PHYSICAL ACTIVITY AS A TRIGGER OF AMBULATORY MYOCARDIAL
ISCHEMIA IN PATIENTS WITH CORONARY ARTERY DISEASE:
ASSESSMENT USING AUTOMATED ACTIVITY MONITORS

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ABSTRACT

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Coronary Artery Disease: Assessment Using Automated Activity Monitors

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This study used automated physical activity monitors to objectively examine the relationship between heightened physical activity levels and the occurrence of daily life ischemia in patients with coronary artery disease (CAD). A total of 54 ischemic episodes were recorded in 21 CAD patients (2.6 ± 2.3 episodes/person) during 883 hours of continuous ECG and activity monitoring. The results of this study indicated that episodes of activity-induced ischemia occurred throughout the day, but tended to peak in the early morning hours due to dramatic shifts in activity and heart rate concomitant to the initiation of morning activities upon arising. In general, gradual increases in physical activity and heart rate were observed during the hour before the onset of ischemia. The findings of this study provide objective corroboration of previous self-report investigations of activity-induced ambulatory ischemia and highlight the potency of increased myocardial oxygen demand as a trigger of daily life ischemia.

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By

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Physical Activity as a Trigger of Ambulatory Myocardial Ischemia in Patients with Coronary Artery Disease: Assessment Using Automated Activity Monitors

Introduction

Coronary artery disease (CAD) is the leading cause of death in the U.S., and is responsible for numerous fatalities due to myocardial infarction (MI) and sudden cardiac death (SCD; American Heart Association, 2000). CAD is characterized by the accumulation of lipid-laden, fibrous plaque (atherosclerosis) in the inner lining of the coronary arteries which, when severe enough, can limit coronary blood supply to large areas of the heart muscle (Guyton & Hall, 1996). Insufficient perfusion of blood to areas of the heart will result in reduced oxygenation of heart muscle cells, or myocytes. In cases where coronary obstruction is complete and myocytes are starved of oxygen, cell death will result in the loss of viable cardiac tissue. This loss of viable tissue, by definition, is an MI or heart attack. In instances where coronary blood flow is rate-limited by CAD, an imbalance may arise between the amount of coronary blood being supplied to myocytes, and their need for oxygen. This imbalance between coronary blood supply and myocardial oxygen demand due to partial coronary obstruction is known as myocardial ischemia. Hence, both MI and myocardial ischemia share a common pathophysiology related to the progression of atherosclerotic disease.

Scientific knowledge of the causes of MI and SCD has increased in recent years and is the current focus of many important research protocols. Before undertaking this type of study however, researchers must consider the fact that heart attacks and episodes of sudden death are relatively rare events to study, despite the large annual loss of life related to their occurrence. An alternative to studying MI and SCD is to investigate the

onset of myocardial ischemia in patients with CAD. Episodes of ischemia are typically non-fatal and occur frequently during daily life. As a result, episodes of ischemia may be more amenable to scientific scrutiny than are MI or SCD. Furthermore, ambulatory ischemia often occurs asymptomatically, unlike many instances of MI, which means that the likelihood for experiencing pain is minimized for research volunteers. Thus, examining the circumstances related to the onset of myocardial ischemia can provide researchers with useful information regarding the deleterious health consequences of CAD.

Precipitation of Myocardial Ischemic Events. The sequence of events leading up to the onset of myocardial ischemia can be complex and may depend upon the interaction of several endogenous and exogenous factors that can provoke or "trigger" ischemia. Despite this complexity, the commonality of all ischemic triggers is that they ultimately lead to the disrupted balance between coronary blood supply and myocardial oxygen demand -- the physiological markers of ischemia. The mechanism of action by which an ischemic trigger operates will therefore depend upon how it alters either side of this supply/demand balance. For example, in patients with CAD, increased sympathetic tone has been shown to paradoxically reduce coronary blood flow by increasing coronary vasoconstriction at the site of atherosclerotic lesions (Selwyn, Raby, Vita, Ganz, & Yeung, 1991; Zeiher, Drexler, Wollschlaeger, Saurbier, & Just, 1989). At the same time however, it is well established that increased sympathetic tone can lead to increased myocardial oxygen demand, as indicated by increases in both heart rate (HR) and blood pressure (BP) levels (Guyton & Hall, 1996). In other words, this first example illustrates how a single endogenous variable, increased sympathetic tone, may influence both

coronary blood supply and myocardial oxygen demand in ways that are conducive to the provocation of ischemia. As will be discussed later, there are several other endogenous variables that are also known to exert similar influences upon this balance.

On the other hand, exogenous factors such as cigarette smoking and postural changes can also disrupt the balance between coronary blood supply and myocardial oxygen demand and lead to the onset of ischemia. For example, cigarette smoking has been shown to increase sympathetic nervous system output, leading to increased cardiac demand (Narkiewicz et al., 1998), while at the same time reducing peripheral blood flow by attenuating vasodilation (Newby et al., 1999). Similarly, postural changes and increased physical activity can increase sympathetic tone, as indicated by a resultant increase in HR (Parker et al., 1994), while also reducing the return of venous blood to the heart as a result of blood pooling in the lower extremities. As would be expected from such findings, previous research has reported that there is an increased risk for ischemia related to cigarette smoking (Gabbay et al., 1996), postural changes, and increased physical activity (Krantz et al., 1996; Parker et al., 1994). Finally, when one considers the interaction among these risk factors, such as the resumption of daily smoking concomitant to arising and initiating morning activities, the complexity by which daily life ischemia can be triggered becomes clearer.

Purpose of the Current Study. Considering the numerous risk factors that may be responsible for the induction of myocardial ischemia in CAD patients, a particularly potent trigger of ischemia appears to be heightened levels of physical activity. For instance, graded exercise stress test protocols serve as a standard by which the vulnerability for ischemia, and presumably the CAD responsible for causing ischemia, is

diagnosed. Furthermore, several self-report studies have found a link between heightened physical activity levels during daily life and the onset of ischemia (Barry, Campbell, Yeung, Raby, & Selwyn, 1991; Gabbay et al., 1996; Krantz et al., 1996; Parker et al., 1994; Pepine, 1991), with "highly active" individuals 4 times more likely to experience morning ischemia and twice as likely to experience afternoon ischemia than subjects with "low" activity levels (Krantz et al., 1996). Yet, despite this evidence, there remain several unanswered questions regarding the nature of activity-induced ischemia which the current study will address. For example, is physical activity an acute trigger of daily life ischemia? Is there an identifiable pre-ischemic increase in physical activity and cardiac demand levels (i.e., heart rate) before the onset of ischemia? Along with several other questions of interest, suffice it to say that the broad goal of this thesis will be to further examine the relationship between physical activity and the onset of daily life ischemia in patients with CAD.

Physical Activity, Cardiac Demand, and the Timing of Daily Life Ischemia. A notable characteristic of myocardial ischemia is the circadian fluctuation of its occurrence. Previous research has shown that in patients with stable CAD, the daily occurrence of myocardial ischemia peaks around morning awakening and to a lesser extent in the late afternoon or early evening (Deedwania & Nelson, 1990; Krantz et al., 1996; Mulcahy et al., 1988; Parker et al., 1994; Pepine, 1991; Rocco et al., 1987). This distribution of ischemic events has been observed in both laboratory and daily life studies of ischemia (Deedwania, 1997), and is similar to the pattern of onset for both MI (Muller et al., 1985; Willich et al., 1989; Willich et al., 1991) and SCD (Willich et al., 1987).

One of the first studies to examine the circadian onset of daily life ischemia was performed by Rocco and colleagues (1987). These investigators showed that when the time of day at which CAD patients had ischemia was adjusted for the time of day at which each patient awoke (i.e., number of hours after awakening), a sharp increase in ischemic frequency was observed during the first three hours subsequent to morning arising. In addition, Rocco et al. (1987) reported that 39% of all ischemic events and 46% of total ischemic time (i.e., total duration, in minutes) occurred in the morning hours, between 0600 and 1200 hours.

The findings of Rocco et al. (1987) led Parker and colleagues (1994) to question whether the peak in morning ischemia was due to an intrinsic mechanism related to awakening, or whether external factors such as the initiation of morning activities and postural changes related to arising also contributed to ischemia. After awaking subjects at the same time of day (8 a.m.), Parker delayed subjects' time of arising from bed by several hours in a counterbalanced fashion over two study days. As a result of this delayed arising, Parker et al. (1994) found that there was a similar observable delay in the onset of the peak in morning ischemia. In other words, by differentiating the time at which people awoke from the time at which people arose to begin their daily activities, Parker et al. (1994) demonstrated that the peak in morning ischemia appeared to be related to the act of arising. Furthermore, Parker reported that 87% of all the ischemic events observed in his study were preceded by HR increases of five or more beats per minute, implicating increases in cardiac demand as the mechanism by which ischemia was being triggered. Moreover, on the days of delayed activity Parker et al. (1994) observed that the peak incidence of HR-related ischemic events was likewise delayed,

demonstrating the correspondence between activity-induced increases in cardiac demand and the onset of ischemia.

More recent correlational studies, such as that by Krantz and colleagues (1996), have shown that 77% of morning events, but also 51% of afternoon daily life ischemic events occurred in patients self-reporting "high" activity levels during these times. "Highly active" patients were almost four times more likely to experience morning ischemia, but also twice as likely to experience afternoon ischemia than patients reporting "low" activity levels. Self-reported activity levels were not related to an increased risk for evening ischemic events however (Krantz et al., 1996), suggesting that a different mechanism of action may be responsible for the provocation of ischemic events during this time of day. The onset of nocturnal ischemia has also been associated with increased physical activity levels, with periods of waking and arising during the night coinciding with the onset of ischemia 67% of the time (Barry et al., 1991). Increases in HR preceding nocturnal ischemia, as well as electrocardiographic (ECG) changes during ischemia, were noted to be similar to those corresponding to morning ischemic events.

It is well documented that daily life ischemia is generally preceded by gradual increases in both HR and BP (Deedwania & Nelson, 1990; McLenachan et al., 1991; Panza, Diodati, Callahan, Epstein, & Quyyumi, 1992), further highlighting the importance of increased cardiac demand as a trigger of daily life ischemia. Thus, the occurrence of daily life ischemia appears to follow a non-random, diurnal distribution characterized, in part, by a peak incidence of early morning ischemic events related to postural changes and the initiation of daily physical activities upon arising. These changes in activity are believed to lead to increases in myocardial oxygen demand levels,

which may trigger episodes of ischemia by offsetting the balance between coronary blood supply and myocardial oxygen demand.

Discordant Findings. Several studies have reported findings that may seem at variance with those reviewed above. For instance, at least two studies have found that the majority of daily life ischemic events occurred at relatively lower HR levels than those observed during exercise-induced laboratory ischemia (Deanfield et al., 1983; Schang & Pepine, 1977). The implication of these findings is that the circumstances related to activity-induced daily life ischemia may be different from those responsible for the induction of laboratory ischemia, such as treadmill exercise testing. Research has shown that people usually spend a large amount of their daily lives performing low intensity activities such as walking or resting (Gabbay et al., 1996; Schang & Pepine, 1977). This finding could partially explain why the majority of daily life ischemic episodes occur at lower HR levels than laboratory ischemia. However, this finding does not adequately explain whether activity-induced daily life ischemia is truly different from exercise-induced laboratory ischemia. Several studies have been conducted to resolve these apparently conflicting results.

In a recent study, Gabbay et al. (1996) found that daily life ischemia occurred most frequently and at a higher onset HR level during periods of moderately intense to intense self-reported activity. This finding is consistent with the pathogenic mechanism believed to precipitate daily life ischemia and was found by correcting for the amount of time people reported spending in activities of relative varying intensity (i.e., low, medium, high). In other words, because so much of daily life is reportedly spent engaged in low intensity activities, adjusting for this fact allowed these researchers to discern the

true relationship between heightened physical activity levels and the onset of daily life ischemia. Similarly, findings from several laboratory studies have demonstrated that when a gradual exercise protocol is employed to slowly increase HR levels and induce ischemia, there is little difference between the onset HR for laboratory and daily life ischemia (McLenachan et al., 1991; Panza et al., 1992). In fact, one study reported that the onset HR for both laboratory and daily life ischemia differed by less than 10 beats per minute for 85% of the recorded events (Panza et al., 1992). Thus, the findings of these studies revealed that episodes of daily life ischemia do appear to result from activity-induced increases in cardiac demand in the same fashion as laboratory-induced ischemia. However, these studies also highlight the comparative difference in the degree of physical exertion related to both laboratory-induced and daily life ischemia. In daily life, few people engage in physical activities with the same sustained intensity and duration as would be required to induce exercise-related laboratory ischemia.

Alternative Explanations for Activity-Induced Ischemia. So far, the present discussion has focused on explaining a cardiac demand-based model for activity-induced ischemia. However, there is also ample evidence linking increased physical activity and postural changes to diminished coronary blood supply via changes in vascular tone (Brezinski et al., 1988; Gordon, Wolfe, Island, & Liddle, 1966; Quyyumi, 1990; Weitzman et al., 1971). For example, Gordon and colleagues (1966) observed that the early morning hours, as well as the postural changes related to morning arising, were associated with increased levels of renin, a powerful endogenous vasoconstrictor. Winther and associates (1992) reported that, regardless of the time of day, changing from a supine to an upright posture increased plasma norepinephrine levels an average of 50%

above baseline levels (Winther et al., 1992). Increased plasma cortisol levels have also been found to occur with physical activity and postural changes (Weitzman et al., 1971), and may act synergistically with heightened morning catecholamine levels (Turton & Deegan, 1974) to alter vasomotor tone. More recently, Quyyumi has reported that vascular tone appears to be increased in the morning hours, particularly after awakening and arising, due primarily to increases in both systemic noradrenergic and renin activity (Quyyumi, Panza, Diodati, Lakatos, & Epstein, 1992). Other factors involved in decreased coronary blood supply, such as increased sympathetic nerve activity (Fujita et al., 1998; Turton & Deegan, 1974), increased platelet aggregability (Brezinski et al., 1988), and decreased fibrinolytic activity (Andreotti et al., 1988; Rosing et al., 1970), are also known to vary across the day and may therefore overlap (e.g., interact) with morning postural changes and increases in physical activity.

In summary, there is strong evidence suggesting that daily life ischemia may be due to factors related to both diminished coronary blood supply, as well as factors related to increased cardiac demand. Because there are no ambulatory techniques available that can suitably assess variations in daily life coronary artery blood supply, the precise physiological basis for activity-induced ambulatory ischemia still remains unclear. The findings cited above suggest that heightened physical activity levels may exacerbate underlying physiological states related to diminished coronary blood supply which, in turn, probably act in concert with activity-induced increases in cardiac demand to induce ambulatory ischemia.

Limitations of Prior Studies Measuring Daily Life Physical Activity and Ischemia. To date, all the available information regarding physical activity and daily life

ischemia has originated from either laboratory-based or self-reported research. While such research designs are widely used and effective methods for collecting data, their findings are nonetheless subjective due to the reliance upon self-reported information and data collected under highly controlled experimental settings. Moreover, published studies examining activity-induced ischemia have often relied upon as few as 1-2 activity assessments per hour in their estimation of the diurnal fluctuation of daily life activity (Krantz et al., 1996). Such facts should raise concerns regarding the precision by which previous self-report and laboratory-based studies have assessed activity levels related to the onset of daily life ischemia.

Use of Activity Monitors. Technological advances in the field of actigraphy have lead to the development of automated activity monitors (Tryon, 1991), which are designed to assess real-time variations in daily life physical activity levels. Activity monitors, or actigraphs, are lightweight, compact, motion-sensing devices that provide objective, unobtrusive, and continuous measurements of daily life physical activity levels. Activity monitors work by directly measuring and recording information about the magnitude and duration of subjects' super-threshold movements. In particular, these devices use a piezoelectric bender element that translates body movements into electric signals, which are then stored in the unit's memory until downloaded onto a personal computer. More intense physical activity levels create stronger electrical signals which, in turn, are translated into a higher number of "activity counts" per user-defined assessment time period. The most current version of activity monitors can provide as many as four activity assessments per minute, providing a wealth of information regarding very precise changes in physical activity. Using such devices to reliably

measure physical activity has also been extensively validated against observational, self-report, and VO$_2$ max. criteria (Patterson et al., 1993). Thus, activity monitors provide researchers with an objective means of measuring very precise changes in daily life physical activity levels, without the methodological restrictions inherent to self-report and laboratory research designs.

Overview and Hypotheses of the Current Study. The purpose of this study is to use automated physical activity monitors to objectively measure the daily life activity pattern of CAD patients undergoing 24-48 hours of unrestricted, ambulatory ECG monitoring. The primary goal of this study is to further examine the relationships among increased physical activity, cardiac demand levels (as measured by HR), and the onset of daily life ischemia. The second goal of this study is to examine whether there are identifiable changes in activity and HR related to the circadian pattern of myocardial ischemia onset. The third goal of this study is to determine whether an increase in activity corresponds to the pre-ischemic increase in HR that previous studies have observed (Deedwania & Nelson, 1990). Finally, this study will examine whether the pre-ischemic increases in activity and HR differ according to the time of day at which ischemia occurs. Based upon the prior literature, four hypotheses will be tested:

1) Activity levels associated with the onset of ischemia will be greater than levels recorded during non-ischemic times of the day.

2) Activity and HR levels associated with the onset of ischemia will differ according to the time of day at which the event occurs, such that afternoon

ischemia will occur at a higher activity and HR levels than ischemic events occurring at other times of the day.

3) There will be a corresponding increase in both activity and HR levels preceding the onset of ischemia.

4) The hypothesized pre-ischemic increase in activity and HR will be greater before the onset of early morning ischemia, concomitant with the initiation of morning activities and postural changes related to arising.

Methods

Subjects. The present sample consisted of 21 patients (20 men; mean age = 57.2 $\pm$ 8.38 years; range: 39-70 years) with documented CAD (based upon angiography, prior myocardial infarction, positive exercise stress test, or a high probability of CAD ($\geq$ 80.0%) according to Bayesian analysis of risk factors and symptoms) (Rozanski et al., 1984). All participants had evidence of daily life ischemia as assessed by 48-hour ambulatory ECG monitoring. Patients were recruited as part of a larger study investigating emotional, physical, and behavioral triggers of myocardial ischemia (Gabbay et al., 1996; Krantz et al., 1996), and were equipped with an automated physical activity monitor (Motionlogger Actigraph™), and a Holter monitor during 24-48 hours of unrestricted daily life activity. All subjects provided written informed consent before participating, and this research was reviewed and approved by the relevant Institutional Review Boards.

Ambulatory ECG monitoring. Patients were titrated off anti-ischemic medications (beta-adrenergic blocking agents > 48 hours, calcium channel blocking agents > 24 hours, long-acting nitrates > 6 hours) prior to monitoring. Patients were permitted to take sublingual nitroglycerin as needed. Following standard electrocardiographic procedures, a two-lead Cardiodata AM recorder was used with bipolar electrodes at V5 and a modified inferior position (see Appendix A). Placement of the exploring electrode was modified to monitor the chest lead with the greatest ischemic response as documented during prior diagnostic exercise testing. An ischemic response was defined as horizontal or downsloping ST segment depression ≥ 1 mm below the isoelectric baseline, occurring 0.08 seconds after the J point and persisting for at least 60 seconds. Two cardiologists interpreted the ECG data in a blinded fashion with disagreements settled by consensus. This analysis provided information about the time of day at which ischemia occurred, its duration, as well as the onset and peak HR for each ischemic event. Heart rates at 60, 10, and 2 minutes prior to each ischemic event were also provided.

Activity monitoring. An accelerometer-based physical activity monitoring device (Motionlogger Actigraph™) was placed on the wrist of the patient's non-dominant arm (see Appendix A). As described earlier, the actigraph monitor uses a piezoelectric bender element to translate body movements into electric signals that are then stored in memory until downloaded onto a personal computer. Motions that fall beyond a pre-set threshold of .05 g and within the range of 0.25-5 Hz are sampled 10 times/second and stored in user-defined time epochs as "activity counts" (Tryon, 1991). This mode of detection, otherwise known as *threshold mode detection*, results in a value representing both the

frequency and intensity of super-threshold linear motion displacements of 20 degrees or greater. The sum of activity counts measured during each user-defined assessment epoch is then expressed as a function of chronological time. Thus, threshold mode detection is appropriate for examining longitudinal changes in physical activity over long periods of time. For this study, 48-hour physical activity data was collected and averaged over 15-minute epochs in order to adequately sample patients' hourly physical activity while also conserving battery life. As previously mentioned, the use of these devices to reliably measure physical activity has been extensively validated against observational, self-report, and VO_2 max. criteria (Patterson et al., 1993).

Statistical Analyses. Before analyzing the data, the time of day at which each ischemic episode occurred was adjusted according to each patients' reported time of awakening (mean wake time = 6:13 a.m.). A Chi-squared test was then used to determine how many hours had passed since awaking before the peak density of ambulatory ischemic events occurred (using successive three hour time blocks). Otherwise, t-tests, oneway analysis of variance (ANOVA), and repeated measure ANOVA were employed to test for differences in activity levels, changes in activity, HR levels, and changes in HR levels. *A priori* contrast testing was used to test specific predictions for significant overall findings. Statistical significance was set at a two-tailed probability level of .05 and results are expressed as mean $\pm$ standard deviation, or as frequencies with percentages.

Definition of Study Time Periods. For circadian analyses in this study, ischemic events were categorized into four six-hour blocks, based upon the time of day each event occurred and corresponding to Morning (0600-1159 hours), Afternoon (1200-1759 hours), Evening (1800-2359 hours), or Nighttime hours (2400-0559 hours). The morning

peak in ischemia was examined by correcting these time blocks for patients' self-reported times of awakening (see Statistical Analyses section above). Physical activity associated with "waking" ischemia, defined as the occurrence of ischemia within the hour awakening (0-59 minutes), was compared with activity levels associated with "morning" (1-6 hours from awakening), "afternoon" (7-12 hours from awakening); "evening" (13-18 hours from awakening), and "nighttime" ischemia (19-24 hours from awakening). Waking ischemic events therefore represent ischemia concomitant with the time of awakening, arising, and initiating morning activities.

Ambulatory Activity and Ischemia Data Reduction. To assess whether there were increases in activity prior to the onset of ischemic episodes, analyses were based on activity data recorded for the hour preceding each event, (i.e., the "pre-ischemic" hour). Since activity was sampled and averaged over 15-minute epochs, the pre-ischemic hour corresponds to activity measurements at 60, 45, 30, and 15 minutes before ischemic onset. Measures were taken to assure that this hour did not also include activity data relating to a previous episode of ischemia. Because multiple events occurred close in time in two patients (within 30 minutes), seven ischemic events were censored from analyses examining the change in activity over the pre-ischemic hour. Additionally, there were four instances in which two ischemic events occurred within 15 minutes of each other in three participants. Because these events fell within the same 15 minute sampling epoch of the actigraph, data for these events were averaged and considered to be single events in all analyses.

Management of Heart Rate Data. In a series of analyses, HR for 60, 10, and 2 minutes before ischemia were compared with HR levels at the onset of ischemia. The

first analysis compared HR levels for all time points, the second analysis compared HR readings recorded at 10 and 2 minutes with onset HR levels, and the last analysis compared HR levels for just 2 minutes and onset. There were 22 events with HR readings for all time points, 34 events with a 10 and 2 minute and onset HR reading, and 52 events with a 2 minute and onset HR reading.

Results

Ambulatory ECG analyses. A total of 883.3 hours of simultaneous Holter and actigraph monitoring were recorded from 21 ischemic CAD patients. Fifty-four ischemic episodes or 2.6 ± 2.3 episodes/person occurred. Nineteen ischemic episodes (35.2%) occurred between 0600-1159 hours, 13 (24.1%) between 1200-1759 hours, and 22 (40.7%) between 1800-2359 hours. No ischemic episodes occurred at night in this sample. Because no nocturnal ischemia was recorded, data for this time period were not analyzed further. All events occurred between 0600 and 2400 hours (range: 0609 to 2307 hours), and within 19 hours after awakening. The average duration of each ischemic episode was 9.9 ± 12.1 minutes, a total of 535 minutes of recorded ischemic time. Ten ischemic events (18.5%) in 5 patients (23.8%) were reportedly accompanied by anginal pain. The remaining events were silent (n=44; 81.5%).

Circadian Distribution of Ischemic Events. Figure 1 illustrates the diurnal pattern of the 54 ischemic events in relation to each patients' time of awakening (mean wake time = 6:13 a.m.). This distribution of ischemic episodes, coalesced in successive three hour time periods, peaked within the first 3 hours after awakening (16 episodes, 29.6%), and with a secondary peak beginning 10-12 hours (12 episodes, 22.2%) after awakening, $(\underline{X}^2 (5) = 13.8, \underline{p} < .05)$.

Comparison of Patients' Ischemic and Non-Ischemic Activity Levels. To test whether subjects' activity levels were higher during ischemic than non-ischemic time periods, average activity data for all ischemia-positive and ischemia-negative 15-minute epochs were compared within subjects (see Table 1 for means and standard deviations). Patients' overall activity levels at the onset of ischemia were found to be significantly higher than their levels during non-ischemic times (t 20 = 4.34, p < .001). The tendency for higher onset activity levels was also observed if analyses were conducted within chronological time blocks. For example, patients with morning ischemia (0600-1159 hours) had higher activity levels during ischemic than non-ischemic times, as did patients with afternoon ischemia (1200-1759 hours) and evening ischemia (1800-2400 hours). However, these differences were not statistically reliable (p's > .05).

Circadian Variation of Activity Levels, HR, and Ischemia. Activity levels at the onset of morning, afternoon, and evening ischemia were compared to assess whether they varied as a function of the chronological time of day (see Table 2 for means and standard deviations). Results showed that afternoon ischemia occurred at higher activity levels than both morning and evening ischemia, but this difference was of marginal statistical significance (F 2,51 = 2.81, p < .07). However, contrast tests revealed that afternoon ischemia occurred at significantly higher activity levels than did evening ischemia (t 51 = 2.37, p < .05). Similar results were found regarding HR (in beats per minute, bpm) at the onset of ischemia. Afternoon ischemia occurred at a somewhat higher, but not significantly higher onset HR than morning and evening ischemia (F 2,51 = 2.17, p = .13). However, similar to activity levels, onset HR for afternoon ischemia was significantly higher than that for evening ischemia (t 51 = 2.37, p < .05). Thus, the onset

activity level for myocardial ischemia was found to vary as a function of the time of day, and this variation was mirrored in onset HR values.

Increases in Activity and HR Preceding the Onset of Ischemia. Figure 2 illustrates the significant increase in physical activity which preceded the onset of ischemia ($\underline{F}$ 4,184 = 8.51, $\underline{p}$ < .001). Contrast tests revealed that activity levels significantly increased between 60 and 45 minutes before ischemia ($\underline{F}$ 1,46 = 10.72, $\underline{p}$ < .005), and between 45 and 30 minutes before ischemia ($\underline{F}$ 1,46 = 5.28, $\underline{p}$ < .05; see Table 3 for means and standard deviations). Activity levels increased slightly from 30 to 15 minutes and to an even lesser extent from 15 minutes to the onset of ischemia, but not significantly ($\underline{p}$'s > .05). Thus, activity was found to plateau at a heightened level from 30 minutes to the onset of ischemia. Further analyses confirmed the presence of this plateau in activity. Activity levels at ischemic onset were significantly higher than levels at 60 ($\underline{F}$ 1,46 = 14.67, $\underline{p}$ < .001) and 45 minutes before ischemia ($\underline{F}$ 1,46 = 6.39, $\underline{p}$ < .05), but were not significantly higher than levels at 30 or 15 minutes before onset ($\underline{p}$'s > .05). Thus, the increase in activity prior to ischemia occurred in the first half of the pre-ischemic hour, and remained heightened yet steady from 30 minutes to the onset of the event. The average increase in activity between 60 and 45 minutes was 28.6 $\pm$ 59.9 counts, between 45 and 30 minutes was 25.6 $\pm$ 76.5 counts, but only 8.4 $\pm$ 73.5 counts between 30 and 15 minutes, and 1.7 $\pm$ 68.1 counts between 15 minutes and onset.

Heart rate also increased over the hour preceding ischemia ($\underline{F}$ 3,63 = 52.30, $\underline{p}$ < .001), such that HR levels at the onset of 22/54 events were significantly higher than levels at 60 minutes ($\underline{F}$ 1,21 = 102.67, $\underline{p}$ < .001), 10 minutes ($\underline{F}$ 1,21 = 20.84, $\underline{p}$ < .001), and 2 minutes ($\underline{F}$ 1,21 = 42.16, $\underline{p}$ < .001) before onset (see Table 4 for means and

standard deviations). Further analysis of HR readings for just 10 and 2 minutes before ischemia (34 events) revealed that onset HR levels were significantly higher than both (p's < .001). Finally, HR at 2 minutes and onset were compared (52 events), revealing that onset HR was significantly higher than the 2 minute reading (t 51 = 6.77, p < .001). These findings are consistent with the observed increase in activity levels over the pre-ischemic hour, yet differ in that HR continued to significantly increase up to the time of onset, while activity did not.

Pattern of Activity and HR Changes for the Hour Preceding the Onset of Ischemia. The pattern of activity preceding waking (n=8 events), morning (n=13 events), afternoon (n=15 events), and evening ischemia (n=11 events) is illustrated in Figure 3 (see Table 3 for means and standard deviations). Again, waking ischemia was defined as the occurrence of ischemic events within the hour of awakening (0-59 min.), and represents the onset of the peak in morning ischemia concomitant to morning awakening, posture changes, and the initiation of morning activities (see Methods section). Results showed that physical activity significantly increased over the hour before waking ischemia (F 4,28 = 19.78, p < .001), but not before morning, afternoon, or evening ischemia (p's > .05). For waking ischemia, activity levels significantly increased between 60 and 45 minutes (F 1,7 = 7.28, p < .05), and between 45 and 30 minutes before ischemia (F 1,7 = 13.72, p < .01). Activity levels also increased between 30 and 15 minutes, and between 15 minutes and the onset of ischemia, but not significantly (see Figure 3 and Table 3).

A significant increase in HR also preceded the onset of waking ischemia (F 3,12 = 28.86, p < .001), such that HR increased between 60 and 10 minutes before ischemia (F

$1,4 = 37.72$, $\underline{p} < .01$), but not between 10 and 2 minutes ($\underline{F}$ $1,4 = 1.93$, $\underline{p} = .24$), or

between 2 minutes and ischemic onset ($\underline{F}$ $1,4 = 3.90$, $\underline{p} = .12$; see Figure 4 and Table 4 for

means and standard deviations). In fact, there was a slight decrease in average HR (6

bpm) which occurred between 10 and 2 minutes before the onset of waking ischemia.

However, these analyses were based upon a small sample of HR (n=5) due to missing HR

data (n=3) and must be interpreted cautiously.

Unlike pre-ischemic activity levels, pre-ischemic HRs increased significantly

during the hour before the onset of morning ($\underline{F}$ $3,18 = 17.37$, $\underline{p} < .001$), afternoon ($\underline{F}$ $3,18$

$= 15.33$, $\underline{p} < .001$), and evening ischemia ($\underline{F}$ $3,16 = 8.38$, $\underline{p} < .05$; see Figure 4 and Table

4). HR significantly increased between 60 and 10 minutes before the onset of morning ($\underline{F}$

$1,6 = 13.56$, $\underline{p} < .05$) and afternoon ischemia ($\underline{F}$ $1,6 = 22.29$, $\underline{p} < .005$), remained

relatively stable between 10 and 2 minutes for these same respective time periods ($\underline{F}$ $1,6$

$= 1.52$, $\underline{p} = 26$; $\underline{F}$ $1,6 = 0.08$, $\underline{p} = .79$), and significantly increased from 2 minutes to the

onset of morning ischemia ($\underline{F}$ $1,6 = 37.50$, $\underline{p} < .005$), and marginally for the onset of

afternoon ischemia ($\underline{F}$ $1,6 = 5.73$, $\underline{p} = .054$). Evening ischemia was preceded by a

significant HR increase only for the 2 minutes immediately preceding the event ($\underline{p} < .05$),

however this finding may be spurious due to the small number of available HR for this

analysis (n = 3).

Comparison of Activity and HR Changes Preceding the Onset of Ischemia.

Figure 5 (left) illustrates the gross change in activity over the hour preceding the onset of

waking, morning, afternoon, and evening ischemia. These values represent the difference

in activity levels measured at ischemic onset, and 60 minutes before onset, for each

wake-time adjusted block (e.g., activity change = onset activity – 60 minute activity).

Results revealed that there was a significant difference in the change in activity over this hour ($\underline{F}$ 3,43 = 9.58, $\underline{p}$ < .001), such that waking ischemia was preceded by a larger increase in activity (214.8 $\pm$ 82.7 counts) than morning ischemia (13.7 $\pm$ 91.1 counts; $\underline{t}$ 43) = 4.84, $\underline{p}$ < .001), afternoon ischemia (66.8 $\pm$ 92.8 counts; $\underline{t}$ 43 = 3.66, $\underline{p}$ < .01), and evening ischemia (11.6 $\pm$ 99.2 counts; $\underline{t}$ 43 = 4.74, $\underline{p}$ < .001). In other words, the onset of the peak in daily life ischemia (i.e., waking ischemia) was preceded by an average increase in activity that was over 15 times greater than that preceding morning ischemia, 3 times greater than that preceding afternoon ischemia, and 18 times greater than that preceding evening ischemia. The fact that this time period also corresponds to the transition from sleep for these subjects suggests that the acts of awakening, arising, and initiating morning activities were most likely responsible for the dramatic increases observed in physical activity levels during the hour preceding the onset of waking ischemia.

Figure 5 (center) illustrates the gross change in HR for the hour preceding the onset of waking, morning, afternoon, and evening ischemia. These values represent the difference in HR values measured at onset, and 60 minutes before onset, for a subset of 22 ischemic episodes. Results indicated that there was no significant overall difference regarding the average change in HR over this hour ($\underline{F}$ 3,18 = 1.45, $\underline{p}$ = .26), although waking ischemia was preceded by a greater increase in HR (40.2 $\pm$ 10.7 bpm) than morning ischemia (28.7 $\pm$ 13.7 bpm), afternoon ischemia (26.0 $\pm$ 16.1 bpm), and evening ischemia (23.3 $\pm$ 5.0 bpm). If these HR change scores are converted to percentage change score (from HR readings at 60 minutes), there is a significant increase in HR for these time periods ($\underline{F}$ 3,18 = 4.24, $\underline{p}$ < .05). Specifically, the percent change in HR preceding

waking ischemia (72.7 $\pm$ 24.3%) was significantly greater than that preceding morning ischemia (36.6 $\pm$ 18.8%; $\underline{t}$ 18 = 2.95, $\underline{p}$ < .01), afternoon ischemia (36.1 $\pm$ 23.3%; $\underline{t}$ 18 = 2.99, $\underline{p}$ < .01), and evening ischemia (29.7 $\pm$ 9.0%; $\underline{t}$ 18 = 2.81, $\underline{p}$ < .05). In other words, when considered in terms of the relative percent change in HR (i.e., percent increase in HR over reading at 60 minutes), there is a two-fold increase in HR preceding waking ischemia compared to other time periods (see Figure 5, right).

Comparing Early Morning Activity Levels of CAD Patients With and Without Waking Ischemia. Patients with and without waking ischemia were compared to see if they differed regarding early morning activity levels (see Figure 6). It was determined that the 8 waking ischemic events recorded in this study occurred in 5 patients, 31.4 $\pm$ 23.8 minutes on average after awakening. This means that, for this study, the onset of the peak in morning ischemia was accounted for by these 5 patients. Twelve CAD patients without waking ischemia comprised the comparison group and the same time frame was examined, namely 30 minutes before and after awakening. Four CAD subjects without waking ischemia were excluded from this analysis due to difficulties in precisely identifying their time of awakening (n = 2), or due to unusual waking patterns related to sickness (n = 1), or early morning business travel (n = 1). Regardless, although not significantly different from the comparison group, patients with waking ischemia had a trend towards higher activity levels, starting 30 minutes before awakening through the onset of ischemia (224.3 $\pm$ 75.2 counts), compared to the 12 comparison patients (140.2 $\pm$ 117.2 counts). Figure 6 illustrates this trend. More importantly, patients with waking ischemia had over a 5-fold increase in activity levels from the time of awakening to the onset of ischemia (105.9 $\pm$ 117.2 counts), than did the comparison group for this same

time period (19.8 ± 79.72 counts). More research is needed but these findings suggest that individual differences in early morning activity may differentiate CAD patients who have waking ischemia from those who do not.

Discussion

This study found that episodes of daily life ischemia were associated with heightened levels of physical activity, as well as heightened indices of myocardial oxygen demand (i.e., heart rate). While previous studies using self-reported activity levels have reported similar results (Barry et al., 1991; Deedwania & Nelson, 1990; Parker et al., 1994), to our knowledge this is the only study to use automated activity monitors to objectively validate this relationship in patients with CAD.

Physical Activity as a Trigger of Ambulatory Ischemia. In this study, CAD patients were found to be significantly more active during ischemic than non-ischemic times throughout the day. CAD patients with morning, afternoon, or evening ischemia also had a trend towards higher ischemia-related activity levels during these periods, compared to respective periods of non-ischemic activity. Both findings are consistent with previous studies of activity-induced daily life ischemia. For example, Gabbay et al. (1996) found that, while people reportedly spent the majority of their days engaged in low intensity activities such as sitting or resting, the likelihood for experiencing ambulatory ischemia was greatest during periods of heightened physical activity. Further analyses of this same set of data revealed a circadian pattern in this relationship, such that episodes of morning and afternoon ischemia were more likely to occur in CAD patients self-reporting higher levels of physical activity (Krantz et al., 1996). In fact, these

researchers reported that during periods of "high activity" CAD patients were four times more likely to experience morning ischemia and twice as likely to experience afternoon ischemia, than during periods of "low activity". Barry and colleagues (1991) showed that nocturnal physical activity (i.e., waking and arising during the night) was associated with the onset of nocturnal ischemic events similar in character to activity-related morning ischemic events. In fact, Barry et al. (1991) found that 67% of all nocturnal arisings corresponded to the onset of an ischemic episode. Thus, several studies, including the current study, have clearly demonstrated an increased risk for ambulatory ischemia associated with heightened levels of daily life physical activity.

The Circadian Distribution of Ambulatory Ischemia. The increased risk for activity-induced ischemia is most obvious during the early morning hours, around the time of awakening. In fact, there are several studies which clearly demonstrate a diurnal peak in ischemic frequency for this time of day (Deedwania & Nelson, 1990; Krantz et al., 1996; Mulcahy et al., 1988; Parker et al., 1994; Pepine, 1991; Rocco et al., 1987). Consistent with this literature, the current study found that the peak in early morning ischemia occurred during the first 3 hours after awakening, with almost 40.0% of all ischemic events occurring within 6 hours of awakening (Deedwania & Nelson, 1990; Pepine, 1991; Rocco et al., 1987). As well, the onset of this peak in early morning ischemia (i.e., waking ischemia) was preceded by an increase in activity that was 15 times greater than that for morning ischemia, 3 times greater than that for afternoon ischemia, and 18 times greater than that for evening ischemia. Moreover, waking ischemia was preceded by a two-fold greater increase in HR changes compared to HR changes preceding ischemia at other times of the day. Thus, the findings of this study

provide further empirical evidence that the shift in cardiac workload related to the act of awakening seems to be a potent trigger of the diurnal peak in ambulatory ischemia. In turn, this shift in cardiac workload could exacerbate underlying factors related to changes in coronary blood supply (Brezinski et al., 1988; Gordon et al., 1966; Quyyumi, 1990; Weitzman et al., 1971), sympathetic nerve activity (Fujita et al., 1998; Turton & Deegan, 1974), and decreased fibrinolytic activity (Andreotti et al., 1988; Rosing et al., 1970) -- all of which have been related to changes in physical activity, all of which are known to fluctuate across the day, and all of which have been implicated in the induction of early morning ischemia.

Preliminary findings from this study also suggest that individual differences in early morning exertion levels may actually differentiate CAD patients who have episodes of waking ischemia from those who do not. CAD patients who had waking ischemia were noted to have a five-fold greater increase in activity subsequent to arising than did CAD patients without waking ischemia. Since the peak incidence of daily life ischemia is in the early morning hours, future research could be directed towards discriminating whether certain individuals are at a greater risk for early morning ischemia than others, simply due to higher levels of exertion related to their morning routines.

Finally, this study found that afternoon ischemia occurred at significantly higher activity and HR levels than did evening ischemia. Activity and HR levels at the onset of morning ischemia were lower, but not significantly lower than afternoon ischemia. Both findings are consistent with previous research examining the circadian variation in ischemic threshold (Quyyumi et al., 1992). In that study, the morning and evening hours were characterized by significantly lower ischemic threshold levels (as measured by HR)

than were the afternoon hours, due primarily to higher levels of coronary vascular resistance. In other words, due to the diurnal variation in vascular resistance, cardiac demand levels associated with the onset of ischemia varied accordingly across the day, being higher in the afternoon than in the morning or evening. This finding is similar to what was found in the current study, except that higher levels of afternoon cardiac demand were also related to higher levels of physical activity. Thus, consistent with previous research, the findings of this study highlight the fact that the onset of daily life ischemia appears to be governed by the circadian fluctuation of both endogenous and exogenous triggers of ischemia.

Pre-Ischemic Increases in Physical Activity and Cardiac Demand. The fact that episodes of daily life ischemia occurred during periods of heightened physical activity and heightened levels of cardiac demand is not a new finding. However, what is novel about this study's findings is the fashion by which activity and HR were noted to increase prior to the onset of ischemia. Specifically, a significant increase in activity occurred between 60 and 30 minutes before the onset of ischemia, followed by a non-significant heightened plateau in activity during the half hour immediately preceding ischemic onset (see Figure 2). In other words, this study found that "onset" levels of activity were attained, as well as maintained, for about thirty minutes before ST-segment changes were noted. Heart rate was also found to gradually increase over this hour, but unlike activity, HR continued to increase in the minutes prior to the onset of ischemia, despite a plateau in activity.

Taken together, these findings seem to suggest that physical activity *per se* was not a proximal trigger of ischemia in the current study. Instead, it appears that the

cumulative effect of sustained, heightened levels of physical activity resulted in gradual increases in cardiac demand levels that, over time, led to the onset of ischemia. Thus, the findings of this study suggest that there is a discernible pattern to the changes in physical activity and HR which precede the onset of daily life ischemia. This sequence of events is corroborated by the results of at least two different laboratory-based studies of exercise-induced ischemia (McLenachan et al., 1991; Panza et al., 1992). These studies demonstrated that laboratory ischemia could be induced by gradual increases in pre-ischemic activity, resulting in pre-ischemic HR levels that were similar to those observed before the onset of ambulatory ischemia. While this finding does not provide direct support for the specific pattern of pre-ischemic activity changes noted in the current study, it does provide a basis for comparing the process by which gradual increases in activity may result in the onset of ambulatory ischemia.

Study Limitations. Although the hypotheses of this study were generally supported by the data, there are several study limitations which need to be addressed. First, the sample for this study was small, consisted mostly of men, and lacked a non-ischemic CAD control group. Thus, the interpretation and generalizability of this study's findings to a broader sample of CAD patient is limited until replicated in a larger, more heterogeneous sample of subjects. As well, future research may wish to employ a between-subjects experimental design in which the activity and HR levels of ischemic CAD patients are compared to those of non-ischemic CAD controls, especially during specific times of the day (i.e., waking hour). The fifteen minute sampling interval of the activity monitor used in this study was relatively wide, as were the intervals at which pre-ischemic HRs were assessed. Future research examining activity and HR on a minute to

minute basis will improve the precision by which the physical activity--cardiac demand relationship is assessed with regard to ambulatory ischemic events.

Future Research. As was previously addressed, the current data suggests that physical activity may trigger ambulatory ischemia via sustained levels of heightened exertion. However, this finding may also be an artifact of the relatively wide, 15-minute sampling interval of the activity monitors used in this study. Technological improvements have provided current activity monitors with enough memory to store several days of minute to minute assessments of activity. Ideally, activity and HR should be measured for shorter epochs than was used in the current study. Using more precise methodologies, future research may find physical activity to be an acute trigger of ischemia.

Second, since the greatest density of hourly ischemia occurs soon after awakening, future research would be remiss in not exploring the possible connection between electroencephalographic (EEG) and ECG correlates of sleep and ischemia. For example, REM density sleep has been shown to occur immediately prior to awakening and is associated with dramatic increases in sympathetic nerve and respiratory activity (Somers, Dyken, Mark, & Abboud, 1993). The implication of these findings, of course, is that pre-waking autonomic disturbances might set the stage for ischemia by increasing arrhythmic vulnerabilities in the face of increased cardiac demand upon arising. Thus, many benefits could arise from research examining the impact of normal EEG activity on the pathophysiological mechanisms underlying abnormal ECG activity.

Finally, the field of chronotherapy could benefit from the use of activity monitors. Since the basis of this field, as well as the study of chronopharmacology and chronokinetics, is the biological rhythm dependencies of medications, the use of activity

monitors could provide relevant information regarding how physical activity alters the efficacy of pharmacologic agents. In turn, findings from such research may provide important clinical information regarding the administration of medications in order to assure therapeutic levels of drug during times of peak ischemic vulnerability.

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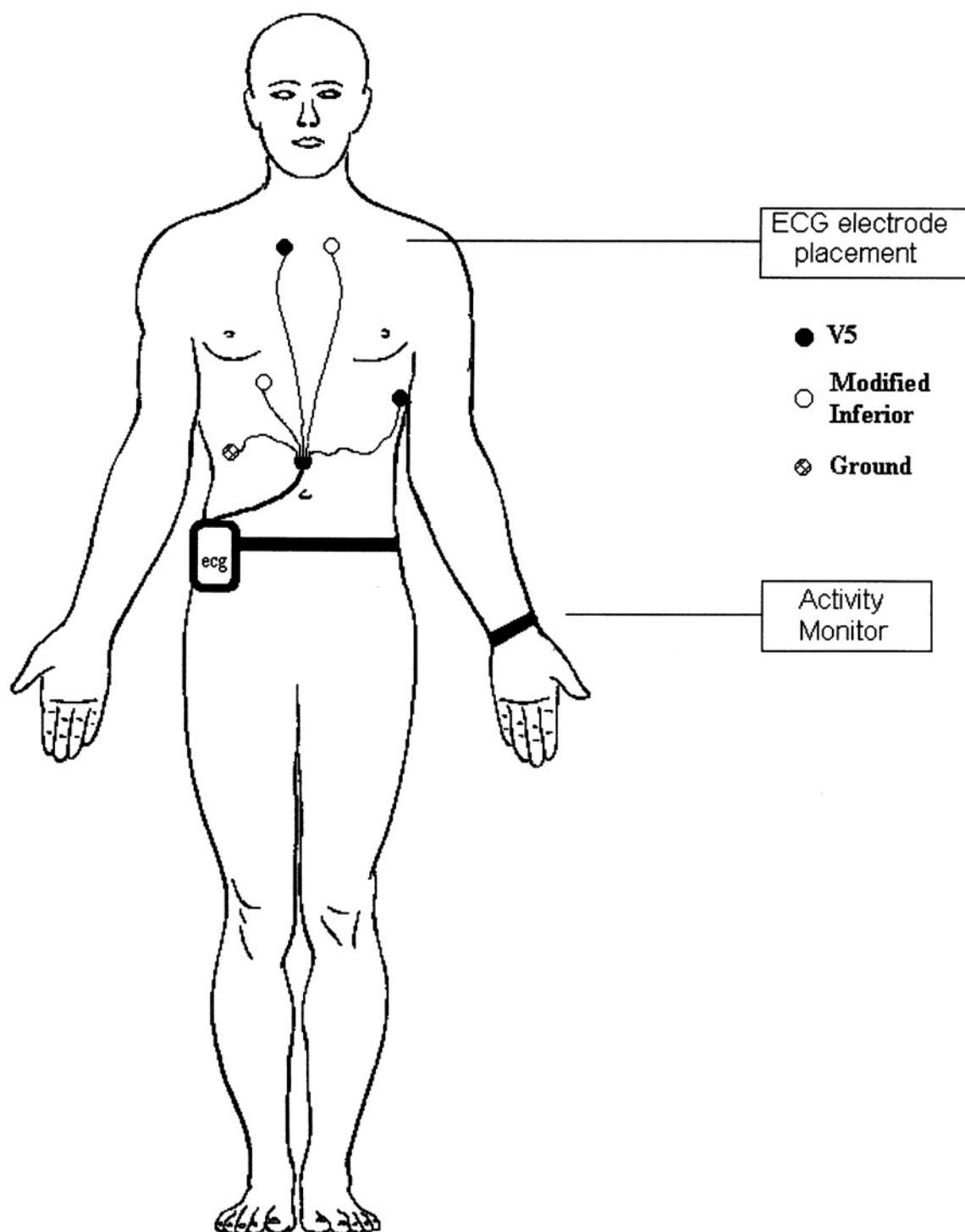

APPENDIX A

Table 1: Within Time Block and Within Subject Comparison of Activity Levels.

	Overall	Morning Ischemic	Afternoon Ischemic	Evening Ischemic
Sample Size *	21	10	8	12
Ischemic Activity (avg. counts)	224.3 ± 104.8	238.8 ± 96.1	275.9 ± 98.4	186.1 ± 99.5
Non-Ischemic Activity (avg. counts)	136.5 ± 38.9	188.5 ± 49.2	202.8 ± 43.3	158.7 ± 71.4
p-value	.001	ns	ns	ns

Values are expressed as mean $\pm$ standard deviation.

* Because some patients had ischemic events in more than one time period, addition of sub-sample sizes will exceed the total (N = 21).

Table 2: Comparison of Physical Activity and Heart Rate Levels Measured at the Onset of Morning, Afternoon, and Evening Ischemic Events.

	Morning Ischemia	Afternoon Ischemia	Evening Ischemia	p-value
Physical Activity (avg. counts)	230.3 ± 83.3	280.2 ± 97.6	203.8 ± 96.2	.07
Heart Rate (bpm)	102 ± 11	107 ± 16	96 ± 16	.13

Values are expressed as mean $\pm$ standard deviation.

Table 3: Activity Levels Measured During the Hour Before Onset of 47 Ischemic Events, Overall and by Wake-time Adjusted Time Block.

Time Period	Sample Size (%)	Pre-Ischemic Activity (counts)					p-value
		60 minutes	45 minutes	30 minutes	15 minutes	Ischemic Onset	
Overall	47 *	175.5 ± 112.0	204.2 ± 109.1	229.8 ± 93.7	238.3 ± 78.3	240.0 ± 96.8	.001
Waking	8 (17.0)	30.3 ± 59.8	77.9 ± 67.0	169.1 ± 102.3	228.3 ± 46.4	245.0 ± 59.7	.001
Morning	13 (27.7)	225.5 ± 94.0	243.4 ± 106.4	267.8 ± 75.3	247.8 ± 56.9	239.2 ± 102.6	ns
Afternoon	15 (31.9)	208.8 ± 78.7	247.1 ± 62.1	251.8 ± 69.0	258.4 ± 64.0	275.6 ± 73.2	ns
Evening	11 (23.4)	177.0 ± 118.5	191.0 ± 122.2	199.0 ± 114.1	206.7 ± 123.2	188.6 ± 125.1	ns

Values are expressed as mean ± standard deviation or as frequencies with (percentages).

* 7 episodes of ischemia were censored from these analyses due to temporal proximity (< 30 minutes) to a preceding ischemic event.

Table 4: Pre-Ischemic Changes in Heart Rate, Overall and by Wake-time Adjusted Time
Block.

	# of Events	Pre-Ischemic Heart Rate (bpm)				p-value
		60 minutes	10 minutes	2 minutes	Ischemic Onset	
Overall	22	73 ± 12	95 ± 11	90 ± 12	103 ± 11	.001
	34		94 ± 11	92 ± 11	104 ± 13	.001
	52			91 ± 12	102 ± 13	.001
Waking	5	57 ± 7	94 ± 10	88 ± 8	97 ± 8	.001
Morning	7	81 ± 9	97 ± 13	95 ± 16	109 ± 13	.001
Afternoon	7	76 ± 9	93 ± 11	93 ± 11	102 ± 13	.001
Evening	3	80 ± 8	98 ± 10	84 ± 8	103 ± 3	.05

Values are expressed as mean ± standard deviation.

Figure 1: Distribution of 54 Ischemic Events in Relation to Time of Awakening in 21 CAD Patients.
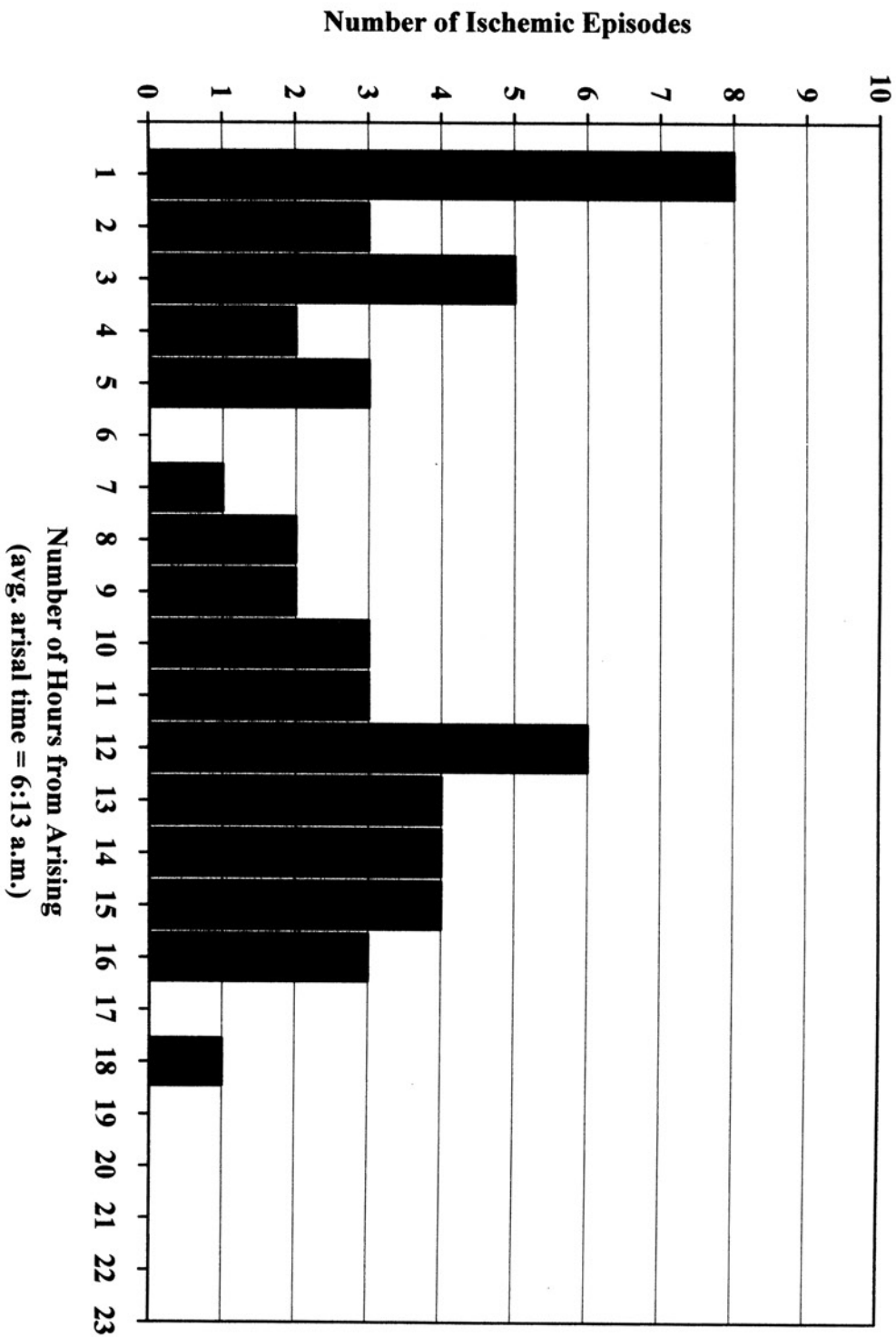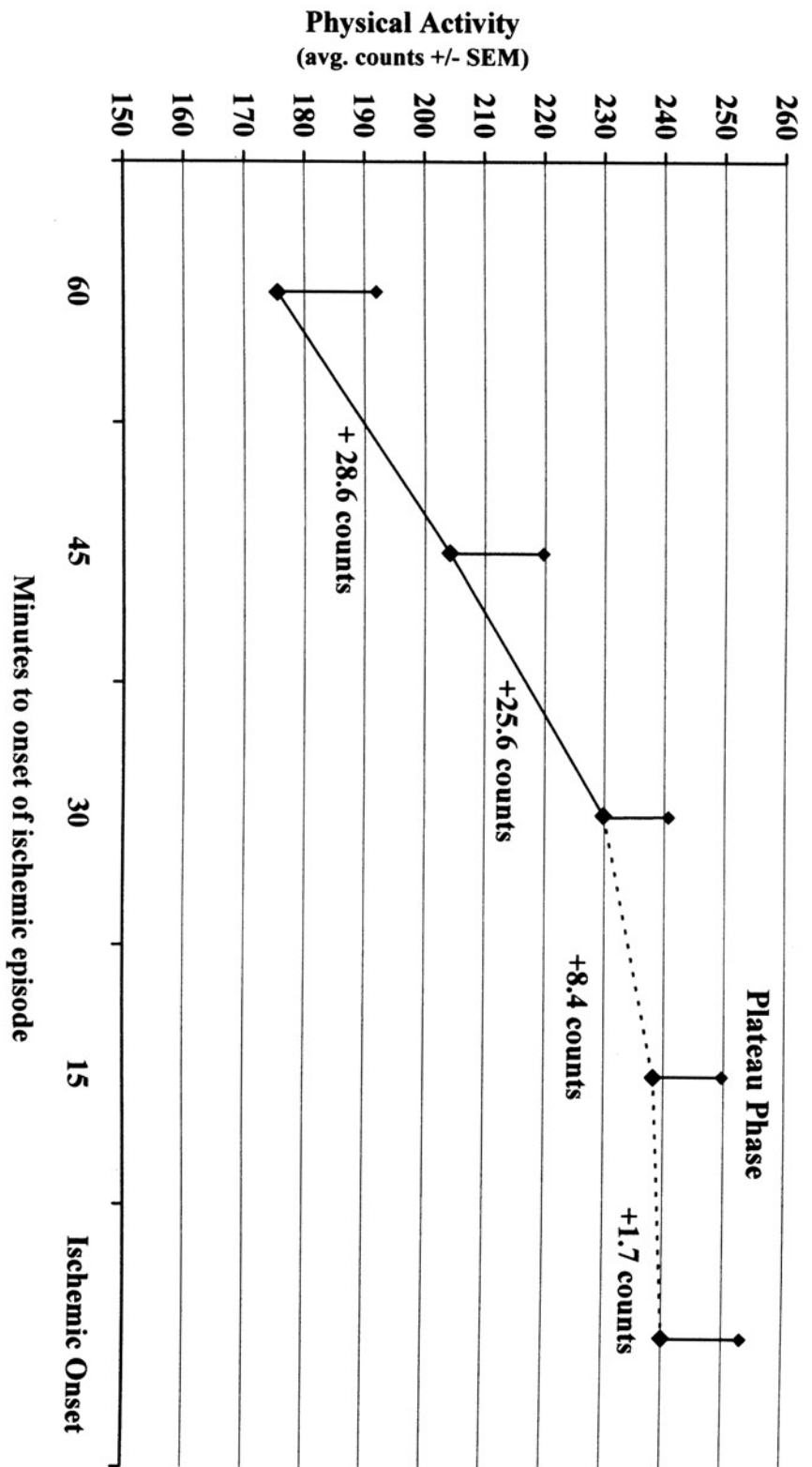
Figure 2: Increase in Average Physical Activity Levels During the Hour Preceding the Onset of 47 Ischemic Events.

Note 1: 7 episodes of ischemia were censored from these analyses due to temporal proximity (<30 minutes) to a preceding ischemic event (see Methods section).

Note 2: Standard Error of the Mean (SEM) is represented by the error bars due to the variability of physical activity levels.

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Figure 3: Pattern of Activity Preceding the Onset of 47 Ischemic Episodes, by Wake-time Corrected Time of Day.
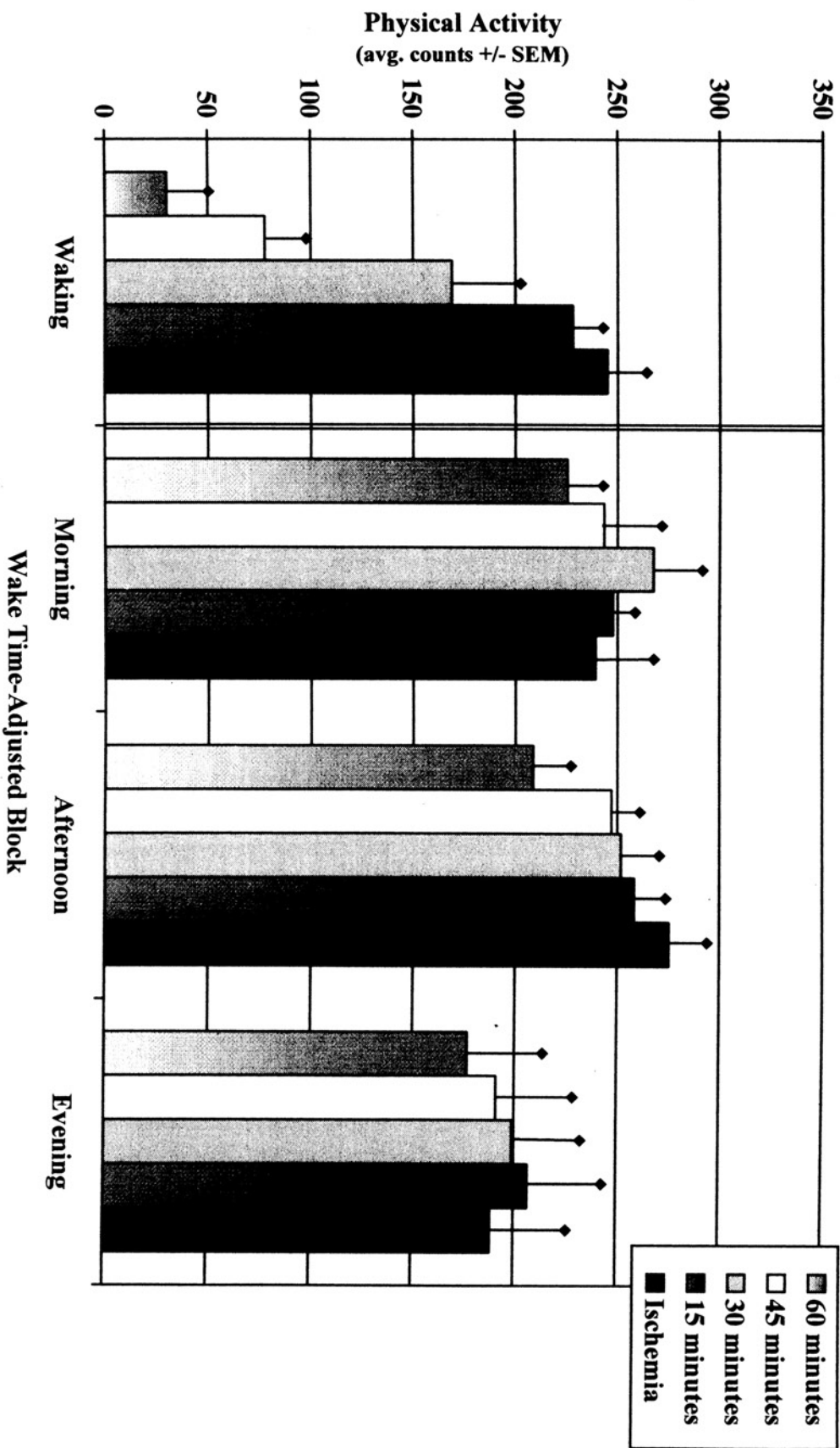
Note 1: Standard Error of the Mean (SEM) is represented by the error bars due to the variability of physical activity levels.

Figure 4: Changes in Heart Rate Preceding the Onset of Ischemia, by Wake-time Corrected Time of Day.
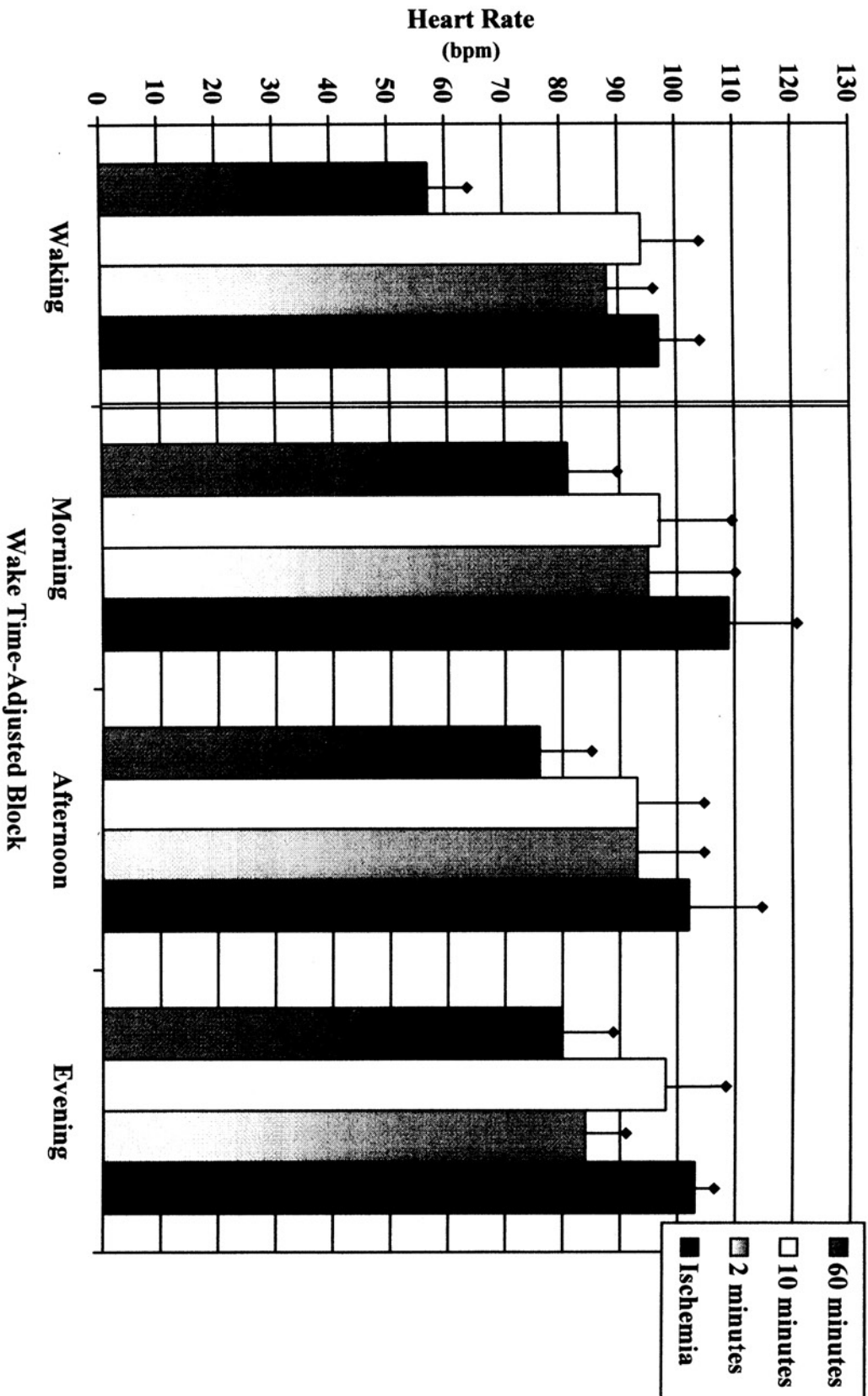
Figure 5: Changes in Activity, HR, and Percent HR over the Hour Preceding Ischemia by Wake-time Corrected Time of Day

W = Waking
M = Morning
A = Afternoon
E = Evening