

Circadian rhythm of heart rate and heart rate variability

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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.

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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.¹ 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.²

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,^{3–7} in adolescents,⁸ but not in neonates.⁹ 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

We analysed 24 hour ECG recordings obtained from 57 healthy infants and children (28 boys and 29 girls), aged 2 months to 15 years. Nine age groups of three subjects, aged respectively 2, 3, 4, and 8 months, and then each year of age, were constituted. None had any known disease or was taking regular medications (including oestrogen) or using tobacco products. Sinus rhythm was confirmed before entering the protocol. The same analysis was performed in the five teenagers with diabetes mellitus, regularly attending our outpatient clinic, with the most severe 24 hour HRV abnormalities but with no clinical vagal neuropathy.¹⁰

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

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

SD, standard deviation.

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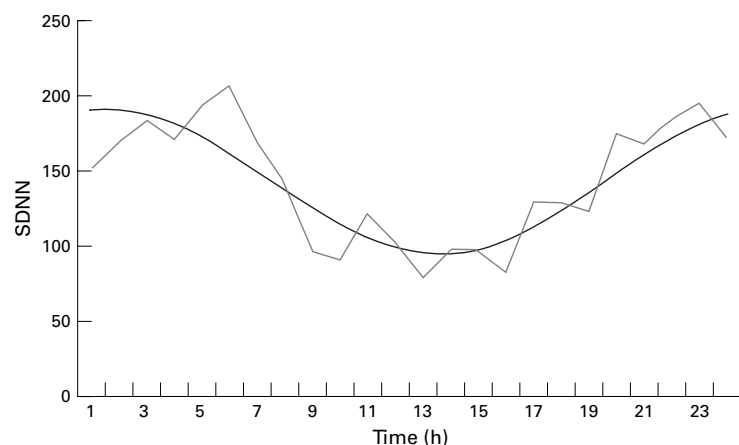


Figure 1 Estimating rhythm parameters by least squares fitting of cosine function to single series of observations. Example with 24 hour cosine function (continuous line), fitted to hourly values of SDNN in 10 year old children.

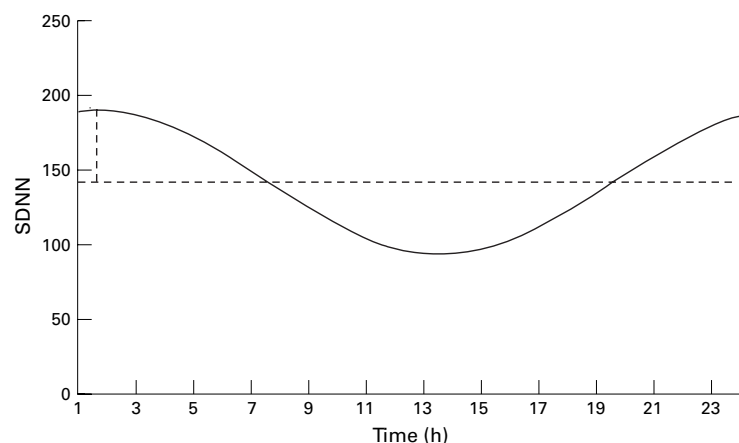


Figure 2 Same example as in fig 1. The continuous line represents the cosine curve. The horizontal dotted line represents the mean value of the curve or mesor (here 142.5) and the vertical dotted line the amplitude (here 48.2) at the time at which the curve reaches its highest value or acrophase (here one hour 36 minutes).

Table 2 Characteristics of the cosine curve

Parameters	Mesor	Amplitude	Acrophase (mean (SD))
SDNN	50.0 Age ^{0.27}	21.1 Age ^{-0.09} (p > 0.05)	03:51 (01:33)
SDNNi	38.1 Age ^{0.27}	7.2 Age ^{0.44}	04:00 (01:22)
rMSSD	26.8 Age ^{0.27}	7.3 Age ^{0.55}	02:45 (01:20)
pNN50	3.8 Age ^{0.27}	2.4 Age ^{0.87}	02:28 (01:16)
VLF	25.8 Age ^{0.31}	5.9 Age ^{0.34}	04:44 (01:13)
LF	20.8 Age ^{0.27}	4.0 Age ^{0.32}	03:37 (01:43)
HF	15.4 Age ^{0.27}	3.9 Age ^{0.62}	03:06 (01:09)
LF:HF	0.01 Age ² -0.18 Age+1.79	0.16 Age ^{0.32}	14:27 (00:49)
mean RR	502.5 Age ^{0.16}	63.3 Age ^{0.75}	02:54 (00:54)

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

reviewed by one analyst and were edited to validate the system's QRS labelling for the duration of the Holter recording. There had to be 24 hours of analysable data for the recording to be accepted for the study. Recordings containing more than five complexes classified as noise or ectopic per hour were rejected. Measures of HRV were calculated employing only normal to normal intervals. Results for individuals were standardised to a starting time of midnight. The data were subdivided into consecutive segments reflecting 60 minutes of real time recording; hourly values of mean RR interval and four time domain indices of HRV (table 1) were calculated. Beat to beat fluctuations were transformed to the frequency

domain by fast Fourier transformation. The specific measures were computed as the square root of the areas under the power spectrum. The mean hourly values of four frequency domain indices calculated over successive five minute spans were then examined (table 1). rMSSD, pNN50, and HF reflect the short term HRV and are predominantly a response to changes in vagal tone. The other indices express the long term HRV and are dually influenced by cholinergic and adrenergic activity, as well as by other physiological inputs.

STATISTICAL ANALYSIS

A mean hourly value for each parameter was obtained in each age group and a chronobiological analysis of those hourly values of mean RR and HRV indices was made by single cosinor method.¹¹ In this model a cosine function curve is fitted to the data by a least squares procedure (fig 1), and a circadian rhythm is defined by three parameters of the curve (fig 2): its mean value or mesor; its amplitude, one half of the difference between the highest and the lowest values; and the time at which the curve reaches its highest value or acrophase. The significance of the derived circadian rhythms was evaluated by the zero amplitude test. The minimal level of significance accepted was $p < 0.05$.

Results

All the variables showed significant circadian rhythms during childhood. LF:HF ratio was greater during the day than at night ($p < 0.05$ from 3 years of age), whereas mean RR interval ($p < 0.0001$ from 4 years, and $p < 0.01$ between 4 months and 3 years of age) and all other HRV indices ($p < 0.05$ from 4 months for SDNNi, pNN50, VLF, and LF; from 1 year for rMSSD and HF; from 2 years for SDNN) increased at night and decreased during the day. An example is given in the figs 1 and 2. Circadian variation disappeared in very young patients, because of fall of LF:HF ratio and rise of other parameters during the daytime sleep episodes characterising infancy and early childhood. The variation of LF:HF had already disappeared in 2 year old children because of the afternoon sleep (fig 3). The mean values of the cosine curves were significantly related to a power of age as shown in table 2, except for the LF:HF ratio where the relation was quadratic. The amplitudes of the cosine curves were also significantly related to a power of age apart from that for SDNN. The acrophases of the curves were not significantly dependent on age. The same chronobiological analysis was performed in diabetic teenagers (see discussion). Circadian variation of heart rate and HRV was similar to that of controls.

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

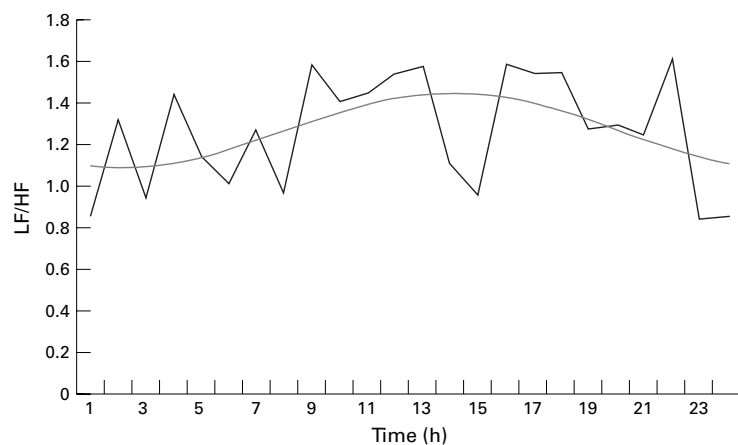


Figure 3 Estimating rhythm parameters by least squares fitting of cosine function to single series of observations. Example with 24 hour cosine function (continuous line), fitted to hourly values of LF:HF ratio in a 2 year old child. Note the decreased values of LF:HF during the afternoon nap.

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 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.⁴

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^{4,11} 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^{12,13} but depends on the age related flexibility of the autonomic nervous system.^{14,15} 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 nightly 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 SDNNi 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,⁴ although these findings are controversial.¹⁶ 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 complication¹⁰ 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 04:00,¹⁷ coinciding with the peak HRV found in this study. However, the response to sympathetic nerve stimulation is slow.¹⁸ It appears unlikely that it could modulate beat to beat changes directly, but it could affect vagal effects on the cardiac cycle.¹⁹

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 adults²⁰ 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.²⁰ 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 studies²⁰ 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.²¹ 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 interfeeding 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 hour and 12 hour periods.²² 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

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,²³ are associated with the disappearance of ultradian sleep rhythms²² 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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Commentary

Some of the statistical measures of variability in this paper may be unfamiliar to readers. The analysis has actually proceeded in two stages. Several measures of heart rate variability within one hour periods have been calculated and the resulting 24 values (averaged over four children in an age group) have been fitted to a cosine curve as shown in fig 1, with a view to showing the circadian rhythm. Before this, however, the question arises of how variability should be measured in data of this kind. The usual standard deviation does not take account of any structure in the variability—this may consist of a mixture of relatively slow trends, approximately regular rhythms possibly associated with respiration or other factors, and high frequency or fairly random activity. The authors' SDNNi aims to eliminate slow trends by measuring the variability only within five minute segments; their rMSSD and pNN50, which compare differences between successive values, also de-emphasise the lower frequencies.

An alternative approach is to model the data as the sum of a large number of cosine waves with frequencies covering a continuous range. Fourier transformation methods then enable the calculation of the so called *power spectrum*, effectively the contributions to the total variance plotted against frequency. The total area under the curve is equal to the overall variance of the data, and the areas in adjacent frequency bands provide the contributions from low, medium, and high frequencies. A purely random sequence ("white noise") has a flat power spectrum, with equal contributions from all frequencies. The paper reports the square roots of the band areas as analogues of standard deviations. This type of *frequency domain* analysis provides a powerful methodology for examining the structure of time series data and is worth further investigation by researchers whose data take this form.

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