Heart rate variability and cardiac reflexes in small for gestational age infants

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Galland, Barbara C., Barry J. Taylor, David P. G. Bolton, and Rachel M. Sayers. Heart rate variability and cardiac reflexes in small for gestational age infants. J Appl Physiol 100: 933–939, 2006. First published November 23, 2005; doi:10.1152/japplphysiol.01275.2005.—To assess the influence of intrauterine growth retardation and postnatal development on heart rate variability (HRV) and cardiac reflexes, we studied 27 healthy small for gestational age (SGA) and 23 appropriate for gestational age (AGA) infants during a nap study. Resting HRV was assessed by point dispersion of Poincaré plots for overall (SDRR) and instantaneous beat-to-beat variability (SDΔRR) and the ratio (SDRR/SDΔRR). Heart rate reflex and arousal responses to a 60° head-up tilt were determined. All tests/measures were repeated twice in quiet and active sleep and in prone and supine sleep positions at 1 and 3 mo of age. SGA infants exhibited higher resting sympathetic tone [SDRR/SDΔRR: 1.9 (95% confidence interval: 1.7, 2.0) and 1.7 (95% confidence interval: 1.5, 1.8) in SGA and AGA, respectively; P = 0.046] and a tendency for a smaller tachycardic reflex response to the tilt [1 heartbeat: 24 beats/min (95% confidence interval: 20, 28) and 30 (95% confidence interval: 25, 34)] in SGA and AGA, respectively; P = 0.06]. HRV indexes were reduced in the prone compared with supine position (P < 0.0001), but reflex tilt responses were unchanged with position. SGA/AGA differences were independent of sleep position. Gestational age weight status did not influence the likelihood of arousal, but prone sleeping per se reduced the odds 2.5-fold. The findings suggest reduced autonomic activity and cardiac reflexes in SGA infants. The finding that the sympathetic component of the control of HRV was higher in SGA infants could link with findings in adulthood of an association between being born SGA and a higher risk of cardiovascular disease.

Heart rate variability; intrauterine growth retardation; prone position; sudden infant death syndrome; supine position; tilting; small gestational age

INDIVIDUALS BORN WITH SMALL WEIGHT for gestational age (SGA) with intrauterine growth retardation are at higher risk of perinatal morbidity/mortality (40, 56) and sudden infant death syndrome (SIDS) (7, 42, 54) and have poor neurological outcomes (41) compared with infants whose weight is average for gestational age (AGA). The strong association between prone sleeping position and SIDS is elevated among SGA infants (42), and of concern is the report that very low birth weight (<1,500 g) is a strong predictor of prone sleep positioning 1 mo after hospital discharge (55). The etiology of SIDS is unknown, but autonomic failure in cardiorespiratory control and in arousal are regarded as likely scenarios for the infant faced with life-threatening challenges that may occur in their sleeping environment.

SGA is associated with increased insulin resistance in children (26) and increased long-term cardiovascular morbidity and mortality (5). Postnatal “catch-up growth” reverses some of the lost ground of intrauterine growth retardation but is positively correlated with high risk of cardiovascular mortality in adulthood. The mechanism may be sympathetic hyperactivity, a known risk factor for cardiovascular disease that can be seen in the muscular vascular beds in young adults born SGA (8). Even at 11–12 wk of infant age, the sympathetic component of heart rate (HR) control is higher in infants who have experienced postnatal catch-up growth as in SGA (36).

SGA is the result of a large variety of clinical conditions. Generally, infants will have experienced intrauterine growth retardation because of adverse fetal, maternal, or environmental events. However, some SGA may be due to short maternal stature, leading to a newborn of small size but following a regular growth pattern in utero. Most studies concerned with small babies do not separate low birth weight from prematurity. This has resulted in difficulties of knowing whether any differences noted there are due to prematurity, growth restriction, or both. Earlier, our laboratory (19) studied term AGA infants and reported findings of reduced autonomic activity in these infants sleeping in the prone position compared with supine. The objectives of the present study were to quantify autonomic activity of term SGA infants through measures of HR variability (HRV) and reflex HR and arousal responses to experimental upright tilting. We tested the hypothesis that SGA infants sleeping prone would be further compromised in this position in terms of their autonomic activity compared with their AGA counterparts.

METHODS

Study groups. Twenty-seven AGA and 23 SGA infants were studied longitudinally around 1 mo (mean ± SD: 3.1 ± 1.6 wk) and 3 mo of age (12.4 ± 1.8 wk). A summary of infant group characteristics is given in Table 1. AGA infants were selected on the basis of being >37 wk of gestation, weighing over 2,500 g, and >25th percentile weight for gestational age, and SGA infants were <10th percentile weight for gestational age and >37 wk of gestation. There were no twins in the study. All infants were recruited from the postnatal wards of the local maternity hospital. Exclusion criteria included living outside the Dunedin area, prenatal or postnatal complications, maternal smoking, and illness or on medication at the time of study. Nonsmoking status was ascertained by questionnaire and maternal salivary cotinine analyses. Idiopathic intrauterine growth retardation was predominant in SGA infants (n = 19; 83%); the remaining four were born to mothers with pregnancy-induced hypertension. The study protocol was approved by the Otago Ethics Committee, Dunedin, New Zealand. Informed, written consent was obtained from the parent(s) of all infants before study.

Infant setup. The nap studies took place after the infants were fed and between the hours of 9 AM and 1 PM and were conducted in a dimly lit nursery with a quiet temperature-controlled atmosphere between 20 and 23°C. Infants were set up with ECG electrodes placed...
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RESULTS

Table 1 shows that the AGA and SGA infants were comparable in regard to age at time of studies and gender mix, but SGA infants were of younger gestational age with smaller head circumference and crown-heel length, weight at birth and at time of studies, and fewer were exclusively/predominantly breast fed. As assessed by least squares means, the weight of SGA babies was lower than AGA babies at each time point by 996 g [95% confidence interval (CI): 80, 1,187] at birth, 808 g (CI: 568, 1,048) at 1 mo, and 757 g (CI: 330, 1,184) at 3 mo, indicating significant SGA catch-up growth (P = 0.029).

Nonsmoking status of the mothers was confirmed from maternal salivary cotinine analyzed by Canterbury Health Laboratories using mass spectral detection (accuracy to 2 g/l); median cotinine levels of 0 ng/ml were obtained from mothers of AGA and SGA infants at the 1- and 3-mo studies.

Baseline HR. Table 2 shows the average baseline HR during the HRV recording and the dependent variables of gestational status, age, sleep state, and sleep position. HR was significantly slower in older aged infants, was faster in AS compared with QS, and was faster when infants were sleeping prone as opposed to supine, but there was no difference between SGA and AGA infants. A significant interaction was found for age with sleep position such that the prone-supine difference was greater in older infants (P = 0.001).

HRV. Table 2 also shows the main effects for HRV variables SDRR and SD\(R^2\)R with and without HR controlled in the model. Without HR controlled for, both SDRR and SD\(R^2\)R were significantly different between AGA and SGA infants. P value* indicates that the P value was controlled for HR.

Table 2. Heart rate variability measures

<table>
<thead>
<tr>
<th>GA status</th>
<th>HR, beats/min</th>
<th>R-R Interval, ms</th>
<th>SDRR, ms</th>
<th>SD(R^2)R, ms</th>
<th>SDRR-to-SD(R^2)R Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGA</td>
<td>135 (131, 139)</td>
<td>447 (434, 454)</td>
<td>20.5 (17.8, 23.3)</td>
<td>12.4 (10.7, 15.0)</td>
<td>1.7 (1.5, 1.8)</td>
</tr>
<tr>
<td>SGA</td>
<td>133 (130, 137)</td>
<td>453 (442, 464)</td>
<td>19.4 (17.3, 21.7)</td>
<td>10.7 (9.1, 12.7)</td>
<td>1.9 (1.7, 2.0)</td>
</tr>
<tr>
<td>P value</td>
<td>0.49</td>
<td>0.47</td>
<td>0.53</td>
<td>0.28</td>
<td>0.12</td>
</tr>
<tr>
<td>P value*</td>
<td></td>
<td></td>
<td>0.18</td>
<td>0.06</td>
<td>0.046</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mo</td>
<td>140 (137, 142)</td>
<td>432 (423, 440)</td>
<td>17.7 (16.1, 19.3)</td>
<td>9.1 (7.9, 10.3)</td>
<td>2.0 (1.8, 2.1)</td>
</tr>
<tr>
<td>3 mo</td>
<td>129 (126, 131)</td>
<td>469 (460, 478)</td>
<td>22.5 (19.9, 23.8)</td>
<td>14.7 (12.8, 16.8)</td>
<td>1.6 (1.5, 1.7)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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<td>&lt;0.0001</td>
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<tr>
<td>P value*</td>
<td></td>
<td></td>
<td>0.79</td>
<td>0.0002</td>
<td>0.001</td>
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<tr>
<td>Sleep state</td>
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<td></td>
</tr>
<tr>
<td>Quiet</td>
<td>132 (130, 135)</td>
<td>457 (448, 465)</td>
<td>15.3 (14.0, 16.8)</td>
<td>10.9 (9.5, 12.4)</td>
<td>1.4 (1.3, 1.5)</td>
</tr>
<tr>
<td>Active</td>
<td>136 (133, 138)</td>
<td>444 (435, 452)</td>
<td>25.9 (23.6, 28.4)</td>
<td>12.2 (10.8, 13.9)</td>
<td>2.2 (2.0, 2.3)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P value*</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sleep position</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Supine</td>
<td>133 (130, 135)</td>
<td>455 (446, 463)</td>
<td>21.8 (19.9, 23.8)</td>
<td>12.9 (11.3, 14.6)</td>
<td>1.7 (1.6, 1.8)</td>
</tr>
<tr>
<td>Prone</td>
<td>135 (133, 138)</td>
<td>446 (435, 454)</td>
<td>18.2 (16.5, 19.9)</td>
<td>10.3 (9.0, 11.6)</td>
<td>1.8 (1.7, 1.9)</td>
</tr>
<tr>
<td>P value</td>
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<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.016</td>
</tr>
<tr>
<td>P value*</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Values are means, with 95% confidence interval in parentheses. All reduced model effects controlled for feeding type. GA, gestational age; HR, heart rate; SDRR, SD of the beat intervals; SD\(R^2\)R, SD of the change between successive beat intervals. *Controlled for HR.

Fig. 2. Example of a HR and R-R interval trace in quiet sleep derived from the ECG during a tilt maneuver. In this example, the baseline HR averaged over 30 s was 113 beats/min (bpm). Tachycardia (maximum HR within 20–30 beats of the tilt) was 125 bpm followed by a rebound bradycardia (minimum HR within the next 25 beats) of 97 bpm. R-R intervals were used to obtain the ratio measure bradycardia (maximum R-R interval)/tachycardia (minimum R-R interval), which in this example was 1.28 (618/480 ms).
increased significantly in older infants and in AS compared with QS, decreased significantly when infants slept prone as opposed to supine, and remained unchanged between SGA and AGA infants. Significant interactions were found for age with sleep position (the prone-supine difference for SDRR and AGA infants. Significant interactions were found for age with opposed to supine, and remained unchanged between SGA and AGA infants.

The magnitude of the reflex response as described by the ratio measure (degree to which the bradycardia exceeds the tachycardia) was smaller in SGA infants (1.21 vs. 1.28). The ratio measure was significantly larger in older than younger infants, predominantly as a result of significantly enhanced tachycardia. AS, compared with QS, enhanced both the tachycardic and bradycardic response, with no change in the ratio measure. There was no significant effect of sleep position on any of the tilt variables under study. There were no significant interactions.

Arousal. The arousal response grades to the tilt were transformed into binary variables for analyses. Thus codes 0 and 0.5 were coded into one variable indicative of no movement at all or startle in response to tilt (but remained asleep), and codes 1.0 to 2.0 coded into another variable indicative of gross movement and/or being woken to the test. Because a startle raises HR, combining codes 0 and 0.5 together as one variable for analyses would have been problematic if fewer or more startles (code 0.5) were represented in the data. Therefore, the arousal responses falling into these individual categories were not significantly different overall or for gestational age status, age, sleep state, or sleep position. Codes 0 to 0.5 resulted in significantly (P = 0.002) less tachycardia (23.6%; CI: 20.4, 26.7) than codes 1 to 2 (30.9%; CI: 26.6, 35.2), but no difference in the arousal response was evident from the rebound bradycardia measure.

Table 4 shows that SGA infants were not significantly more likely to wake to the test than AGA infants, nor were older infants compared with younger infants, but a trend in this direction was evident. Waking, however, was significantly more likely in AS than QS (P < 0.0001). The prone sleep position opposed to supine significantly (P = 0.025) decreased the likelihood of waking by 2.5-fold [univariate odds ratio for waking in the prone position was 0.4 (CI: 0.17, 0.94)].

**DISCUSSION**

The findings that term SGA infants with no maternal smoking history have reduced HRV and HR reflex responses at 1
and 3 mo of age suggests immaturity of autonomic cardiovascular control and component reflexes compared with their term AGA counterparts. Similarly, reduction of HRV and poor arousal responses in the prone sleep position support the view that sleep position can alter autonomic control (18–20, 45). However, the finding that sleep position did not interact with SGA suggests that the SIDS postnatal risk factor of sleeping prone in relation to lowered autonomic responsiveness is independent of the prenatal risk factor of being born SGA. SIDS has been independently associated with prone sleeping position and intraternal growth retardation (42).

As in our laboratory’s previous study (21), we found no difference in baseline HR between SGA and AGA infants, although a study by Spassov et al. (50) reported HR to be higher in newborn SGA infants. Their below 3rd percentile cutoff compared with ours at the 10th percentile resulted in a higher in newborn SGA infants. Their below 3rd percentile cutoff compared with ours at the 10th percentile resulted in a higher HR (1). Unfortunately, although a study by Spassov et al. (50) reported HR to be higher in newborn SGA compared with AGA infants, although we are unaware of any studies that have linked bottle feeding to depressed autonomic activity through HR or HR-derived measures, it has been implied through findings of depressed arousal responses involving activation of the autonomic nervous system (27).

The finding that HR reflex responses to the tilt-test stimulus were reduced is also indicative of a less mature or compromised autonomic nervous system and means, under normal circumstances, that SGA infants may not respond as readily to blood pressure challenges during sleep. Although the tilt test may be considered an artificial stimulus to apply during horizontal sleep, sudden drops in blood pressure may be a very real hazard, supported by published respiratory recordings of infants who died of SIDS showing a progressive bradycardia with continued breathing movements (36), suggesting maintenance of circulatory control may be a crucial factor in survival.

It was expected that the ability of the SGA infants to arouse from the cardiovascular provocation would be impaired in light of the fact that a poorer cardiovascular reflex response was elicited. However, SGA infants demonstrated equally as good behavioral waking responses as AGA infants. The only other comparable study is of SGA/AGA newborn twin sets, where SGA infants showed a trend for more spontaneous startles than AGA infants and a higher incidence of vigorous limb movements (44). Those findings suggest a higher state of alertness in newborn SGA compared with AGA infants that was not apparent in our infants studied at 1 and 3 mo of age. Studies where functional maturation of CNS control in SGA has been tested in relation to brain stem auditory-evoked responses produce conflicting findings where both advanced development (43) and a subtle degree of central neural dysfunction (28, 29) associated with small head size (28) have been reported. SGA infants compared with AGA infants do not differ with respect to resting respiratory rate (21, 12), sleep-state organization (11), or sleep-state cycling (44). The present study would also suggest that SGA infants do not differ in regard to resting HRV, and HR reflexes discriminated across sleep state and maturing age.

Maturation of the autonomic nervous system through HRV measures and HR reflex responses to the tilt were evident over the 1- and 3-mo age range. Many other studies have demonstrated maturation of the autonomic nervous system through measures of HRV and HR responses to provocation showing a higher variability as the infant matures (19, 35, 38, 46). Similarly, in healthy children and adolescents, there is a pro-

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Table 4. Number of tilt tests that resulted in subjects waking (arousal codes 1 to 2)

<table>
<thead>
<tr>
<th>Factor</th>
<th>N, %</th>
<th>Univariate OR†</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGA</td>
<td>59 (28)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>SGA</td>
<td>64 (31)</td>
<td>1.18</td>
<td>0.56, 2.47</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mo</td>
<td>83 (28)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>40 (33)</td>
<td>1.15</td>
<td>0.59, 2.21</td>
</tr>
<tr>
<td>Sleep state</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QS</td>
<td>10 (5)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>AS</td>
<td>113 (51)</td>
<td>18.8</td>
<td>8.6, 41.3</td>
</tr>
<tr>
<td>Position</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>74 (36)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Prone</td>
<td>49 (24)</td>
<td>0.4</td>
<td>0.17, 0.94</td>
</tr>
</tbody>
</table>

Values are means (SD). The model controlled for feeding type. *Values represent raw data. †Estimated values from mixed-model analyses, taking into account repeated measures. OR, odds ratio.
gressive decrease in HR and increase in overall HRV reflecting progressive development of the autonomic nervous system with age (48). The HRV increase with age noted here was attributed, to a large extent, to the baseline HR itself since once baseline HR was controlled for, the age effect, although still significant, was considerably reduced.

Head-up tilting has been a classical tool to test for maturation of baroreflex activity in infancy as reviewed by Gootman and Gootman (22). Limitations are that the test is concerned with short-term regulation of arterial BP only, involves provocation, and risks ending the study period of sleep by fully waking the infant. Although we were able to obtain information on maturation of the HR reflex response, recent more advanced technology has been recommended to overcome these limitations where spontaneous oscillations in beat-to-beat blood pressure concomitant with HR have been used to test maturation of baroreflex sensitivity (13). This approach allows the dynamics of the system to be studied noninvasively, and the technique has been used to test maturation of baroreflex sensitivity in term and preterm infants (23).

Sleep-state differences in HRV using time or frequency domain measures have been reported in many studies where rapid eye movement or AS is associated with more variability than non-rapid eye movement or QS. AS tends to have a sympathetic predominance (2) borne out in the HRV results from this study and represents a time of heightened arousal. The odds of waking to the tilt test were increased almost 19-fold compared with QS. HRV has a close relationship with sleep stages and the sleep cycle, and there is even some suggestion that the changes in HRV may precede electroencephalogram arousal for at least 10 beats (9), forming the basis for research into activities of the different physiological systems in the sequence of sleep transition from state to state.

Maternal smoking during pregnancy as a confounder was eliminated because, where heavy smoking in combination with intrauterine growth restriction are apparent, there are indications for suppression of autonomic activity in utero and beyond through measures of resting HR (49), HRV (17, 49), HR and BP responses to stress stimuli (10, 53), and arousal responses to external stressors (17). In studies of SGA vs. AGA infants, it is rare to find that maternal smoking has been eliminated.

Our findings suggesting less mature autonomic responses in SGA infants have implications for SIDS, but our evidence for higher sympathetic tone in SGA infants suggest the mechanism(s) that engender long-term metabolic and cardiovascular disturbances that develop later in life, such as increased percentage of body fat mass (32), Type 2 diabetes (4), higher systolic BP (51), and increased cardiovascular mortality (5).

Autonomic responsiveness is reduced in many of these conditions (31, 37, 39), and although our findings do not allow us to speculate SGA/AGA differences beyond the 3-mo age period, studies concerned with this form of autonomic testing could consider SGA as an early source of compromise. Massin et al. (35), in a large study of 546 healthy infants aged 5–12 wk, demonstrated among other things a significant positive correlation between HRV indexes and postnatal weight gain that was mostly influenced by sympathetic activity at 11–12 wk. Their work also supports other evidence that there might be a link between impaired growth in fetal and infant life to high blood pressure and other cardiovascular disease in later life (the Barker hypothesis) (5).

In summary, this research found that healthy SGA infants exhibited less mature autonomic activity compared with AGA infants that potentially could increase their vulnerability to SIDS. However, sleeping SGA infants prone as opposed to supine did not add further to this vulnerability. This could be due to an independent association between prone sleeping and SGA. Of importance also was the finding that the sympathetic component of the control of HR variability was higher in SGA infants at 1 and 3 mo of age. This suggests an encoding influence on autonomic control early in life, which could link with an association between being born SGA and a greater risk of high blood pressure and other cardiovascular disease in adulthood, particularly where postnatal catch-up growth is evident. Further longitudinal studies need to be carried out to determine cause and effect.

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GRANTS

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REFERENCES

HEART RATE VARIABILITY IN SGA INFANTS


