Pathophysiology of Silent Myocardial Ischemia During Daily Life
Hemodynamic Evaluation by Simultaneous Electrocardiographic and Blood Pressure Monitoring

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The role of myocardial oxygen demand in the genesis of silent myocardial ischemia was evaluated by measuring the heart rate and blood pressure changes preceding the silent ischemic events during daily life in 25 men with proven coronary artery disease. Simultaneous 24–48-hour ambulatory electrocardiographic and blood pressure monitoring were performed during unrestricted daily activities. Of the 92 transient ischemic events recorded during monitoring, 85 (92%) were silent. Sixty-one percent of the silent events were preceded by an increase in the heart rate of 5 beats/min or more. Seventy-three percent of the silent ischemic events showed an average increase of 10 mm Hg in systolic blood pressure within 6 minutes preceding the onset of ST segment depression. The silent ischemic events showed a circadian pattern with a high density (34% of total events) between 6:00 AM and noon. The increase in heart rate and blood pressure paralleled the increase in silent ischemic events during these hours. These results showing significant (p<0.001 for both) increases in heart rate and blood pressure preceding a majority of silent ischemic events suggest that increase in myocardial oxygen demand plays a significant role in the genesis of silent ischemia. This pathophysiological mechanism has important therapeutic implications. (Circulation 1990;82:1296–1304)

Although silent myocardial ischemia during daily life occurs frequently in patients with coronary artery disease,1–5 the precise mechanism responsible for it has not yet been established.6,7 It has been shown that silent ischemia during unrestricted daily activity occurs at heart rates significantly less than those observed during exercise testing.4 Also, some studies have reported that there are relatively small changes in the heart rate preceding silent ischemic events.4,8 Based on these data, it has been postulated that silent myocardial ischemia occurs predominantly because of a decrease in coronary blood supply. However, two separate reports9,10 have recently demonstrated that a majority of silent ischemic events are preceded by an increase in the heart rate. Furthermore, several recent studies have shown that β-blockers are effective in reducing both the frequency and duration of silent ischemia.7,11–16 Because of these conflicting data, it is not clear whether an increase in myocardial oxygen demand plays a significant role in the genesis of silent myocardial ischemia. Although heart rate and blood pressure are both major determinants of myocardial oxygen demand, little information is currently available regarding the simultaneous changes in heart rate and blood pressure preceding silent ischemic events during daily activity. In this study, we performed simultaneous ambulatory electrocardiogram (ECG) and blood pressure monitoring to evaluate the role of heart rate and blood pressure changes in the genesis of silent myocardial ischemia during unrestricted daily activity.

Methods

Patient Population
We evaluated 25 men aged 48–76 years (mean, 61 years) with a history of chronic stable angina and previously documented silent myocardial ischemia; a dual-channel frequency-modulated ambulatory ECG recorder (Medilog MR 20, Oxford) was used for this evaluation. All patients had documented coronary artery disease as evidenced by at least a greater than 70% occlusive lesion of a major coronary artery on angiography or a reversible thallium defect on exercise thallium-201 scintigraphy. Furthermore, all patients

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had diagnostic ST segment depression (≥0.1 mV at 80 msec from the J point) during a maximal exercise treadmill test using a standard Bruce protocol.

Each patient gave informed consent to participate in the study, which had been approved by the Institutional Review Board. All patients had been maintained on the same doses of antianginal medications for 3 months before entering the study. Patients underwent simultaneous ambulatory frequency-modulated ECG and continuous blood pressure monitoring for a minimum of 24 hours. Patients were educated to keep an accurate account of daily activities (including awake and sleep times) and symptoms in a specially developed diary during the monitoring period. They were instructed to note the time of onset and description of chest pain, associated activity, and use of sublingual nitroglycerin.

**Ambulatory ECG Monitoring Technique**

Continuous 24-hour ECG monitoring was performed to record two bipolar ECG leads on the dual-channel frequency-modulated monitor. The patient’s skin was prepared by removing surface oil with ethanol, shaving, and applying a mild abrasive. The ECG electrode positions were selected to provide the recording of the same two standard leads showing the greatest ST segment changes during prior monitoring periods and exercise testing. The electrode placement was considered unacceptable if the electrical impedance was greater than 5 kΩ. Baseline recordings, including hyperventilation, were obtained in the left and right lateral, supine, and standing positions. Patients with ST segment abnormalities observed during hyperventilation or positional changes were excluded. Patients were instructed to activate the event marker for any anginal symptoms.

**Continuous Ambulatory Blood Pressure Monitoring**

Simultaneous blood pressure monitoring was performed by the arm-cuff method using an ambulatory blood pressure device (model ICR-5200, Space Laboratories). The patient’s blood pressure was also measured by the standard arm-cuff method using a mercury sphygmomanometer and was compared with that simultaneously measured by the device. Based on the previous pattern of ischemic activity during Holter monitoring, the device was programmed to provide more frequent measurements during the periods of anticipated silent ischemic activity. The blood pressure monitoring device was activated at an exact time corresponding to the time on a watch given to the patient, which had previously been synchronized with the 24-hour ambulatory ECG.

**Analysis of ECG Tapes**

All 24-hour tape recordings were visually analyzed by two experienced technicians at 60 times real speed on an Oxford Medilog (model MA-20) playback unit. The ECG complexes were analyzed to provide a printout of a 24-hour trend of beat-to-beat variation of heart rate and amount of ST segment depression at 80 msec after the J point compared with the PR segment. All periods associated with ST segment depressions of 0.1 mV or more from the baseline were individually sampled from both channels. Only episodes free of artifact and with ST segment depression meeting the established criteria (downsloping or horizontal ST segment depression of ≥0.1 mV persisting for 80 msec after the J point and lasting for 60 seconds or longer) were included for analysis. Individual episodes were defined when separated by a minimum of 2 minutes between the two events associated with diagnostic ST segment depression. The degree of ST segment shift was confirmed by both the ST segment trend and by direct measurement on the ECG strips obtained at 25 mm/sec. The onset of an episode was measured beginning at the point of initial shift from baseline, and termination was defined at the point when the ST segment level returned to baseline. ECG strips (25 mm/sec) were obtained 1 minute before onset, at the onset, at 2–5-minute intervals throughout, at peak, and at termination of each event.

The heart rate was determined from the ECG trend charts and was also calculated from the ECG strips. All events associated with diagnostic ST segment depression were categorized as silent or symptomatic based on correlation with symptoms recorded in the diary. Separate baseline heart rates were obtained from the average RR interval measured during a minimum 2-hour event-free period for sleep and awake periods.

**Analysis of Blood Pressure Data**

The blood pressure data were retrieved from the recorder storage unit by using the Space Laboratories computer-based retrieval system (model ICR-5300). A printout of the systolic, diastolic, and mean arterial blood pressure and heart rate for all individual recordings was obtained. Each systolic blood pressure value was plotted on the 24-hour heart rate and ST segment trends. The baseline systolic blood pressure was calculated separately for sleep and awake periods by averaging all the systolic blood pressure values recorded during a minimum 2-hour event-free interval.

Subsequently, 24-hour ECG and blood pressure data were tabulated to obtain the heart rate, systolic blood pressure, and double product at baseline and before, during, and at termination of transient ischemic events. Also, the average hourly heart rate, systolic blood pressure, double product, and number of transient ischemic events were plotted for the 24-hour period to evaluate the circadian pattern.

**Comparison of Exercise and Ambulatory Monitoring Data**

During exercise testing, the heart rate and systolic blood pressure at baseline, 1-mm ST segment depression, peak exercise, and maximum ST segment depression were obtained. These exercise parameters were
compared with the corresponding hemodynamic values obtained during ambulatory monitoring. The hemodynamic values during exercise testing and ambulatory monitoring are expressed as mean±1 SD.

Method of Data Analyses and Statistics

To evaluate the magnitude of circulatory changes, heart rate and blood pressure data were analyzed before onset, at the onset, at peak, and at termination of each ischemic event. The preevent heart rate measurement was made 1 minute preceding the onset of ST segment depression. The preevent blood pressure value was evaluated only if the measurement had been made within a 10-minute period preceding the ischemic event.

As a nonischemic comparison control value, heart rates were measured at 1 minute preceding the two designated control periods at 30 and 60 minutes before the onset of an episode of ischemic ST segment depression. Similarly, blood pressure values were evaluated within 10 minutes preceding these control periods. This was done to ensure that the changes in heart rate and blood pressure immediately preceding the ischemic episode were not random occurrences. To avoid effects of ischemia on the control heart rate and blood pressure data, these were measured only if there was no ischemic episode between the designated control period and its corresponding ischemic episode.

For each episode, baseline heart rate was subtracted from the heart rate at 31- and 61-minute control periods and from the preischemic and peak-ischemic heart rate. These four differences were tested to determine their difference from 0 with a paired t test. Similar analysis was performed for the blood pressure data.

An increase of heart rate by 5 beats/min or more was considered important. For each of the above three time periods, the number of events with an increase equal to or greater than this value was tabulated. Then two χ² analyses were performed. The first analysis involved 1-minute preischemic values versus values at ischemia minus 31 minutes; the second analysis involved 1-minute preischemic values versus values at ischemia minus 61 minutes. A similar analysis was done for blood pressure values, in which a 10-mm Hg increase in systolic blood pressure was chosen as the cutoff value. Differences were considered significant at p<0.05.

Results

Of the 30 enrolled patients, 25 had interpretable data for a total monitoring period of 627 hours (25.1 hours per patient; range, 17.08–46.48 hours) during normal, unrestricted daily activity. During the monitoring period, a total of 92 transient ischemic events were observed; 85 (92%) of these events were silent, and seven were symptomatic. Seventy-nine percent of patients had one or more silent ischemic events. The mean number of ischemic episodes per patient was 4.4±2.8, and the median was 4.0 (range, 1–10). Ninety-five percent and 100% of the patients provided heart rate and blood pressure data, respectively, for the designated control periods that were free of ischemic events.

Exercise Testing

All patients had a positive exercise treadmill test with a mean ST segment depression of 0.22±0.12 mV. Table 1 shows the changes in heart rate, blood pressure, and double product at 1-mm ST segment and peak segment depressions during exercise. Compared with baseline, all these parameters showed significant increases (p<0.001) during exercise testing.

Circulatory Changes During Ambulatory Monitoring

An example of simultaneous ambulatory ECG and blood pressure monitoring data is shown in Figure 1. The systolic blood pressure values, heart rate, and ST segment changes have been plotted against time to show the relation of circulatory changes before, during, and at peak ischemic activity. Of the seven transient ischemic events shown in this example, two (marked with an asterisk in Figure 1) were accompanied with chest pain and required the use of sublingual nitroglycerin. The first symptomatic ischemic event began at 8:37 PM while the patient was closing a garage door, and the second event began at 1:25 AM and awakened him from sleep. It is interesting to note that in these two symptomatic events the ST

| TABLE 1. Comparison of Heart Rate, Systolic Blood Pressure, and Double Product at Baseline and at 1-mm and Peak ST Depression During Exercise Treadmill Test |
|----------------------------------|------------------|------------------|------------------|
|                                  | Baseline         | At 1-mm ST depression | At peak ST depression |
| Heart rate                       | Mean  SD         | Mean  SD          | Mean  SD         |
| Mean  SD                         | Mean  SD         | Mean  SD          | Mean  SD         |
| Heart rate                       | 75.2  12.1       | 110.6*  18.2      | 122.7*  22.4     |
| Δ Heart rate                     | 35.9  16.0       | 47.5  18.6        |
| Systolic BP                      | 141.3  19.6      | 155.9*  22.8      | 163.2*  25.7     |
| Δ Systolic BP                    | 13.7  21.6       | 22.0  25.4        |
| Double product                   | 10,647  2,443    | 17,594*  4,931    | 20,250*  5,830   |
| Δ Double product                 | 6,914  3,868     | 9,603  4,629      |

Δ, Change from baseline value; BP, blood pressure; double product, heart rate multiplied by systolic BP. *p<0.001 compared with corresponding baseline value.
segment depression began 5 and 9 minutes, respectively, before the onset of chest pain and persisted for 9 and 10 minutes, respectively, after the relief. The remaining five ischemic episodes were silent. The heart rate and systolic blood pressure increased before the onset of all but one of these ischemic events. This change in heart rate and blood pressure showed a further increase during the episode and gradually returned to baseline with resolution of the ST segment depression.

The hemodynamic data showing the circulatory changes during the 85 silent ischemic events are shown in Table 2. During the monitoring period, 2,232 blood pressure recordings were obtained; there was an average of 2.7 recordings/hr from midnight to 6:00 AM and 4.2, 4.6, and 4.1 recordings/hr from 6:00 AM to noon, from noon to 6:00 PM, and from 6:00 PM to midnight, respectively. Only blood pressure recordings obtained within 10 minutes before the onset of a silent ischemic event were used as preevent data. The maximum systolic blood pressure response is the greatest value recorded during an ischemic event. Fifty-six silent ischemic events had a blood pressure value recorded within a mean of 5.6 minutes before the onset of ST segment shift. Because of the known circadian variation in the heart rate and blood pressure, the changes in these parameters during the ischemic events were compared with the corresponding sleep and awake baseline values in each patient.18,19

**Hemodynamic Changes Preceding Silent Ischemic Events**

Both heart rate and systolic blood pressure showed significant increases preceding the silent ischemic events (Table 2). Of the 85 silent ischemic events, 61% were preceded (1 minute before ischemia) by an average increase in the heart rate of greater than or equal to 5 beats/min ($p<0.001$ compared with base-

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**Figure 1.** Simultaneous ambulatory electrocardiographic and blood pressure monitoring data in man with coronary artery disease. Systolic blood pressure (SBP), heart rate (HR), and ST segment changes (ST) are plotted against time. The data reveal an increase in HR and SBP preceding and during most events. *Transient ischemic event accompanied by chest pain requiring use of sublingual nitroglycerin (indicated by arrow).“

**Table 2.** Heart Rate, Systolic Blood Pressure, and Double Product During Ambulatory Monitoring at Baseline, Before Onset of ST Depression, at 1-mm, and at Peak ST Depression

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Before onset of ST depression</th>
<th>At 1-mm ST depression</th>
<th>At peak ST depression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Awake</td>
<td>Sleep</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Heart rate</td>
<td>72.8</td>
<td>12.7</td>
<td>58.9</td>
<td>8.0</td>
</tr>
<tr>
<td>Δ Heart rate</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>121.2</td>
<td>14.9</td>
<td>110.6</td>
<td>15.4</td>
</tr>
<tr>
<td>Δ Systolic BP</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Double product</td>
<td>8,818</td>
<td>1,885</td>
<td>6,522</td>
<td>1,289</td>
</tr>
<tr>
<td>Δ Double product</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Δ, Change from baseline value (calculated by comparison with the corresponding sleep or awake baseline value); BP, blood pressure; double product, heart rate multiplied by Systolic BP.

*p<0.001 compared with corresponding baseline value.
TABLE 3. Comparison Between Number of Episodes With Heart Rate Increase Preceding Silent Ischemic Episodes Versus Those Preceding Designated Control Periods

<table>
<thead>
<tr>
<th>Episodes of change in heart rate</th>
<th>Before ischemia</th>
<th>Total episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥5 beats/min</td>
<td>52 (61%)</td>
<td>85</td>
</tr>
<tr>
<td>&lt;5 beats/min</td>
<td>33 (39%)</td>
<td></td>
</tr>
</tbody>
</table>

Numbers in parentheses indicate percent of episodes with corresponding change. Control periods are 31 and 61 minutes before ischemia.

*p<0.001 by χ² analysis.

The circulatory response during the seven symptomatic ischemic events was separately analyzed. During the symptomatic events, heart rates before the event and at 1-min and maximum ST segment depression were, respectively, 72±14, 91±20, and 103±21 beats/min. The corresponding systolic blood pressure values were 115±21, 133±17, and 149±17 mm Hg. We also compared the extent of circulatory changes between asymptomatic and symptomatic episodes within the same patient. Of the seven symptomatic events, only four had systolic blood pressure recordings obtained before the onset of ST segment depression. Two of these events had a hypotensive response before the onset of ST segment depression. Both events occurred midday, and thus, it is unlikely that hypotension was due to postural changes.

All seven symptomatic events had an increase in heart rate (mean, 6.6 beats/min) 1 minute before the onset of ST segment depression. Within each patient, comparison of net ST segment depression between asymptomatic and symptomatic ischemic events did not reveal any specific pattern; in only two patients were the symptomatic events associated with the greatest (5.6 and 2.9 mm) ST segment depression. Interestingly, ST segment depression preceded the onset of chest pain in all seven symptomatic events. In summary, comparison of the circulatory changes between the asymptomatic and symptomatic episodes in our study did not reveal any significant differences.

Comparison Between Silent and Symptomatic Ischemic Events

As shown in Table 1, the absolute heart rate, systolic blood pressure, and double product values were greater during exercise testing. However, due to the significant differences in the baseline heart rate and systolic blood pressure values during the exercise test and ambulatory monitoring, the changes in these parameters were compared by evaluating the percent change in the values from their respective baselines. This comparison revealed significant differences only in the heart rate and double product at 0.1 mV ST segment depression (Figure 2). It is interesting to note that, despite a greater ST segment depression during exercise testing compared with that during ambulatory monitoring (0.22±0.11 versus 0.15±0.06 mV; p<0.001), there was no significant difference between the relative percent increase in these parameters at peak ST segment depression.

Comparison of Circulatory Response During Exercise Testing and Ambulatory Monitoring

As shown in Table 2, these changes were not significant except for the maximum systemic blood pressure response to nitroglycerin. Thus, it is likely that the hypotension seen during exercise testing is due to postural changes. This finding is consistent with the proposal that hypotension is a component of the tachycardia response to exercise.

TABLE 4. Comparison Between Number of Episodes With Systolic Blood Pressure Increase Preceding Silent Ischemic Episodes Versus Those Preceding Designated Control Periods

<table>
<thead>
<tr>
<th>Episodes of change in blood pressure</th>
<th>Before ischemia</th>
<th>Total episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥10 mm Hg</td>
<td>41 (73%)</td>
<td>56</td>
</tr>
<tr>
<td>&lt;10 mm Hg</td>
<td>15 (27%)</td>
<td></td>
</tr>
</tbody>
</table>

Numbers in parentheses indicate percent of episodes with corresponding change. Control periods are 40 and 70 minutes before ischemia.

*p<0.001 by χ² analysis.

Effect of β-Blocker Therapy on Circulatory Changes

To evaluate the effects of β-blocking agents on heart rate and blood pressure, we compared the degree of circulatory changes in patients on β-blockers (n=10) versus those not on β-blockers (n=15). Although at baseline, heart rate and blood pressure values were significantly lower (p<0.05) in patients receiving β-blockers, the percent increase in
both parameters during the ischemic episodes was comparable except for a lesser magnitude ($p<0.05$) of increase in blood pressure at 1-mm ST segment depression during silent ischemic episodes.

**Circadian Pattern of Silent Ischemic Events**

The 24-hour distribution of the 92 transient ischemic events and the heart rate, systolic blood pressure, and double product values is illustrated in Figure 3. The circadian pattern of the circulatory changes and transient ischemic events during the 24-hour monitoring period is quite evident. The total number of silent ischemic events abruptly increases during the morning hours, with 34% of the ischemic activity occurring between 6:00 AM and noon. The heart rate, systolic blood pressure, and double product show simultaneous and abrupt increases that parallel the increases in silent ischemic activity during these hours. There is a second peak in silent ischemic events between 8:00 and 9:00 PM. This distribution of silent ischemic events mirrors the circadian pattern of the circulatory changes.

**Circulatory Response During Silent Ischemic Events**

During the silent ischemic events, the heart rate increased in 100% and blood pressure increased in 89% of the events. There was an increase in the heart rate of greater than 10 beats/min in 75% of the silent ischemic events. The systolic blood pressure increased by 10 mm Hg or more in 78% of the silent events. The heart rate increased by 45% during the asymptomatic events and was comparable with the 52% increase during the symptomatic events. Similarly, the systolic blood pressure increased by 18% and 26%, respectively, during the symptomatic and silent ischemic events. Eight of the 73 silent ischemic events with blood pressure recordings during the events had either a decline or no change in the
systolic blood pressure from baseline. When comparing these events with the remaining 65 ischemic events in which there was an increase in the systolic blood pressure, there were no significant differences in the mean 1-minute preevent heart rate (74±17 versus 72±14 beats/min), mean peak heart rate (97±22 versus 97±18 beats/min), mean event duration (22.1±14.5 versus 28.5±16.6 minute), and mean maximum ST segment depression (1.2±0.3 versus 1.5±0.5 mm). However, there was a significant difference between these events when comparing the mean baseline systolic blood pressure (137±28 versus 117±17 mm Hg; p<0.01) and the percent change in systolic blood pressure from baseline to 1 mm (−12.8±12.0% versus 20.4±22%; p<0.001) and, as expected, at peak ST segment depression (−12.6±11.4% versus 24.8±21.5%, p<0.001).

**Discussion**

Our results show that, in patients with chronic stable angina, the vast majority of silent ischemic events during unrestricted daily activity are preceded by an increase in the heart rate and systolic blood pressure. Previous reports evaluating the possible mechanisms contributing in the genesis of silent myocardial ischemia have primarily focused on the analysis of the heart rate changes anywhere between 1 and 15 minutes preceding the onset of ST segment depression. These studies have provided inconclusive and conflicting results. Although some investigators have reported increases in the heart rate before onset of ST segment depression in a minority of episodes, others have reported increases before episode onset in the majority of cases. In view of the conflicting nature of these studies, the precise mechanism of myocardial ischemia during daily activity remains unclear. Furthermore, these studies lack simultaneous evaluation of blood pressure, which is an important determinant of myocardial oxygen demand.

**Hemodynamic Changes Before the Onset of Silent Ischemic Events**

This study, which uses simultaneous ambulatory ECG and blood pressure monitoring, demonstrates a significant increase in both the heart rate and systolic blood pressure before the onset of ST segment depressions. Sixty-one percent of the silent ischemic events were preceded by a significant increase in the heart rate, and 73% of the episodes with available blood pressure data showed an average increase of 10 mm in the systolic blood pressure preceding the silent ischemic events. These findings demonstrate that, in a majority of silent ischemic episodes, significant increases in heart rate and blood pressure precede the onset of ST segment depression and must play a significant role in the genesis of these events. However, it should be noted that despite all measures taken by us to avoid the effects of a previous ischemic episode on the heart rate and blood pressure responses preceding the subsequent ischemic epi-sode, it is not possible to ensure total independence of observations within a given patient.

It is of interest to note that in our study 39% and 27% of the silent ischemic events were not preceded by such a significant increase in the heart rate and blood pressure, respectively. It is possible that these episodes occurred secondary to other mechanisms that led to a reduction in myocardial oxygen supply. Also, seven of the eight events associated with a hypotensive response were not preceded by an increase in the systolic blood pressure within a mean of 7.1 minutes before the onset of ST segment depression. It is conceivable that, as reported by Nabel et al., alteration in coronary blood flow is primarily responsible in the genesis of these episodes.

**Hemodynamic Changes During Silent Ischemia**

We also evaluated the hemodynamic consequences of silent ischemia during unrestricted daily activity. The circulatory response to myocardial ischemia detected during ambulatory monitoring in our study is similar to that reported by Roughgarden, Littler et al., and Figueras et al. Similar to observations by Figueras et al and Littler and associates, we found that some ischemic events are not associated with a significant increase in the systolic blood pressure and may actually show a decrease in systolic blood pressure during the episode. The exact mechanism of the hypotensive response observed during the eight silent ischemic events in our study is not clear. Based on the time of onset, it seems unlikely that hypotension was secondary to postural changes. Furthermore, it is also unlikely that these events were associated with more severe ischemia since we did not demonstrate a difference between the duration and magnitude of ischemia during these episodes.

The progressive increase in the circulatory changes during myocardial ischemia, whether silent or symptomatic, provides good evidence of the associated hemodynamic consequences of ischemia. It is possible that these hemodynamic changes may further increase the intensity and duration of myocardial ischemia, which could eventually lead to cellular damage or death if left uncontrolled for prolonged periods.

**Comparison of Hemodynamic Changes During Exercise Testing Versus Ambulatory Monitoring**

Myocardial ischemia induced during exercise treadmill testing is widely assumed to occur as a result of an increase in myocardial oxygen demand. Thus, a comparison of hemodynamic changes observed during exercise testing with those noted during ambulatory monitoring is of interest in defining the role of increased myocardial oxygen demand in the genesis of silent ischemic events during daily life. Although of a lesser magnitude than during exercise testing, the net change in heart rate and systolic blood pressure during silent ischemic events showed significant increases from their corresponding baseline values. As expected, the numerical figures for both heart rate and blood pressure during
exercise-induced ischemia were higher than those noted during the silent ischemic events recorded on ambulatory monitoring. However, when the corresponding baseline values were taken into account, there was no significant difference between the relative percent increase in systolic blood pressure at 1-mm ST segment depression during exercise and ambulatory monitoring. These similarities in circulatory changes between exercise-induced ischemia and those observed during unrestricted daily activity in our study further support the concept that an increase in myocardial oxygen demand plays a significant role in the genesis of silent myocardial ischemia.

**Circadian Pattern of Silent Ischemia**

Finally, the circadian pattern of silent ischemic events in our study is similar to that reported by Rocco et al. We observed a bimodal distribution with peaks of silent ischemic activity in the morning and evening hours. This circadian pattern of silent ischemic events is quite similar to that described for out-of-hospital sudden cardiac deaths and onset of acute myocardial infarction and may suggest that increased frequency of silent myocardial ischemia during the morning hours acts as a trigger for these events. Interestingly, the morning surge of silent ischemic events in our study was associated with abrupt and simultaneous increases in the heart rate and systolic blood pressure. This surge in circulatory response previously has been shown to be associated with increased sympathetic activity leading to high levels of plasma catecholamines and cortisol. Although other factors, such as increased platelet aggregability, enhanced coronary vasomotor tone, endothelial dysfunction, and decreased intrinsic fibrinolytic activity, may also play a role, the marked increase in heart rate and blood pressure shown in our study must contribute in the genesis of silent ischemic activity during the morning hours. The simultaneous surge in systolic blood pressure and transient ischemic events during the morning hours could lead to plaque rupture, ultimately resulting in irreversible events such as myocardial infarction and sudden cardiac death.

**Implications**

The findings of our study have significant clinical implications. Our results demonstrate that increase in heart rate and blood pressure frequently precedes the onset of silent ischemic events during daily life. The circulatory changes observed before the onset of silent ST segment depressions closely resemble those involved in the pathophysiology of angina pectoris. Our findings also help explain the underlying mechanism of recently demonstrated efficacy of β-adrenergic blockers in reducing the number and duration of silent ischemic events. Finally, since the morning surge in heart rate and blood pressure parallels the increase in ischemic activity, it is conceivable that these could be effectively suppressed by appropriate β-adrenergic blocking agents and may help reduce the increased risk of myocardial infarction and sudden cardiac death during this period.

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**References**


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