Circadian Profile of Systemic Hemodynamics

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Abstract We determined the continuous 24-hour profile of mean arterial pressure, heart rate, stroke volume, cardiac output, and total peripheral resistance in eight healthy ambulatory volunteers. Beat-to-beat intra-arterial blood pressure was recorded with the Oxford system; subjects were ambulant during daytime and slept at night. Beat-to-beat stroke volume was determined by the pulse contour method from the arterial pulse wave. During the nighttime, compared with the daytime average, there was a decrease in blood pressure (9 mm Hg), heart rate (18 beats per minute), and cardiac output (29%); stroke volume showed a small decrease (7%), and total peripheral resistance increased unexpectedly by 22%. When subjects arose in the morning a steep increase in cardiac output and decrease in total peripheral resistance were found. Comparable changes were seen during a period of supine resting in the afternoon, whereas physical exercise caused opposite changes in hemodynamics. This pattern was observed in all subjects. We conclude that the circadian pattern of cardiac output and total peripheral resistance originates from the day-night pattern in physical activity: during the nighttime, blood flow to the skeletal muscles is decreased through local autoregulation, which increases total peripheral resistance and decreases cardiac output compared with the daytime. (Hypertension. 1995;25:55-59.)

Key Words • circadian rhythm • hemodynamics • blood pressure • heart rate

Increasing attention has focused on 24-hour rhythms of the cardiovascular system. The main reason is the consistent finding of a circadian pattern in the occurrence of cardiovascular events. During the early morning hours there are more episodes of myocardial ischemia, more myocardial infarctions, and more cerebrovascular accidents than during any other segment of the day. The circadian variation observed in these epidemiological studies has been associated with the circadian variation of blood pressure (BP) and heart rate (HR) and with the variation in several other physiological parameters such as plasma norepinephrine, platelet aggregation, and fibrinolytic activity. It has been well established that BP and HR are lower during the night than during the day and increase sharply at the moment of arising in the morning. It has been suggested that the sudden increase in HR and BP might act as a trigger for the rupture of atherosclerotic plaques or for platelet aggregation, thereby causing the acute development of a cardiovascular event. Most studies on circadian hemodynamics are solely concerned with changes in BP and HR. However, our understanding of these rhythms would increase by the study of the circadian variation of stroke volume (SV), cardiac output (CO), and total systemic vascular resistance.

Methods

Subjects

Continuous intra-arterial ambulatory 24-hour BP recordings from eight healthy normotensive volunteers (sitting BP by mercury sphygmomanometry <140/90 mm Hg) were used in this study. The age of the subjects was on average 24 years (range 18 to 32 years). All subjects were male; no one used medication. All subjects gave written informed consent. The protocol was approved by the medical ethics committee of the Academic Medical Centre.

Measurements

Intra-arterial BP was measured through a polytetrafluoroethylene cannula with a length of 11 cm and internal diameter of 1 mm. After local anesthesia with 1% lidocaine, the cannula was inserted into the brachial artery of the nondominant arm with the Seldinger technique. The cannula was connected via a 70-cm-long polyethylene tube to the transducer of an Oxford Medilog Mark II system (Romulus Technology Ltd.) The average overall resonance frequency of the combined system was 19 Hz (range 14 to 30 Hz). For storage of the intrabrachial signal, an instrumentation cassette recorder (HR-10J, TEAC Corp) was used.

Protocol

Subjects were hospitalized for the 24-hour recording period, during which several strictly controlled activities were carried out: sleeping time during the night was also controlled. On the first day of the registration, arterial cannulation was performed between 9 and 10 AM. The actual protocol started at 1 PM and lasted until 1 AM of the next day. Controlled activities comprised a supine period (2:30 to 3:30 PM), during which the subjects rested on a bed but did not sleep; a 30-minute period of cycling at 50 W, 50 to 60 rpm on a bicycle ergometer (4:45 to 5:15 PM); and two periods of walking outside the hospital from 9:30 to 11:30 AM with a period of 30 minutes of quiet sitting in between. During the night the subjects stayed in bed from 10 PM to 7 AM.

Data Analysis

The magnetic tapes on which the 24-hour BP signal was recorded were replayed. The analog BP signal was digitized for further processing by computer at 100 Hz with 0.25 mm Hg resolution. HR, mean arterial blood pressure (MAP), left ventricular SV, CO, and total peripheral resistance (TPR) were determined beat-to-beat by a signal-analysis program, and hourly averages of these parameters were calculated.

The hemodynamic parameters SV, CO, and TPR were calculated with the pulse contour algorithm of Wesseling (Sprangers et al; Wesseling et al; and Smith et al), dis-
cussed briefly below. All pulse contour methods are, explicitly or implicitly, based on a model. Most models are hemodynamic in nature, relating an arterial pressure or pressure difference to a flow or volume via the impedance through which the flow is driven. If the systemic circulation is considered to be a Wind- kessel model, SV can be calculated from the pressure as the driving force for flow during the ejection time:

\[ SV = A_{\infty} / Z_{\infty} \]

where SV is the pulse contour SV of the heart, \( A_{\infty} \) the area under the systolic portion of the pressure wave, and \( Z_{\infty} \) the characteristic impedance of the aorta.

Obviously, this model for the human circulation is too simple. However, sufficient information on human arterial hemodynamics is available today to provide an extension of this model.\(^{12,13}\) MAP is used for the correction of pressure-dependent nonlinear changes in the cross-sectional area of the aorta, and HR is used to correct for reflections from the periphery. (If the time for the pressure wave to travel forward and backward is longer than the ejection time, no correction is needed.) These corrections for pressure and rate are furthermore age dependent. A detailed description can be found in the article by Wesseling et al.\(^{13}\) Basically, the computation can be written as

\[ CO_{p} = HR \cdot A_{\infty} / Z_{\infty} \]

\[ Z_{\infty} = a + (b + (c \cdot P_{max}) + (d \cdot HR)) \]

where \( CO_{p} \) is the pulse contour CO, \( P_{max} \) is the MAP, and \( a, b, c, \) and \( d \) are age-dependent parameters. An initial estimate of \( Z_{\infty} \) is computed if age, MAP, and HR are available. The actual characteristic impedance \( Z_{\infty} \) is not known and must be determined for each subject by comparison with an absolute CO estimate such as thermodilution. However, without such calibration one can still determine the relative changes in CO in a subject with the same precision as mentioned below.\(^{12,13}\)

CO measured by this method was found to be in good agreement with dye dilution measurements when radial and brachial artery waveforms of young adult subjects were used, when MAP, HR, and CO were varied over wide ranges by pharmacological interventions.\(^{14}\) We have shown previously that when intrabrachial measurements on standing are repeated within a short time period, almost identical responses are obtained for both the arterial pressure measurements and the pulse contour computations.\(^{15}\) On comparison of CO by this method with thermodilution during changes in BP and HR in open-heart surgery, a standard deviation of the difference between the two methods of 10.6% (± 0.54 L/min) was found.\(^{16}\)

The circulatory circadian profile was analyzed in two ways: (1) To determine the changes of SV, CO, and TPR throughout the whole recording period, we used the entire 24-hour average as the reference level. The percentage of hourly deviations from this reference level were calculated to describe the circadian patterns of these three parameters. (2) The effects of sleep and physical activity were determined by calculating the difference of MAP, HR, SV, CO, and TPR with their daytime averages for the following time periods: the afternoon supine resting period, the nighttime period (10 PM to 7 AM), the walking and cycling periods, and the period of sitting between the two walking periods. For this purpose the daytime average was defined as follows: 1 to 10 PM of the first day combined with 7 AM to 1 PM of the second day. We excluded the nighttime from this reference level as it was one of the periods to be compared. Of course, the height of the chosen reference level may influence the magnitude of the changes in hemodynamic parameters. However, this does not influence the interpretation of the results. Our data consist of relative changes, and the variation of the changes in hemodynamic parameters alters concomitantly with the chosen height of the reference level. Also, the directions of these changes do not change irrespective of any reference level. All results are presented as averages and 95% confidence intervals (95% CI).\(^{17}\) The effects of sleep and physical activity were compared with the daytime average by the Wilcoxon signed rank test. A value of \( P < 0.05 \) was considered significant.

### Results

All eight subjects showed the well-known circadian profile of MAP and HR. Nighttime BP and HR decreased substantially compared with daytime values (Fig 1, Table), followed by a large increase starting at around 7 AM when the subjects were awakened by the investigator and got out of bed.

SV showed relatively small changes throughout the entire 24-hour measuring period (Fig 1). Only in the early morning hours after subjects arose did a large increase in SV occur, which lasted until about 11 AM. Compared with the daytime average, nighttime SV showed a decrease of 7% (95% CI, −2% to −12%; \( P < 0.05 \)). Because of the large decrease in HR and small change in SV, a large decrease in CO of 29% (95% CI, −24% to −34%; \( P < 0.01 \)) was observed during the night (Figs 1 and 2), ranging in individual subjects between −16% and −42%. In the early morning hours CO showed a large increase, with a peak between 10 and 11 AM (Fig 1). The circadian profile of TPR was the mirror image of the BP, HR, and CO profiles (Fig 1). TPR gradually increased when the subjects went to bed and showed a steep decrease when they rose. This pattern was seen in all eight individuals. The average increase in TPR during the night (Figs 1 and 2) was 22% (95% CI, 29% to 66%; \( P < 0.01 \)). TPR increased in all subjects.

### Changes in Hemodynamic Parameters During Day and Night

<table>
<thead>
<tr>
<th></th>
<th>MAP, mm Hg</th>
<th>HR, bpm</th>
<th>SV, %</th>
<th>CO, %</th>
<th>TPR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Night</td>
<td>−9</td>
<td>−15</td>
<td>−7</td>
<td>−29</td>
<td>+27</td>
</tr>
<tr>
<td>(−6 to −11)</td>
<td>(−14 to −22)</td>
<td>(−2 to −12)</td>
<td>(−24 to −34)</td>
<td>(20 to 18)</td>
<td></td>
</tr>
<tr>
<td>Supine resting</td>
<td>−9</td>
<td>−15</td>
<td>1</td>
<td>−17</td>
<td>+8</td>
</tr>
<tr>
<td>(−6 to −13)</td>
<td>(−9 to −17)</td>
<td>(8 to −6)</td>
<td>(−11 to −23)</td>
<td>(15 to 0)</td>
<td></td>
</tr>
<tr>
<td>Sitting</td>
<td>+9</td>
<td>+3</td>
<td>−6</td>
<td>−2</td>
<td>+13</td>
</tr>
<tr>
<td>(12 to 6)</td>
<td>(8 to 2)</td>
<td>(2 to −10)</td>
<td>(2 to −7)</td>
<td>(17 to 9)</td>
<td></td>
</tr>
<tr>
<td>Walking</td>
<td>+7</td>
<td>+22</td>
<td>+32</td>
<td>+94</td>
<td>−41</td>
</tr>
<tr>
<td>(10 to 4)</td>
<td>(34 to 22)</td>
<td>(39 to 26)</td>
<td>(69 to 68)</td>
<td>(−36 to −46)</td>
<td></td>
</tr>
<tr>
<td>Bicycling</td>
<td>+5</td>
<td>+29</td>
<td>+24</td>
<td>+74</td>
<td>−38</td>
</tr>
<tr>
<td>(7 to 3)</td>
<td>(26 to 23)</td>
<td>(50 to 18)</td>
<td>(50 to 57)</td>
<td>(−32 to −44)</td>
<td></td>
</tr>
</tbody>
</table>

MAP indicates mean arterial pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; and TPR, total peripheral resistance. Changes in hemodynamic parameters during various activities are compared with daytime average (1 to 10 PM of the first day combined with 7 AM to 1 PM of the second day). Results are group averages (n=8) (95% confidence interval).

\( P < 0.01, \, ^{TP} < 0.05 \) vs daytime.
The direction of the changes in hemodynamics during the afternoon supine resting period was comparable to that observed during the night, although the changes were of smaller magnitude (Fig 2, Table). BP and HR dropped as expected, and CO also decreased. TPR increased, although the increase of 8% (95% CI, 15% to 1%; P<0.05) was smaller than that seen during the night. During the period of sitting, TPR also increased compared with the daytime average; CO did not differ from the daytime average (Fig 2, Table). During periods of mild physical activity such as walking or cycling, HR and SV increased considerably, resulting in a large increase in CO (Fig 3, Table). As TPR decreased during both periods of physical activity, MAP increased only modestly.

**Discussion**

In our normotensive healthy subjects we found a normal day-night pattern in BP and HR. MAP dropped on average 9 mm Hg and HR on average 18 beats per minute during the night (Figs 1 and 2). Analysis of the hourly averages of the continuously computed SV, CO, and TPR (Fig 1) revealed that the nightly fall in BP was related to a substantial decrease in CO, mainly through a decrease in HR. SV also decreased in the night, but this fall was of a much smaller magnitude than that of HR. Somewhat surprisingly, and in contrast to what is usually assumed, TPR increased considerably during the night compared with the daytime, followed by a sharp decrease when subjects arose on the second day.

However, reports from animal experiments in primates tend to agree with our findings in humans. In monkeys a hemodynamic circadian rhythm was found that was comparable with our findings in humans. In these animals CO fell during the night because of a decrease in HR, resulting in a decrease in BP, whereas TPR increased during the night.

Several studies in humans have measured systemic hemodynamics at various instances during the night. However, none of these studies determined SV, CO, or TPR for the entire 24 hours in ambulatory subjects, and the data from these studies are contradictory. Miller and Harvath found a decrease in CO during sleep comparable to our findings and a decrease in SV, with no change in HR. These authors could not calculate vascular resistance, as they did not measure BP. Khatri and Freis found that the nightly decrease in CO was mediated by a decrease in HR, with no change in SV compared with the waking hours. TPR increased during the night, although not significantly. The results of these studies contrast with the results of Bristol et al, who found no change in CO although BP and TPR decreased during the night.

The differences between these results and our findings can at least in part be explained by the fact that in the above-cited studies in humans hemodynamics during waking time were measured while the subjects were heavily instrumented and resting, whereas our sub-
Fig 3. Plots show changes in mean arterial pressure (MAP), heart rate (HR), stroke volume (SV), cardiac output (CO), and total peripheral resistance (TPR) during walking and cycling of all individual subjects compared with daytime averages (all hours except between 10 PM and 7 AM). The averaged changes of all subjects and 95% confidence interval bars are also shown.

The circadian rhythm of BP depends on physical activity; sleeping was one of the activities in their study. Figs 2 and 3 illustrate that in our subjects the changes in CO and TPR induced by moderate physical activity, as during ordinary everyday life, are exactly opposite to those seen during the night. During quiet supine resting in the daytime, CO and TPR change in the same direction as during nighttime sleeping, albeit to a lesser degree (Fig 2).

Decreased demand for oxygen, especially by skeletal muscles, during nighttime sleep may provide the physiological basis for the relation between the activity pattern and the circadian variation in hemodynamics. The existence of a circadian pattern in oxygen consumption in humans has been established. The amount of peripheral flow and thus CO is regulated by local autoregulation in the tissues, in proportion to their need for oxygen and other nutrients. Muscle blood flow can increase manyfold during exercise—from 1.2 L/min at rest to 22 L/min during maximal exercise—and responses of the autoregulation in active skeletal muscle can occur within seconds. The heart plays a permissive role, allowing CO to be regulated at any level below its maximum limit. Thus, a circadian pattern in activity and in peripheral demand for flow may lead to a circadian pattern in venous return and CO. As the level of blood flow is regulated by peripheral vasoconstriction and vasodilatation, a decreased need for blood flow (during the nighttime) implies an increase in peripheral resistance. This reasoning makes our finding of an increased TPR during the nighttime plausible.

Another factor that may contribute to the nightly drop in CO is a reduction in effective circulating blood volume during the night compared with the day. The nightly increase in peripheral resistance will then be explained as a compensatory response to the decrease in CO. The decrease in effective circulating volume may be due to a translocation of blood to the periphery secondary to a fall in venous tone. It has been shown that in humans venous tone declines during sleep. Also, an absolute reduction in plasma volume may occur during the night because of a loss of water volume in expired air, insensible perspiration, and urine formation that is not replaced, causing a negative water balance. This hypothesis is supported by the finding that in monkeys central venous pressure declines and hematocrit increases during the night. However, as the reduction in plasma volume develops gradually, this would contradict our finding of more or less instantaneous changes in CO and peripheral resistance at the beginning and end of the sleep period.

The sympathetic nervous system probably plays only a minor role in the regulation of the circadian pattern of BP and related hemodynamics. During nighttime hours the activity of the sympathetic nervous system decreases, which has been considered to induce a decrease in peripheral resistance during sleep, in contrast to our findings. However, in monkeys neither α- nor β-blockade nor a combined α- and β-blockade could eliminate the circadian pattern of decreased MAP and HR and increased TPR during the night. Also, in patients with continuously high levels of circulating catecholamines due to pheochromocytoma, the circadian drop in BP is still present.

We found a large increase in BP and HR in the morning after subjects had risen. This increase in BP was related to an increase in SV and CO larger than the decrease in TPR (Fig 1). The extent of these hemodynamic changes coincided with a brisk, 90-minute walk outside the hospital. This probably amplified the changes in hemodynamics that normally occur at that time, as shown in Fig 3. During a period of quiet sitting in the morning, MAP, HR, SV, CO, and TPR levels did not differ from their daytime averages, confirming that circadian hemodynamics are mainly determined by the intensity of physical activity and not by the clock hour.

The change in TPR and CO we observed after subjects had risen is different from that found during the cardiovascular laboratory after they had stood up from a supine position. During quiet standing, CO is decreased and TPR increased compared with values during the supine position. However, this only holds when subjects remain standing quietly without moving, whereas our subjects were engaged in normal daily activities after arising. The physical activity explains these differences in hemodynamics.

The large and rather steep increase in BP and CO after arising results in a sudden increase of the workload.
of the heart. These factors may contribute to the onset of acute cardiovascular events in the morning, as they increase the oxygen demand of the myocardium at that time of day.\(^{26}\)

The large hemodynamic differences between day and night may have consequences for the treatment of hypertension. Our subjects were all young and normotensive, and as yet we have no similarly detailed information on the circadian profile of CO and TPR in hypertensive subjects. However, as the circadian profile of BP and HR differs only quantitatively between normotension and hypertension,\(^{8}\) the results of this study suggest that different antihypertensive drugs for day and night, with differing hemodynamic mechanisms, may be needed to ensure adequate BP control for the entire 24 hours.

References