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Characterization of the relationship between spontaneous locomotor activity and cardiovascular parameters in conscious freely moving rats

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HIGHLIGHTS

- Cardiovascular parameters and spontaneous locomotor activity are linked by the negative exponential function.
- Both the heart rate and mean blood pressure reach maximal values when locomotor activity is relatively low.
- The phase of daily cycle affects heart rate in conscious rats independent of locomotor activity.

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ABSTRACT

In freely behaving rats, variations in heart rate (HR) and blood pressure (BP) are coupled closely with changes in locomotor activity (Act). We have attempted to characterize this relationship mathematically. In 10- and 16-week-old rats, HR, BP and Act were recorded telemetrically every minute for 2 days under 12 h:12 h light–dark cycling. After examining data for individual rats, we found that the relationship between Act and HR could be approximated by the negative exponential function $HR(Act) = HR_{max} - (HR_{max} - HR_{min}) * \exp(-Act / Act_e)$, where HR_{max}, HR_{min}, and Act_e are constants. These constants were calculated separately for light and dark periods by non-linear curve fitting. HR corresponding to maximal locomotion was similar during the light and dark phases, while HR at rest during the dark phase was higher than during the light phase. The range of HR variability associated with Act during the dark phase was similar in young and older animals, but minimal HR was significantly lower in older rats. The relationship between Act and BP was approximated with a similar function. We have found no differences between BP at rest and at maximal locomotion between light and dark and between 10-week and 16-week-old rats. Our results indicate that in rats, cardiovascular parameters are coupled to locomotion to a high degree; however both the HR and the BP reach maximal values when locomotor activity is relatively low. We also found that the phase of daily cycle affects HR in conscious rats independent of locomotor activity.

1. Introduction

Radiotelemetry provides a powerful non-invasive means for long-term monitoring of physiological parameters [1,2]. Most often this technique has been employed to characterize rhythmic circadian and/or ultradian patterns in individual parameters for which a variety of methods have been employed, including autocorrelation, power spectrum analysis (Fourier transform) and cosinor analysis. However, much less attention has been directed to a particularly powerful feature of telemetry: the ability to assess and correlate two (or more) physiological parameters simultaneously.

A potentially significant relationship that has received limited attention is that between spontaneous locomotor activity and the primary cardiovascular endpoints of heart rate and blood pressure. Meinrath and D'Amato [3] and Schlatter et al. [4] reported high correlations between heart rate and locomotor activity. Waterhouse et al. [5] studied the sensitivity of blood pressure to locomotor activity where a linear relationship between these parameters was assumed. Lemmer et al. [6] applied a "purification" technique, which was developed earlier for circadian variability of body temperature, to dynamics of heart rate and blood pressure. In this study, the authors tried to recover "endogenous" circadian variations masked by activity using the proximity of the recovered endogenous curve to the cosine curve as a goal. One of the assumptions in such an approach is that the correction coefficients for locomotor activity are the same during dark and light periods [6,7]. The conclusions of these studies suggest only that the heart rates of

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rodents are higher at night when locomotor activity is present [8] or involve untested assumptions about the relationship [5].

Thus, the relationship of spontaneous locomotor activity to cardiovascular endpoints has never been subjected to careful mathematical analysis that might permit the quantitative estimation of the contribution of locomotor activity to blood pressure and heart rate on a minute-to-minute basis with any degree of precision. Such an analysis would be of considerable interest from the perspective of basic physiology but might also prove to have considerable utility in factoring out effects on locomotion when assessing cardiovascular changes in a given experimental paradigm. For example, when examining the effects of an experimental antihypertensive agent that alter behavior, the contribution of observed changes in locomotion could be quantitatively assessed with regard to changes in blood pressure and heart rate.

To estimate the functional relationships between locomotion and cardiovascular parameters, we collected data on blood pressure, heart rate, and locomotor activity from chronically instrumented rats, then prepared and examined appropriate scatter plots of our data. All graphs clearly demonstrated a consistent but non-linear linkage between spontaneous activity and cardiovascular parameters. We then analyzed mathematically the relationship between two pairs of parameters — locomotor activity and heart rate, and locomotor activity and mean blood pressure. Using this information, we developed a technique to calculate locomotion-independent values of mean blood pressure and heart rate. Our newly developed approach was compared with a previously published technique to calculate heart rate and blood pressure associated with inactivity.

Either differences in the intensity of spontaneous locomotion or differences in mathematical parameters that determine behavioral-cardiovascular coupling [5] could ultimately affect cardiovascular parameters. Therefore, we tested our technique by analyzing and comparing datasets (1) from two periods that differed markedly with respect to levels of spontaneous locomotor activity day (light) vs. night (dark), and (2) from rats of different ages (10 weeks versus 16 weeks) which were serendipitously noted to have similar patterns and levels of locomotor activity but differed significantly with respect to cardiovascular status.

2. Methods

2.1. Animals

Male Sprague–Dawley rats from three litters were used. Female rats were obtained from Harlan (Indianapolis, IN) at the 15th day of pregnancy and maintained under standard animal housing conditions with lights on 07-00–19-00. All deliveries occurred within 2 consecutive days. All litters were reduced to 11 pups on day 5 and weaned at the 21st day of age. Animals were housed at three animals per cage until the implantation of the telemetric probe. After the surgery, animals were housed singly. All procedures were in accordance with protocols approved by the Indiana University School of Medicine IACUC.

2.2. Telemetric probe implantation

Male rats were randomly selected for surgery from all three litters at 9 weeks (250–300 g) or 15 week (350–400 g). Rats were anesthetized with Nembutal (50 mg/kg, ip). The flexible catheter of the telemetric transmitter (PhysioTel® PA-C40 Small Animal Transmitter, Data Sciences Intl., St.Paul, MN) was secured surgically in the abdominal aorta with the tip just below the renal arteries. The transmitter was sutured to the abdominal wall. After the surgeries, the animals received an injection of buprenorphine (0.05 mg/kg, s.c.) and were monitored until recovery from anesthesia. Rats were housed in individual cages and allowed to recover from surgery for at least seven days to restore normal daily rhythms [9,10].

2.3. Recording of telemetric data

Rats in their home cages (non-transparent cages with dimensions 40 × 20 × 20 cm) were placed over the receiver plates in a separate room. The rats were unrestrained and free to move within their cages with unlimited access to standard chow and tap water. Animals were left undisturbed for 2 days except for replenishment of food and water.

Hemodynamic data were sampled for 10 s every minute and average heart rate, mean arterial blood pressure, and locomotor activity were stored. Rats were allowed to adapt to this new environment for at least 5 h. Recording started before 7 pm on the first day and finished after 7 am on the third day of recording. Therefore, the total duration of undisturbed continuous recording subjected to analysis was at least 36 h and included one complete 12-h light period and two complete 12-h dark periods.

For proper interpretation of data, it is important to understand how the telemetric system records various data. In the “scheduled sampling” mode, physiological parameters like blood pressure or heart rate are acquired only for a predefined period of time each cycle. They are then averaged and recorded at the end of the acquisition period. For example, we had configured the system to record cardiovascular parameters each minute by averaging data obtained over 10 s. This means that every minute, mean blood pressure and heart rate were recorded for 10 s (for example, from 0 to 10 s) and stored at the end of the interval (at 10 s). Unlike physiological parameters, locomotor activity is calculated from the intensity of the telemetric signal. The intensity changes depending on the distance of the probe from the receiving coils and the angle between the probe and the coils. The hardware follows the strength of the signal and generates an event when the strength changes for more than a threshold. The algorithm was designed in the following way: if the animal walks with a constant speed of 1 cm/s for the entire minute, it is measured as 1 locomotor unit. Thus, according to this scale, 10 units is equivalent to 6 m/min, and 30 units to 18 m/min.

Monitoring signal strength, and as a consequence locomotor activity, is performed throughout the entire cycle (in our case 1 min). The software records the information about locomotion in the beginning of the monitoring periods. In the analysis module, new activity data appear at the beginning of the monitoring period, while cardiovascular data are added after the end of the monitoring interval. Therefore, in our dataset, an array of data for a specific cycle consisted of cardiovascular parameters measured between 0 to 10 s while activity was “counted” for the period from −60 to 0 s. It is interesting that crosscorrelation between activity and heart rate is maximal at +1 min, while there is no shift between the activity and the blood pressure. Thus, despite the fact that activity recorded for a particular data point is on average collected 30 s before heart rate, it still takes an extra minute for the heart rate to respond to a change of locomotion.

2.4. Processing of the data

All data processing, calculations and fittings were performed in Microsoft Office Excel. First, the data from individual recordings was averaged for 60 min intervals to reveal daily rhythmicity. Then, original minute-by-minute data from individual recordings was analyzed for auto- and crosscorrelation using Statistica for Windows (Statsoft Inc., OK). Intervals of 640 min (from 7–40 to 6–20) from light and dark periods were used for analysis with lags from 0 to 240 min for autocorrelation and from −240 to 240 min for crosscorrelation. Data from the two dark periods were averaged.

Finally, minute-to-minute data from individual recordings was averaged for intervals of 10 min starting every 5 min (for example 5:00–5:09; 5:05–5:14; 5:10–5:19 etc.). An abrupt change of lighting between day and night is an external stimulus, which affects the level of anxiety for up to 20 min [11]. Therefore, considering that our aim was to examine the correlation between spontaneous activity and cardiovascular parameters, the data around light–dark phase change (30 min before and