Circadian rhythm of heart rate and heart rate variability

Martial M Massin, Krystel Maeysns, Nadia Withofs, Françoise Ravet, Paul Gérard

Abstract

Background—Measurements of heart rate variability (HRV) are increasingly used as markers of cardiac autonomic activity.

Aim—to examine circadian variation in heart rate and HRV in children.

Subjects—A total of 57 healthy infants and children, aged 2 months to 15 years, underwent ambulatory 24 hour Holter recording. Monitoring was also performed on five teenagers with diabetes mellitus and subclinical vagal neuropathy in order to identify the origin of the circadian variation in HRV.

Methods—The following variables were determined hourly: mean RR interval, four time domain (SDNN, SDNNi, rMSSD, and pNN50) and four frequency domain indices (very low, low and high frequency indices, low to high frequency ratio). A chronobiological analysis was made by cosinor method for each variable.

Results—A significant circadian variation in heart rate and HRV was present from late infancy or early childhood, characterised by a rise during sleep, except for the low to high frequency ratio that increased during daytime. The appearance of these circadian rhythms was associated with sleep maturation. Time of peak variability did not depend on age. Circadian variation was normal in patients with diabetes mellitus.

Conclusion—We have identified a circadian rhythm of heart rate and HRV in infants and children. Our data confirm a progressive maturation of the autonomic nervous system and support the hypothesis that the organisation of sleep, associated with sympathetic withdrawal, is responsible for these rhythms.

Keywords: heart rate; heart rate variability; circadian rhythms

Many physiological measures are continuous variables that are subject to the influence of external stimuli and internal homeostatic control mechanisms. Despite the controlling influences of the latter kind, many variables fluctuate considerably in the short, medium, and long term. The most common variation is that of a 24 hour cycle and is defined as circadian. Many parameters have been studied extensively compared with that of cardiovascular variables, often because of the assumption that the latter closely follow the activity cycle of the subject. If measurement of clinically important values, such as cardiac autonomic function, varies widely and in a consistent pattern throughout the 24 hour cycle, considerable precision can be added by qualifying measurements by the time of day when they were made.

Heart rate variability (HRV), as determined from 24 hour Holter recordings, represents a non-invasive parameter for studying cardiac autonomic control. Studies have recently described a circadian variation in HRV in adults, but not in neonates.

No data are available for children. We aimed to investigate whether heart rate and HRV independently have a circadian rhythm in healthy children, and to determine the differences as a function of age.

Subjects and methods

Subjects and methods

METHODS

The 24 hour ambulatory tape recording was obtained using a two channel Holter monitor (MR45 Oxford) while the subjects went about their normal daily routines. All Holter tapes were subsequently analysed with use of a Medilog Excel computer program to identify and label each QRS complex. All data were

Table 1 Definition of HRV indices

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN</td>
<td>Standard deviation of all RR intervals</td>
</tr>
<tr>
<td>SDNNi</td>
<td>Mean of the SD of all RR intervals for all five minute segments</td>
</tr>
<tr>
<td>rMSSD</td>
<td>Square root of the mean of the sum of squares of differences between adjacent RR intervals</td>
</tr>
<tr>
<td>pNN50</td>
<td>Percentage of differences between adjacent RR intervals that are greater than 50 msec</td>
</tr>
<tr>
<td>VLF</td>
<td>Very low frequency index (0.004–0.04 Hz) (msec)</td>
</tr>
<tr>
<td>LF</td>
<td>Low frequency index (0.04–0.15 Hz) (msec)</td>
</tr>
<tr>
<td>HF</td>
<td>High frequency index (0.15–0.4 Hz) (msec)</td>
</tr>
<tr>
<td>LF:HF</td>
<td>Ratio of LF to HF</td>
</tr>
</tbody>
</table>

SD, standard deviation.
Table 2: Characteristics of the cosine curve

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean Age</th>
<th>Amplitude</th>
<th>Acrophase (mean (SD))</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN</td>
<td>50.0 Age</td>
<td>21.1 Age</td>
<td>03:51 (01:33)</td>
</tr>
<tr>
<td>SDNNi</td>
<td>38.1 Age</td>
<td>7.2 Age</td>
<td>04:00 (01:22)</td>
</tr>
<tr>
<td>rMSSD</td>
<td>26.8 Age</td>
<td>7.3 Age</td>
<td>02:45 (01:20)</td>
</tr>
<tr>
<td>pNN50</td>
<td>3.8 Age</td>
<td>2.4 Age</td>
<td>02:28 (01:16)</td>
</tr>
<tr>
<td>VLF</td>
<td>25.8 Age</td>
<td>5.9 Age</td>
<td>04:44 (01:13)</td>
</tr>
<tr>
<td>LF</td>
<td>20.8 Age</td>
<td>4.0 Age</td>
<td>03:37 (01:43)</td>
</tr>
<tr>
<td>HF</td>
<td>15.4 Age</td>
<td>3.9 Age</td>
<td>03:06 (01:09)</td>
</tr>
<tr>
<td>LF:HF</td>
<td>0.01 Age-0.18 Age+1.79</td>
<td>0.16 Age</td>
<td>14:27 (00:49)</td>
</tr>
<tr>
<td>mean RR</td>
<td>502.5 Age</td>
<td>63.3 Age</td>
<td>02:54 (00:54)</td>
</tr>
</tbody>
</table>

Time domain indices and LF:HF in absolute values; LF, HF, and mean RR in msec, age in years.

Discussion

In the general population, autonomic activity shows a circadian rhythm with a prevalence of sympathetic tone during the day and a considerable relative increase in parasympathetic tone during the night and in the first hours after awakening. Heart rate variation and variability depend on the influence of sympathetic and parasympathetic nervous system activity.
parasympathetic activity on the sinus node and reflect spontaneous changes in autonomic activity. HRV measures have received a great deal of attention with regard to the autonomic control of heart rate, even if their interpretation is sometimes controversial because specific components may be related to different mechanisms in different conditions and because the interaction between heart rate, HRV, and other biological signals have to be considered.

In this study, we have characterised the circadian variation of heart rate and HRV. We observed that a substantial fluctuation of autonomic function occurs during sleep. Similar findings were reported in adults, using a similar method with ambulatory monitoring. A slowing of heart rate during sleep is well established, though few studies have undertaken a detailed analysis of the circadian properties of the curve. Previous reports in adults reported a peak in RR interval length between 4 and 5 o’clock and their results are consistent with ours. Heart rate and HRV both depend on the autonomic nervous system. However, the circadian variation of heart rate persisted in infants from 4 months of age, whereas that of HRV is not observed for most of the parameters below 1 year of age. This observation in infants reinforces the generally admitted opinion that HRV does not simply reflect the overall heart rate but depends on the age-related flexibility of the autonomic nervous system.

When computed over hourly intervals, SDNN is likely to undergo circadian changes related to the wave form of the circadian rhythm in heart rate itself: a larger variability is anticipated and found around awakening, when heart rate changes rather abruptly from low nighttime to much higher daily values (the actual transition usually starts earlier, but any anticipatory rise preceding awakening and the transition in the evening are usually smoother and slower). The interference by the circadian waveform of heart rate with HRV is reduced when SDNN is computed on five minute spans which is why SDNN was also calculated.

The origin of the circadian variation in HRV seems more likely to be sympathetic withdrawal rather than a parasympathetic effect because it was maintained in the presence of vagal neuropathy in diabetic and alcoholic adults, although these findings are controversial.

Discrepancy between these studies could be a result of the fact that most diabetic adults have other illness complications which can influence HRV and circadian rhythms. Persistence of circadian rhythms of heart rate and HRV in our teenagers with diabetes mellitus and subclinical vagal neuropathy but no overt illness complication reinforces the sympathetic withdrawal hypothesis. The sympathetic effect may be mediated through a direct nervous effect or by a reduction in circulating catecholamines, which also show a circadian variation with a trough occurring at 04:00, coinciding with the peak HRV found in this study. However, the response to sympathetic nerve stimulation is slow. It appears unlikely that it could modulate beat to beat changes directly, but it could affect vagal effects on the cardiac cycle.

There is normally a characteristic rise of HRV at night. It would be interesting to know what factors might be responsible for this. The first candidate for modifying HRV is that of a built-in diurnal clock but it has been shown in adults that the daytime HRV is higher while subjects are on night shift and sleeping during the day, and that 24 hour HRV is normal but without day/night difference during periods of sleep deprivation. As the disappearance of the circadian variation of HR and HRV is associated with young age and sleep immaturity, other candidates are the immobility associated with sleep and sleep itself. HRV pattern has been shown to be normal in immobile young men after injury. This suggests that being confined to bed is not a factor influencing the HRV. The third candidate for modifying HRV is that of sleep itself. The results from both the sleep deprivation and the night duty studies support this mechanism. The parallelism between the developmental course of sleep and the appearance of circadian rhythms of autonomic activity is very impressive in our study, reinforcing the hypothesis that sleep itself and the maturation of its “biological clock” are implicated in the mechanism of autonomic regulation. That “clock”, which resides in the hypothalamic suprachiasmatic nucleus, has an important role in both the timing and organisation of sleep, and in the coordination of sleep with other physiological rhythms such as autonomic balance. The newborn infant sleeps about 16 to 18 hours a day, and its sleep is widely distributed. By 4 months of age, the total amount of sleep drops to about 14 or 15 hours a day and a clear diurnal pattern emerges. The lengthening of the interfacing interval then corresponds with an increased consolidation of sleep during the night and the appearance of circadian rhythms associated with the maturation of the “biological clock”. A circadian sleep rhythm appears, but is not evident because of more rapid rhythms with four and 12 hour periods. From that age we also observed the appearance of circadian rhythms for heart rate and for some parameters of HRV. The daily sleep quota then remains

Figure 3 Estimating rhythm parameters by least squares fitting of cosine function to single series of observations. Example with 24 hour cosine function (continuous line), fitted to hourly values of LF:HF ratio in a 2 year old child. Note the decreased values of LF:HF during the afternoon nap.
relatively constant but REM (rapid eye movement) sleep amount declines throughout the first two years of life from more than 50% to less than 25%, a figure which then remains constant throughout childhood and adulthood. Lengthening of night-time sleep, shortening and decrease of daytime sleep episodes, associated with increased influence of parasympathetic activity during non-rapid eye movement sleep, are associated with the disappearance of ultradian sleep rhythms and the appearance of circadian rhythms for the other indices of HRV during that period. A further gradual decline of sleep then occurs from 3 years throughout childhood and adolescence until the adult pattern is approximated. The shortening and afterwards the disappearance of the last daytime sleep episode is associated with the appearance of circadian rhythms for the balance LF:HF.

CONCLUSION
We have identified a circadian rhythm of heart rate and HRV in children. Our data confirm a progressive maturation of the autonomic nervous system and support the hypothesis that the organisation of sleep, associated with sympathetic withdrawal, is responsible for those rhythms. No continuous data are available for children. Our findings provide a new and powerful tool to examine the effects of underlying disease processes or therapy on cardiac autonomic tone and its circadian modulation.

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