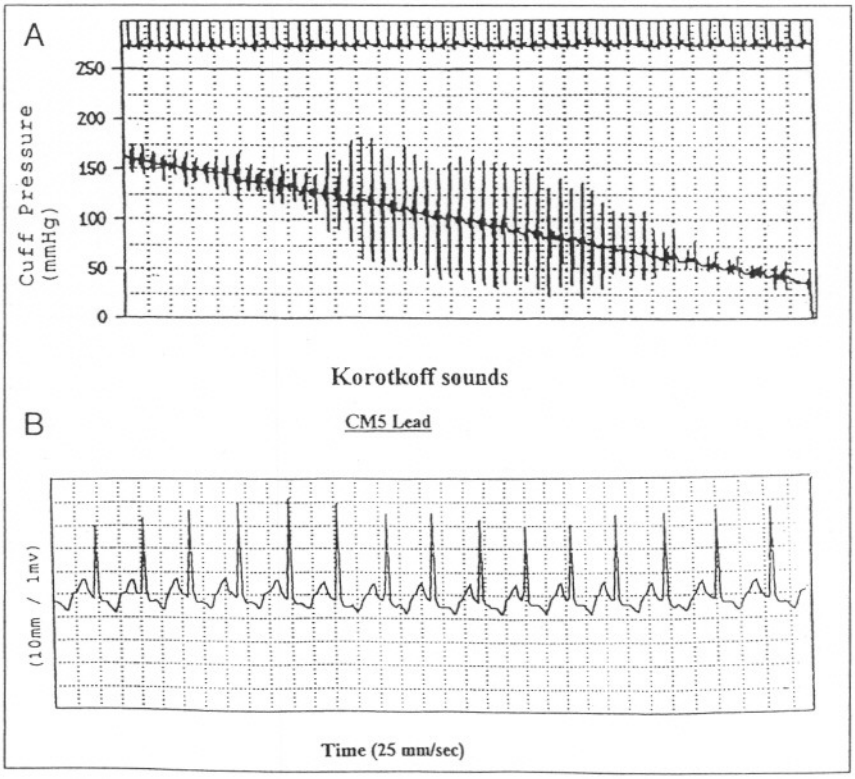


**FIGURE 1. Printing required by the observer to check the quality of blood pressure measurements by printing the Korotkoff sounds recorded during cuff deflation *(A)*, and the electrocardiographic signal by checking the full disclosure and editing the ST-segment depression *(B)*.**

**TABLE II** Comparison of Blood Pressure Values Between Patients With and Without ST-Segment Depression

| Blood Pressure (mm Hg) | Patients With ST-Segment Depression (n = 23) | Patients Without ST-Segment Depression (n = 77) |
|---|---|---|
| Office | | |
| Systolic | 163 ± 18 | 159 ± 17 |
| Diastolic | 102 ± 7 | 101 ± 8 |
| 24 Hours | | |
| Systolic | 135 ± 14 | 129 ± 15* |
| Diastolic | 84 ± 8 | 79 ± 10† |
| Daytime (0700–2200) | | |
| Systolic | 141 ± 15 | 136 ± 15 |
| Diastolic | 89 ± 9 | 85 ± 11* |
| Nighttime (2200–0700) | | |
| Systolic | 126 ± 15 | 119 ± 16 |
| Diastolic | 76 ± 9 | 71 ± 11* |

*p <0.05; †p <0.01.
Values are expressed as mean ± 1 SD.

after the onset due to the time required by the device to inflate and deflate the cuff. BP measurements triggered by the detection of ST-segment depression were used to calculate BP changes observed during ST depression. Two BP changes were calculated: BP modification between values during ST depression and mean 24-hour levels in the same patient; and (2) BP modification between values during ST depression and BP values recorded just before ST depression outset (<15 minutes before outset of ST depression since BP recordings were obtained automatically every 15 minutes).

**Echocardiography:** Echocardiography was performed by the same specialist according to American Society of Echocardiography guidelines[18] using a Sigma 44 color Doppler echocardiograph (Kontron Instruments, Basel, Switzerland). Left ventricular dimensions and ventricular septal and posterior wall thicknesses were measured in the parasternal view. Triplicate measurements were obtained over 3 consecutive cardiac cycles and the mean used to calculate left ventricular mass was determined according to the Devereux formula.[19] The mean was divided by the body surface area to give the normalized ventricular mass ($g/m^2$). Left ventricular hypertrophy was defined as an index of >133 $g/m^2$ in men and >110 $g/m^2$ in women.[19] Reproducibility of these measurements has been evaluated in our laboratory and published elsewhere.[20] Accurate echocardiography and reliable measurements of the left ventricular mass were obtained in 52 patients (28 men and 24 women).

**Statistical analysis:** Statistical analysis of mean ± SDs was performed using the NCSS program (Kaysville, Utah). Patients with and without episodes of ST-segment depression were compared using the chi-square test for qualitative parameters and Student's *t* test for quantitative parameters, with a significance level of $p < 0.05$.

## RESULTS

Ambulatory recordings were uninterpretable in 14 patients (technical problems with BP and with the electrocardiogram in 9 and 5 patients, respectively); thus, 100 patients (50 men and 50 women) were included in the analysis. Mean age ± SD was 51 ± 8 years,mean weight was 70 ± 14 kg, and mean body mass index was 24.9 ± 4.0 $kg/m^2$. Twenty-eight patients were daily cigarette smokers and 36 admitted regular drinking habits. Total plasma cholesterol was 6.08 ± 1.04 mmol/L and plasma glucose was 5.55 ± 0.72 mmol/L. Casual measurements were: mean systolic BP 160 ± 17 mm Hg, mean diastolic BP 101 ± 8 mm Hg, and mean heart rate 71 ± 12 beats/min. Mean 24-hour systolic and diastolic BP were 130 ± 15 and 80 ± 10 mm Hg, respectively; mean 24-hour heart rate was 77 ± 10 beats/min. The mean Sokolow-Lyon index (resting electrocardiogram) was 25 ± 9 mm; the left ventricular mass index obtained in 52 of 100 analyzed subjects was 114 ± 35 $g/m^2$ (men, 119 ± 35 $g/m^2$; women, 107 ± 35 $g/m^2$).

**Prevalence of ST-segment depression episodes:** Twenty-three patients (15 men and 8 women) had a total of 72 episodes of ST-segment depression, distributed as follows: ≥1 episode, 23 patients; ≥2 episodes, 21 patients; ≥3 episodes, 14 patients; ≥4 episodes, 7 patients; ≥5 episodes, 4 patients; and ≥6 episodes, 3 patients. The mean duration of episodes was 132 ± 65 seconds, and mean amplitude 1.51 ± 0.55 mm. During the ST-segment depression, systolic and diastolic BP values were 143 ± 24 and 90 ± 15 mm Hg, respectively, and concomitant heart rate was 78 ± 21 beats/min. The distribution of episodes showed circadian variation with 2 peaks, around awakening and in the late afternoon (Figure 2).

**Relation between clinical parameters, risk factors, and prevalence of ST-segment depression:** Table I compares

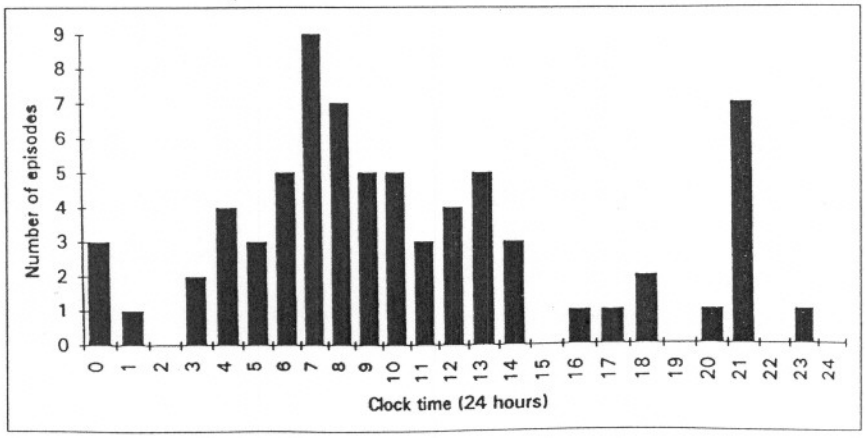


FIGURE 2. Circadian distribution of all 72 ST-segment depressions observed in the 23 patients.

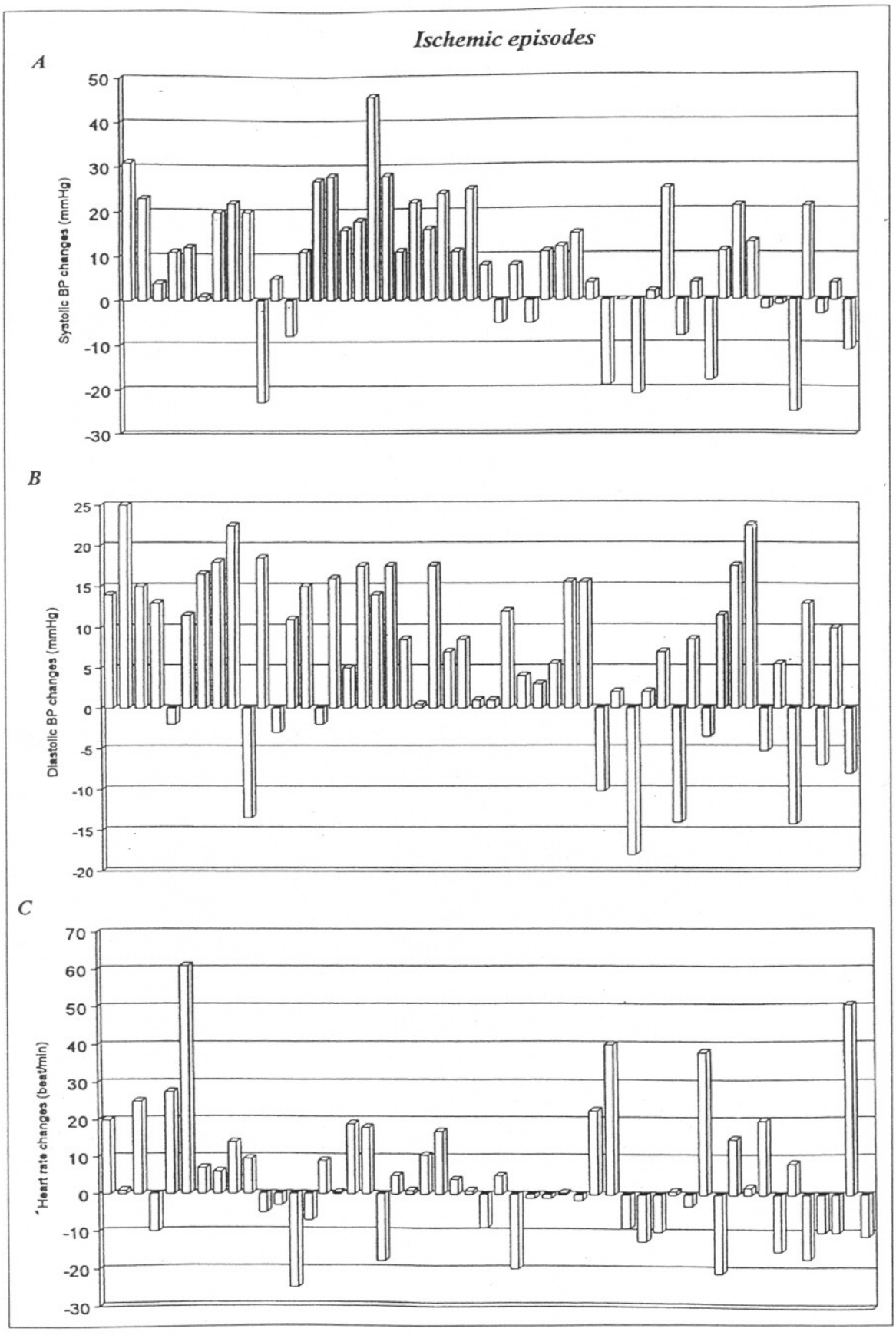


FIGURE 3. Changes in systolic *(A)* and diastolic *(B)* blood pressure (BP) and heart rate *(C)* observed during each recorded ST-segment depression and compared with 24-hour mean values (value during the ST-segment depression) in the same patient.

clinical parameters and the cardiovascular risk factors between patients with and without ST-segment depression. Risk factors differing between the 2 groups of patients were blood glucose (5.83 ± 0.70 vs 5.46 ± 0.71 mmol/L; p = 0.04) and self-rated, work-related stress (22% vs 13%; p = 0.03).

**Relation between ambulatory blood pressure and prevalence of ST-segment depression:** Table II shows that the mean ambulatory BP level was higher in patients with ST-segment depression. Al-though the difference was present at various times during the day, it was statistically significant over the entire 24 hours for both systolic and diastolic BP (135 ± 14 vs 129 ± 15 mm Hg; p <0.05, and 84 ± 8 vs 79 ± 10 mm Hg; p <0.01, respectively). There was a significantly higher proportion of patients with elevated ambulatory BP values, as defined by the international consensus reference values (>137/87 mm Hg), in the group with than without ST-segment depression (57% vs 31%; p <0.05). No difference in office BP measurements was noted between the 2 groups.

**Blood pressure and heart rate during ST-segment depression:** BP and heart rate variations during ST depression episodes can be analyzed with respect to either the mean 24-hour value or to the value preceding the ST-segment depression outset. For the 72 recorded ST episodes, 51 BP measurements were available during the ST depression. For 21 episodes, BP measurements were not obtained because of technical impossibilities.

**Variation from 24-hour mean values:** Figure 3 plots the differences between values recorded during ST-segment depression and the 24-hour mean for the systolic BP, diastolic BP, and heart rate. It shows that ST depression episodes were mainly associated with systolic and diastolic BP elevation, and that some occurred concomitantly with low-variation amplitude or even a decrease in BP. The pattern in heart rate variation was less clear, with an average change of <10 beats/min. The mean elevations in systolic and diastolic BP were 9 ± 15 and 7 ± 11 mm Hg, respectively, and in heart rate 5 ± 18 beats/min.

**Variation from the pre-ST-segment depression value:** Results were similar to those observed, with changes calculated on the basis of 24-hour mean values. Mean elevations (value during ST depression preceding value) of systolic and diastolic BPs were 6 ± 14 and 4 ± 10 mm Hg, respectively, and for heart rate 3 ± 15 beats/min.

## DISCUSSION

**Prevalence of ST-segment depression:** In this study, we used 24-hour monitoring as recommended by Tzivoni et al[17] who showed that a 1-day recording appears to be sufficient for evaluation of ischemia during daily activities. These results and criteria of ≥1 mm and 60 seconds have been confirmed by Zehender et al[5] after 4 weeks of placebo. A variety of factors can affect ST-segment changes and lead to false-positive findings[21] which can be ruled out in this study. According to this methodology, ST-segment depression was observed in 23% of patients; this frequency is slightly less than that in published reports: between 27% and 33%.[2,5,11] Older patients were involved in the previous studies and, as shown by other investigators, the incidence of ST-segment and T-wave abnormalities increase progressively with age.[2,4,14] Mirvis et al[12], in a multivariate model, showed a significant correlation between ST-T-wave abnormalities and hypertension. These episodes of ST depression, which are suggestive of silent ischemia when there is no arteriographic evidence of coronary disease, are reported as "false-positive." However, because a normal coronary angiogram will only exclude coronary macroangiopathy, these so-called false-positive findings could be due to alterations in subendothelial coronary microvessels or reflect reduced coronary flow reserve and other well-known functional and structural microvessel diseases that have been described in studies of the coronary circulation of hypertensive patients with or without left ventricular hypertrophy.[9–11,22–24] Picano et al[6] showed that dypiridamole-induced ischemic-like ST-segment depression does in fact reflect reduced coronary flow reserve and microvascular disease in asymptomatic hypertensive patients with normal coronary angiograms.

**Circadian pattern of ST-segment depression:** The pattern of the 72 episodes of ST-segment depression observed in our study shows circadian variations with clustering around morning awakening and late afternoon periods. This circadian distribution is very close to those described by others in similar populations[4,5] and in patients with proven coronary artery disease.[13,25] These early morning and late afternoon peaks of ST-segment depression observed in both hypertensive subjects and patients with coronary artery disease mimic the circadian variations of myocardial infarction and sudden cardiac death.[26] A similar rhythm has also been found in several physiologic processes,[27] which could contribute to and even trigger the onset of cardiovascular events: Blood fibrinolytic activity is lower in the early morning hours; platelet aggregability, plasma epinephrine and norepinephrine levels, plasma renin activity, and the rate of cortisol secretion are higher. Elsewhere, Panza et al[28] showed the presence of a circadian rhythm in vascular tone that is associated with, and probably causally related to, increased α-sympathetic activity in the morning. Increased α-adrenergic vasoconstrictor activity has been demonstrated in a number of cardiovascular conditions including hypertension and coronary stenosis.

**Comparison between patients with and without ST-segment depression:** As reported by others,[4,14] the 2 groups had similar clinical characteristics with respect to age, gender, weight, and duration of hypertension. Patients with ST-segment depression had higher blood glucose and self-rated work stress levels, 2 well-known coronary heart disease risk factors. No differences were observed for smoking, alcohol consumption, and total plasma cholesterol. This result should be analyzed with caution. First, the investigation was limited to patients with mild plasma lipoprotein abnormalities. Second, smoking and alcohol consumption were only qualitative parameters (yes or no) based on what the patient declared on the investigation day. Third, the self-rated stress scale only indicates the nature of the stress and not the magnitude of perceived stress.

Whereas casual BP measurements values were similar in patients with and without ST-segment depression,

ambulatory BP monitoring showed higher mean BP levels in patients with ST-segment depression. This apparent discrepancy can be easily explained by the well-established highest sensitivity of the ambulatory method.

Despite the well-established interrelations between BP, left ventricular hypertrophy, and coronary disease, we as well as other workers[14,22,23] could not demonstrate a difference in left ventricular mass between patients with and without ST-segment depression. This important result must be interpreted carefully. In fact, we did observe a trend toward higher left ventricular mass index values in patients with ST-segment depression. Pringle et al[8] found the highest incidence of ST-segment depression in hypertensive patients with left ventricular hypertrophy. In contrast, Antony et al[23] showed that coronary reserve was reduced in untreated hypertensive patients with normal myocardial masses and normal epicardial coronary arteries. This suggests that abnormalities of the coronary microvasculature may occur before left ventricular hypertrophy. Furthermore, Scheler et al[22] suggested that the alteration in coronary microcirculation could be primary and independent of left ventricular hypertrophy.

**Changes in blood pressure and heart rate during ST depression:** Important data on changes in BP and heart rate during episodes of ST depression were obtained through simultaneous BP and Holter monitoring in this study. Analysis of data can shed light on the pathophysiology of painless episodes of ST depression. Fifty-five percent of ST depression episodes were preceded by an increase (10 mm Hg) in systolic BP; a similar trend was observed for diastolic BP, with an increase (5 mm Hg) in 65% of the episodes, and a concomitant increase in heart rate was observed in only 17% of patients. With regard to heart rate changes, there was no clear-cut trend because 41% of the episodes were preceded by a decrease, 31% by a clear increase (10 beats/min), and 21% by a smaller increase (<10 beats/min).

Significant increases in both heart rate and BP during silent episodes have been reported in 2 studies, the first in patients with angina pectoris and the second in elderly hypertensive patients without coronary disease[13,14]; these results suggest that an increase in myocardial oxygen demand could play a significant role in silent ischemia. However, previous studies based on heart rate changes alone reported conflicting results that could be explained either by an increase in myocardial oxygen demand or by a decrease in coronary blood supply as the determinant factor in silent ischemia episodes.[9,13,27–29] In our study, because BP and heart rate were not significantly modified during the ischemic episodes in nearly 50% of patients, it could be concluded that a decrease in coronary blood supply is involved in the genesis of ischemia during daily activities. Three mechanisms could explain this decrease in coronary blood supply: decreased coronary vasodilator reserve, elevated coronary microvasculature resistance, and abnormal endothelium-dependent coronary vasodilation with progressive dysfunction, as observed in different early stages of coronary atherosclerosis.[22–24,27,28]

ST-segment depression during ambulatory Holter mo-nitoring was recorded in 23% of untreated hypertensive patients. These ST depression episodes were mainly recorded around awakening and in the late afternoon periods and were associated with an increase in BP and, to a lesser degree, with heart rate. Patients with ST-segment depression had a higher level of BP; in fact, ST-segment depression occurred more often in hypertensive patients. Patients with ST depression had a higher ambulatory BP load than patients without ST depression. ST depression occurred mainly during the day when BP was higher, and an increase in BP was mainly noted during ST depression. In this study, there was no treatment or follow-up period, and further studies are needed to assess how this established risk[2,5] can be lowered with drug therapy.

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