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Reactivity of Ambulatory Blood Pressure to Physical Activity Varies With Time of Day

Helen Jones, Greg Atkinson, Andrew Leary, Keith George, Michael Murphy, Jim Waterhouse

Abstract—Blood pressure (BP) fluctuates over a 24-hour period, but it is unclear to what extent this variation is governed completely by changes in physical activity. Our aim was to use a BP “reactivity index” to investigate whether the BP response to a given level of physical activity changes during a normal sleep–wake cycle. Hypertensive patients (n=440) underwent simultaneous 24-hour ambulatory BP, heart rate (HR), and activity monitoring. BP and HR were measured every 20 minutes. Actigraphy data were averaged over the 15 minutes that preceded a BP measurement. Individual BP and HR reactivity indices were calculated using least-squares regression for twelve 2-hour periods. These indices were then analyzed for time-of-day differences using a general linear model. Systolic BP and HR were generally more reactive to physical activity than diastolic BP. The highest reactivity of systolic BP (mean \pm SE = 4 ± 1 mm Hg per logged unit change in activity) was observed between 8:00 AM and 10:00 AM ($P=0.014$). Between 10:00 AM and 12:00 PM, BP reactivity then decreased ($P=0.048$) and showed a secondary rise in the early afternoon. These 24-hour changes in BP reactivity did not differ significantly between groups formed on the basis of early and late wake times ($P=0.485$), medication use, age, and sex ($P>0.350$). In conclusion, under conditions of normal living, the reactivity of BP and HR to a given unit change in activity is highest in the morning and shows a secondary rise in the afternoon. (*Hypertension*. 2006;47:778-784.)

Key Words: exercise ■ blood pressure monitoring, ambulatory ■ heart rate ■ circadian rhythm

The onset of acute cardiovascular events varies according to time of day. Myocardial infarction, sudden cardiac death, and stroke show peak incidences between 6:00 AM to 12:00 PM and the lowest incidences during the nighttime hours.^{1–4} A secondary peak in the incidence of some cardiac events has also been reported in the afternoon or evening. For example, the onset of angina pain shows a rise in incidence between 6:00 PM to 7:00 PM that is secondary in magnitude to the morning peak.¹

The rupture of an atherosclerotic plaque leading to thrombosis is a mechanism that has been postulated for the peak occurrence of the above sudden cardiac events and stroke at the above times of day.⁵ Possible triggers of plaque rupture in the morning include increases in platelet aggregation, catecholamine, and cortisol levels, as well as increases in arterial blood pressure (BP) at this time of day.¹ Resting BP exhibits similar 24-hour variation to that of the incidence of cardiovascular events, with the lowest values of BP being observed during nocturnal sleep. After waking, BP increases markedly,⁶ a phenomenon that has been coined the “morning surge.”⁷

It has been hypothesized that the morning surge in BP may disrupt vulnerable plaques causing rupture and thrombosis leading to a cardiovascular or cerebrovascular incident.^{6,8} This hypothesis is supported by the results of a study by

Muller et al,³ who found that those elderly hypertensive patients who experienced larger-than-average morning surges in BP were also at an increased risk of stroke. Changes in BP at times of day other than the morning period may also be important. For example, a secondary fall and rise in BP has been demonstrated in the afternoon in the elderly, including those who are hypertensive.^{9,10} This pattern is also observed in people who take an afternoon “siesta.”¹¹ Interestingly, the siesta has been identified as a separate risk factor for sudden cardiac events,¹² but it is not known whether it is the daytime sleep, the increase in activity after the nap, or both components that mediate unfavorable BP changes. Therefore, the question arises as to whether the rises in BP observed after waking from a night’s sleep or a siesta are wholly because of the increased amounts of activity at these times or is there, in addition or alternatively, an increased sensitivity of BP to the effects of activity at these times?

One way to examine the internal influences on human circadian rhythms is by controlling physical activity at minimal levels via a constant routine of bed rest.¹³ If a circadian rhythm is still apparent under such conditions, then it follows that the rhythm is, in part at least, endogenously mediated. The results of a very recent constant routine study suggest that the 24-hour variation in BP does have an endogenous component,¹⁴ although

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this finding disagrees with those of other earlier researchers.^{15,16} The present study is concerned with a question that cannot be answered using a constant routine protocol, that is, whether there is any 24-hour variation in the response of BP to a change in activity.

Kario et al¹⁷ introduced a statistical index to investigate the reactivity of BP to physical activity when measured during normal living conditions. This index describes the change in BP per unit change in activity during a given period of data collection. Kario et al¹⁷ calculated reactivity indices during separate periods of sleep and wakefulness. Our aim is to use this same index to investigate whether the reactivity of BP to a given level of activity differs with time of day. A similar investigation has been reported previously for a nocturnal animal model,¹⁸ but any 24-hour variation in the reactivity of BP has not been investigated in human participants living normally.

Methods

Participants

All of the participants (n=440) were referred for the evaluation and monitoring of BP to Mercy Hospital, Cork. The sample of participants was heterogeneous (Table) and was originally examined in a previous study,¹⁹ which, nevertheless, concentrated solely on the data recorded during the morning period. Participants were referred for ambulatory BP monitoring for various reasons, including confirmation of diagnosis of hypertension (versus "white coat" hypertension) and for the assessment of BP status after receiving medication for already diagnosed hypertension.

Research Design

After providing informed consent, participants underwent noninvasive ambulatory BP and activity monitoring for 24 hours on a normal weekday. The equipment was fitted during a visit to the hypertension clinic at the hospital. Participants were instructed to follow their normal daily routine when they left the hospital and to return to the clinic the following day. All of the procedures were in accordance with institutional guidelines and were approved by an institutional review committee.

Measurements

A Quiet-Trak ambulatory BP monitor (Tycos-Welch-Allyn Inc) was fitted to each participant according to guidelines outlined by Staessen et al.²⁰ The nondominant arm was used for measurement using an appropriate-sized cuff. If the arm circumference was >31 cm, a large cuff was used. The monitor was calibrated by direct comparison with

3 BP readings by a trained nurse using a mercury sphygmomanometer in the sitting position according to British Hypertension Society guidelines.²¹ The monitor recorded BP and heart rate (HR) measurements every 20 minutes both during waking and sleep via auscultation. Subjects were asked to keep the arm still during the recording of each measurement.

After the ambulatory BP monitor was set up, an actigraph (Gaehtler Electronics) was placed on the participant's dominant wrist. This site was chosen because the results of previous research have shown that motor activity measured at the dominant wrist is the most appropriate²² and also correlates best with general physical activity.²³ The internal clock of the ambulatory BP monitor was set on the same computer. The actigraph device weighed 68 g and recorded suprathreshold motor activity (acceleration >0.1 g with filtering of the analogue sensor signal by a bandpass filter of 0.25 to 3.00 Hz) at an 8-Hz sampling frequency. The accelerometer produced an electrical current that increased in magnitude as the degree of motion increased. Every 10 s, the device converted the motor activity into an activity score on an arbitrary scale that ranged from 0 to 253 U.

All of the participants were given a standardized activity diary to complete during the monitoring period. Subjects recorded significant actions (eg, driving) around the time of each automated BP reading. This information was compared with the actigraph data as a general cross-validation of the measurements. Participants also used the diary to record the time of going to bed at night and time of waking in the morning. Waking time was defined as the time closest to diary wake time at which there was onset of regular activity scores of >0. This definition of waking time has been adopted in previous studies.²⁴⁻²⁶

Data Reduction

All of the BP readings rejected by the Quiet-Trak software as being artifacts were excluded from the analyses. Mean activity data were calculated, and the score was logarithmically transformed to correct for positive skew.^{17,27,28} In previous research work, the correlation between activity and BP has been found to be strongest when the activity data are averaged over the 15-minute period that precedes each BP measurement.²⁷ Therefore, this method of summarizing the activity data was chosen. The BP and activity data were partitioned into twelve 2-hour time periods starting at 12:00 AM to 2:00 AM in order to calculate the reactivity indices. For each participant and each time period, a least-squares regression slope for the relationship between BP, or HR, and activity was calculated¹⁷ using a minimum of 3 and a maximum of 6 data points for each time period. This slope described the individual BP and HR reactivity to physical activity over the 12 periods of the day that were studied. Data selected from a random subsample of 42 participants were explored for goodness-of-fit of the reactivity indices. Pearson's correlation coefficients were 0.51 ± 0.08 , 0.49 ± 0.08 , and 0.53 ± 0.08 for the systolic BP, diastolic BP, and HR reactivity indices, respectively (mean \pm SE).

Participants were grouped by sex, age, and medication status. Participants were ranked according to age and allocated to 3 age categories: (1) 15 to 41 years (n=148), (2) 42 to 55 years (n=155), and (3) 56 to 81 years (n=137). Participants who were receiving antihypertensive therapy or a combination of therapies (including β -blockers, calcium antagonists, angiotensin-converting enzyme inhibitors, α -blockers, diuretics, angiotensin II antagonists, and centrally acting agents) were classified as receiving medication (n=271). Participants were additionally categorized into 2 groups of either normotensive (n=123) or hypertensive (n=46) subjects for a secondary analysis. Participants were deemed normotensive if their average 24-hour ambulatory BP reading was systolic BP ≤ 135 mm Hg and diastolic BP ≤ 85 mm Hg²⁹ and if they were not taking antihypertensive medication. Participants who had an average 24-hour ambulatory BP reading above these levels and were not receiving antihypertensive therapy were classed in the hypertensive group.

We attempted to examine the influence of individual differences in wake times using 2 subanalyses. First, the data for each individual were reorganized so that the first time point for analysis was the first complete 2-hour period of reactivity calculations after the time of waking. For example, if an individual woke at 7:30 AM, the first reactivity index calculation was the period 8:00 AM to 10:00 AM. This meant that the act

Characteristics of Patients

Patient Characteristics	No. (n=440)
Age, y	48 \pm 14
Men, %	48
Current smoker, %	14
Antihypertensive medication, %	62
Weight, kg	77.0 \pm 14.4
Height, m	1.69 \pm 0.10
Body mass index, kg/m ²	26.6 \pm 4.5
Ambulatory systolic BP, mm Hg	132 \pm 16
Ambulatory diastolic BP, mm Hg	81 \pm 10
Wake time, h	8.0 \pm 1.2

Statistics for continuous measures are shown as mean \pm SD. For categorical measures, such as sex and antihypertensive medication, percentage of total sample is shown.

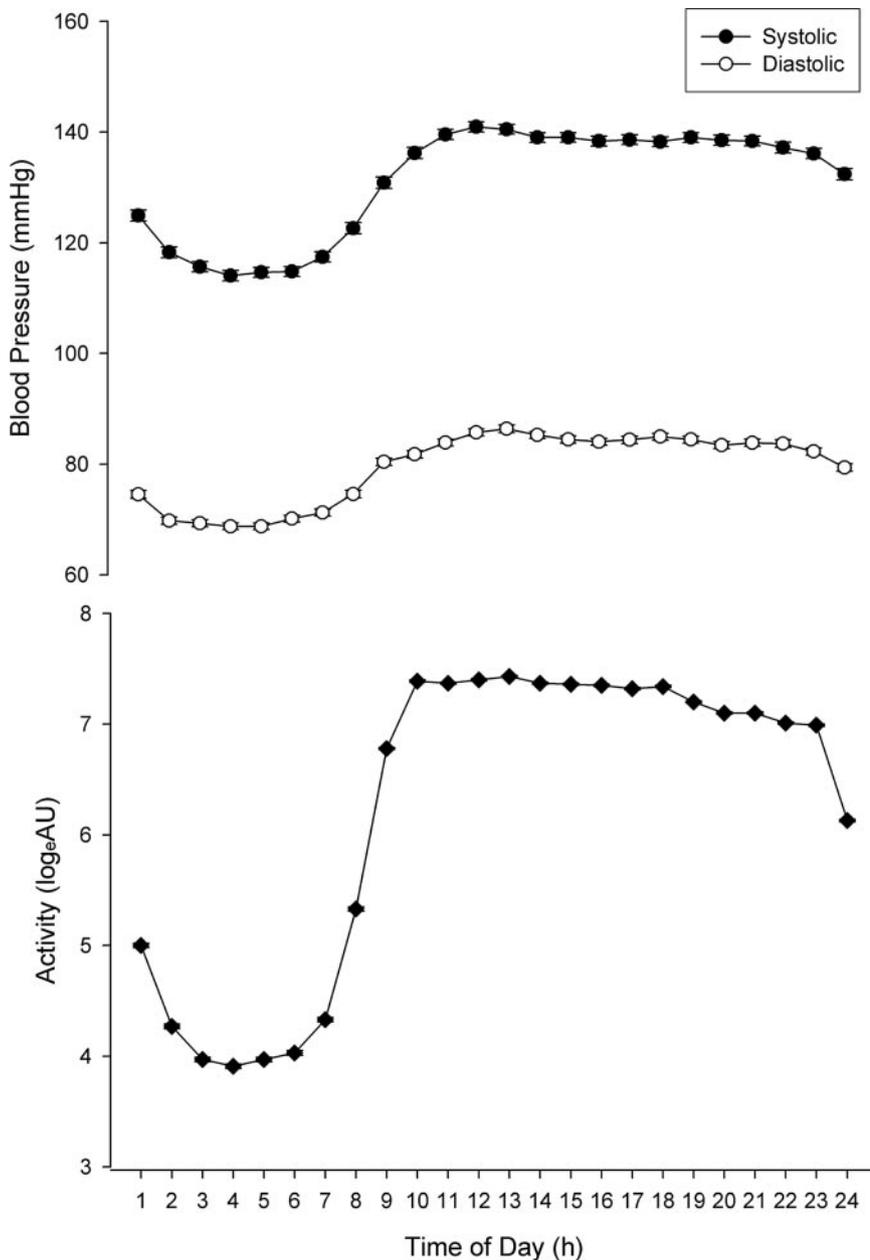


Figure 1. Twenty-four hour variation of systolic and diastolic BP and activity. Data are mean \pm SE.

of waking was not apparent in any calculation of reactivity. Because of individual differences in wake time, the first period of data used for calculation of reactivity could have begun between 1 and 120 minutes after waking. Such short-term (≤ 4 hours) BP responses to the act of waking have been examined in a previous study, which involved a portion of our data set.¹⁹ Second, we performed an analysis that compared the 24-hour variation in BP and HR reactivity between individuals with early and late wake times. Two subgroups were formed on the basis of their wake times occurring before or after the sample median. There was an “early wakers” group (wake time: 4.03 to 7.95 hours, $n=221$) and a “late wakers” sample (wake time: 7.97 to 11.62 hours, $n=219$). This between-subjects factor was added to our general linear model in the statistical analysis.

Statistical Analysis

A general linear model was used to examine differences in the mean reactivity indices between the time periods. There was a repeated measures factor of time with 12 levels (or 11 levels when reactivity periods were timed relative to waking) and between-subject factors of age, sex, medication status, and wake time. Because the sample size was

large, the multivariate method of repeated-measures analysis was selected for maximum statistical power.³⁰ This multivariate method also has the advantage that the repeated-measures assumption of sphericity is not relevant and so does not have to be corrected for. Significant main effects of time of day were followed up with a repeated measures contrast, which compares the mean value of each dependent variable at each time point with that recorded at the previous time point (with the exception of the first).³¹ All of the data were analyzed using SPSS version 12. Data are presented in the text and figure as mean \pm SE, and exact P values are cited (values of P of 0.000 provided by the statistics package have been recorded as <0.0005).

Results

Systolic and diastolic BP varied over 24 hours in a typical fashion; both 24-hour profiles were characterized by a rise in the morning with a peak at noon and a nadir during sleep (Figure 1). In absolute terms, the rise in diastolic BP was less marked than that in systolic BP. Activity followed a similar 24-hour pattern to that of BP (Figure 1).

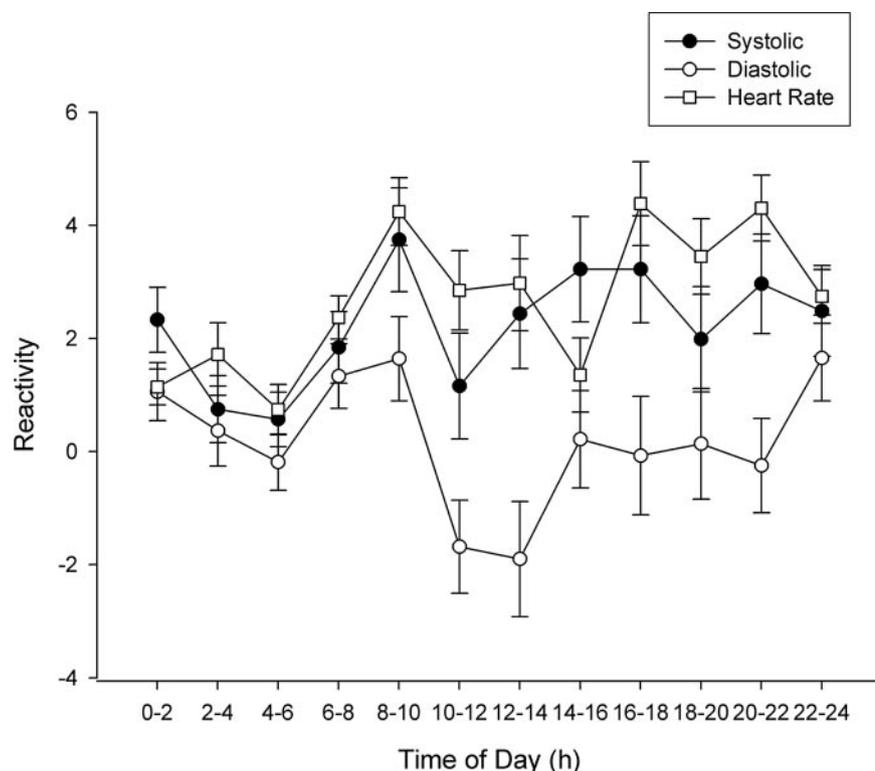


Figure 2. The reactivity of systolic and diastolic BP and HR to activity calculated over 12 2-hour periods. Data are mean \pm SE.

When the reactivity indices were calculated and analyzed, the reactivity of systolic BP to activity was found to change significantly over the 24-hour study period ($P=0.014$). The highest mean \pm SE reactivity index of 4 ± 1 mm Hg systolic BP per logged unit change in activity was observed between 8:00 AM and 10:00 AM ($P=0.048$). Reactivity then decreased between the hours of 10:00 AM and 12:00 PM ($P=0.043$; Figure 2). The between-subject factors of sex ($P=0.370$), age ($P=0.814$), and medication ($P=0.537$) did not affect these 24-hour changes in systolic BP reactivity. Furthermore, the 24-hour changes in reactivity of systolic BP did not differ significantly between hypertensive and normotensive individuals ($P=0.966$).

The reactivity of diastolic BP to activity also varied with time of day ($P=0.014$). The highest mean \pm SE reactivity index of 1 ± 1 mm Hg diastolic BP per logged unit change in activity was observed between 8:00 AM and 10:00 AM (Figure 2; $P=0.002$). Interestingly, diastolic BP showed a slightly negative reactivity index between 10:00 AM and 12:00 PM after the peak period of reactivity. The between-subject factors of sex ($P=0.582$), age ($P=0.950$), and medication ($P=0.801$) did not affect these 24-hour changes in BP reactivity. No difference was found between the 24-hour profiles in diastolic BP reactivity between the normotensive and hypertensive individuals ($P=0.393$).

HR showed a time-of-day effect in reactivity ($P<0.0005$), and the highest mean \pm SE HR reactivity index was 5 ± 1 beats per minute per logged unit change in activity (Figure 2). This peak in reactivity was observed at 8:00 AM to 10:00 AM ($P=0.008$) and 4:00 PM to 6:00 PM ($P=0.002$). The main effect of the between-subject factor of sex was statistically significant ($P=0.014$), with women showing greatest HR reactivity in general. Age ($P=0.602$), medication ($P=0.688$), and BP status ($P=0.983$) did not affect these 24-hour changes in HR reactivity.

Twenty-four hour variation in the reactivity of systolic BP ($P=0.025$) and HR ($P<0.0005$) was still apparent when the data were reorganized so that the first time period of reactivity calculation was that which occurred after the individual time of waking (Figure 3). Nevertheless, this was not the case for diastolic BP ($P=0.269$). As expected, 24-hour profiles in activity levels were significantly different between samples formed on the basis of early and late wake times ($P<0.0005$; Figure 4). Although the increase in activity during the morning period was delayed by ≈ 2 hours in the late compared with the early risers, the 24-hour profiles in the reactivity of systolic BP ($P=0.485$) and diastolic BP ($P=0.591$) did not differ between these subgroups (Figure 4). There was evidence ($P=0.086$) that the 24-hour changes in HR reactivity differed between the early and late risers (Figure 4); the morning increase in reactivity was delayed by ≈ 2 hours in the later risers compared with the early risers.

Discussion

The main finding unique to this study is that the reactivity of BP to a given unit change in physical activity shows 24-hour variation in humans living normally. This result complements the finding from a recent constant routine study¹⁴ that 24-hour variation in BP does not appear to be completely explained by changes in activity. Rather than physically controlling activity at minimal levels during a constant routine, our data were collected while participants went about their everyday activities and slept normally. Therefore, we were interested in estimating the magnitude of the rise in BP in response to a given change in activity in these conditions. This estimation can be made using least-squares regression, which is the statistical basis for the "reactivity index"¹⁷ that we used.

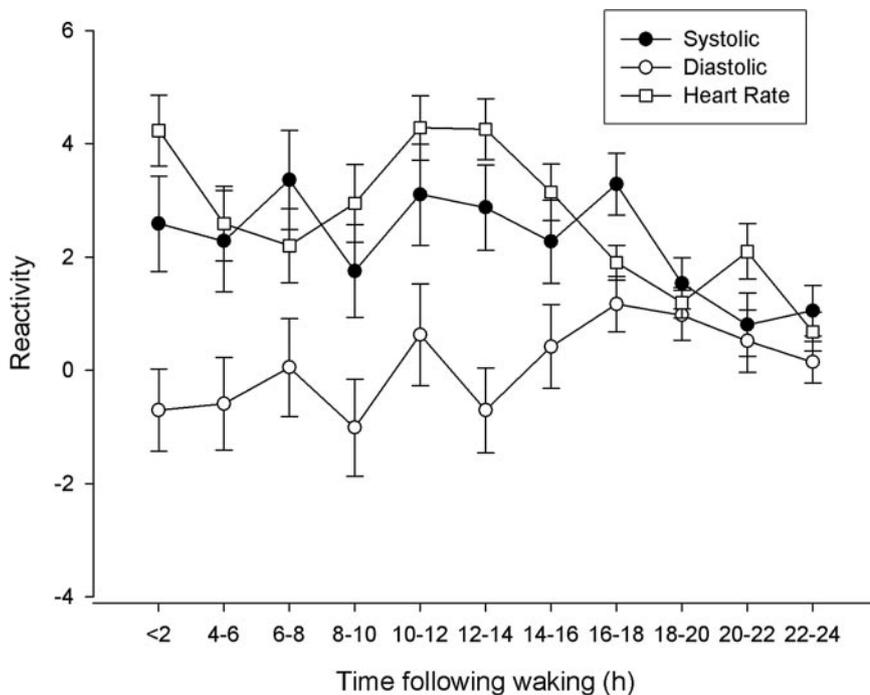


Figure 3. The reactivity of systolic and diastolic BP and HR to physical activity. The first reactivity time period shown is that which occurred after the individual time of waking. Data are mean \pm SE.

In the present study, absolute values of BP showed typical 24-hour variation (Figure 1), characterized by a peak in the morning and a nocturnal decline of similar magnitude to that observed in a study conducted by Staessen et al.³² The 24-hour rhythm of activity visually mirrored that of BP, which suggests a general relationship between activity and BP. This relationship has, in fact, been examined in many previous studies. Using simple correlation methods applied to time-series data, previous researchers^{17,23,27,33} have found that activity measured 1 to 30 minutes before a BP measurement was related to that measurement of BP. Nevertheless, we were concerned with whether the nature of such a correlation changes with time of day, that is, whether the slope of the activity–BP relationship shows 24-hour variation.

We found that the magnitude of the BP–activity regression slope fluctuates over a 24-hour period, with the highest values of this reactivity index being observed in the morning. Leary et al¹⁹ and Khoury et al³⁴ reported that increases in BP in the morning hours are related to changes in activity. However, these latter researchers only studied the morning period and did not examine whether the strength or characteristics of the activity–BP relationship differs in the afternoon or evening. When studied over a full 24-hour period, we found that the reactivity of systolic BP and diastolic BP follows a similar pattern (Figure 2) but that they differ in “amplitude” (the magnitude of variation in reactivity over 24 hours).

In the late morning, there was evidence of a transient decline followed by an afternoon peak in BP reactivity. This secondary fall and rise in BP reactivity was not as marked as that observed in the morning. A secondary afternoon peak in absolute values of BP has been found previously for elderly subjects.^{6,9} Our data suggest that this peak could be mediated by a greater reactivity to changes in activity at this time, such as those resulting from an afternoon nap.¹² Participants did not keep detailed records of exactly when lights were switched on or off or when an upright

posture was adopted after waking. Therefore, it is difficult to unravel the influence of these factors on BP reactivity. Interestingly, Carrington et al³⁵ found that the largest fall in BP occurs between lights-off and the onset of sleep. It is not known whether, paradoxically, the increase in BP after waking from sleep is explained mostly by switching the lights on.

HR showed significant changes in the response to activity throughout the day. Peaks in HR reactivity coincided with the peaks in BP reactivity. Interestingly, diastolic BP showed some negative values in reactivity between 10:00 AM and 2:00 PM. Although these negative values of reactivity were not significantly different from 0, the reactivity between 10:00 AM and 12:00 PM was significantly different from that calculated during the preceding time period (8:00 AM to 10:00 AM). Unlike systolic BP, the responses of diastolic BP to a given bout of exercise have been found to be variable, ranging from a slight decrease during light exercise to an increase of 10 to 20 mm Hg during intense exercise.^{36,37} The participants in our study were mainly performing light, everyday activities.

When the reactivity index time periods were ordered in terms of time after waking, systolic BP and HR still showed statistically significant 24-hour variation in reactivity. Reactivity transiently declined 6 to 10 hours after waking. Reactivity also declined during the night 14 to 20 hours after waking. These fluctuations seemed to be timed slightly earlier, relative to wake time, for HR compared with systolic BP reactivity (Figure 3). More evidence to suggest that the 24-hour variation in reactivity was not fully explained by the act of waking came from the wake-time subgroup analysis; the variation in reactivity did not differ significantly between early and late “wakers” for any of the reactivity indexes (Figure 4). Nevertheless, to control fully for the influence of wake time, per se, an experimental rather than observational study is required. Some factors, for example, changes in posture, lighting condition, and meal times, might not

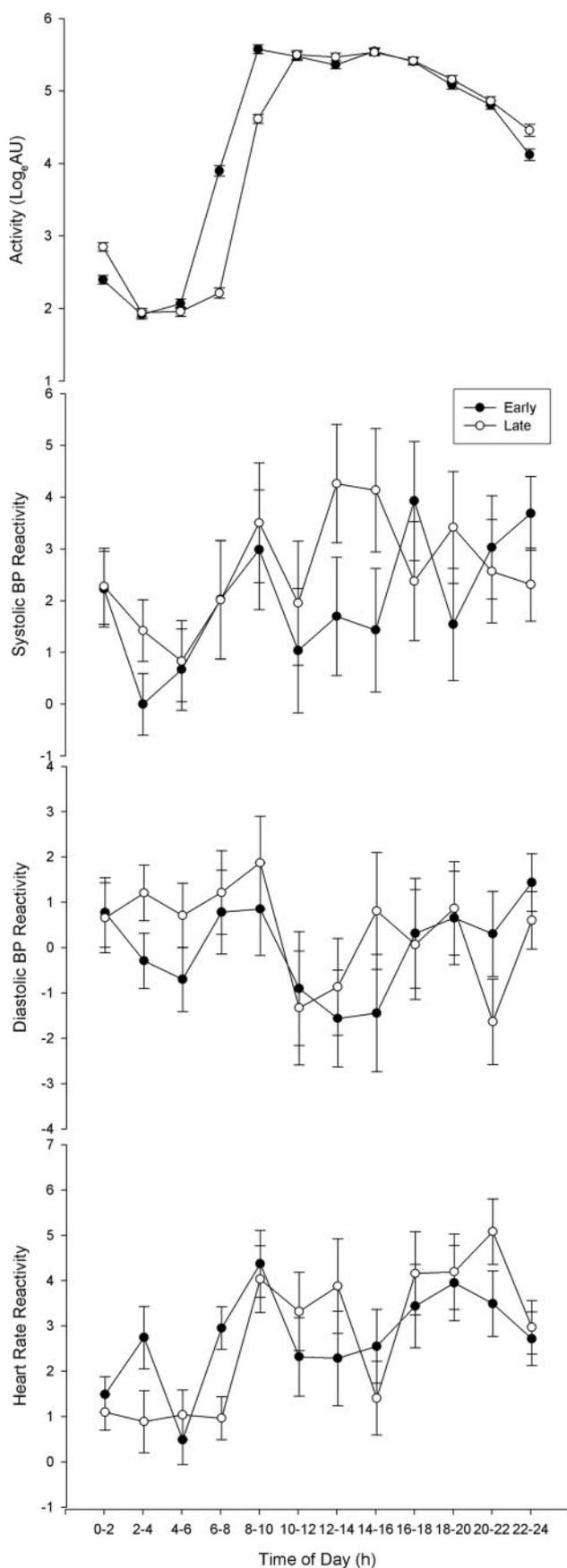


Figure 4. The 24-hour variation in physical activity and the reactivity of systolic BP, diastolic BP, and HR to physical activity

be directly linked to the timing of waking. For example, an individual might wake but then read in bed. Such a future experimental study should be designed to separate the influences of all of these factors on BP reactivity in the same way as that adopted by Winther et al,³⁸ who examined platelet aggregation and fibrinolytic activity between 8:00 AM and 12:00 PM. Exercise was systematically introduced toward the end of this period, which included previous interventions with posture. Exercise was found not to increase platelet aggregation to levels beyond that produced by the upright posture. Nevertheless, exercise, per se, was associated with a marked increase in fibrinolytic activity, which disagrees with the findings of Dag et al.³⁹

The finding that there were no differences in the 24-hour variation in BP reactivity between the normotensive and hypertensive groups suggests that the morning rise in the response of BP to activity is present irrespective of BP status. This result supports previous researchers,¹⁷ who found that dipping status did not affect the reactivity of BP to activity in normotensive people. The fact that 24-hour variation in BP reactivity exists in hypertensive patients may have implications for the prescription of exercise to these patients. It may be that hypertensive patients should ideally avoid the morning period for vigorous physical exertion. Recently, Floras⁴⁰ critically analyzed the observational evidence for the notion that physical activity is the fundamental link between circadian variations in hemodynamics and sudden cardiac events. He estimated that <6% of the morning increase in BP could be attributed to concurrent increases in physical activity. Nevertheless, Floras⁴⁰ thought that several “sensible cautions” should be applied, including the advice that morning exercise is taken regularly rather than infrequently; that isometric exercise, which tends to increase BP markedly, should be avoided in the morning; and that patients at risk should be screened.

The descriptive nature of our study cannot rule out the importance of changes in physiological variables for sudden cardiac events other than BP, such as sympathetic nervous activity, platelet hyperactivity, hypercoagulability and hypofibrinolysis, blood viscosity, and increased vascular spasm.^{1,41–44} All of these variables have been found to show circadian variation when studied at rest and have also been linked to the major pathophysiological processes underlying sudden cardiac death and myocardial infarction.^{1,45} Nevertheless, other than the study by Winther et al,³⁸ there is a lack of research on whether 24-hour variation exists in the responses of these variables to physical activity.

Perspectives

We used a recently formulated statistical index to investigate the magnitude of rise of BP in response to a given change in the level of physical activity measured during normal living. In light of the possible link between activity-mediated changes in BP and circadian variation in the incidence of sudden cardiac events, our aim was to ascertain whether the

compared between 2 groups formed on the basis of wake time. These 2 groups differed significantly in terms of the timing of the increase in activity in the morning, but no significant differences were found in terms of the timing of the increase in BP or HR reactivity in the morning.

reactivity of BP to physical activity shows 24-hour variation. We found that, irrespective of individual differences in wake times, BP status, medication use, age, and sex, systolic BP reactivity is highest in the morning and shows a secondary rise in the afternoon. Although the underlying reason for this 24-hour variation in BP reactivity has not been determined in this observational study, our findings support concerns about individuals at risk of a sudden cardiac event performing vigorous exertion in the morning soon after waking. Our future research work will now focus on separating the effects of factors such as changes in posture, light condition, and physical activity on the reactivity of BP in the morning.

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