Altered Cardiovascular Rhythmicity in Children Born Small for Gestational Age

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Abstract—Low birth weight is frequently associated with a disproportionately high incidence of cardiovascular disease, diabetes mellitus, and kidney disease in adulthood. Epidemiological studies have identified an inverse association between low birth weight or being small for gestational age and hypertension in adulthood. We hypothesized that children born with low birth weight might have altered circadian and ultradian cardiovascular rhythmicity independent of the prevailing blood pressure level. Twenty-four-hour ambulatory blood pressure and heart rate rhythmicity was prospectively evaluated by Fourier analysis in a cohort of healthy children born with low birth weight and compared with normative pediatric data. Seventy-five children born small for gestational age (mean age, 8.1 ± 2.2 years) and 139 controls matched for age and sex were investigated. In addition to increased 24-hour, daytime, and especially nighttime blood pressure levels (P < 0.05), children born small for gestational age exhibited blunted circadian (24-hour) and ultradian (12-, 8-, and 6-hour) blood pressure rhythmicity (P < 0.05). In a multivariate analysis including children born with low birth weight and controls, being born with low birth weight independently influenced ultradian blood pressure rhythmicity, whereas in a multivariate analysis including children born with low birth weight only, circadian and ultradian rhythms were independently influenced by catch-up growth, gestational age, and blood pressure level. This study demonstrates blunted circadian and ultradian cardiovascular rhythmicity in prepubertal children born small for gestational age, independent from the presence of arterial hypertension. Circadian and ultradian rhythms may be sensitive indicators for detecting subtle early abnormalities of cardiovascular regulation. (Hypertension. 2012;60:865-870.)

Key Words: small for gestational age ■ low birth weight ■ child ■ blood pressure ■ circadian and ultradian cardiovascular rhythmicity

Elevated blood pressure (BP) has become increasingly recognized as a major health threat in the adult population and among adolescents. In parallel, survival of premature or small for gestational age (SGA) newborns because of intrauterine growth restriction has improved, resulting in an expanding group of infants with low birth weight (LBW; ie, < 2500 g). LBW is frequently associated with a disproportionately high incidence of cardiovascular disease, arterial hypertension, diabetes mellitus, and kidney disease in adulthood.

The precise mechanisms that underlie the link between reduced fetal growth and increased cardiovascular risk remain complex and insufficiently understood. The “fetal programming hypothesis” proposes that fetal adaptation in utero to adverse intrauterine conditions increases the fetus’s chance of survival but permanently alters physiology and metabolism causing increased disease susceptibility later in life.

Among other mechanisms, the association between LBW and congenital nephron deficit supporting salt and water retention might contribute to the relationship between LBW and arterial hypertension. Moreover, there is a growing body of evidence that children born SGA have a higher sympathetic tone in infancy, childhood, and as adults.

These mechanisms may not only cause higher BP values but also contribute to a disturbed cardiovascular rhythmicity, which has also been related to an increased risk of cardiovascular disease. We hypothesized that, independent of the BP level, children born with LBW have a disturbed circadian and ultradian cardiovascular rhythmicity. To evaluate our hypothesis, we analyzed 24-hour ambulatory BP and heart rate rhythmicity in a cohort of otherwise healthy SGA children and compared the results with normative data obtained from healthy children.

Methods

Subjects
Healthy SGA children born term or preterm between October 1997 and December 2004 at the University of Heidelberg Women’s Hospital, currently aged 5 to 11 years and living within the Heidelberg area, were eligible to enter the study. SGA was defined as a birth weight more than 2 SD scores (SDSs) below the mean for

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the local population.13 Children who are SGA because of congenital infections, such as cytomegalovirus, dystrophism, severe cerebral palsy, congenital heart disease, or syndromal intrauterine growth retardation, were excluded. Gestational age was determined by a recollection of the last menstrual period and confirmed or corrected by an ultrasonographic examination before the 20th week of gesta-
tion using the crown-rump length. Correction of the gestational age using the measured length was made when a difference of 5 days from the menstrual age was recognized. Moreover, parents were asked to complete a structured questionnaire about (familial) cardiovascular disease. Parents were considered hypertensive if they reported to have been told by a physician that they had elevated BP or were currently treated for arterial hypertension.

The control group consisted of 139 age- and sex-matched healthy German subjects aged 5 to 11 years who were described else-
where12,14,15 representing the whole spectrum of BP values (ie, also including children with BP values below the 5th or above the 95th percentile for height on 24-hour ambulatory BP monitoring (ABPM)) and of birth weight of the healthy childhood population. The protocol was approved by the local ethical review board and fulfilled the criteria of the Declaration of Helsinki. All of the participating children and their parents gave informed consent.

Clinical Measurements
All of the SGA children attended the Center for Pediatrics and Adolescent Medicine of the University of Heidelberg. Height and weight were measured, and body mass index (BMI) was calculated; BMI, weight, and height centiles were computed according to the German national growth charts.16,17 A physical examination was performed, including assessment of puberty stage (Tanner stages), and office BP and heart rate were measured in sitting position on the right arm with a validated oscillometric automated device (Dinamap)18 using an appropriate cuff size after 5 minutes of rest in a quiet room. The means of 3 independent measurements was calculated, as proposed by current guidelines. BP SDS values were calculated; elevated BP was defined according to the American reference data.1

Waist and hip circumferences were measured, and triceps and subscapular skinfold thickness measurements at the right-hand side were taken using Harpenden calipers. Three readings were obtained and the mean values used to calculate percentage of body fat by the formula of Slaughter et al.19

ABPM Measurements
All of the included children received 24-hour ABPM measurement, which was assessed oscillometrically using the SpaceLabs Monitor 90207 device with the most appropriate cuff applied on the nondominant arm. Readings were taken every 15 to 20 minutes during the day and every 20 to 30 minutes at night, recordings lasting ≥22 hours with ≥80% of successful readings, and cumulative recording gaps no greater than 2 hours were considered as valid and were included in the analysis. Absolute BP values obtained from ABPM were subsequently transformed into SDSs based on normative ABPM values.20 Because during oscillometric measurements only mean arterial BP (MAP) is measured (representing the BP value with the greatest oscillations) and systolic and diastolic BPs are mathematically derived from device-specific algorithms, the analysis was restricted to the MAP data.

The night period was defined from 12:00 AM until 6:00 AM. The daytime period was defined as 8:00 AM until 8:00 PM.

BP nighttime dipping status was analyzed by calculating the ratio of MAP during the day in relation to nighttime MAP (MAP daytime/nighttime). Similar to the study by Wühl et al,15 the MAP lowering during the night >10% was considered as dipping. MAP nighttime dipping of <10% (MAP daytime/nighttime <1.1) was considered as nondipping. Similarly, the heart rate (HR) nighttime dipping was described with the daytime/nighttime ratio.

Rhythm Analysis
Rhythm analysis was performed according to the procedure described elsewhere.12,20 In short, the 24-, 12-, 8-, and 6-hour MAP and HR rhythms were analyzed using Fourier analysis. First, the 24-hour circadian rhythm was checked using least-squares analysis and was considered to be present if a cosine function within 24 hours could be fitted with a significance of $P<0.05$. Then, shorter ultradian rhythms were tested in the same manner. The following parameters were calculated for each significant rhythm: (1) MESOR, which is the median value midway between the lowest and highest values of the fitted cosine curve; (2) amplitude, which is the difference between MESOR and highest value; and (3) acrophase, which is the time from midnight to the highest value of the curve during the rhythm.

Statistical Analysis
Subject characteristics and results are presented as mean±SD. BMI and BP values were expressed both as absolute values and as SDSs corrected for age and sex. Comparison of prevalence between the groups was performed using the $\chi^2$ test.

Variables with a normal distribution were compared by the Student $t$ test for independent variables. Values with nonnormal distribution were compared by the Mann-Whitney U test and the Kruskal-Wallis test in case of multiple group comparison. Correlation analysis was done with Pearson test for variables with parametric distribution and Spearman test for variables with nonparametric distribution. Forward stepwise multivariate linear regression analysis was performed to identify the significant independent factors influencing BP values and BP rhythms. A $P$ value <0.05 was regarded as significant.

Results
Characteristics of the Study Population
Eighty-six SGA children were recruited between January and May 2009; 75 healthy, prepubertal SGA children were included in the final analysis. Eleven ABPM readings had to be excluded from the study because of an incomplete recording length of <22 hours or gaps between measurements ≥2 hours (Figure 1).

Forty-three children were born preterm (mean gestational age, 35±2 weeks) and 32 at term (mean gestational age, 39±1 weeks). The mean birth weight was 2036±469 g (SDS, −2.2±0.7 g) and the mean birth length 44.9±4.6 cm (SDS, −1.77±1.20 cm). The clinical characteristics of the SGA children and control subjects are given in Table 1. Despite a similar age distribution in the 2 groups, children born SGA were significantly smaller and lighter at the time of the study compared with control subjects. In children born SGA, catch-up growth, defined as current weight SDS – birth weight SDS, was +2.0±1.1.

Office BP Measurements
Mean office BP of SGA children was systolic 107.1±10.1 mmHg (0.8±1.0 SDS) and diastolic 62.5±6.9 mmHg (0.4±0.7 SDS). The values were significantly ($P<0.001$) higher when compared with the normal population.

SA children born 10/97–12/04 784
Excluded (medical or organizational issues) 629 (80%)

Children eligible for the study 155 (20%) Excluded (incomplete recording) 11 (13%)

Children with ABPM recording 86 (55%)

Included in analysis 75 (87%)

Figure 1. Flow chart of the small for gestational age (SGA) children considered in the study.
ABPM 24-Hour, Daytime, and Nighttime BP, and Nocturnal BP Fall
Mean 24-hour, daytime, and nighttime MAP values are summarized in Table 2. MAP SDS was significantly higher in the SGA group compared with the control group for 24-hour (P=0.003), daytime (P=0.02), and nighttime (P<0.001). Twenty-four–hour MAP SDS correlated with birth length SDS (r=0.31; P=0.007) in the SGA group and with BMI (r=0.34; P<0.001) and BMI SDS (r=0.38; P<0.001) in the control group. Daytime MAP SDS correlated with percentage of body fat (r=0.25; P=0.04). BP values of SGA subjects did not correlate with catch-up growth, waist/hip ratio, or parental hypertension.

Children born SGA had a significantly reduced nocturnal MAP decline (daytime/nighttime ratio, 1.18±0.1 versus 1.21±0.1; P=0.04; Table 2) and smaller circadian BP amplitude (9.3±2.9 versus 10.8±3.9 mmHg; P=0.03) compared with control subjects. The prevalence of nondipping was nearly the same in the 2 groups (15% versus 14%; P=0.96).

Circadian and Ultradian BP Rhythms (Fourier Analysis)
The prevalence of circadian and ultradian BP rhythmicity was comparable between the children born SGA and the controls (24 hours, 96% versus 89%, P=0.09; 12 hours, 33% versus 32%, P=0.89; 8 hours, 41% versus 36%, P=0.44; 6 hours, 31% versus 22%, P=0.18). The prevalence of HR rhythms was similarly distributed without significant differences compared with the control group.

Children born SGA had blunted MAP and HR amplitudes compared with control subjects for all of the rhythms (Table 3 and Figures 2 and 3). Acrophases of children born SGA were similar compared with controls (Table 3). Although in the control group the different circadian and ultradian MAP amplitudes correlated with each other (r=0.36–0.75, P=0.006–0.020; data not shown), in children born SGA only a correlation between the 24-hour MAP amplitude and the 12-hour MAP amplitude was found (r=0.43; P=0.03). The 24-hour MAP amplitude correlated with the 24-hour HR amplitude in the control group (r=0.25; P=0.006) and in children born SGA (r=0.25; P=0.006).
born SGA ($r=0.32; P=0.009$). MAP rhythms did not correlate with HR rhythms for the ultradian amplitudes.

Five SGA children had abnormally diminished 24-hour MAP amplitudes ($<5$th percentile$^{12}$); 4 of them were nondippers. Nine children had abnormally diminished ($<5$th percentile$^{12}$) ultradian amplitudes (12 hours, n=5; 8 hours, n=3; 6 hours, n=1).

Correlations Between Circadian or Ultradian Rhythms With Anthropometric Characteristics or BP Level in Univariate or Multivariable Analyses

In the SGA subjects, BP dipping was associated with BMI ($r=0.26; P=0.02$), BMI SDS ($r=0.26; P=0.03$), body fat ($r=0.31; P=0.009$), and catch-up growth ($r=0.27; P=0.01$), whereas in the controls no correlations were found. Both in the group of SGA children and in controls, the 24-hour MAP amplitude was positively correlated with the BMI SDS (SGAs, $r=0.25, P=0.04$; controls, $r=0.24, P=0.008$), which means that thinner children had a smaller circadian amplitude. In SGA children, 24-hour MAP amplitude was positively correlated with catch-up growth ($r=0.27; P=0.02$). In addition, in the control group the 6-hour MAP amplitude was correlated with current BMI ($r=0.4; P=0.02$), height ($r=0.43; P=0.02$), and height SDS ($r=0.5; P=0.004$). The univariate analyses of other factors possibly associated with BP rhythmicity, like sex, gestational age, SDS of birth weight or birth length, body fatness, or genetic predisposition for hypertension did not disclose significant correlations.

In both groups the circadian MAP amplitude was correlated with the daytime MAP SDS (SGA, $r=0.43, P<0.001$; controls, $r=0.36, P<0.001$) and nighttime MAP SDS (SGA, $r=-0.31, P=0.008$; controls, $r=-0.24, P=0.007$), respectively. No correlation was found between 24-hour MAP level (absolute values or SDS) and circadian amplitudes. Amplitudes of the 12-, 8-, and 6-hour ultradian rhythms showed no correlation to either mean 24-hour, daytime, or nighttime MAP levels (absolute values or SDSs) in either SGA children or in the control group. The nighttime MAP SDS was negatively correlated with the 12- and 8-hour MAP acrophases in controls ($r=0.34, P=0.02; r=-0.34, P=0.01$, respectively) and positively with the 8-hour MAP acrophase in the SGA children ($r=0.39; P=0.03$).

In a multivariate stepwise regression analysis including birth weight SDS, gestational age, catch-up growth, BMI SDS, height SDS, and 24-hour MAP SDS of children born SGA into the model, catch-up growth and 24-hour MAP SDS were independently correlated with 24-hour MAP amplitude, gestational age, and 24-hour MAP SDS with 24-hour MAP acrophase, gestational age with 8-hour MAP amplitude only, and catch-up growth with nocturnal dipping (Table 4). In a multivariate stepwise regression model including SGA children and controls in addition to sex, age, height SDS, BMI SDS, and 24-hour MAP SDS, being born SGA was the only independent predictor of ultradian MAP rhythmicity (12 hours, $r^2=0.125, P=0.003$; 8 hours, $r^2=0.185, P<0.0001$; and 6-hour amplitude, $r^2=0.127, P=0.008$).

**Discussion**

The main finding of our study is that children born SGA display significantly altered circadian and ultradian cardiovascular rhythmicity, even before hypertension becomes manifest. In addition, we confirm that prepubertal SGA children display increased 24-hour, daytime, and especially nighttime BP levels compared with the healthy control population.

The rhythm of cardiovascular functions is generated by a principal pacemaker probably located in the suprachiasmatic nuclei and is transmitted through efferent sympathetic nerves.$^{21}$ Additionally, there are several peripheral oscillators, and the interaction is tuned by neuroendocrine and metabolic cues.$^{22}$

The shorter, ultradian rhythms are more dependent on sympathetic activity caused by external and behavioral stimuli.$^{23}$

The most commonly used marker of BP rhythmicity is nocturnal dipping that has been shown to be an important independent risk factor for cardiovascular disease.$^{11,24}$ Our results confirm that the nighttime dipping of BP is reduced in children born SGA, as already found in prepubertal, low birth weight children,$^{25,26}$ and in children with primary$^{27}$ or secondary hypertension attributed to chronic kidney disease.$^{28,29}$
In addition to the conventional dipping analysis, Fourier analysis of ABPM profiles permits the description of the circadian (24-hour) and the ultradian (12-, 8-, and 6-hour) cardiovascular rhythmicity by the amplitudes and acrophases of the derived cosine curves. The prevalence of BP rhythmicity was similar between the children born SGA and control subjects. In contrast, both nocturnal BP fall and magnitude of circadian and ultradian amplitudes were considerably decreased in the SGA group compared with the controls. These alterations were not the consequence of higher BP values in the former group as demonstrated in the multivariate analysis including both groups of children. These results are consistent in extent to children with primary hypertension and chronic kidney disease. With respect to the observed similar prevalence but decreased amplitude size of the rhythms, one might speculate that abnormal cardiovascular regulation starts with a reduction of amplitudes, evolving to abolished rhythms later in life.

In children born SGA, BMI was positively associated with mean BP level, nocturnal dipping, and the circadian amplitude of BP but not with ultradian rhythms. A negative correlation between dipping and BMI SDS has been reported previously in adolescents.

Our data indicate that children born SGA with low BMI and missing (or reduced) catch-up growth are at risk of blunted cardiovascular rhythmicity. The pathophysiological mechanisms underlying this phenomenon are not completely understood but may involve sympathoadrenal overactivity and/or abnormalities of kidney function. Findings suggestive of a higher sympathetic tone in SGA born individuals could be the link to a disturbed BP rhythmicity, endothelial dysfunction, and an increased cardiovascular risk. Among other mechanisms, salt sensitivity, which has been associated with LBW, probably because of a reduced kidney size and nephron number, has been proposed as a possible reason for the changes in BP rhythmicity.

The only moderate agreement between circadian and ultradian amplitudes in our SGA cohort is in accordance with previous data from children with chronic kidney disease and supports the autonomy of rhythms with different period length, probably influenced by different pathophysiological effects. HR rhythms showed analogous abnormalities to BP rhythms with decreased amplitude size compared with controls, but only the 24-hour HR and -BP amplitudes correlate positively with each other. It remains unclear whether HR changes lead to the development of BP rhythms or alternatively involve separate physiological mechanisms. A decreased beat-to-beat HR variability has been shown to be an adverse prognostic marker for cardiovascular outcome. Galland et al reported a decreased HR variability attributed to a reduced autonomic activity and cardiac reflex in SGA infants. The abnormalities of more easily accessible ultradian rhythms detected on noncontinuous HR and BP monitoring found in our study may also have been influenced by disturbances of the autonomic nervous system and have prognostic significance on cardiovascular health.

The limitations of our study are the lack of data on possible target organ damage to establish a potential relationship between altered BP rhythmicity and early, subclinical injury in children born SGA and the absence of data about perinatal factors (birth weight, birth length, and gestational age) in the control group and about kidney function, renal size, or sympathetic activity to detect a possible etiology of the disturbed cardiovascular rhythmicity.

**Perspectives**

This study demonstrates a blunted circadian and ultradian cardiovascular rhythmicity in prepubertal children born SGA, independent from the presence of arterial hypertension. This may suggest that circadian and ultradian rhythms are early and sensitive markers for detecting subtle abnormalities of cardiovascular regulation. These findings are important because being born SGA is frequently associated with a disproportionately high incidence of cardiovascular diseases in adulthood.

In perspective, it would be of interest to prospectively assess whether, after the development of a disturbed circadian and ultradian BP rhythmicity, arterial hypertension and cardiovascular diseases would become manifest in subjects born SGA. These studies would confirm the hypothesis that an altered circadian or ultradian BP rhythmicity is an early marker for the assessment of cardiovascular diseases. Moreover, it would be of interest to test whether the ultradian cardiovascular rhythmicity bears prognostic implications on target organ damage in children born SGA, as it has been shown for the circadian profiles.

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**Disclosures**

None.

**References**

What Is New?

- Children born SGA exhibit blunted circadian and ultradian cardiovascular rhythmicity.
- Catch-up growth, gestational age, and 24-hour BP independently influence circadian and ultradian BP rhythmicity.

What Is Relevant?

- These data provide further evidence for the fetal origins of adult disease.

Novelty and Significance

These results support the importance of continued surveillance of children born SGA to early detect cardiovascular diseases.

Summary

This study demonstrates blunted cardiovascular rhythmicity in prepubertal children born SGA, independent from the presence of arterial hypertension. Circadian and ultradian rhythms may be sensitive indicators for detecting subtle early abnormalities of cardiovascular regulation.
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