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# Heart Rate and Heart Rate Variability during Sleep in Small-for-Gestational Age Newborns

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**ABSTRACT. To assess the influence of intrauterine growth retardation on heart rate (HR) and HR variability during sleep, we performed polygraphic recordings in 10 small-for-gestational age (SGA) and 16 appropriate-for-gestational age (AGA) newborns. Both groups were clinically and neurologically normal and were at 37 to 41 wk conceptional age. RR intervals were analyzed using the short-time Fourier transform in three frequency bands: *1*) high frequency, with a period 3–8 heartbeat; *2*) mid frequency, with a period 10–25 heartbeat; and *3*) low frequency, with a period 30–100 heartbeat. In both active and quiet sleep, SGA newborns significantly differed from AGA newborns by having a shorter RR interval ($p < 0.01$) and lower amplitude of HR variability in all bands ($p < 0.05$) except low frequency in quiet sleep. Quiet sleep differed from active sleep by having a longer RR interval ($p < 0.05$), higher high-frequency variability ($p < 0.02$) in both SGA and AGA newborns, and lower low-frequency variability ($p < 0.005$ for AGA newborns). Our data give evidence of clear modifications of both sympathetic and parasympathetic HR control in the at-risk SGA population. Similarity of between-state characteristics suggests maintained CNS control of HR in SGA as well as in AGA newborns. We speculate that between-group HR and HR variability differences may be related to augmented metabolic rate in SGA compared with AGA newborns. (*Pediatr Res* 35: 500–505, 1994)**

### Abbreviations

**AGA, appropriate-for-gestational age**
**ANS, autonomic nervous system**
**AS, active sleep**
**hb, heartbeat**
**HR, heart rate**
**HRV, heart rate variability**
**HF, high frequency**
**IUGR, intrauterine growth retardation**
**LF, low frequency**
**MF, mid frequency**
**QS, quiet sleep**
**REM, rapid eye movement**
**SGA, small-for-gestational age**

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SGA newborns are considered a risk group because of the higher incidence of neonatal complications (1) and higher morbidity during the first years of life, including augmented incidence of sudden infant death syndrome (2). In recent years, improved obstetric monitoring has led to a decrease in the birth rate of premature infants, but the percentage of SGA newborns remains unchanged [data in a French population (3)].

There is no consensus concerning the maturity of SGA infants born after IUGR. With different criteria for CNS maturation, they have been considered *1*) similar to normal AGA newborns according to EEG patterns (4), body motility (5), and sleep state organization (6); *2*) retarded according to muscle tone, general excitability (7), and auditory responsivity (8); or *3*) advanced according to neurologic development (9). SGA newborns also are known to have accelerated lung maturation and a lower incidence of hyaline membrane disease (10). However, to our knowledge, there are no data in the literature concerning HRV in different frequency bands in healthy SGA newborns.

HR and HRV have been reported to be closely dependent on the ANS control: short-term (or HF) variability is related to parasympathetic vagal activity, whereas long-term (or LF) variability depends on both sympathetic and parasympathetic branches of the ANS (11, 12). In healthy newborns, HF HRV is higher in QS than in AS, whereas the LF HRV is higher in AS than in QS (13–16). HRV has been used to discriminate sleep states (14, 16) and to discriminate premature newborns from full-term newborns (13).

Disturbance of HR patterns is associated with apparent life-threatening events and sudden infant death syndrome (17, 18).

The aim of the present prospective study was to evaluate HR and HRV in different frequency bands in SGA newborns (never before studied in this at risk group of infants) and to compare them with HR and HRV in AGA newborns.

## MATERIAL AND METHODS

*Subjects.* We studied 26 healthy full-term newborns at 2 to 10 d of postnatal life (conceptional age 37–41 wk): 16 were AGA and 10 SGA. Conceptional age of the infants was defined as gestational age plus postnatal age at the day of the recording.

Mean birth weight was 3142 g (SD 432 g, range 2285–3910 g) in AGA newborns and 1978 g (SD 243 g, range 1550–2340 g) in SGA newborns; birth weights were thus between the 10th and 75th percentiles for AGA newborns and under the 3rd percentile for SGA newborns according to the curves for a French population (19).

All infants had *1*) normal clinical and neurologic examinations (20), *2*) normal EEG patterns for conceptional age (4), and *3*) polygraphic results without cardiac or respiratory abnormalities. Pregnancies were carefully followed in all cases, each infant's Apgar score was at least 9 at 5 min of life, and no infant was receiving drug therapy (except mineral or vitamin supplements) between birth and the date of the recording.

SGA infants included only those with idiopathic IUGR (five cases) or born to mothers with mild pregnancy-induced arterial hypertension (five cases) with diastolic pressure less than 100 mm Hg. Three of the hypertensive mothers received $\alpha$-methyldopa (known to have a 10- to 20-h plasma half-life in newborns) and two received labetalol (known to be rapidly cleared) (21). Infants born to mothers who were heavy smokers (more then 10 cigarettes/d) or mothers with diabetes mellitus, chronic illness other than mild hypertension, or chronic intoxication (alcohol, drugs, *etc.*), as well as those with a documented infection or congenital abnormality, were not included in the study. To avoid any possible drug effect in infants of mothers who were treated for arterial hypertension or received medication during delivery (21), the recordings were performed after 2 d postnatal age.

All studies were performed after approval of the hospital ethical committee. Parental consent was obtained after detailed explanations of the recording methods and the aim of the study had been given.

*Polygraphic recordings.* Simultaneous paper and analog magnetic tape polygraphic recordings were performed in the sleep laboratory, close to the maternity department, after a morning meal (between 0900 and 1300 h). All infants were normally dressed and lying supine in a room temperature of 25–26°C. The recordings included EEG, REM, ECG (a bipolar chest lead), chin electromyogram, surface electromyography of the diaphragm, nasal and oral airflow, thoracic and abdominal respiratory movements, and upper and lower limb movements. Recordings were performed during spontaneous sleep and lasted until spontaneous awakening of the infant.

*Sleep-state coding.* Sleep states were coded on paper tracings, as described by Curzi-Dascalova and Peirano (6), according to the concordance between the EEG patterns (4) and the REM criteria (REM present in AS and absent in QS). Each infant had at least one complete sleep cycle, including both AS and QS.

*ECG processing.* ECG tape recordings were sampled off line at 286 Hz and processed by a signal-to-noise ratio algorithm to obtain RR interval series, which were then stored in 512-hb epochs (22). Artifacts were recognized by RR intervals above or below predefined thresholds and by large (>30%) differences from adjacent RR values. They were removed by replacing the actual values with the trend RR value in the region. Only epochs containing less than 10% artifacts before removal were processed. Each infant had at least one 512-hb epoch in QS and one in AS.

Each 512-hb epoch was processed by the short-time Fourier transform, a nonstationary spectral analysis procedure that provides "instantaneous" evaluation of spectral amplitude in a given frequency band (16, 22). We studied three frequency bands: *1*) HF (variations with the period ranging from 3 to 8 hb); *2*) MF (the period from 10 to 25 hb); and *3*) LF (the period from 30 to 100 hb), which have been previously described (16, 22).

Means per 512-hb epoch and means per infant for RR interval, HF, MF, and LF (16) are given in this report.

*Statistical analysis.* Because the distribution of data is not normal, statistical analyses include two levels. First, at the level of the population of babies, we computed means over each sleep state in every newborn for RR and each HRV variable. These means were used in the following nonparametric tests: *1*) the Spearman rank correlation test, which was used to study the influence of birth weight on HR and HRV variables and of HR on HRV variables; *2*) the Mann-Whitney *U* test, used to compare RR and HRV variables between SGA and AGA infants; and *3*) the Wilcoxon matched-pairs rank test, used for the comparison between QS and AS in both groups. These tests were performed on raw data and after correcting RR for birth weight (by dividing RR interval values by birth weight) and HRV variables for HR (by dividing HRV variables by RR interval). Then factor analyses were performed at the level of the population of all 512-hb epochs: normed principal component analysis and linear discriminant analysis were performed (13, 23).

## RESULTS

A total of 303 epochs of 512 hb were obtained as follows: *1*) 211 epochs (75 in QS and 136 in AS) were recorded in AGA newborns, and *2*) 92 epochs (38 in QS and 54 in AS) were recorded in SGA newborns. In SGA newborns, data obtained were similar in infants born to treated mothers and in those born to nontreated mothers. Table 1 presents means for RR interval, HF, MF, and LF in both AGA and SGA groups for both sleep states.

The analysis of the correlation between birth weight and RR and HRV variables, and between RR and HRV variables, showed no consistent tendencies. The hypothesis tests using data corrected for birth weight and HR did not change any statistical significance of the differences found. Thus, only results using raw, uncorrected data will be presented.

*Between-group comparison.* In both AS and QS, SGA newborns showed significantly different values for RR interval and HRV in the three frequency bands with the exception of LF in QS ($p = 0.07$) compared with AGA newborns (Fig. 1).

The contribution of each HRV variable to the total variance of the statistical cloud of means over 512-hb epochs in the three-dimensional (HF, MF, LF) space was examined by principal component analysis (Fig. 2). In both AS and QS, the first factor (on the $x$ axis) shows an equally weighted combination of all three HRV variables and explains 75.9% (in AS) and 66.6% (in QS) of the total variance of the statistical cloud. According to this factor, most epochs of the SGA newborns are placed on the left side of the center of gravity of the statistical cloud (the crossing point of the $x$ and $y$ axes), whereas AGA epochs are more randomly distributed. The equation given on the $x$ axis (which displays correlation coefficients of the first factor x, with HRV variables) shows that the first factor appears as a "group factor," depending on the sum of all three HRV variables. According to it, SGA newborns appear as a more consistent group than AGA newborns.

The possibility of discriminating between SGA and AGA newborns was evaluated by a linear discriminant analysis of the same data set. Data presented in Table 2 show that in both sleep states the percentages of correctly classified epochs were higher for SGA epochs (84.2% in QS and 83.3% in AS) compared with AGA epochs. The correlation coefficients of the discriminant linear functions with HRV variables, presented in this table, all vary in the same direction; they all are strongly correlated with the discriminant function. This means that the whole HRV (of both sympathetic and parasympathetic origin) is involved in this discrimination.

*Between-sleep-state comparison.* SGA and AGA newborns showed qualitatively similar between-sleep-state differences for all the variables studied (Fig. 3). In both groups, QS was contrasted from AS by longer RR interval, higher amplitude of HF variability, and smaller amplitude of LF variability. However, the degree of significance for between-sleep-state differences was lower in SGA than in AGA newborns.

Principal component analysis showed a distinction between QS and AS epochs in both AGA and SGA newborns almost entirely in the y direction (y is factor 2, Fig. 4). Thus, this factor can be considered a "state factor." It explains only 21.4% (in SGA newborns) and 30.8% (in AGA newborns) of the total variance. The equation of the $y$ axis represents opposing effects of HF and LF in both groups with a negligible coefficient for MF.

Table 1. *Means and SD of RR intervals and HF, MF, and LF HRV in AGA and SGA newborns in QS and AS*

| Group | State | RR (ms) | HF (ms) | MF (ms) | LF (ms) |
|---|---|---|---|---|---|
| AGA (n = 16) | QS | 498.0 (35.2) | 16.2 (6.4) | 16.0 (5.3) | 18.4 (6.9) |
| | AS | 471.9 (29.9) | 10.8 (2.4) | 17.5 (4.7) | 23.1 (6.1) |
| SGA (n = 10) | QS | 440.5 (36.3) | 11.7 (6.6) | 11.4 (4.4) | 13.6 (4.5) |
| | AS | 424.7 (27.7) | 8.7 (3.4) | 11.5 (3.3) | 15.6 (3.0) |

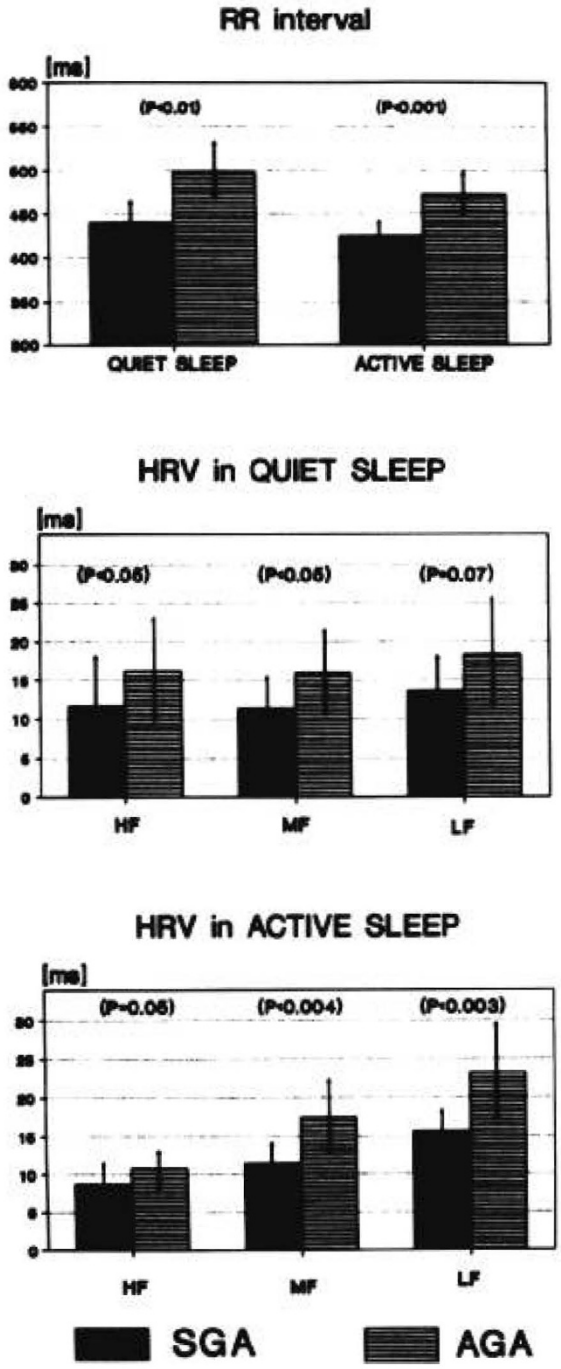


Fig. 1. Comparison between SGA and AGA infants in both sleep states for RR interval in QS and AS (*top*): HF, MF, and LF in QS (*middle*); and HF, MF, and LF in AS (*bottom*). Degree of significance is shown in parentheses. *Black bars* are SGA infants, *dashed bars* are AGA infants, and *vertical lines* indicate SD.

Linear discriminant analysis (Table 3) showed a similar discrimination between sleep states in SGA and AGA newborns. In both groups, the percentage of well-classified epochs in AS was higher than the percentage of well-classified epochs in QS. Because the correlation coefficient with the discriminant function varied in opposite directions for HF and LF, one may suggest that between-state discrimination is based on the opposition HF *versus* LF HRV, *i.e.* on the opposition between sympathetic (higher in AS) and parasympathetic (higher in QS) tones.

Thus, despite higher HR and lower amplitude of HRV in SGA than in AGA newborns, HRV allows a comparable degree of sleep state discrimination in both groups.

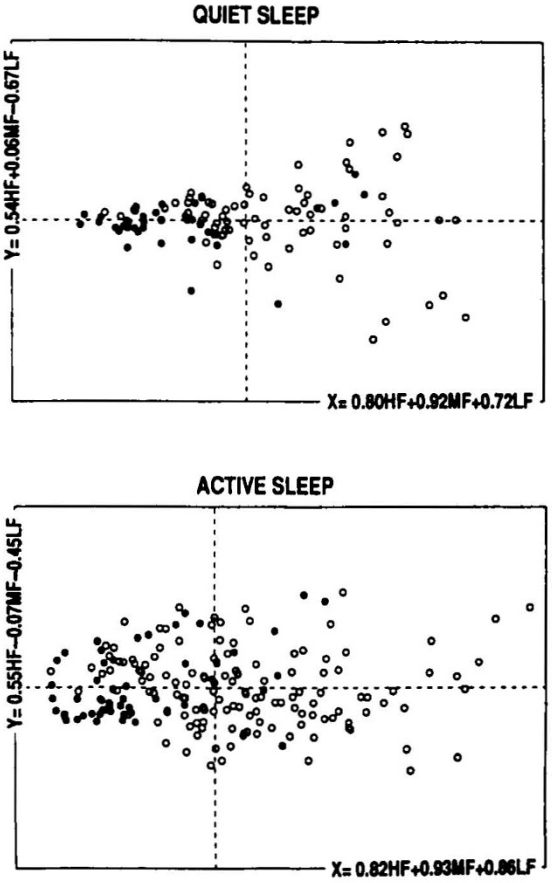


Fig. 2. Principal component analysis according to HF, MF, and LF variability in QS (*top*) and AS (*bottom*). All 512-hb epochs belonging to SGA (*filled circles*) and AGA newborns (*open circles*) are projected onto the principal factor plane (x, y). The equation coefficients represent the weights of variables in the definition of the factors x and y. Note that most of the SGA epochs are on the left side of the figure (see text for details).

Table 2. *Discrimination between AGA and SGA groups of newborns in QS and AS, according to HF, MF, and LF HRV (analysis based on all 512-hb epochs)*

| State | Group | Number of epochs analyzed | Percentage of correctly classified epochs | Correlation coefficient of DLF with HRV variables* |
|---|---|---|---|---|
| QS | AGA | 75 | 61.3 | +0.824 (HF)<br>+0.969 (MF) |
| | SGA | 38 | 84.2 | +0.529 (LF) |
| AS | AGA | 136 | 71.3 | +0.743 (HF)<br>+0.970 (MF) |
| | SGA | 54 | 83.3 | +0.859 (LF) |

* DLF, discriminant linear function.

## DISCUSSION

Our data demonstrate that, with respect to HR and HRV, SGA newborns are different from AGA newborns. In both QS and AS, SGA newborns showed a shorter RR interval and a lower amplitude of the HRV in all three frequency bands than AGA newborns.

Data concerning HR control in SGA newborns are rare. In the study of Watanabe *et al.* (24), five of the low-birth-weight infants were SGA. However, the data reported for these infants were only for HR, and SGA infants were excluded from subse-

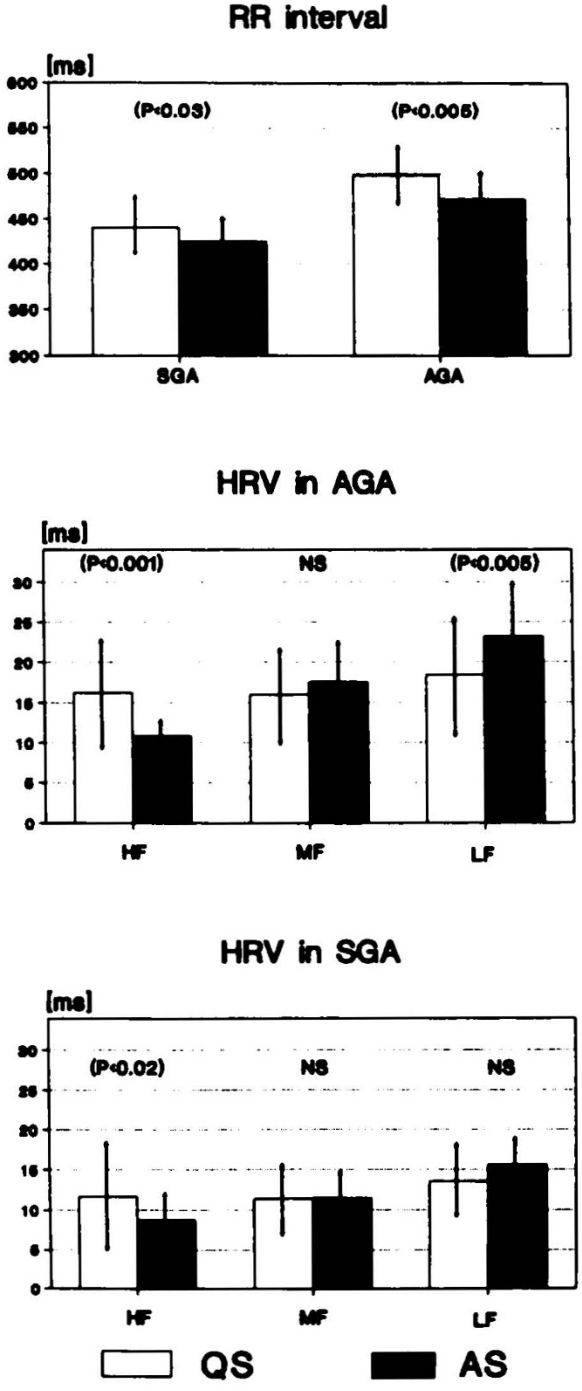


Fig. 3. Between-sleep-state comparison of the means per infant of RR interval (*top*); HF, MF, and LF HRV in AGA newborns (*middle*); and HF, MF, and LF HRV in SGA newborns (*bottom*). *White bars* are QS, *black bars* are AS, and *vertical lines* indicate SD.

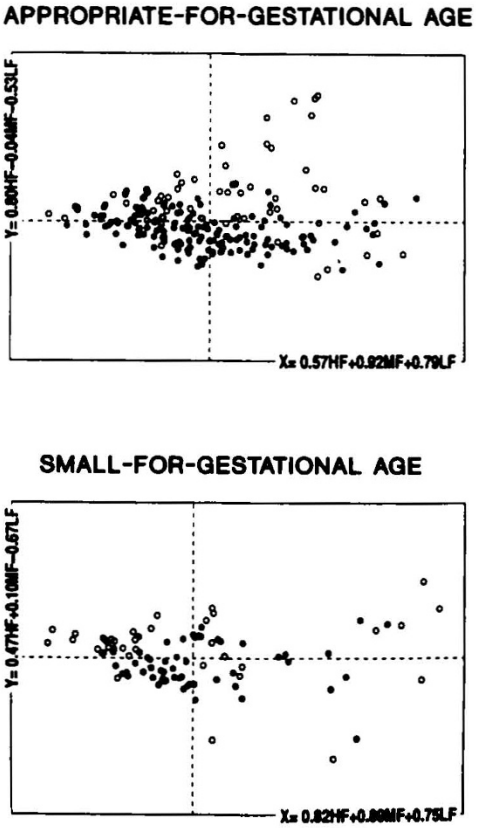


Fig. 4. Principal component analysis in relation to sleep states in AGA (*top*) and SGA newborns (*bottom*). *Filled circles* are AS, *open circles* are QS (see Fig. 2 and text for details).

Table 3. *Discrimination between sleep states (QS vs AS) in AGA and SGA newbowns according to HF, MF, and LF*

| Group | State | Number of epochs analyzed | Percentage of correctly classified epochs | Correlation coefficients of DLF with HRV variables* |
|---|---|---|---|---|
| AGA | QS | 75 | 66.7 | +0.809 (HF)<br>−0.197 (MF) |
| | AS | 136 | 81.6 | −0.379 (LF) |
| SGA | QS | 38 | 65.8 | +0.543 (HF)<br>−0.259 (MF) |
| | AS | 54 | 77.8 | −0.351 (LF) |

* DLF, discriminant linear function.

quent analyses. Van Ravenswaaij-Arts *et al.* (25) investigated four premature, 30- to 31-wk chronologic age SGA infants. There is no information on the neurologic status of these infants. They had faster HR compared with age-matched AGA premature infants. Furthermore, data on HRV and between-state differences are given only for AGA and not for SGA premature infants.

Differences in HR and HRV observed in SGA newborns, when compared with AGA newborns, give evidence of significant modification of both sympathetic and parasympathetic ANS control. These modifications can be related to *1*) modifications in the maturation of the CNS structures involved in cardiac control; *2*) metabolic rate modifications; and *3*) a possible influence of residual drug effects of maternal therapy on HR and HRV that was excluded *a priori* because, in our study, all recordings were made after 2 d postnatal age (21, 26). In addition, RR interval and HRV variables in SGA infants born to treated mothers were similar to those in SGA infants born to nontreated mothers.

Data from the literature on animal models of IUGR have shown that the brain is the organ least affected by nutrient restriction (27, 28). In humans, Larroche and Korn (29) described normal brain development in newborns with IUGR as far as weight, gross configuration, cytoarchitecture, and myelination are considered.

Data from the literature on functional maturation of CNS control in SGA newborns are controversial. Arguments for advanced development have been reported by Amiel-Tison (9), on the basis of neurologic examination, and by Pettigrew *et al.* (30), on the basis of brainstem auditory evoked potentials. Some other

data on brainstem auditory evoked response suggest a delay in brainstem maturation in SGA newborns (18, 31). Finally, data on respiratory rate in QS (32), motor activity (5), and sleep state organization (6) showed that SGA newborns do not differ from AGA newborns.

Our data, showing similar between-sleep-state differences in HR and HRV for AGA and SGA newborns, are consistent with the thesis suggesting similarity of CNS control in SGA and AGA newborns.

An increase of HR is known to be related to an augmented metabolic rate. SGA newborns have a higher metabolic rate than AGA newborns during both wakefulness and sleep (33). SGA newborns also manifest higher oxygen consumption in AS than in QS, as observed in AGA newborns (33–35). These data support the hypothesis that there is a metabolic origin for the differences in HR observed in our study between SGA and AGA newborns.

According to the literature, the relationship between HR and HRV is still controversial. Harper *et al.* (14) found a negative correlation between HR and respiratory sinus arrhythmia. Baldzer *et al.* (36) described a decrease in total HRV when HR decreased. Correlations between RR interval and amplitude of HRV in the three frequency bands showed inconsistent tendencies and did not offer convincing arguments for the lower amplitude of HF, MF, and LF variability in SGA newborns by the shorter RR intervals in this group. Thus, the lower amplitude of HRV in SGA newborns seems to be a specific characteristic of these infants rather than determined by faster HR.

Finally, our data do not answer the question of whether SGA newborns are advanced or delayed compared with AGA newborns. Values for RR and HRV variables obtained in SGA newborns are close to those described in premature infants (16, 37, 38). Recent data from Peirano and Monod (39) demonstrate persistent HR pattern modification in SGA infants at 13 wk postnatal age. This could support the hypothesis of immaturity of the ANS in SGA infants. However, at the same time, 1-mo-old infants are reported to have higher HR (13) and lower HRV (40) compared with 1-wk-old newborns. Data obtained from 1-mo-old infants are similar to our data from SGA newborns, which could support the opposite hypothesis of an advance in ANS maturation in SGA newborns.

In conclusion, SGA newborns differ from AGA newborns by higher HR and lower HRV. Because of similar between-sleep-state differences of HR and HRV in SGA and AGA newborns, our data do not support the idea of a modification in CNS control of heart rhythm in SGA newborns. It may be possible that differences observed between the two groups of newborns are related to an augmented metabolic rate in SGA newborns. Higher HR and lower amplitude of HRV may be suspected as risk factors for SGA infants. Similar diminished HRV in different frequency bands has also been shown in sudden infant death syndrome victims (17, 18). Further investigation of HR and HR reactivity to stimulation and changes in environmental conditions may offer information concerning the underlying mechanisms that determine higher vulnerability in this at-risk population.

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# Announcement

## VII International Congress of Pediatric Dermatology

The VII International Congress of Pediatric Dermatology will be held in Buenos Aires, Argentina, from September 26th to October 1st, 1994. The main themes will be Atopic Dermatitis, Nutritional Disorders, AIDS, and Genodermatoses. *For further information, please contact* Dr. Adrián Pierini, President, VII International Congress of Pediatric Dermatology, Arenales 1446 Ap. 1 B, (1061) Buenos Aires, Argentina, phone (54.1) 814-4068, fax (54.1) 812-9255.