Normative Values for Circadian and Ultradian Cardiovascular Rhythms in Childhood

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Abstract—To assess the prevalence and characteristics of physiological circadian (24-hour) and ultradian (12-, 8-, and 6-hour) rhythms of mean arterial blood pressure (BP) and heart rate (HR), we analyzed 24-hour ambulatory BP profiles from 938 healthy school children aged 5 to 18 years. Cosine harmonics were fitted by Fourier analysis, and an amplitude and acrophase (time of peak) were calculated for each rhythm. Ninety percent of children displayed circadian rhythmicity of BP, independent of age, whereas circadian HR rhythmicity decreased with puberty from 96% to 87% (P<0.0001). Puberty had marked effects on the prevalence of ultradian rhythmicity: 12- and 6-hour rhythms increased for BP (27% to 47%, P<0.0001; 18% to 25%, P=0.01) and HR (36% to 47%, 17% to 31%, both P=0.001), whereas 8-hour BP rhythms decreased (34% to 23%, P=0.002). Median amplitudes were 10.1, 5.9, 5.6, and 5.2 mm Hg for the 24-, 12-, 8-, and 6-hour BP rhythms, respectively, and 13.4, 7.7, 6.8, and 6.4 bpm for HR. The acrophase occurred at approximately 14:00 hours, 8:00 hours, 5:30 hours, and 2:00 hours (military time) for the four BP rhythms, and at 13:30 hours, 08:30 hours, 01:50 hours, and 02:00 hours for HR. For the combined curve, the peak–trough difference was 25.9 mm Hg and 35 bpm for BP and HR, respectively, with the peaks occurring at 13:50 hours and 13:10 hours. There was marked association between BP and HR rhythms, both for prevalence (P<0.0001 for coupling of BP and HR rhythms of the same period length) and timing, with a median time lag of BP after HR acrophase of only 21, 16, 13, and 5 minutes for the four rhythms, respectively. (Hypertension. 2004;43:547-554.)

Key Words: blood pressure ■ heart rate ■ children ■ adolescents ■ ambulatory blood pressure monitoring

The introduction of ambulatory 24-hour blood pressure monitoring (ABPM) has led to an increasing interest in the diurnal changes of blood pressure (BP), their physiological origins, as well as their pathophysiological and prognostic relevance. Various mathematical approaches have been used to analyze the large amount of data generated by each ABPM measurement. Linear analyses, such as dividing the 24-hour period into day and night intervals, either arbitrarily or according to a patient diary, allow a quantification of the nocturnal BP fall, or “dipping,” both in absolute and relative terms. Alternative methods include the calculation of cumulative sums,1 chronobiological cosinor analysis,2 and Fourier analysis, which is the simultaneous application of several cosine functions.3

Even though definitions of “non-dipping” are thus still varied, some prognostic relevance of the non-dipping phenomenon has been shown in adults with renal failure4 and in the general population.5 Controversy persists about the physiological basis of the generation of BP rhythms. Evidence from shift workers suggests that BP rhythms are determined largely externally by various physical activity.6–9 However, the fact that disturbances of the diurnal BP pattern have been demonstrated in a variety of pathological conditions9,10 has led to the suggestion that an endogenous rhythm of autonomic nervous activity is at least partly responsible for the generation of the circadian BP rhythmicity. With respect to this ongoing debate, Fourier analysis appears less biased than linear analysis because there is no need to define day and night intervals, which presuppose an activity-related origin of BP variations. Also, the combination of several rhythms allows a more detailed and flexible description of the 24-hour period than does the original cosinor method.

However, defined normal ranges are required to evaluate changes in groups of subjects with specific pathological conditions. The need for normative data applies especially for children, because BP is known to change with age and body size. For linear analysis, valid reference data are available for European children,11 and an early study considered the nocturnal fall in primary school children.12 However, only very few studies have applied Fourier analysis in healthy
children and were too limited in numbers or age range to provide reference values throughout childhood. In addition, published pediatric studies have considered varying numbers of rhythms (one, two, or four), yet provided only data for overall amplitudes and acrophases. The parameters of individual rhythms have only been described for adults so far.

In this study, we have analyzed the ABPM profiles of 938 children, giving the detailed dimensions for each of the 24-, 12-, 8-, and 6-hour Fourier curves and for the overall cardiovascular rhythms. To evaluate potential age-related effects, the prevalence and magnitude of each of the rhythms was examined for relationship to gender, height, and puberty. The aim was to provide reference values of use for detailed chronobiological study and for clinical trials examining the effects of diseases and pharmacological agents on BP.

**Methods**

**Patients**

ABPM profiles from 1141 healthy white school children and adolescents, recorded in a multicenter trial by the German Working Group on Pediatric Hypertension, were considered for this analysis. None of the children had any medical history of diseases or treatments affecting BP. Children aged 5 to 18 years with a minimal ABPM record length of 22 hours and cumulative recording gaps no greater than 2 hours were included in this analysis. These prerequisites were fulfilled by 938 profiles (49% boys). Informed consent was obtained from all children and parents. The study was approved by the local ethical committees, legal authorities, and the State Ministries of Education.

**BP Recordings**

Measurements were taken with a standard oscillometric ABPM device (SpaceLabs Monitor 90207). The most appropriate of three cuff sizes was applied to the non-dominant arm. Testing was commenced at approximately 10:30 hours on regular school days, which typically started at 08:00 hours. The children went about their normal daily activities but were instructed to rest the arm during recordings. Readings were taken every 15 to 20 minutes during the day and every 30 to 50 minutes at night. BP values are given as mean arterial pressure (MAP) throughout, because this is measured directly by the device, whereas systolic and diastolic BP are calculated via algorithms.

**Rhythm Analysis**

ABPM profiles were examined for the presence of a circadian (24-hour) rhythm by cosinor analysis. Additionally, 3 shorter ultradian rhythms with period lengths of 12, 8, and 6 hours, respectively, were also fitted by Fourier analysis. A circadian rhythm was considered to be present if a cosine function within a 24-hour period could be fitted with a significance of $P<0.05$ by least-squares analysis. The residual differences were then tested in the same manner for the presence of a significant ultradian rhythm (Figure 1a–1d). The following parameters were calculated for each rhythm of BP and heart rate (HR) by the ABPMfit software: the midline estimating statistic of rhythm (MESOR), which is the value midway between the highest and lowest values of the fitted cosine curve, amplitude (the distance between MESOR and the highest value of the cosine curve), and acrophase (time of the highest value of the cosine curve, expressed as hours after midnight). Whereas the MESOR is closely related to the 24-hour mean BP, the amplitude measures the magnitude of the rhythmic change, and the acrophase describes its timing. If more than one rhythm was present, then the amplitude and acrophase are given separately for each cosine curve, whereas the MESOR remains the same. The overall curve was calculated from the addition of all four rhythms according to the following formula:

\[
\text{MESOR} = \frac{1}{4} \left( A_1 + A_2 + A_3 + A_4 \right)
\]

\[
\text{Amplitude} = \frac{1}{4} \left( A_1 + A_2 + A_3 + A_4 \right)
\]

\[
\text{Acrophase} = \frac{1}{4} \left( \phi_1 + \phi_2 + \phi_3 + \phi_4 \right)
\]

**Figure 1.** a to e, Steps of the Fourier analysis and parameters calculated to describe rhythms.
where \( y \) is BP or HR at time \( t \) (in hours). Because the overall curve is not necessarily symmetrical, it is not possible to describe it solely with one amplitude and acrophase; instead, the difference between the peak and trough value, as well as the timing of the peak, are given (Figure 1e).

### Statistical Analysis

Data were stored and analyzed with SAS (SAS Institute, Cary, NC). Categorical variables, such as prevalence, were compared using the \( \chi^2 \) test. The Shapiro-Wilk test was used to test for normal distribution. The majority of amplitudes and acrophases were not normally distributed, and non-parametric tests were used throughout for further statistical analysis. Group comparison was performed with the Wilcoxon two-sample test and the Kruskal-Wallis test in case of multiple groups. Median score tests were additionally performed for confirmation; \( P<0.05 \) was considered significant, and the Bonferroni adjustment for multiple testing was used when relevant. Correlation coefficients were calculated using Spearman rank order correlation.

### Reference Standards

Normal values for height and BMI for the calculation of standard deviation scores (SDS) were taken from Prader et al\(^{19} \) and Schaefer et al,\(^{20} \) respectively. Boys younger than age 11 years and girls younger than age 10 years were considered prepubescent. BP SDS were calculated using the LMS tables of Wühl et al.\(^{21} \)

### Results

#### Dimensions and Prevalence

**MESOR**

Mean values and MESORs for MAP and HR are given in Table 1. The MESOR and the 24-hour integrated mean were very closely related, with a correlation coefficient of \( r=0.96 \) for BP and \( r=0.97 \) for HR (both \( P<0.0001 \)). The 95% confidence interval for the difference between the MESORs and the 24-hour means were only 6.1 mm Hg for MAP and 8.2 bpm for HR.

**Circadian Cardiovascular Rhythms**

Circadian BP rhythmicity was observed in 851 children (90%), without significant differences between genders or height groups (Figure 2). The size of the 24-hour BP amplitude and acrophase was also independent of height and gender. Distribution percentiles are given in Figure 3a and 3b and in Table 2. The 24-hour amplitude was positively correlated to daytime MAP expressed in absolute values (\( r=0.38, P<0.0001 \)) or SDS (\( r=0.43, P<0.0001 \)), and negatively to nighttime MAP (\( r=-0.30, P<0.0001 \)) or MAP SDS (\( r=-0.27, P<0.0001 \)). Accordingly, children exhibiting 24-hour rhythms had higher daytime and lower nighttime MAP (\( P<0.0001 \) for day/night MAP and SDS). Interestingly, children who did not have circadian BP rhythmicity had a lower daytime HR (\( 87\pm12 \) versus \( 90\pm11 \) bpm, \( P=0.01 \)) even after adjusting for gender and height (\( P=0.04 \) for HR SDS) compared with children who displayed this rhythm.

In absolute terms, the nighttime MAP fall was \( 15.1\pm6.2 \) mm Hg (for systolic BP \( 15.3\pm7 \) mm Hg; diastolic \( 16.5\pm6.7 \) mm Hg), whereas the day/night MAP ratio was \( 1.22\pm0.1 \) (Table 1). The absolute fall and the day/night ratio were not normally distributed (both \( P<0.0001 \)), but there were no significant relationships to gender or absolute and relative height and weight.

![Figure 2. Prevalence of circadian and ultradian BP and HR rhythms before and during puberty.](image-url)
Significant circadian rhythmicity of HR was detected in 90% of subjects, with prevalence decreasing from 96% in pre-pubertal to 87% in pubertal subjects ($P<0.0001$; Figure 2). In line with the age-related decrease in prevalence, 24-hour HR amplitudes were smaller in pubertal children ($P<0.0001$), and the distribution of acrophases widened with age ($P<0.0001$).

**12-Hour Cardiovascular Rhythms**

The prevalence of 12-hour rhythms increased with puberty for BP (28% to 46%, $P<0.001$) and HR (36% to 46%, $P=0.001$) and was independent of gender. In line with the age-related increase in the prevalence of 12-hour rhythmicity, the BP acrophase occurred later and had a narrower population distribution in pubertal children (interquartile range of 108 versus 138 minutes). In contrast, the magnitude and timing of BP amplitude and the HR rhythms were not related to height or puberty.

When children with 12-hour BP rhythmicity were compared with those without, as expected they were on average older ($P<0.001$) and more likely to be girls ($P=0.001$). However, even after correction for gender and height, they also had higher daytime and 24-hour MAP SDS ($P=0.01$ for both), but not nighttime MAP SDS.

**8-Hour and 6-Hour Cardiovascular Rhythms**

Eight-hour rhythmicity was found in approximately one-third of children. Prevalence was stable at ~30% for HR, but decreased from 34% to 23% during puberty for BP ($P=0.0004$). For BP and HR, the 8-hour amplitude was smaller in pubertal children ($P<0.0001$ for BP and $P=0.002$ for HR), and the acrophases were independent of age and body size (Figure 3).

The prevalence of 6-hour rhythms was higher in pubertal children (25% for BP; 31% for HR) than in the younger age group (18% for BP, $P=0.01$; 17% for HR, $P<0.0001$). However, the dimensions of the acrophases and amplitudes were not dependent on age, stage of puberty, or gender. Children who exhibited 6-hour BP rhythmicity had significantly higher 24-hour MAP ($P=0.02$) and MAP SDS.

**Figure 3.** Population distribution of amplitudes and acrophases for blood pressure (MAP) and heart rate. Boxes indicate 25th to 75th percentile; lines, 10th and 90th percentile.
overall 24-, 12-, 8-, and 6-hour rhythmicity

The dimensions of the overall amplitude and acrophase could be calculated for 892 children (95%) who had at least one BP rhythm and the same number who had at least one HR rhythm. The peak and trough values increased with body height for HR \((r = -0.36\) and \(r = -0.29\), respectively) and BP \((r = 0.17\) and \(0.25\), all \(P < 0.0001\)). This relationship persisted when pre-pubescent and pubescent children were considered separately. The characteristics of the overall rhythm were most strongly influenced by the circadian rhythmicity in terms of prevalence and dimensions. Changes in prevalence were similar to those observed in the 24-hour rhythm, with a constant proportion of BP rhythms and a decrease in HR rhythm prevalence from 99% before puberty to 93% in pubescent children. The peak–trough difference was more closely correlated to the daytime BP SDS; HR: \(r = 0.48\) to 24-hour amplitude; HR: \(r = 0.57\) to 24-hour amplitude; all \(P < 0.0001\).

### Coupling of Cardiovascular Rhythms

**Interaction of Circadian and Ultradian Rhythms**

There were several significant associations of the circadian and ultradian rhythms among each other, which are summarized in the first two columns of Table 3. Although the prevalence of most HR rhythms was significantly associated with each other, among BP rhythms only the 12-hour rhythm was coupled to the other rhythms. Correlation of the amplitudes was closer than that of the acrophases and more pronounced among the shorter rhythms.

### Coupling of BP to HR Rhythms of the Same Period Length

There was a very significant association of the HR rhythms with the BP rhythms of the same period length in terms of prevalence and timing. In the presence of any given BP rhythm, the corresponding HR rhythm of the same period length was present more often than expected by chance (see

### Table 2: Population Distribution Percentiles of Individual and Combined Fourier Harmonics for Blood Pressure and Heart Rate

<table>
<thead>
<tr>
<th>Rhythm</th>
<th>Parameter</th>
<th>Group</th>
<th>Group</th>
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<th>25th</th>
<th>50th</th>
<th>75th</th>
<th>95th</th>
<th>5th</th>
<th>25th</th>
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<th>75th</th>
<th>95th</th>
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<td>10.1</td>
<td>12.4</td>
<td>16.9</td>
<td>6.6</td>
<td>10.1</td>
<td>13.4</td>
<td>17.0</td>
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<td>...</td>
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<td>12.3</td>
<td>15.4</td>
<td>19.1</td>
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<tr>
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<td>13.9</td>
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<td>16.7</td>
<td>10.5</td>
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<td>13.5</td>
<td>14.6</td>
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<td></td>
<td>Acrophase</td>
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<td>5.9</td>
<td>7.2</td>
<td>10.4</td>
<td>4.2</td>
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<tr>
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<td>6.4</td>
<td>7.8</td>
<td>8.7</td>
<td>10.5</td>
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<tr>
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<td>Amplitude</td>
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<td>4.4</td>
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<td>10.2</td>
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<tr>
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<td></td>
<td>Pre-pubescent</td>
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<td>5.1</td>
<td>6.1</td>
<td>7.5</td>
<td>10.5</td>
<td>4.3</td>
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<tr>
<td></td>
<td></td>
<td>Pubescent</td>
<td>3.3</td>
<td>4.1</td>
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<td>6.5</td>
<td>9.3</td>
<td>3.7</td>
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<tr>
<td>8-h</td>
<td>Amplitude</td>
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<td>3.4</td>
<td>4.4</td>
<td>5.2</td>
<td>6.6</td>
<td>9.7</td>
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<td>4.4</td>
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<tr>
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<td>Pre-pubescent</td>
<td>0.5</td>
<td>1.5</td>
<td>2.0</td>
<td>3.0</td>
<td>4.8</td>
<td>0.7</td>
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<td>Combined 24, 12, 8, and 6-h</td>
<td>Peak–trough</td>
<td>All</td>
<td>12.2</td>
<td>19.9</td>
<td>25.9</td>
<td>31.8</td>
<td>42.2</td>
<td>16.4</td>
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<td>...</td>
<td>...</td>
<td>20.0</td>
<td>29.4</td>
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<tr>
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<td>13.8</td>
<td>16.6</td>
<td>19.4</td>
<td>7.8</td>
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<td>15.4</td>
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<tr>
<td></td>
<td>Time of peak</td>
<td>All</td>
<td>9.4</td>
<td>12.2</td>
<td>13.9</td>
<td>16.7</td>
<td>18.9</td>
<td>9.0</td>
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<td>12.6</td>
<td>14.9</td>
<td>19.4</td>
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</tbody>
</table>

Acrophases are given as hours after midnight, amplitudes, and peak–trough differences as mm Hg for mean arterial pressure (MAP) and bpm for heart rate (HR). Separate values for pre-pubescent and pubescent children are only given if the difference was statistically significant.

\((P = 0.04)\), as well as MAP MESORs \((P = 0.01)\) compared with those lacking 6-hour rhythmicity.
third column of Table 3) and there was a high correlation of acrophases (r between 0.56 and 0.66). For the coupling of circadian with ultradian rhythms there was a stronger correlation of amplitudes than acrophases.

The time lag between the acrophases of BP and HR showed a narrow population distribution (Table 4)(Annex 2) and was independent of gender as well as HR and BP level. For 24-, 8-, and 6-hour rhythms the BP acrophase occurred after the HR peak (median 21 minutes for 24-hour, 12 minutes for 8-hour, and 5 minutes for 6-hour rhythm) and vice versa for the 12-hour rhythm (median 16 minutes). Age did not have a pronounced effect on median time lag for any rhythm, but in the pubescent population there was a wider spread for the 24-hour rhythm.

The overall BP and HR rhythms also showed significant association, albeit less pronounced than for the individual rhythms. Correlation was only r=0.22 for the peak BP and HR values and r=0.3 for the time of the peaks (both P<0.0001). The median time difference between the BP and HR peaks was similar to that of the individual rhythms but was dependent on age (10 minutes before puberty, 20 minutes during puberty) and showed a much wider population distribution than time lags of individual rhythms (interquartile range of 223 and 274 minutes for pre-pubescent and pubescent children; Table 4).

**Discussion**
This study aimed to determine the distribution of the prevalence, magnitude, and timing of cardiovascular rhythms across childhood to investigate possible developmental changes and provide pediatric reference data for the evaluation of BP rhythms in states of disease. To this end, we analyzed ABPM profiles from a large representative cohort of healthy Middle European children aged 5 to 18 years. We observed significant ultradian or circadian cardiovascular rhythmicity in 95% of healthy children. During or near puberty, the dominant frequency of ultradian BP rhythms changed from 8-hour to 6-hour and 12-hour patterns.

We chose to screen each individual ABPM profile for a maximum of four superimposed sinusoidal rhythms to establish respective normative values of use in a variety of settings. The use of four harmonics to model the overall BP curve has been recommended to standardize the degree of analysis and to strike an acceptable balance between the accuracy and complexity of the mathematical procedures involved. It should be emphasized that the repeatability of Fourier analyses can be influenced by methodological issues such as the sampling frequency and the rate of measurement errors. Notably, Yetman et al, using sampling intervals nearly twice as long as those used here, detected either a circadian or a 12-hour rhythm in only 33 of 100 healthy children in contrast to 92% in this study.

The observed prevalence and dimensions of the 24-hour BP rhythm were remarkably constant across childhood, with a uniformly high prevalence at ≈90% and amplitudes and acrophases comparable to those of an earlier small study with a very strict synchronization schedule. The circadian rhythmicity component was the major determinant of the overall BP curve fitted by the combination of up to four harmonics. Lurbe et al, who analyzed four rhythms in a population with a similar age range, found comparable values for the overall Fourier parameters, except for slightly smaller systolic amplitudes (13.4±5.4 versus 12.5±4.2 mm Hg, P=0.025), possibly related to sociocultural differences between the Spanish and Middle European populations.

In contrast to the constant circadian rhythmicity of BP, 24-hour HR rhythms showed a small but consistent decrease...
of prevalence and amplitude with puberty. The dissociation of circadian BP and HR rhythmicity during puberty may be related to changes in lifestyle and sleeping habits; this interpretation is in line with the stronger relationship of HR, compared with BP, to activity during ABPM that has been described previously.23

We observed significant ultradian rhythmicity in 63% of children for BP and 66% for HR, which was usually (95%) superimposed on the circadian rhythm. Ultradian amplitudes were significantly more pronounced than those previously described in adults,16 even in the pubescent children (up to 3 mm Hg for systolic and diastolic amplitudes). The mechanisms underlying ultradian cardiovascular rhythmicity are largely unknown and may include behavioral patterns of physical activity and neurogenic fluctuations of the cardiovascular tone. The autonomic nervous system has been implicated in studies in animals24,25 and humans26,27 as a regulator of circadian BP variation. Its role in the generation of ultradian cardiovascular rhythms is also suggested by our interesting observation that children displaying rhythmicity of any period length had consistently higher daytime, but not nighttime, HR than those in whom BP or HR did not fluctuate periodically. Of note, a higher degree of coupling was observed among the amplitudes of the individual ultradian rhythms than between the ultradian and the circadian rhythms. This may point to different mechanistic principles operative in the temporal organization of circadian and ultradian rhythmicity, respectively.

We observed marked nonlinear changes of the prevalence and/or magnitude of individual ultradian cardiovascular rhythms around the time of puberty (summarized in Figure 4). Although the 12-hour and 6-hour rhythmicity of BP and HR became more prominent, 8-hour BP rhythmicity decreased. The peripubertal changes in the prevalence, magnitude, and timing of rhythms were concordant for BP and HR, and trends in prevalence paralleled changes in amplitude.

It is tempting to speculate about the factors responsible for the observed changes of ultradian cardiovascular rhythmicity. The intrinsic activity of the autonomic nervous system changes around puberty;28 this has been implicated in the physiological increase of BP during adolescence29 and may affect ultradian BP rhythmicity as well. Endocrine factors may also be involved in view of the dramatic peripubertal increase in sex hormone production, which also follow ultradian cyclical patterns30 and affect BP by various mechanisms. The differential cardiovascular effects of male and female sex steroids are reflected by the gender difference of absolute and MESOR BP levels observed from the onset of puberty onwards. However, in agreement with previous studies,13–15 we found no gender differences in the prevalence, magnitude, or timing of any of the cardiovascular rhythms.

### Table 4. Population Distribution Percentiles for the Time Lag of the MAP Acrophase After HR Acrophase

<table>
<thead>
<tr>
<th>Rhythm</th>
<th>Group</th>
<th>5th</th>
<th>25th</th>
<th>50th</th>
<th>75th</th>
<th>95th</th>
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<td>−29</td>
<td>21</td>
<td>76</td>
<td>184</td>
<td>105</td>
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<td></td>
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<td>54</td>
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<tr>
<td></td>
<td>Pubescent</td>
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<td>32</td>
<td>88</td>
<td>200</td>
<td>110</td>
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<tr>
<td>12-h</td>
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<td>−16</td>
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<td>88</td>
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<tr>
<td></td>
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<td>5</td>
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<tr>
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<tr>
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<td>103</td>
<td>10</td>
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<td>66</td>
<td>20</td>
<td>208</td>
<td>560</td>
<td>274</td>
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</tbody>
</table>

MAP indicates mean arterial pressure; HR, heart rate; IQR, interquartile range.

Figure 4. Synopsis of age-related changes in prevalence and dimensions of cardiovascular rhythms across childhood. — indicates no age-related changes; ↑, increases with age; ↓, distribution narrows with age; <, distribution broadens with age; ↘, decreases with age (earlier acrophase).
Perspectives

We have described circadian cardiovascular rhythmicity in the majority of healthy children and adolescents with an attenuation of 24-hour HR periodicity during puberty. In addition, ultradian rhythms were found in a large proportion, with a shift of BP rhythmicity from 8-hour to 6-hour or 12-hour with age. The provision of detailed reference values is an important step in the identification of subtle abnormalities in pediatric patients with defined pathologies. Several new observations should stimulate further investigations, such as the greater ultradian BP amplitudes in children compared with adults as well the major changes in the temporal organization of cardiovascular rhythmicity during puberty.

Acknowledgments

This analysis was supported by the European Commission (5th Framework Programme, QLG1-CT-2002-00908), the Boehringer Ingelheim Foundation, the Baxter Extramural Grant Program, and Aventis Pharma.

References


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Normative Values for Circadian and Ultradian Cardiovascular Rhythms in Childhood
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the German Study Group for Pediatric Hypertension

_Hypertension_. 2004;43:547-554; originally published online January 26, 2004;
doi: 10.1161/01.HYP.0000116754.15808.d8
_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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