Circadian Blood Pressure Changes and Myocardial Ischemia in Hypertensive Patients With Coronary Artery Disease

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Objectives. We sought to evaluate whether different circadian blood pressure (BP) changes could influence the occurrence of ischemic episodes in untreated and treated hypertensive patients with stable coronary artery disease (CAD).

Background. In hypertensive patients with CAD the occurrence of myocardial ischemia could be influenced by either high or low BP values. Ambulatory monitoring has shown that circadian BP profile is not uniform in hypertensive patients.

Methods. Twenty-one patients with a nighttime BP fall <10% (“nondippers”), 35 with a nighttime BP fall between >10% and <20% (“dippers”) and 14 with a nighttime BP fall >20% (“overdippers”) with CAD underwent simultaneous ambulatory BP and electrocardiographic monitoring before and during drug therapy with nitrates and atenolol or verapamil in a prospective, randomized, open, blinded end point design.

Results. Daytime BP was not significantly different among the groups both before and during therapy. Nighttime BP was different by definition. Treatment significantly reduced BP values in each group (p < 0.05). Daytime ischemic episodes did not differ among the groups either before or during therapy. Drug therapy significantly reduced daytime ischemia (p < 0.05). In untreated patients, nighttime ischemia was more frequent in nondippers than in dippers and overdippers (p < 0.05). Drug therapy significantly reduced nocturnal ischemia in nondippers (p < 0.05), had no significant effect in dippers and significantly increased nighttime ischemia in overdippers (p < 0.05). During treatment, nighttime ischemia was more frequent in overdippers than in dippers and nondippers (p < 0.05). The same results were achieved when ischemic episodes were defined with more restrictive criteria (ST segment depression ≥2 mm).

Conclusions. Circadian BP changes can influence the occurrence of myocardial ischemia in untreated and treated hypertensive patients with CAD. Nocturnal ischemia was found to be more frequent in nondippers among untreated patients and in overdippers among treated patients, potentially suggesting different therapeutic approaches based on circadian BP profile.

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Hypertension is one of the major risk factors for coronary artery disease (CAD). In hypertensive patients, however, the occurrence of cardiac ischemic episodes could be influenced either by high blood pressure (BP) levels, through an increase of myocardial oxygen demand or by low BP values, through a reduction of coronary perfusion due to an upward shift of the lower limit of coronary autoregulation in the subendocardium (1–6). Moreover, several studies (7–10), but not all (11,12), have also reported a J-shaped relation between diastolic BP and risk of myocardial infarction in treated hypertensive patients with CAD. In the same context, Floras (13) has hypothesized that unrecognized nocturnal hypotension may be one reason why treatment has not diminished the risk of coronary events in patients with hypertension. Ambulatory BP monitoring has shown that the circadian BP profile is not uniform in hypertensive patients. Indeed, some patients do not exhibit a nocturnal BP fall and have been called “nondippers,” whereas others show a nighttime BP reduction and have been defined as “dippers” (14–16). Among the latter group, in addition, we and other investigators (17) have noticed that some subjects have a marked nocturnal BP fall and could be defined as “overdippers” or “extreme dippers.” Episodes of myocardial ischemia, either symptomatic or silent, have been detected by ambulatory electrocardiographic (ECG) monitoring in normotensive patients with CAD, as well as in hypertensive patients with or without clinical evidence of stable CAD (18–26). Various studies (18–21,26), but not all (22,23), have reported that ambulatory ischemia is associated with an adverse prognosis in patients with stable CAD. To our knowledge, no study has investigated a possible relation between circadian BP profile and frequency of myocardial ischemia in hypertensive patients with CAD.

The aim of this study was to evaluate whether different circadian BP changes could influence the occurrence of ischemic episodes in untreated and treated hypertensive patients with stable CAD.

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Methods

Patients. Patient selection is reported in Figure 1. Twenty-one patients with a nighttime BP fall <10% (“nondippers”), 35 with a nighttime BP fall between >10% and <20% (“dippers”) and 14 with a nighttime BP fall >20% (“overdippers”) with CAD underwent simultaneous ambulatory BP and ECG monitoring before therapy and 1 month later in a prospective, randomized, open, blinded end point design. Groups were well matched in terms of age, gender, employment and coronary anatomy and received the same drugs (atenolol 50 to 100 mg/day, verapamil 240 to 360 mg/day, sustained release isosorbide mononitrate 30 to 60 mg/day, aspirin 100 mg/day and sublingual nitroglycerin as necessary). Exclusion criteria for entry in the study were previous myocardial infarction, unstable angina, congestive heart failure, valvular heart disease, cardiomyopathy, obesity, left bundle branch block, preexcitation syndrome and ECG evidence of left ventricular (LV) hypertrophy with strain. The study was done in accordance with the Second Declaration of Helsinki and was approved by the Institutional Committee on Human Research. All subjects gave written informed consent.

Abbreviations and Acronyms

BP = blood pressure
CAD = coronary artery disease
ECG = electrocardiogram, electrocardiographic
LV = left ventricle, left ventricular

Figure 1. Patient selection. DBP = diastolic blood pressure; Dippers = patients with nighttime BP fall between >10% and <20%; Nondippers = patients with nighttime BP fall <10%; Overdippers = patients with nighttime BP fall >20%; SBP = systolic blood pressure.
Office BP measurements. Clinical systolic and diastolic BP recordings were performed according to standard technique. Clinical hypertension was defined as BP >140/90 mm Hg.

Ambulatory BP monitoring. Ambulatory monitoring was performed with a noninvasive recorder (SpaceLabs 90207) on two consecutive days (48 h) of typical activity. Technical aspects have been previously reported (27). Ambulatory BP readings were obtained automatically at 15-min intervals from 6 AM to midnight and at 30-min intervals from midnight to 6 AM. Patients were asked to go to bed and to get up at approximately the same time on the two consecutive days. Eight nondippers, 14 dippers and 11 overdippers were mild to moderate smokers (<15 cigarettes every day or some days) and were asked to smoke as little as possible during monitoring and to report the number of cigarettes smoked in their diary. Average daytime (awake period), average nighttime (asleep period) and average 24-h systolic and diastolic BPs were evaluated. Awake and asleep periods were determined from the patients’ diaries. According to the reduction of the average BP values from day to night, patients were arbitrarily defined as nondippers (<10%), dippers (>10% and <20%) and overdippers (>20%) (15,17). Some patients who were nondippers for systolic BP and dippers for diastolic BP, and some others who were dippers for systolic BP and overdippers for diastolic BP, were classified according to diastolic BP changes because of the importance of diastolic BP in coronary perfusion. “Ambulatory” hypertension was defined as daytime BP >134/90 mm Hg (28). All patients included in the study had recordings of good technical quality.

Echocardiography. Echocardiograms were recorded with a Hewlett-Packard 77030A ultrasound imaging system. Measurements were made according to the American Society of Echocardiography recommendations (29). LV mass was calculated using the formula introduced by Devereux et al. (30). Individual values for LV mass were indexed by body surface area (LV mass index). LV hypertrophy was defined as LV mass index >125 g/m² in men (31) and >110 g/m² in women (32).

Exercise stress testing. Exercise testing was performed on a bicycle ergometer. The work load was increased by 25 W every 3 min up to a symptom-limited maximum. The test was considered positive if there was horizontal or downsloping ST segment depression ≥1 mm at 80 ms after the J point.

Dipyridamole echocardiography. Dipyridamole echocardiography was performed to evaluate whether ST segment depression observed during exercise stress testing could be related to CAD or other factors (33), except in patients with a positive exercise ECG at a low to intermediate work load or in those with a suboptimal acoustic window. The test was performed as previously reported (34) and was considered positive when transient dysynergy (a marker of CAD) was detected.

Coronary angiography. Selective coronary arteriography was performed in multiple projections using the Judkins technique. Significant stenosis was considered present when there was ≥70% diameter narrowing of a major coronary vessel or ≥50% narrowing of the left main stem.

Ambulatory ECG monitoring. Continuous ECG monitoring on two consecutive days (48 h) was performed with a Hewlett-Packard 43400B recorder and analyzed by an experienced physician (A.M.) who was unaware of the ambulatory BP monitoring data or drug therapy. After careful preparation of the patient’s skin, electrodes were positioned to obtain lead V3 and a modified inferior lead (35). To exclude positional ECG changes, initial ECG recordings were made with the patient in different positions and while hyperventilating. Ischemic ST segment changes were defined as horizontal or downsloping ST segment depression ≥1 mm occurring 80 ms after the J point, lasting for >1 min and separated from other episodes by at least 1 min. Changes in T wave configuration alone were not considered significant for ischemia. Only episodes with no artifacts were included in the analysis. To enhance the specificity of ambulatory ECG changes, ischemic episodes were also reclassified, taking ST segment depression ≥2 mm as the reference limit. All selected patients had recordings of good technical quality.

Statistical analysis. Data are expressed as the mean value ± SD. Ambulatory BP and ECG data for daytime and nighttime are reported as an average of the values of the 2 days. One-way analysis of variance followed by a multiple comparison test, chi-square test or Fisher exact test; two-way repeated measures analysis of variance followed by a multiple comparison test; the Kruskal-Wallis test followed by the Mann-Whitney U test for multiple comparisons; and the Wilcoxon signed-rank test were all used as appropriate (36). Analyses were made with the use of the SYSTAT package implemented on an Apple Macintosh SE/30 personal computer. Statistical significance was defined as p < 0.05.

Results

Study group data. Gender distribution, age, body mass index, prevalence of diabetes and hypercholesterolemia, family history of CAD and therapy did not differ among the groups (Table 1). A smoking habit was more frequent in overdippers than in dippers and nondippers (p < 0.05). The average daily cigarette consumption was 6 (range 2 to 11), and there was no difference among smokers of the three groups. No patient smoked during the nighttime. The duration of sleep was similar among nondippers, dippers and overdippers (6.3 ± 0.4 vs. 6.4 ± 0.5 vs. 6.5 ± 0.5 h, respectively).

Echocardiographic and angiographic findings. LV mass index was significantly higher in nondippers than in overdippers (Table 1). The prevalence of LV hypertrophy was progressively higher from overdippers to nondippers but did not attain statistical significance. The frequency distribution of one-, two- and three-vessel disease was similar among the groups (Table 1).

Clinical and ambulatory BP data. Clinical and daytime BP values were not significantly different among the groups, both before and during drug therapy (Table 2). Nighttime and 24-h BP values were progressively higher, by definition, from overdippers to nondippers, both before and during therapy. Clini-
Table 1. Characteristics of the Study Group

<table>
<thead>
<tr>
<th></th>
<th>Nondippers (n = 21)</th>
<th>Dippers (n = 35)</th>
<th>Overdippers (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>16/5</td>
<td>27/8</td>
<td>11/3</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54 ± 6</td>
<td>53 ± 6</td>
<td>55 ± 5</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27 ± 3.2</td>
<td>26.8 ± 3.0</td>
<td>26.6 ± 3.1</td>
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<tr>
<td>Risk factors</td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>21 (100)</td>
<td>35 (100)</td>
<td>14 (100)</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>8 (38)</td>
<td>14 (40)</td>
<td>11 (79)*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5 (24)</td>
<td>8 (23)</td>
<td>3 (21)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>8 (38)</td>
<td>14 (40)</td>
<td>6 (43)</td>
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<tr>
<td>Family history of CAD</td>
<td>6 (29)</td>
<td>11 (31)</td>
<td>4 (29)</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
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<tr>
<td>Atenolol</td>
<td>8 (38)</td>
<td>14 (40)</td>
<td>6 (43)</td>
</tr>
<tr>
<td>Verapamil</td>
<td>13 (62)</td>
<td>21 (60)</td>
<td>8 (57)</td>
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<td>Nitrates</td>
<td>21 (100)</td>
<td>35 (100)</td>
<td>14 (100)</td>
</tr>
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<td>Aspirin</td>
<td>21 (100)</td>
<td>35 (100)</td>
<td>14 (100)</td>
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<td>Echocardiographic findings</td>
<td></td>
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<tr>
<td>LV mass index (g/m²)</td>
<td>121 ± 18</td>
<td>110 ± 20</td>
<td>103 ± 20†</td>
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<tr>
<td>LV hypertrophy</td>
<td>10 (48)</td>
<td>14 (40)</td>
<td>5 (36)</td>
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<td>Fractional shortening (%)</td>
<td>37 ± 5</td>
<td>38 ± 5</td>
<td>37 ± 5</td>
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<td>Coronary angiographic findings</td>
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<td>5 (24)</td>
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<td>Two-vessel disease</td>
<td>13 (62)</td>
<td>21 (60)</td>
<td>9 (64)</td>
</tr>
<tr>
<td>Three-vessel disease</td>
<td>3 (14)</td>
<td>5 (14)</td>
<td>2 (14)</td>
</tr>
</tbody>
</table>

*p < 0.05 versus dippers and nondippers. †p < 0.05 versus nondippers. Data presented are mean value ± SD or number (%) of patients. CAD = coronary artery disease; Dippers = nighttime blood pressure fall between >10% and >20%; LV = left ventricular; Nondippers = nighttime blood pressure fall <10%; Overdippers = nighttime blood pressure fall >20%.

cal, daytime, nighttime and 24-h BP values were significantly reduced by drug therapy in each group, both in patients treated with atenolol and in those treated with verapamil. The circadian BP pattern was similar on the two consecutive days in all the patients. Daytime and nighttime heart rates were not different among the groups, either before or during treatment. Drug therapy significantly reduced heart rate during both the daytime and nighttime.

**Ambulatory ECG data.** The same trend was observed when ischemia was classified as ST segment depression of either ≥1 mm, 198 episodes during the daytime (61 in nondippers, 97 in dippers and 40 in overdippers) and 33 episodes during the nighttime (20 in nondippers, 10 in dippers and 3 in overdippers) were recorded in untreated patients; in treated hypertensives, 100 episodes during the daytime (30 in nondippers, 50 in dippers and 20 in overdippers) and 27 episodes during the nighttime (7 in nondippers, 7 in dippers and 13 in overdippers) were recorded. Considering ischemic episodes as ST segment depression ≥1 mm, 60 patients during the daytime (18 nondippers, 30 dippers and 12 overdippers) and 26 patients during the nighttime (13 nondippers, 10 dippers and 3 overdippers) had ischemic episodes before therapy; during therapy, 54 patients during the daytime (16 nondippers, 28 dippers and 10 overdippers) and 23 patients during the nighttime (6 nondippers, 7 dippers and 10 overdippers) had ischemic episodes. Two nondippers, two dippers and two overdippers with daytime ischemic episodes at baseline had no episodes during treatment, and all the other patients with ischemia, in each group, had a reduction of daytime ischemia. Seven nondippers with nighttime ischemia at baseline had no ischemia during therapy, and six nondippers had a reduction of nighttime ischemic episodes during therapy. Three dippers with nighttime ischemia at baseline had no ischemia during therapy, and seven dippers with nighttime ischemia at baseline did not show changes during therapy. Three overdippers with nighttime ischemia at baseline showed an increase of nighttime ischemic episodes during therapy, and seven overdippers with no ischemia at baseline showed nighttime ischemia during therapy.

Of the total ischemic episodes recorded during monitoring (231 before and 127 during therapy), 93% were silent; the prevalence of silent ischemia was not different among the groups.

Of the daytime ischemic episodes (198 before and 100 during therapy), 90% were preceded by an increase of heart rate (>10 beats/min) and BP (>10 mm Hg), when BP values were available during the 5 to 10 min preceding the ischemic episode; these findings were similar in the three groups. In untreated patients, 7 of the 20 nighttime ischemic episodes in nondippers, 3 of the 10 in dippers and 1 of the 3 in overdippers were associated with heart rate changes (>10 beats/min). In treated patients, three of the seven nighttime ischemic episodes in nondippers, two of the seven in dippers and none in overdippers were associated with heart rate changes. In the treated overdipper group, the increase of ischemic episodes during nighttime occurred in the period with the lowest BP values (105 ± 5 mm Hg for systolic and 58 ± 5 mm Hg for diastolic).

When ischemic episodes were reclassified as ST segment depression ≥2 mm, 99 episodes during the daytime (31 in nondippers, 48 in dippers and 20 in overdippers) and 18
...nighttime blood pressure fall between HR

$ST \text{ seg fall}$

Nighttime HR 68

Daytime HR 79

Nighttime SBP 146

Daytime SBP 154

Clinical SBP 157

Clinical DBP 100

Daytime SBP 154

Daytime DBP 98

Nighttime SBP 146

Nighttime DBP 91

24-h SBP 151

24-h DBP 96

Daytime HR 79

Nighttime HR 68

24-h DBP 96

Nighttime DBP 91

24-h SBP 151

Daytime SBP 154

Clinical DBP 100

Diabetes at baseline showed nighttime ischemia during therapy. Two overdippers with nighttime ischemia at baseline showed an increase of nighttime ischemic episodes during therapy, and four overdippers with no ischemia at baseline showed nighttime ischemia during therapy.

The duration of daytime and nighttime ischemia, both before and during therapy, followed the same trend in terms of the number of ischemic episodes (Table 2).

During the daytime most of the ischemic episodes occurred in the morning and in the evening, both before and during therapy. During the nighttime most of the episodes occurred between midnight and 4 AM only in the treated overdiaper group.

Discussion

Main findings. In this study we have evaluated the relation between circadian BP changes and the occurrence of ischemic episodes in untreated and treated hypertensive patients with proven CAD. No difference was found among nondippers, dippers and overdippers concerning daytime myocardial ischemia, either before or during treatment. On the contrary, a different pattern was observed during the nighttime. Indeed, nighttime ischemia was significantly more frequent in nondippers than in dippers and overdippers among untreated patients, whereas it was significantly more frequent in overdippers than in dippers and nondippers among treated ones.

Daytime ischemia. In the present report, characteristics of daytime ischemia are essentially similar to those found previously (24–26,37–39) and do not seem to deserve comment. In agreement with Lee et al. (40,41), the reduction of ambulatory
ischemia tended to be more evident in those patients with a better control of ambulatory BP.

**Nighttime ischemia.** This is apparently the first study describing a relation between a nighttime BP pattern and the occurrence of cardiac ischemic episodes in hypertensive patients with CAD. Notably, myocardial ischemia is less frequent during the nighttime than during the daytime. In this context, however, we have found that hypertensive patients with a different nighttime BP profile show differences in the frequency of nighttime ischemia.

Some investigators (35,42) have reported that nocturnal ischemia could be related to an increase of myocardial oxygen demand (increased heart rate and BP due to disturbed or rapid eye movement sleep, postural changes and raised LV diastolic pressure). Other investigators (43–45), in contrast, argue that nocturnal ischemia could be due to a reduction of coronary flow resulting from increased coronary tone and vasospasm; indeed, these workers (43–45) have reported a lower ischemic threshold during the nighttime.

Both nighttime ischemic episodes associated with a heart rate or BP increase and those without such changes were more frequent in untreated nondippers than in untreated dippers and overdippers. It could be hypothesized that, in nondippers, persistent hypertension during the nighttime favors myocardial ischemia through an increased oxygen demand; this phenomenon could occur even in the presence of mild heart rate or BP changes, or both, which do not usually trigger ischemia in other subjects. In contrast, it could be hypothesized that persistent hypertension during the nighttime could be associated with a more severe vascular dysfunction resulting in increased coronary tone and vasospasm. Indeed, it has been reported (46) that hypertensive patients show coronary endothelial dysfunction leading to enhanced coronary tone and vascular resistance; according to some investigators (46), this phenomenon is a consequence of hypertension and appears to be related to the degree of BP elevation. An interplay of the two mechanisms (i.e., increased oxygen demand and decreased oxygen supply) may also be involved in the pathogenesis of increased nocturnal ischemia in nondipper hypertensive patients. The aforementioned considerations could help explain the higher frequency of nighttime ischemia in untreated nondippers as compared with dippers and overdippers.

Myocardial ischemia increased during the nighttime in the treated overdippers, and this change was associated with the lowest BP values. Thus, it seems that such a phenomenon is related to drug-induced excessive BP lowering, which reduces the driving pressure in the coronary arteries, leading to hypoperfusion in the presence of significant coronary artery stenoses. Moreover, in hypertensive patients coronary autoregulation in the subendocardium is shifted toward higher pressure (1–6,13), probably owing to LV hypertrophy and functional and structural alterations in the small coronary vessels (1–6,47–49). In the presence of drug-induced relative hypotension, such coronary autoregulation dysfunction may lead to myocardial ischemia, especially in hypertensive patients with LV hypertrophy or coronary artery stenoses, or both (1–6,13).

We have observed an increase of nighttime ischemia both in overdippers treated with atenolol and in those treated with verapamil, further suggesting that this phenomenon is related to low BP per se and not to drug characteristics.

Ambulatory ischemia, regardless of the cause, has been reported to be associated with an adverse prognosis (18–21,26), even though the mechanism is not yet completely clear. In experimental studies, it has been reported that repeated episodes of ischemia damage the collagen matrix (50,51), increase the interstitial fibrous tissue (52) and produce small but distinct areas of subendocardial necrosis (53). It is also possible that ischemia may precipitate lethal ventricular arrhythmias.

Some investigators have hypothesized that, in the presence of altered coronary autoregulation, myocardial infarction could occur without coronary occlusion (1–6,13) in patients with LV hypertrophy or CAD, or both, and drug-induced hypotension. In this regard, it is interesting to note that, in contrast to Q wave infarction, total coronary occlusion of the infarct-related vessel is infrequently observed in non–Q wave infarction (54). This finding could be interpreted in several ways (54); an intriguing possibility is that the infarct-related artery is never occluded and non–Q wave infarction represents a severe imbalance between oxygen demand and supply in the presence of a severely narrowed coronary vessel and reduced coronary pressure (54). However, other factors could also be involved in the pathogenesis of non–Q wave myocardial infarction (55).

We have found more frequent nighttime ischemic episodes among untreated nondippers and treated overdippers both in patients with three-vessel disease, who generally undergo coronary artery bypass graft surgery, and in those with two-vessel disease, who frequently undergo medical treatment. Thus, it seems important to tailor drug therapy according to the circadian BP pattern to avoid undertreatment in nondippers and overtreatment in overdippers. Our data suggest that nondippers should receive 24-h active therapy; however, excessive BP lowering during the nighttime seems to be contraindicated in overdippers. Overdippers, and probably dipper hypertensive patients as well, could benefit from a novel therapeutic system that is administered in the late evening and delivers the drug in the early morning (56). This hypothesis should be tested in prospective studies.

**Study limitations.** 1) It has been reported (32) that the presence of hypertension lowers the specificity of ECG changes for the diagnosis of ischemia due to CAD either during exercise stress testing or ambulatory monitoring. To overcome this problem, we performed (when indicated and feasible) dipyridamole echocardiography in patients with a positive exercise test and we selected only those hypertensive patients with a positive dipyridamole echocardiographic test (a marker of CAD). All selected patients, in addition, had angiographic evidence of significant coronary artery stenosis. Moreover, to increase the specificity of ECG modifications during monitoring, we also reclassified the ischemic episodes using more restrictive criteria (ST segment depression...
nighttime blood pressure and myocardial ischemia

Conclusions. Our study shows that different circadian BP changes can influence the occurrence of ischemic episodes in hypertensive patients with CAD. Nighttime ischemia was found to be more frequent in nondippers among untreated patients and in overdippers among treated ones, potentially suggesting that these groups should receive a different therapeutic approach based on their circadian BP profile. In this setting, ambulatory BP monitoring could be helpful and should be recommended in hypertensive patients with CAD before treatment assignment.

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