Cardiac autonomic balance in small-for-gestational-age neonates

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Schäffer L, Burkhardt T, Müller-Vizentini D, Rauh M, Tomaske M, Arlettaz Mieth R, Bauersfeld U, Beinder E. Cardiac autonomic balance in small-for-gestational-age neonates. Am J Physiol-Heart Circ Physiol 294: H884–H890, 2008. First published December 7, 2007; doi:10.1152/ajpheart.00318.2007.—The cardiac sympathetic nervous system is one putative key factor involved in the intrauterine programming of adult cardiovascular disease. We therefore analyzed cardiac autonomic system activity in small for gestational age (SGA) neonates. Heart rate variability (HRV) from 24-h ECG recordings were analyzed for time-domain and frequency-domain parameters in 27 SGA neonates [median 261 (240–283) days of gestation] compared with 27 appropriate for gestational age (AGA) neonates [median 271 (240–294) days of gestation]. Overall HRV was not significantly different in SGA neonates compared with AGA neonates (SD of all valid NN intervals: P = 0.14; triangular index: P = 0.29), and the sympathovagal balance [low frequency (LF)/high frequency (HF) ratio] was similar (P = 0.62). Parameters mostly influenced by sympathetic activity did not reveal significant differences: (SD of the average of valid NN intervals: P = 0.27; average of the hourly means of SDs of all NN intervals: P = 0.66, LF: P = 0.83) as well as vagal tone-influenced parameters were unaltered (average of the hourly square root of the mean of the sum of the squares of differences between adjacent NN intervals: P = 0.59; proportion of pairs of adjacent NN intervals differing by >50 ms: P = 0.93; HF: P = 0.82). Median resting levels for α-amylase were not significantly different in SGA neonates (P = 0.13), and a neonatal stress stimulus revealed similar stress response patterns (P = 0.29). HRV and salivary α-amylase levels as indicators of cardiac autonomic activity were not altered in SGA neonates compared with AGA neonates. Thus, it appears that the intrauterine activation of the sympathetic system in SGA fetuses does not directly persist into postnatal life, and neonatal sympathovagal balance appears to be preserved.

intrauterine programming; cardiovascular; amylase; heart rate variability; sympathovagal balance

THERE IS EVIDENCE that the development of adult cardiovascular disease is initiated by unfavorable conditions during intrauterine fetal life among genetic and environmental factor interactions. This hypothesis of a fetal origin of adult diseases as initially proposed by Barker et al. (7) has been reinforced by epidemiological evidence of an inverse correlation between birth weight and the risk for cardiovascular disease (17, 23, 30). Cardiovascular system regulation strongly depends on sympathetic autonomic control. Sympathetic activity is believed to play an important role in the pathogenesis of essential hypertension (15, 32, 33). During intrauterine life, malfunction of the placenta is the major cause of undernutrition of the developing fetus. The fetus survives by adaptation of metabolic and cardiovascular systems mediated in part by the activation of the sympathetic component of the autonomous system (38). Thus, growth-restricted fetuses show increased levels of catecholamines and glucocorticoids (16, 63). These adaptive events occur at a developmental time when major regulating systems of the organism are believed to still contain flexible set points.

In low-birth-weight adults, surrogates for altered autonomic cardiovascular control, such as an increased pulse rate (18, 45) and, more specifically, altered blood pressure and heart period variability (28, 60), have been described. Several animal models support the connection of an intrauterine adverse environment and alterations of the sympathoadrenergic system (26, 37, 48). Cardiovascular disease is associated with alterations in the activation of the sympathoadrenergic system in the adult (12, 13). Thus, the cardiac autonomic system balance may be permanently altered according to the concept of fetal programming. During the early postnatal period, one may speculate that temporary upregulated systems normalize in response to a normal postnatal environment, whereas permanently altered systems may become apparent, making this time important for analysis.

Heart rate (HR) variability (HRV) is a well-established noninvasive measure of cardiac autonomic control (22, 29). The aim of this study was to analyze the cardiac autonomic balance in small for gestational age (SGA) newborns by HRV measurements. These electrophysiological findings were supplemented by salivary α-amylase measurements in response to a stress stimulus. Salivary α-amylase has been suggested to be a surrogate for cardiovascular autonomic system balance correlating well with HRV parameters (10, 41), thereby making this parameter a promising indicator for cardiac autonomic function.

METHODS

The study was approved by the Research Ethics Committee of the University of Zurich and the Federal Ethics Commission of the canton of Zurich. Written maternal consent was obtained. SGA was defined as newborn weight below the fifth percentile of the gender-specific newborn reference chart (58). Newborn weights of >10th and <90th percentiles were required for appropriate for gestational age (AGA) infants. Only healthy newborns delivered after 34 wk of gestation (>238 days postmenstruation) without intensive care requirements, invasive procedures, or malformations were included. Since mothers did not always give consent for both ECG and saliva sample collection, two separate populations had to be analyzed.

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HRV Measurements

A total of 54 children was recruited for 24-h Holter ECG measurements containing 27 AGA and 27 SGA neonates. Gestational age at delivery did not differ between groups (P = 0.27). A summary of newborn data is shown in Table 1. Three-channel Holter monitors (LifeCard, Delmar Reynolds Medical, Hertford, UK) were placed within the fourth postnatal day. Ectopic beats, noisy data, and artifacts were manually identified and excluded from the HRV analysis. For the calculation of HRV parameters, HRV Analysis software (version 9.3.0) from Nevrokard (www.nevrokard.eu) was applied.

According to the recommendations of the Task Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology (55) and the literature for neonatal HRV measurements (5, 19, 47, 57), the following parameters were analyzed.

Time-domain parameters. Time-domain parameters included the following: 1) as an estimate of overall HRV, the SD of all valid NN intervals (SDNN); 2) parameters mostly influenced by parasympathetic activity, including the ratio of the number of all pairs of adjacent NN intervals differing by >50 ms and the total number of RR intervals (s-NN50), those differing by >27 ms and the total number of RR intervals (s-NN27), and those differing by >20 ms and the total number of RR intervals (s-NN20) as well as the average of the hourly square root of the mean of the sum of the squares of differences between adjacent NN intervals (r-MSSD); and 3) parameters mostly influenced by sympathetic activity, including the SD of the average of valid NN intervals (SDANN) in 5-min segments in the recording and the average of the hourly means of SDs of all NN intervals (SDNNi) in 5-min segments. As a geometric index, the HRV triangular index, defined by the total number of all NN intervals divided by the height of the histogram of all NN intervals measured on a discrete scale with bins of 7.8125 ms as an estimate of overall HRV, was calculated.

Frequency-domain parameters. Power spectral analysis was calculated by fast Fourier transformation (Hamming window) in four frequency bands. To account for the neonatal physiology, frequency bandwidths were adjusted according to the literature (19, 47); high frequency (HF) was 0.24–1.04 Hz, representing parasympathetic activity; low frequency (LF) was 0.04–0.24 Hz, representing both sympathetic and parasympathetic activity; very low frequency (VLF) was 0.003–0.04 Hz, mainly resulting from parasympathetic activity; and ultra LF (ULF) was 0.000–0.003 Hz. Total power (in ms²) as well as the ratio of LF to HF power (LF/HF), considered as a marker of sympathetic-parasympathetic system balance, were analyzed.

α-Amylase Measurements

Salivary α-amylase levels of 36 AGA and 18 SGA infants were analyzed. The infant’s age at delivery did not differ between groups (P = 0.8). A summary of newborn data is shown in Table 2.

To analyze sympathetic autonomic nervous system activity and reactivity to stress, salivary α-amylase samples were collected using a routinely performed blood sampling (heel prick test) 72–96 h postpartum as a pain-induced stress factor. This procedure has been shown to be a significant stressor for the newborn (31, 34), and salivary α-amylase has been suggested as a measure of endogenous adrenergic activity and changes in the autonomic nervous system in general (11, 41) and specifically for cardiac autonomic balance (10, 21, 41). Saliva samples were collected from each infant 10 min before and 5 and 20 min after stress induction. Collection time was based on experiments revealing peak α-amylase responses between 5 and 10 min after stress induction (41, 42). A cotton swab was placed in the neonate’s mouth for a collection time of 5 min. Samples were placed in saliva collection tubes (Salivette, Sarstedt, Nümbrecht, Germany) and stored frozen at −20°C until further analysis.

We used the amylase 4,6-ethylidene-p-nitrophenyl-α-D-maltolheptaoside method from Roche Diagnostics (Mannheim, Germany) for the measurement of α-amylase concentrations in saliva. The diluted saliva samples (1 + 9) were analyzed with integra system 800. The assays showed good performance characteristics (intra-assay coefficients of variation of <1.0% and interassay coefficients of variation of ±1.3% at concentrations of 79.9 and 198 U/l).

All statistical analyses were performed with STATA 9 statistics/data analysis software (Stata, College Station, TX) according to Altman’s and Matthews et al.’ recommendations (3, 36). Baseline characteristics of SGA and AGA infants were compared using the Mann-Whitney test and χ²-test when appropriate. Since HRV parameters were not normally distributed as analyzed by the Shapiro-Wilk test, we compared SGA and AGA values using the Mann-Whitney test. A stepwise multiple regression was conducted to analyze the impact of gender, gestational age, birth weight independent of gestational age, and mode of delivery (spontaneous vaginal, operative vaginal, and cesarean section). α-Amylase data were log transformed to normalize the distribution. The difference between α-amylase baseline levels and the time point of “5 min post” was calculated, and differences revealed no deviation from a normal distribution (P = 0.49, Shapiro-Francia W-test). A paired Student’s t-test for unequal samples was used to analyze alterations of log-transformed data between study groups. The Mann-Whitney test was used for the comparison of raw baseline α-amylase levels. Stepwise multiple regression was applied to test for putative influencing factors of α-amylase values such as gestational age, birth weight independent of gestational age, mode of delivery (spontaneous vaginal, operative vaginal, and cesarean section), and gender. The level of statistical significance of all analyses was set at P < 0.05.

RESULTS

HRV

Median birth weight of SGA infants was 2,210 g, corresponding to the 1.0st weight percentile, compared with 3,170 g, corresponding to the 53rd percentile in AGA infants. The median gestational age in both groups was comparable (261 vs. 270 days, P = 0.27). A summary of study population characteristics is shown in Table 1.

Time-domain parameters as an estimate of overall HRV, such as SDNN and the triangular index, were not significantly shown to differ between groups. The α-amylase concentration of SGA infants was 1.3% lower than that of AGA infants, corresponding to the 98th percentile. A summary of newborn data is shown in Table 2.

Table 1. Infant basic characteristics for heart rate variability measurements

<table>
<thead>
<tr>
<th>Gestational age, days</th>
<th>AGA</th>
<th>SGA</th>
<th>P Value</th>
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<tbody>
<tr>
<td>270 (239–293)</td>
<td>261 (240–283)</td>
<td>0.272</td>
<td></td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>3,170 (2,000–3,830)</td>
<td>2,210 (1,340–2,760)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight percentile</td>
<td>54.8 (15.2–82.6)</td>
<td>1.0 (0.1–4.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>7/20</td>
<td>12/15</td>
<td>0.154</td>
</tr>
</tbody>
</table>

Values are medians with ranges in parentheses; n = 27 Apple appropriate for gestational age (AGA) neonates and 27 small for gestational age (SGA) neonates.
different in SGA neonates compared with AGA neonates ($P = 0.14$ and $P = 0.29$, respectively). The same was found for parameters mostly influenced by sympathetic activity, such as SDANN and SDNNi ($P = 0.34$ and $P = 0.22$, respectively). Again, parameters mostly influenced by the vagal tone, such as r-MSSD ($P = 0.99$) as well as the proportion of pairs of adjacent NN intervals differing by $> 50$, $> 27$, and $> 20$ ms ($P = 0.93$, $P = 0.98$, and $P = 0.91$, respectively), revealed no significant differences between SGA and AGA neonates (Table 3). Analysis of all frequency-domain parameters again revealed no significant differences in SGA infants. Thus, HF, representing vagal activity ($P = 0.82$), LF, representing both sympathetic and vagal activity ($P = 0.82$), VLF ($P = 0.05$), ULF ($P = 0.06$), total power ($P = 0.06$), and LF/HF, representing sympathovagal balance ($P = 0.62$), were comparable in SGA and AGA infants (Table 3). LF/HF similarly decreased with advancing gestational age in both SGA and AGA infants (not shown). To test for a putative influence of gestational age, gender, birth weight independent of gestational age, and mode of delivery on HRV parameters, a stepwise multiple regression was conducted, revealing an influence of gestational age ($P = 0.02$) and gender ($P = 0.02$) but not of birth weight ($P = 0.95$) or mode of delivery ($P = 0.34$) for LF/HF. For other time- and frequency-domain parameters, only gestational age remained as an influencing factor, but not gender.

**Infant α-Amylase Levels**

The median birth weight of SGA children was 2,265 g, corresponding to the 1.6th weight percentile, compared with 3,425 g, corresponding to the 48.2th percentile in AGA children. A summary of the characteristics of the study population is shown in Table 2.

Medians for baseline α-amylase levels were slightly lower but not significantly different in SGA neonates compared with AGA neonates ($P = 0.13$; Fig. 1). After the application of the stress stimulus, α-amylase levels both slightly increased in AGA and SGA neonates at the time point of “5 min post,” not revealing statistically significant differences ($P = 0.3$; Fig. 2).

To control for an influence of mode of delivery, gender, gestational age, and birth weight independent of gestational age, a stepwise multiple regression was performed, revealing no significant influence ($P = 0.81$, $P = 0.16$, $P = 0.22$, and $P = 0.47$, respectively).

**DISCUSSION**

We have shown that indicators of cardiac autonomic nervous activity, such as HRV, are preserved in SGA neonates and that the stress-induced α-amylase response is not significantly altered. Thus, our results suggest normal sympathoadrenergic cardiovascular activity in SGA neonates.

<table>
<thead>
<tr>
<th>Table 3. Time- and frequency-domain heart rate variability parameters in AGA and SGA infants</th>
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<tr>
<td><strong>Heart rate, beats/min</strong></td>
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<td>---------------------------</td>
</tr>
<tr>
<td>Median</td>
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<td>Minimum</td>
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<td>Maximum</td>
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$s$-NN50, ratio of the number of all pairs of adjacent NN intervals differing by $> 50$ ms and the total number of RR intervals; $s$-NN27, ratio of the number of all pairs of adjacent NN intervals differing by $> 27$ ms and the total number of RR intervals; $s$-NN20, ratio of the number of all pairs of adjacent NN intervals differing by $> 20$ ms and the total number of RR intervals; SDNN, SD of all valid NN interval; SDNNi, average of the hourly means of SDs of all NN intervals; r-MSSD, average of the hourly square root of the mean of the sum of the squares of differences between adjacent NN intervals; SDANN, SD of the average of valid NN intervals; HF, high frequency; LF, low frequency; VLF, very LF; ULF, ultra LF.
There is evidence from animal studies that an unfavorable prenatal environment may alter the sympathetic autonomic system balance, which seems to persist into postnatal life. As such, prenatal stress has been shown to result in increased basal and stimulated circulating catecholamine levels in adult rats (26, 61), and compromised intrauterine blood flow did result in a downregulation of epinephrine levels in sheep (1, 43, 51). Conversely, chronic prenatal hypoxia has been shown to be associated with sympathetic hyperinnervation (48, 49). Thus, chronic intrauterine hypoxemia may suppress the adrenaline synthetic capacity of the adrenal medulla (37, 43, 51), whereas increased circulating norepinephrine concentrations seem to derive from hyperinnervated sympathetic nerve terminals of fetal vessels and tissues (37).

More specifically for the cardiovascular system, growth-restricted newborn rats displayed significantly increased basal cardiac sympathetic neuronal activity, as determined by [3H]norepinephrine tracer and α-methyltyrosine techniques (51). In the same species, intrauterine exposure to exogenous steroid levels produced persistent abnormalities of cardiac noradrenergic innervation (8).

In the human, Flanagan et al. (18) found an inverse relationship between adult resting pulse rate as an index related to sympathetic activity and birth weight. Recently, markers of impaired fetal growth were related to autonomic cardiovascular control in adults involving modulation of both sympathetic and parasympathetic function. Accordingly, blood pressure, HR, its spectrum analysis, and baroreflex sensitivity in response to psychological stress were found to be altered in low-birth-weight women but not in men of an Australian prospective cohort study (28, 59). Cardiac sympathetic nerve activity as analyzed by cardiac preejection period and respiratory sinus arrhythmia has been shown to be increased in adolescents born growth restricted (24). In contrast, inconsistent results on muscle vascular bed sympathetic nerve traffic have been reported in low-birth-weight adults (9, 62).

HRV is a well-established noninvasive measure of cardiac autonomic control that has been shown to be related to hypertension (22, 29) and to predict future adverse cardiovascular events in adults (2) and has been suggested for putative prognostic use in children (54). While blood pressure as a cardiovascular risk factor has been shown to be inversely related to birth weight in adults, to our knowledge, a systematic analysis of HRV parameters according to standardized methods (55) so far has not been performed in adults with low birth weight. Alterations of HRV in adults, however, may not necessarily represent a prenatal initiated event according to the concept of fetal programming considering the close interaction with other neuroendocrine systems such as the hypothalamic-pituitary-adrenal (HPA) axis (8).

We did not find significant alterations of HRV parameters in SGA neonates. These findings are consistent with the study of Mehta et al. (39), who found no significant correlation between various HRV parameters and birth weight in a population of 96 healthy newborns, although these authors may not have applied appropriate frequency bands for the frequency-domain analyses (19). In contrast, a small study by Spassov et al. (52) described significantly decreased HRV parameters in term SGA newborns during sleep at 2–10 days of postnatal life and found significantly shorter NN intervals in SGA neonates, which we did not observe despite similar SGA criteria. The reason for these differing results is not clear but may be explained by the small sample size and the different experimental setting of that study. Indeed, it has been shown that HR increases steeply after the 5th day of life with a maximum on the 10th day, indicating distinct changes in cardiovascular control (40). Therefore, it cannot be excluded that group differences in postnatal age may have had an important influence on these results. Furthermore, single HRV parameters could not be compared directly since long-term recordings for time- and frequency-domain parameters were calculated in our study as opposed to the short-term frequency-domain recordings in the study of Spassov et al. (52). Nevertheless, these parameters seem to correlate well (39, 55). Galland et al. (20) did not observe significant differences in NN intervals in SGA infants, confirming our data. They found an increased resting sympathetic tone using Poincaré plot data analysis, however, lying at the limits of significance (P = 0.046) only after controlling for HR at 1 and 3 mo of age and attributed these findings to an immaturity of the autonomic nervous system. Studies on functional central nervous system maturation in SGA infants, however, have revealed conflicting results (4, 27, 44). There is evidence that HRV correlates with birth weight in 11- to 12-wk-old infants but not in younger infants (35). These data suggest alterations of the cardiac autonomic nervous system rather beyond the neonatal period. Therefore, one tends to speculate that the cardiac autonomic nervous system rather appears to be vulnerable during the postnatal development due to conditions induced by putative permanently altered regulatory systems such as the HPA axis (46) and influence of postnatal catchup growth (35). In support of this notion, it has been shown in human fetuses that antenatal glucocorticoids transiently lower short- and long-term fetal HRV (14). Alternatively, we cannot exclude that prenatal induced alterations are too small to detect in the neonatal period and only become apparent with increasing system maturation postnatally. Even more, different methods thought to represent cardiac autonomic activity may have different selectivity for sympathetic system subunits (25), and different methods of stress induction may produce different results (28).

Statistical analysis of our HRV parameters revealed three frequency-domain parameters (total power, VLF, and ULF) to be close to the level of statistical significance (Table 3). These
parameters are closely connected as VLF and ULF components correspond to up to 95% of the total power. Putative reductions in total power as an estimate for autonomic nervous system global activity and VLF might indicate a decrease in parasympathetic modulation. The physiological correlate of VLF and ULF, however, is not truly well established (55). Therefore, although a false negative result cannot be completely excluded for these parameters and a definitive conclusion may not be drawn due to a relatively small sample size, all remaining frequency- and time-domain parameters did not suggest statistical significant differences of HRV in SGA neonates.

Direct comparison of these components with results from the literature is rather difficult due to different experimental settings and HRV calculations; however, Galland et al. (20) reported a higher resting sympathetic tone analyzing 23 SGA infants using a Poincaré method for standard deviation of the beat intervals (SDRR) and the standard deviation of the change between successive beat intervals (SDΔRR). However, only the SDRR/SDΔRR ratio reached the limit of statistical significance (P = 0.046), whereas the remaining parameters were not statistically different. In the study of Spassov et al. (52), short-term HRV with different frequency bands in 10 SGA infants were analyzed; however, not all frequency parameters (LF) reached statistical difference, and HR was significantly increased in SGA neonates, potentially contributing to these findings. In contrast, Galland et al.’s and our analysis did not observe increased HR in SGA neonates.

There is evidence that autonomic cardiovascular control and size at birth may be gender specific. Accordingly, adult low-birth-weight women showed altered autonomic and baroreflex parameters in response to psychological stressors, but not men (28, 60). In our study, which conducted a stepwise multiple regression, we found an influence of gender when analyzing the entire data only for LF/HF but not for the remaining time and frequency domains, making a gender effect at this time of development rather questionable. However, gender was unequally distributed between groups, and subgroups were comparatively small; therefore, a definitive conclusion may not be drawn. It is possible, however, that gender-specific hormonal influences may manifest during adolescence and adulthood in SGA infants.

To supplement our electrophysiological findings with a neuroendocrinological approach, we analyzed salivary α-amylase levels during resting conditions and after a stressful stimulus. Acan cells in the salivary glands are richly innervated by both sympathetic and parasympathetic nerve fibers, influencing the release of salivary α-amylase by classic neurotransmitters (56). Studies in humans and animals have suggested that the activation of the autonomic nervous system leads to a high activity of salivary α-amylase (6, 11, 50, 53). Furthermore, α-amylase levels have been found to be associated with cardiovascular autonomic system balance (21). Bosch et al. (10) found a significant negative correlation between the parasympathetically-influenced HRV parameter r-MSSD and α-amylase levels during stress induction in adults. Furthermore, a positive correlation between α-amylase levels and LF/HF as a surrogate for sympathetic tone has been shown (41), thereby making this parameter a promising indicator for cardiac autonomic function.

To our knowledge, α-amylase levels in SGA neonates have not been studied before. Although studies on cardiovascular autonomic physiology using α-amylase measurements have not been validated in neonates, several analyses from children support the strong relationship between salivary α-amylase and sympathetic/parasympathetic nervous system activation in younger individuals (21). The comparable α-amylase levels during resting conditions in AGA and SGA neonates in our study and the absence of significant differences in response to stress induction support the notion that the sympathetic autonomic cardiovascular system seems not to be permanently altered postnatally regarding the fetal origin hypothesis. The sympathetic nervous system, however, is composed of multiple function-specific subunits (25), and programming of sympathetic nervous system function is believed to occur regionally rather than on a global basis, suggesting that subdivisions of the sympathetic nervous system may be influenced by different sets of environmental variables (64). Therefore, we cannot exclude that other subunits of the sympathetic nervous system may be permanently altered in SGA neonates. Furthermore, with regard to HRV techniques as well as α-amylase measurements, although in general use as research tools for the assessment of cardiac autonomic activity, it is not entirely clear to what degree they truly represent autonomic activity in neonates.

In conclusion, HRV and salivary α-amylase levels, as indicators of cardiac autonomic activity, are not altered in SGA neonates compared with AGA neonates. Thus, the neonatal sympathovagal balance appears to be preserved in SGA neonates.

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