Diurnal Cardiovascular Patterns in Spontaneously Hypertensive and Wistar-Kyoto Rats

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This study was designed to determine whether diurnal patterns of blood pressure, heart rate, or locomotor activity differed among two substrains of Wistar-Kyoto rats, derived originally from Charles River or Taconic Farms stock, or the spontaneously hypertensive rat. Cardiovascular parameters were continuously monitored over 24 hours. Resting systolic and diastolic blood pressure values were statistically different among the three groups both during the lights-on (rest) and lights-off (active) phases of the cycle with blood pressure of spontaneously hypertensive rats greater than that of Wistar-Kyoto rats from Taconic Farms, which was greater than that of Wistar-Kyoto rats from Charles River. The largest difference in arterial pressure between Wistar-Kyoto/Taconic Farms and Wistar-Kyoto/Charles River was during the lights-on period. Heart rates of all rats decreased during the lights-on period; Wistar-Kyoto/Charles River had the largest decrease (—70±5 beats/min), Wistar-Kyoto/Taconic Farms had the least (—17±2 beats/min), and in spontaneously hypertensive rats the decrease was intermediate (—29±3 beats/min). The pronounced diurnal variation in pressure and heart rate exhibited by Wistar-Kyoto/Charles River was not present in either Wistar-Kyoto/Taconic Farms or spontaneously hypertensive rats. Blood pressure magnitude correlated with locomotor activity during both periods, although all groups showed minimal activity during the rest period. Observed differences between Wistar-Kyoto/Charles River and Wistar-Kyoto/Taconic Farms were not due to a lack of or an abnormality in baroreceptor reflex function. Because most investigations that use these rat strains are performed during the lights-on phase of the diurnal cycle, the results demonstrate the need for a careful analysis of individual experimental protocols as well as the determination of the appropriate control for the spontaneously hypertensive rat. (Hypertension 1990;16:422-428)

The suitability of the Wistar-Kyoto (WKY) inbred rat strain as the appropriate control for the spontaneously hypertensive rat (SHR) has been questioned by several groups within the past 2 years. Our concerns were raised in the early 1980s when we noted differences between WKY rats purchased from different vendors.

After completion of a period of inbreeding by the National Institutes of Health (NIH) (20 generations of brother-sister mating), distribution of Wistar-derived SHR obtained initially from Okamoto and Aoki1 commenced in 1969.2 The SHR strain has since achieved wide acceptance as an experimental model for essential hypertension.2-4 For a control rat strain for the SHR, most investigators have used descendants of normotensive WKY rats from which the SHR had been derived.4 As a result of standardized breeding practices, virtual uniformity has resulted in SHR supplied by major commercial vendors.5 However, the rigorous procedures that had been applied to the initial inbreeding and subsequent distribution of the SHR were not used for the WKY rat, and many animals were distributed to commercial suppliers as early as the 10th generation.3 Further, subsequent breeding was not standardized; some suppliers (including Charles River) continued brother-sister matings4 and others (including Taconic Farms) used an outbred protocol.6

The lack of standardized breeding along with the failure to completely inbreed WKY rats before dissemination by NIH has led to questions in the literature regarding the appropriate control animal for the SHR.3,7-9 Studies have compared WKY rats obtained from Charles River (WKY-CR) and Taconic Farms (WKY-TF) and demonstrated pro-
nounced genetic differences and basal daytime cardiovascular differences.\textsuperscript{3,10} Our own laboratory noted altered consummatory behavior and morphological characteristics between these normotensive animals, including an enhanced salt preference in WKY-TF as early as 1984.\textsuperscript{11} This disparity between the inbred and outbred strains of WKY rats has been monitored within our colony of animals for more than 12 generations, and observations in our laboratory on consummatory behavior made in 1982–1984 have recently been confirmed (unpublished observation).

A recent comparison of cardiovascular and behavioral responsivity to a novel alerting stimulus by our laboratory (unpublished observation) revealed a difference in the heart rate response between WKY-CR and WKY-TF rats. Behavioral factors play an important role in blood pressure variability, circadian rhythm of blood pressure, and potentially, development of primary hypertension.\textsuperscript{12} Because WKY-CR and WKY-TF rats exhibited pronounced differences in their heart rate response to an air puff stimulus, the possibility of variant patterns of diurnal cardiovascular and locomotor activity patterns existed. Such variances could complicate interpretation of results from comparative cardiovascular studies. Therefore, the present studies examined diurnal cardiovascular and locomotor patterns of WKY rat strains derived from the two major commercial distributors of rats, Taconic Farms and Charles River, and compared them with SHR derived from Charles River.

\section*{Methods}

Rats used for cardiovascular and behavioral testing were weight-matched (230–260 g). All animals were bred and maintained (12-hour diurnal cycle) within our breeding colony, which is located within the Animal Care Facility at University of California, San Diego. WKY rats were from stock originally purchased from either Taconic Farms, Germantown, N.Y. or Charles River, Wilmington, Mass. and bred in accordance with the procedure of that particular supplier. At the time of the present studies, WKY-CR were in the 13th generation of brother-sister mating, and WKY-TF were in the 12th generation of random matings at our facility. SHR were from Charles River stock in the 13th generation of brother-sister mating in our colony.

Four days before testing, each rat was anesthetized with halothane and instrumented with a chronic femoral arterial catheter. The catheter was exteriorized at the top of the head and guided through a plastic luer-lock hub. The hub was fixed in place on top of the skull with quick drying dental acrylic. After recovery, the rat was placed in an 18×18 in. activity cage inside an acoustic isolation cabinet, which allowed simultaneous measurement of cardiovascular function. The cabinet was illuminated on the same light/dark cycle as the colony. Rats were tested singly and supplied with food and water ad libitum. A small fan located in the top of the cabinet provided fresh air and low level background white noise. The wire bottom of the activity cage was designed to measure locomotor activity. Spontaneous movement of the rat was measured by an electromechanical device that determined movement of the rats across quadrants inside the behavior cage. The sum of these movements was recorded over the 12-hour lights-off and lights-on period. To monitor blood pressure and heart rate, the catheter was fed via the luer-lock hub through a lightweight spring to a single channel fluid swivel. The spring allowed free movement of the rat about the cage but prevented chewing of the catheter. A period of 24 hours was allowed to equilibrate each rat to the cage. Blood pressure and heart rate were then sampled every minute for the next 24 hours by computer, using the Gould Data Acquisition System (Gould, Inc., Cleveland, Ohio). The data was condensed by averaging to one data point for each half-hourly period and analyzed by analysis of variance or \textit{t} test for repeated measures using SYSTAT.

To determine whether intrastrain variation in outbred animals confounded determination of group differences, homogeneity of variance for cardiovascular data was assessed independently by Hartley's test followed by Bartlett's analysis for between-group data.

In another group of WKY-CR and WKY-TF rats, baroreceptor reflex activity was assessed during the lights-on (rest) phase. These rats were instrumented with a femoral artery and venous catheter as described above. After a 3-day recovery period, the rats were acclimated to a 10 in. acrylic tube for testing. Thirty minutes were allowed for equilibration, after which randomized doses of phenylephrine (7–60 µg/kg) were administered intravenously by an infusion pump. Doses were given at 15-minute intervals, ensuring the disappearance of the physiological effects of the previous dose. Heart rate and blood pressure were measured during this period with the drug-induced peak blood pressure (mm Hg) versus heart rate interval (msec) analyzed by a least-square regression analysis to determine baroreceptor reflex gain and set point.

\section*{Results}

\subsection*{Locomotor Activity}

Each of the three groups of animals exhibited pronounced diurnal variation in locomotor activity (Figure 1); the greatest variation of activity by strain was between the lights-off (active) values. SHR were significantly (\textit{p} < 0.01) more active during the lights-off period than WKY-TF rats, which were more active than WKY-CR rats (\textit{p} < 0.01). The same comparative level of activity was apparent during the lights-on period, but the magnitudes of activity were much less and differences between the strains were smaller and correlated less with cardiovascular parameters.

\subsection*{Blood Pressure Variation}

When arterial pressure measurements were averaged over the lights-on and lights-off periods, WKY-
CR rats exhibited the greatest differences between the two time periods (8.4±0.8 mm Hg systolic and 9.2±0.9 mm Hg diastolic, n=11) (Table 1). Coincident with initiation of the lights-off period, systolic and diastolic pressure rose significantly and remained elevated throughout the majority of the cycle (Figure 2, top panel). There was no significant difference between the initial lights-off value of either systolic or diastolic pressure and subsequent time points through the lights-off cycle until 1 hour before the lights-on period. At this point, WKY-CR rats appeared to anticipate the beginning of the lights-on period and reduced toward the lights-on values both systolic pressure (142.8±1.7 at 5:30 AM to 135.8±2.6 at 6:00 AM, p<0.004) and diastolic pressure (101.6±1.8 at 5:30 AM to 95.9±2.6 at 6:00 AM, p<0.02). Just before the decrease in pressure, WKY-CR rats exhibited their maximal systolic and diastolic pressures; at 5:30 AM systolic pressure was 142.8±1.7 mm Hg compared with 136.8±1.7 at 6:30 PM (p<0.01) and diastolic pressure was 101.6±1.8 mm Hg compared with 97.3±2.2 mm Hg at 6:30 PM (p<0.03). Similar to the WKY-CR rats, there was not significant variation in systolic or diastolic pressures during the dark or light phases.

In contrast to WKY-CR rats, WKY-TF rats (n=11) did not exhibit a large variation of either systolic or diastolic pressure over the 24-hour period or a difference between the lights-off and lights-on periods (Figure 2, middle pattern). A 2.3±0.5 mm Hg decrease (p<0.05) in average diastolic pressure was observed for the WKY-TF rats during the lights-on (rest) period (Table 1 and Figure 2, middle panel), whereas systolic pressure did not show significant day-night variation. Similar to the WKY-CR rats, there was not significant variation in systolic or diastolic pressures during the dark or light phases.

The profile of arterial pressure for SHR (n=11) was distinct from that observed in either strain of WKY rats (Figure 2, bottom panel). Similar to WKY-CR rats, systolic and diastolic pressure was significantly elevated (p<0.01) at the first time point during the lights-off period (186.5±2.3 mm Hg systolic at 7:00 PM versus 195.5±2.7 at 7:30 PM, p<0.01; 130.1±2.2 at 7:00 PM versus 136.9±2.4 mm Hg diastolic at 7:30 PM, p<0.02). However, SHR demonstrated a continued and gradual increase in pressure throughout the lights-off period such that the maximum lights-off differences at 5:00 AM were 20.6±4.9 mm Hg systolic (p<0.001) and 13.1±3.0 mm Hg diastolic (p<0.006) greater than the pre-lights-off time point. Initiation of the lights-on period resulted in a gradual but significant decrease in systolic (F<sub>3.235</sub>=6.1, p<0.001) and diastolic (F<sub>3.235</sub>=2.5, p<0.01) pressure in SHR, which continued throughout the lights-on period. The rate of decrease in either parameter was approximately 2 mm Hg/hr. As a result of the gradual increase in pressure during the lights-off period and gradual decrease in pressure during the lights-on period, the average pressure for the entire lights-off period was not significantly different from the average for the lights-on period (Table 1).

Averaged systolic and diastolic pressures were significantly different among the three groups of rats...
TABLE 1. Summary of Cardiovascular Parameters and Locomotor Activity

<table>
<thead>
<tr>
<th>Parameter measured (12-hour average)</th>
<th>WKY-CR</th>
<th>WKY-TF</th>
<th>SHR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lights on</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic pressure</td>
<td>130.5±0.6</td>
<td>144.2±0.2*</td>
<td>195.5±1.0†</td>
</tr>
<tr>
<td>Diastolic pressure</td>
<td>90.3±0.6</td>
<td>102.2±0.3*</td>
<td>136.3±0.7†</td>
</tr>
<tr>
<td>Heart rate</td>
<td>333±2</td>
<td>380±2*</td>
<td>328±2*†</td>
</tr>
<tr>
<td>Locomotor activity</td>
<td>2.1±0.3</td>
<td>3.2±0.3*</td>
<td>6.9±1.1†</td>
</tr>
<tr>
<td><strong>Lights off</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic pressure</td>
<td>138.8±0.4</td>
<td>145.6±0.3*</td>
<td>197.9±1.2†</td>
</tr>
<tr>
<td>Diastolic pressure</td>
<td>99.4±0.4</td>
<td>104.5±0.2*</td>
<td>136.6±0.7†</td>
</tr>
<tr>
<td>Heart rate</td>
<td>403±3</td>
<td>398±2</td>
<td>356±2*†</td>
</tr>
<tr>
<td>Locomotor activity</td>
<td>18.3±1.7</td>
<td>26.6±3.0*</td>
<td>57.7±4.8†</td>
</tr>
<tr>
<td><strong>Differential</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic pressure</td>
<td>8.4±0.8‡</td>
<td>1.4±0.4</td>
<td>2.3±2.1</td>
</tr>
<tr>
<td>Diastolic pressure</td>
<td>9.2±0.9‡</td>
<td>2.3±0.5‡</td>
<td>0.3±1.1</td>
</tr>
<tr>
<td>Heart rate</td>
<td>70±5‡</td>
<td>17±2‡</td>
<td>29±3‡</td>
</tr>
<tr>
<td>Locomotor activity</td>
<td>16.2±1.5‡</td>
<td>23.5±3.0‡</td>
<td>50.7±3.9‡</td>
</tr>
<tr>
<td>Baroreceptor reflex gain (msec/mm Hg)</td>
<td>0.67; r=0.79</td>
<td>0.72; r=0.63</td>
<td>Not tested</td>
</tr>
</tbody>
</table>

Systolic and diastolic blood pressure and heart rate values represent average values±SEM of 24 measurements during lights-off or lights-on period. WKY, Wistar-Kyoto; CR, Charles River; TF, Taconic Farms; SHR, spontaneously hypertensive rat.

*Significantly different from WKY-CR, p<0.05.
‡Significantly different from WKY-TF, p<0.05.
§Significant difference between lights-off and lights-on periods, p<0.05.

during both the light and dark phases of the diurnal cycle (Table 1) with the rank order of: SHR greater than WKY-TF rats greater than WKY-CR rats. Because of the lack of a decrease in arterial pressure during the lights-on period in WKY-TF rats, the disparity between the two WKY rat substrains was most substantial during the day (lights-on) when the WKY-TF rats had a 13.7±0.6 mm Hg higher systolic pressure (p<0.01) and a 11.9±0.6 mm Hg higher diastolic pressure (p<0.01) than WKY-CR rats.

**Heart Rate Variation**

In WKY-CR rats, the increase in blood pressure during the lights-off period was accompanied by a dramatic increase in heart rate of 70±5 beats/min, lights-off versus lights-on average (Figure 3). The onset of the heart rate increase was rapid, reaching the statistical maximum (417.7±10.0 beats/min, 8:30 PM) within 1½ hours. The heart rate remained stable throughout most of the lights-off period. As seen in the pattern of blood pressure changes, heart rate appeared to reflect an anticipatory response to the start of the lights-on phase by demonstrating a significant decrease 1 hour before initiation of the lights-on period (414.4±11.4 versus 384.2±12.0 beats/min at 5:30 and 6:00 AM, respectively, p<0.05) at which time a stable plateau was obtained for the duration of the lights-on period.

WKY-TF rats exhibited a much smaller variation in heart rate over the 24-hour period compared with WKY-CR rats (Figure 3). The increase in heart rate during the lights-off period was only 17±2 beats/min. Because of the large increase in heart rate in WKY-CR rats, the absolute heart rate level of WKY-TF rats was not statistically different from WKY-CR rats during the lights-off cycle. However, during the lights-on phase WKY-TF rats were significantly higher than WKY-CR rats (380±2 versus 333±2 beats/min, F<sub>1,46</sub>=4.18, p<0.01). WKY-TF rats, therefore, demonstrated much less diurnal variation as a result of their apparent inability to decrease heart rate during the lights-on period.

Although SHR showed gradual diurnal variation in blood pressure, the heart rate profile demonstrated an abrupt increase (336.7±5.3 beats/min at 7:00 PM versus 366.4±8.2 beats/min at 7:30 PM) on initiation of the lights-off period. Average lights-off versus
lights-on heart rate values for SHR showed a 29±3 beats/min increase in heart rate during the lights-off period (Table 1). A relatively stable lights-off period was terminated with an anticipatory response similar to that seen in WKY-CR rats. Lights-on heart rate values for the SHR versus WKY-CR rats were not significantly different, but were elevated (p<0.05) throughout this cycle compared with WKY-TF rats (Table 1).

Although resting pressure and heart rate values between the WKY-CR and WKY-TF rats were different during the lights-on periods, baroreceptor reflex gain was not significantly different. Baroreceptor reflex sensitivity for the two groups determined with graded phenylephrine infusions was 0.67 and 0.72 msec/mm Hg, respectively.

**Group Homogeneity**

Hartley's test for homogeneity of variance was used to determine whether significant differences in the group variances existed in cardiovascular parameters over the 24-hour test session. Such a variance would be indicative of within-strain variation. However, this test failed to detect significant differences in the variance of systolic or diastolic pressure or heart rate for any of the three strains of animals over the test period. F values for the outbred WKY-TF rat strain are as follows: systolic \( F_{1,17} = 4.65 \), diastolic \( F_{1,17} = 5.27 \), and heart rate \( F_{1,17} = 4.65 \). In addition, the variability among the three groups of rats was compared by Bartlett's test, which performs a time point comparison. This test revealed 43 of 48 systolic, 45 of 48 diastolic, and 43 of 48 heart rate values exhibited uniform variability. These data indicate that the lack of observed circadian rhythm of blood pressure in the WKY-TF rats does not reflect masking of hour-to-hour changes by within- or between-animal variation.

**Discussion**

A major finding of our study is the presence of distinct differences in diurnal cardiovascular and activity patterns of WKY rats originating from Taconic Farms and Charles River. Such differences are independent of intrastrain and lot-to-lot variation. WKY-CR rats exhibited a pronounced variation in arterial pressure and heart rate between the light (rest) and dark (active) portions of a 24-hour cycle, whereas WKY-TF rats demonstrated very little variation. The greatest disparity in cardiovascular parameters among the normotensive strains occurred during the lights-on phase of the circadian cycle. The lack of a decrease in arterial pressure during this period for the WKY-TF rats is not due to an alteration of baroreceptor reflex function, as there was no statistical difference between baroreceptor reflex gain exhibited by WKY-CR and WKY-TF rats. Although baroreceptor reflex data was not obtained during the lights-off phase, this period represents the time of closest approximation of cardiovascular parameters between the two substrains of WKY rats. Further, the standard errors of the blood pressure data showed no difference in minute-to-minute variation between the two groups, suggesting intact baroreceptor mechanisms during this active phase.13,14

Although abnormalities in baroreceptor reflex gain are not responsible for the differences between WKY-CR and WKY-TF rats, the invariant arterial pressure seen in WKY-TF rats may still reflect the absence of a centrally mediated resetting of basal cardiovascular parameters during the lights-on phase. Specifically, a diminished diurnal cycle in the WKY-TF rats seems to reflect the absence of a diminution in heart rate and blood pressure, present in WKY-CR rats, during the lights-on period. Further, averaged dark-phase values, though statistically different between the substrains, were much closer than averaged lights-on phase values. The lack of diurnal variation observed in WKY-TF rats cannot be attributed to interanimal variation as all three groups demonstrated homogeneity of variance in heart rate and systolic and diastolic pressures. Because most investigations that use these rat strains are performed during the lights-on phase of the diurnal cycle, the importance of these discrepancies becomes acutely profound.

A second major finding of our study is that the SHR exhibits significant differences in diurnal patterns relative to either WKY rat substrain. Only marginal 24-hour variations in blood pressure and heart rate were observed for SHR in this study; the variation between lights-off and lights-on values were intermediate compared with the variation of the WKY rat substrains. Again, the basis of the diminished variation is not immediately explicable. One possibility may relate to the recognized deficit of this strain in baroreceptor resetting.15 Alternatively, recent studies in monkeys suggest that decreased blood volume secondary to insensible fluid loss during the rest phase produces a gradual lowering of blood pressure and heart rate.16

A growing number of studies have recently reported discrepancies in WKY rats from separate commercial
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WKY-CR rats approximately 1 hour before the lights-on period. There is some evidence that cardiovascular function is difficult to determine. For example, humans studied under total bed rest still maintain a rhythm in cardiovascular function totally dependent on the sleep/wake cycle. Further, rabbits show little blood pressure variation over a 24-hour period, which may be attributable to the observation that this species exhibits periods of spontaneous activity during all hours of the day. In our study, both WKY-TF rats and SHR exhibited much more locomotor activity during the lights-off than the lights-on period; yet there were only minor differences in arterial pressure between the two periods. Conversely, WKY-CR rats had the smallest difference between lights-on and lights-off locomotor activity but demonstrated the largest circadian variation of arterial pressure. Although this would argue against a direct linkage between motor activity and arterial pressure, the caveat is that we could only monitor gross locomotor activity. Other activities, such as grooming and consummatory behaviors, could not be quantified with our system but could significantly alter cardiovascular function.

In agreement with our results in WKY-CR and WKY-TF rats, Messerli et al reported that normotensive patients exhibit a stable systolic pressure during their active phase, whereas essential hypertensive patients do not. Hypertensive humans show a downward drift during the active phase and an opposite drift during sleep with no plateau. In SHR, we observed arterial pressure drift during the 24-hour cycle without plateau phases, but the pattern was reversed such that SHR show an upward drift during the active phase and downward drift during the sleep phase in agreement with the recent reports of Talan and Engel in primates. Again, species differences in behavior during the two time periods may underlie the opposite trends.

Normotensive and hypertensive humans during their inactive phase do not exhibit different heart rates. A similar finding was made in our study for WKY-CR rats and SHR. During the active phase, heart rate rose significantly for both groups of rats with the magnitude increase and absolute level highest in WKY-CR rats. A similar disparity is observed between normotensive and hypertensive individuals during the active phase.

The question of which strain, WKY-CR or WKY-TF, is the appropriate control for SHR is partly addressed by our findings. As summarized above, a growing bulk of evidence from different laboratories indicates that these two commercially available WKY rat strains are very different in several physiological parameters including cardiovascular performance. Because these animals are most widely used as experimental controls for the SHR, it may be desirable to match as many parameters as possible to the SHR with the exception of arterial pressure. Our study points out that each of the substrains has potential liabilities and benefits. WKY-CR rats demonstrate lower lights-on arterial pressure and exhibit greater circadian rhythm than WKY-TF rats; however, they do not exhibit the same level of locomotor activity as the SHR. WKY-TF rats, on the other hand, have a higher level of locomotor activity and less circadian rhythm. In these two factors, the WKY-TF rats appear more like the SHR. In addition, lights-on arterial pressure of WKY-TF rats are higher than WKY-CR rats and show minimal circadian rhythm like the SHR. This may be quite important, as most studies using these animals are performed during the lights-on phase of the circadian cycle.

Our findings do not necessarily indicate that the WKY-TF rat is preferred over the WKY-CR rat as the control rat strain for SHR. WKY-TF rats are currently maintained as an outbred strain. Despite this outbreeding, their phenotype continues, after several years of breeding, to reflect many similarities to the SHR phenotype except for the development of...
hypertension at an early age. These animals may likely contain many of the SHR alleles except for those dictating excessively high blood pressure. As we will report elsewhere, they pattern very closely the effects dictating excessively high blood pressure. As a "borderline hypertensive rat." The use of an inbred control, the WKY-CR rat, for the inbred SHR is requisite for molecular genetic studies where intrasstrain differences must be circumvented. We conclude that both WKY rat strains have in uses in studies of SHR hypertension. Although further studies are needed, our findings should be taken into account when choosing the appropriate control animal. In addition, investigators should make every effort to identify the supplier of animals used in their studies.

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References


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