Development and Maturation of the Autonomic Nervous System in Premature and Full-Term Infants Using Spectral Analysis of Heart Rate Fluctuations

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ABSTRACT

The changes in the power spectra of heart rate (HR) fluctuations, in particular the total power (within 0.02–2.0 Hz) and the power in the low- (0.02–0.2 Hz) and high- (0.2–2.0 Hz) frequency ranges, were computed from the ECG and respiratory signals of 59 premature and full-term infants. The objective of the study was to investigate the development and maturation of the autonomic nervous system from the first day of extrauterine life to several weeks of postnatal age. The study population was divided into four age groups. Group A: seven 1-d-old premature infants with gestational age of 34–35 wk. Group B: 28 premature infants 7–49 d old with a conceptional age of 34–35 wk. Group C: seven 1-d-old full-term infants of 39–41 wk gestation. Group D: six premature infants 35–97 d old with a conceptional age of 39–40 wk. Mean HR ($\pm$ SEM) of groups C and D combined, *i.e.* 135 ± 2 bpm, was significantly lower compared with groups A and B, *i.e.* 152 ± 2 ($p < 0.01$). The mean ($\pm$ SEM) of the low- to high-frequency power ratio obtained from the HR power spectrum decreased progressively from 71 ± 31 in group A to 34 ± 8 in group B, 16 ± 3 in group C, and 17 ± 2 in group D. The mean low to high ratio for the combined groups C and D, 17 ± 1 , was significantly lower compared with the combined group A and B, *i.e.* 44 ± 9 ($p < 0.01$). The respiratory signals showed two types of breathing patterns: a single peak in the respiratory spectrum centered around the respiratory frequency (mature type,

typically found in adults); and a second type showing two separate peaks, one centered around the respiratory frequency and the other at the much lower breath amplitude modulation frequency. In both respiratory modes, the HR power spectrum usually showed a dispersed, wide pattern of the power in the high-frequency range. The progressive decline in mean HR and in low- to high-power ratio indicates a decrease in sympathovagal balance with gestational and postnatal age. This maturation might be associated with a gradual focusing into a single respiratory peak, both in the respiratory and the HR power spectrum. (*Pediatr Res* 37: 294–302, 1995)

Abbreviations

GA, gestational age
PA, postnatal age
CA, conceptional age (CA = GA + PA)
LFB, low-frequency band (0.02–0.2 Hz)
HFB, high-frequency band (0.2–2 Hz)
HR, heart rate
HRV, heart rate variability
ANS, autonomic nervous system
RSA, respiratory sinus arrhythmia
BASA, breath amplitude sinus arrhythmia

HRV is affected by numerous factors including blood pressure, temperature, respiration, biochemical influence of acid-base balance, state of oxygenation, ventilation, and psychologic parameters. It is a reflection of the cardiovascular control exerted by the ANS and a direct result of ANS functioning.

Using spectral analysis to investigate the frequency content of HR fluctuations, it has been shown that short-term fluctua-

tions are concentrated in two principal frequency ranges (1–5). The high-frequency peak (HFB, above 0.2 Hz) is centered around the respiratory frequency and shifts with changes in the respiratory rate (1, 3–5). The LFB of the power spectrum (below 0.2 Hz) is composed of two not always distinct contributions (6, 7). It contains the mid-frequency fluctuations between 0.09 and 0.15 Hz, corresponding to what are sometimes called Mayer waves, which have been related to the baroreceptor reflex (7). The other peak at the low-frequency end of the spectrum occurs typically within the 0.02–0.09 Hz range and has been ascribed to thermoregulatory fluctuations and variations in vasomotor tone (6). The HFB reflects parasym-

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pathetic activity, whereas the LFB is influenced by combined sympathetic and parasympathetic control (1). Their ratio is thus a reflection of the sympathovagal balance (8).

Previous animal research (9) suggests that the spectral approach may provide a description of the neurologic development, in particular certain aspects of autonomic function such as the sympathetic to parasympathetic balance. Assali *et al.* (10) studied the autonomic control of cardiovascular functions in a sheep model and followed the varying of maturation rates of both the sympathetic and parasympathetic systems. They found that the sympathetic nervous system matures earlier in fetal life than does parasympathetic control, whereas the cholinergic and adrenergic tones exerted on the resting HR at term are nearly balanced. This study also showed a pronounced increase of the parasympathetic tone after birth, whereas the adrenergic tone becomes less prevailing than in the fetus. Baldzer *et al.* (11) studied a group of full-term neonates using this spectral approach and found that a difference in breathing pattern affects the HRV.

The aims of our work are 1) to study the changes in the HR power spectrum and the contributions of HRV to the various relevant frequency ranges in preterm and full-term infants from the first day of extrauterine life to several weeks PA to obtain information about autonomic maturation and, in particular, about sympathetic to parasympathetic balance; and 2) to study the mode of respiration observed in premature and full-term infants and its impinging effect on HRV.

The broad objectives of this investigation were to establish normative data for neonatal HRV, to determine the usefulness of spectral analysis as an aid to perinatal care, and to learn more about the development and maturation of the autonomic nervous system in newborns.

METHODS

Subjects. The study included 72 infants investigated during the period June 1988 to November 1990. The infants were recorded during 20-min epochs. Some of them were followed and recorded during several such recording sessions, taken weeks apart as they matured.

All infants were healthy, requiring no oxygen administration and no medications except for xanthine therapy for apnea of prematurity in some subjects. Those who received xanthine showed a normal blood level of 7–12 mg/L. All had fewer than three episodes of apnea in a period of 24 h, all of which resolved spontaneously. Their head ultrasonogram did not demonstrate any intraventricular hemorrhage.

The recordings started at least 24 h after birth, when the newborns had completed adaptation to extrauterine life successfully. The ECG and respiration recordings were performed in the neonatal intensive care unit and in the regular nursery using ECG electrodes attached in the standard three-lead manner. The full-term infants remained in their own cribs, whereas the premature infants' recordings were made in their incubators, which were adjusted to provide skin or air temperature according to standard criteria. Only those recordings made when the infants were either sleeping or awake but quiet were included in the analysis. No attempt was made to distinguish

active from quiet sleep. Informed parental consent was obtained for each infant before the recording.

ECG recording and HR spectral analysis. The ECG was measured with a Mennen Medical 740 neonatal monitor (Mennen Medical Ltd., Science Park, Rehovot, Israel). The analog ECG signals were recorded on a Hewlett-Packard 3968A FM magnetic tape recorder (Hewlett-Packard Co., Palo Alto, CA) at a tape speed of $1\frac{5}{16}$ inch per second.

Spectral analysis of fluctuations in HR was performed off-line on 256-s-long stationary segments of the ECG. These segments were sampled at a frequency of 500 Hz and analyzed using a PDP 11–23 minicomputer (Digital) with an analog to digital converter. The R-waves were detected, and the values of RR intervals were saved. The number of RR intervals within a time window of 0.5-s width were used to provide a low pass-filtered series of instantaneous HR values, sampled at equal time intervals according to a previously described algorithm. A smooth time series of instantaneous HR sampled at frequency $f = 4$ Hz was thus created. Stationarity of these HR traces was established by subdividing the traces into four subtraces and assessing that the mean HR value and the variance of the HR fluctuations computed for each subtrace were not significantly different.

Next, the HR power spectrum was estimated based on the computation of a fast Fourier transform of the HR time series. This approach was chosen because relatively long (256 s) and steady traces are considered (2). The power spectrum was smoothed with a five-point Hanning window and normalized by mean HR squared (1). The HR power spectrum thus obtained is presented in units of Hz^{-1} , and the integrals over specific frequency bands are thus unitless (1).

Frequency ranges of interest. Neonates exhibit HRV fluctuations in a wide range of frequencies as shown in a typical power spectrum (Fig. 1). We investigated the entire bandwidth up to 2 Hz except for the very low (0–0.02 Hz) band, which was discarded to avoid the possible contribution of slow trend artifacts. The examined 0.02–2.0 Hz range was divided into several frequency bands, the main divisions being the LFB (0.02–0.2 Hz) and the HFB (0.2–2.0 Hz).

The HFB contains primarily the reflection of the respiratory activity (1, 3–5). The LFB includes at least two contributions (1, 3–8), the thermoregulatory fluctuations tone (below 0.09 Hz) and the baroreceptor control fluctuations (typically occurring between 0.09 and 0.15 Hz). The LFB also possibly may contain fluctuations due to breath amplitude modulation (12).

Respiratory data analysis. Whenever available for research, a Mennen Medical 744 neonatal monitor was used, also providing us with a respiratory recording. In those cases that allow examination of both HR and respiration, both signals were recorded and digitized simultaneously.

The respiratory signal was sampled at 4 Hz, after analog low-pass filtering. The respiratory power spectrum, computed similarly to the HR signal, provided the exact frequency limits of the respiratory frequency band, which did not exceed the upper limit of 50–60 breaths per minute. The power spectra of both HR and respiratory signals were used to ascertain whether common frequency patterns occur in these signals.

Figure 1. A, An example of a typical HR time series for a newborn (group D, number 43). B, Corresponding power spectrum (in units of 1/Hz) of HR fluctuations, displaying regions of power both in the HFB (0.2–2.0 Hz) and in the LFB (0.02–0.2 Hz).

Statistical analysis. Differences between the mean values for the various age groups were analyzed by the *t* test; $p < 0.05$ was accepted as statistically significant. Linear regression was performed to achieve a linear fit and find the coefficient relating the low to high ratio as well as the HFB power to the postnatal age.

RESULTS

Age distribution of infants. From the 72 infants with 110 recording sessions, 59 infants with 85 recordings were analyzed and included in the study. Twenty-five recording sessions of 13 infants were excluded for bad quality signals with many artifacts that did not allow adequate analysis.

Clinical data for the investigated population are shown in Table 1. During the analysis of the recordings, the population was grouped according to GA and PA (Table 2): group A: seven preterm infants, GA 34–35 wk, recorded 24 h after birth; group B: Twenty-eight preterm infants born at 27–34 wk GA with a PA of 1–7 wk for a CA (CA = GA + PA) similar to that of group A (33–35 wk); group C: Seven full-term infants, GA 39–41 wk, recorded 24 h after birth; and group D: Six preterm

Table 1. Clinical data

GA (wk)	No. in group	Birth weight mean (g)	Birth weight SD (g)	Mean Apgar score
26	3	695	90	6
27	4	950	160	8.25
28	2	1280	170	7
29	3	1210	120	9
30	5	1290	110	8
31	6	1337	105	8.3
32	4	1525	350	8.5
33	3	2023	377	7.7
34	11	1920	170	8.7
35	6	1950	126	8
36	5	2190	575	8.5
39	1	4100	0	9
40	4	3400	76	9.25
41	2	3510	152	9

infants born at 27–34 wk GA with a PA of 5–14 wk for a CA similar to that of group C (39–41 wk).

An additional group of infants ($n = 11$) that did not belong to the four age groups were not included in the study. Their data are not displayed in Table 2; however, the data are available upon request.

Mean HR. First, we present the mean HR values because this is the most direct, basic, and well-accepted parameter that we can extract from our data. It is the first approximation of what can be learned from HR about the development of autonomic control in premature *versus* full-term babies. The results of the spectral analysis go one step further to a second-order approximation of what HR can teach us by focusing on its fluctuations.

Comparing the mean HR ($\pm$ SEM) among the age groups (Fig. 2, Table 2), we find the highest HR in group B with 156 ± 2 bpm followed by group D with an HR of 146 ± 7.5 bpm; both groups had a PA of more than 1 wk, and the 1-d-old neonates in groups A and C showed a lower mean HR of 133 ± 4 and 124 ± 4 bpm, respectively (Fig. 2). As shown in Figure 2, *t* test comparison of mean HR reveals a statistically

Figure 2. Mean HR of the four age groups and the combined age groups; their SEM are presented in Table 2. A significant difference ($p < 0.01$) is observed between groups A and B, groups C and D, and the combined groups AB and CD.

significant difference between groups A and B ($p < .001$) as well as between groups C and D ($p = 0.02$).

The combined mean HR ($\pm$ SEM) found for the combined group AB was 152 ± 2 bpm, significantly different from the CD group, which had 135 ± 2 bpm ($p < 0.01$).

The general conclusion is that HR decreases and thus vagal activity becomes more predominant with GA ($HR_{AB} > HR_{CD}$). Also, vagal control seems to develop better in the womb, as indicated by the comparison of mean HR within groups having the same CA in which HR is higher for higher postnatal ages ($HR_A < HR_B$ and $HR_C < HR_D$).

Neonatal variability. Two typical modes of neonatal HR power spectra are observed.

Figure 1A, is an example of a neonatal HR time series with Figure 1B showing the corresponding HR power spectrum. This spectrum is typical for one of the two main modes found in neonatal power spectra. In this mode we find a wide but clear respiratory peak. The high-frequency respiratory variations in HR are expressed by the peak centered at 0.8 Hz. The high-frequency power is not limited here to a narrow and sharp peak appearing in the HR power spectrum as has been found in adults, but rather it is a wider band of dispersive type spreading almost throughout the entire HFB. When considering the HR power spectrum from 256-s traces, it is rare to find in newborns, and particularly in premature neonates, a narrow, well-defined respiratory peak such as in adults; actually, in our study, none were found.

Figure 3A shows another example of an HR time series of 256 s. The instantaneous HR varies periodically with oscillations 10 and 20 s long. Figure 3B displays the corresponding power spectrum. As can be seen, there is not much power above 0.2 Hz in the HFB, which in adults usually displays the reflection of the respiratory activity. The LFB shows two typical peaks at 0.04 Hz and 0.11 Hz. The high-frequency range displays an undefined, wide, and very small respiratory peak that is not even apparent in the HR power spectrum.

Because the two recording sessions presented in Figures 1 and 3 were from the same infant at a time interval of 1 wk, a comparison between their spectra emphasizes the problem of nonuniformity and variability in neonatal HR power spectra.

Table 2 displays the spectral information for all subjects in the four age groups and emphasizes the considerable changes that may occur in the HR power spectrum in the different frequency bands when comparing subjects, both within and across the various groups. Considering the LFB (0.02–0.2 Hz), in which most of the power is concentrated for neonates, we find that the mean power for group C (full-term infants) is $0.33 \pm 0.1 \times 10^{-3}$ (mean $\pm$ SEM), displaying a very large variability within the group. A similar variability is found in the power in other spectral bands and in the total power, when comparing within the group. In Table 2, we thus showed, for each infant, the percentage column next to the absolute power in every band, representing the power in the specific band as a proportion of the total power. The mean percentage power in the LFB for group C is $93.4 \pm 1\%$ (mean $\pm$ SEM), presenting a much lower variability.

Group D, including preterm neonates at full-term CA, resembles group C. Although on an absolute scale group D has

Figure 3. A, An example of another HR time series for the same infant as in Figure 1A (group D, number 43). B, Corresponding power spectrum of HR fluctuations, displaying the main region of power to be in the LFB (0.02–0.2 Hz), where several peaks appear.

slightly more than twice the total power (compared with group C), the mean LFB percentage reaches $94.2 \pm 0.6\%$ (mean $\pm$ SEM). Again the SEM of the mean total power is very large, possibly hinting at the various modes of CNS activity through which the infant may switch.

This wide variability agrees with the large changes in power that also are found in the same infant during different recording sessions (Figs. 1B and 3B).

Age dependence or maturation. A clear dependence of neonatal autonomic control on CA, GA, or both is found in this study, as displayed by the changes in sympathovagal balance expressed by the ratio of LFB to HFB power. Table 2 gives the average low- to high-power ratio for each age group with the SEM.

Group A, which includes 1-d-old preterm infants with a GA of 34 and 35 wk, has an average ratio of 71 ± 31 (mean $\pm$ SEM). Group B, 33–35 wk CA with PA in the range of 1–7 wk, shows a mean low to high ratio of 34 ± 8 . Group C, full-term infants recorded 24 h after birth, presents a ratio of 16 ± 3 . The mean ratio for group C is obtained by omitting the two extreme ratios, marked “—” near their name in Table 2; a similar general trend was observed when including these two excluded infants. Group D, 39–41 wk CA, reaches a similar ratio of 17 ± 2 , although its average HR was higher than that for group C.

Table 2. Results of spectral analysis for all subjects and averaged over groups

Name	GA (wk)	PA (d)	CA (wk)	Mean HR	Total power	Low (0.02–0.2)	High (0.2–2)	Low to high ratio	0.05–0.09 Hz (%)	0.09–0.15 Hz (%)	Low (%)	High (%)
Group A												
1	34	1	34	143	0.150	0.111	0.039	2.9	35.9	17.2	74.0	26.0
2	34	1	34	150	0.008	0.008	0.000326	24.0	47.7	29.5	96.0	4.0
3	34	1	34	114	0.456	0.454	0.002	227.0	60.1	8.4	99.6	0.4
4	34	1	34	127	0.482	0.420	0.0614	6.8	41.1	12.3	87.3	12.7
5	35	1	35	133	0.914	0.482	0.4317	1.1	23.0	10.2	52.7	47.3
6	35	1	35	133	0.134	0.133	0.00153	86.9	55.6	23.9	98.9	1.1
7	35	1	35	133	0.624	0.620	0.0041	151.2	50.5	17.9	99.3	0.7
Mean	34.4	1	34	133	0.40	0.32	0.08	71.4	44.8	17.0	86.8	13.2
SEM	0.2	0.0	0.2	4.0	0.1	0.1	0.1	30.9	4.4	2.7	6.2	6.2
Group B												
8	34	7	35	149	0.210	0.208	0.0016	130.0	49.5	19.8	99.2	0.8
9	32	8	33	161	0.049	0.048	0.001	48.2	50.1	32.8	98.1	1.9
10	32	9	33	157	0.290	0.262	0.028	9.4	23.8	19.3	90.3	4.5
11	33	9	34	140	0.629	0.595	0.0345	17.2	38.4	23.6	94.5	5.5
12	34	9	35	158	0.167	0.150	0.017	8.8	23.4	9.6	89.8	5.4
13	32	10	33	157	0.157	0.097	0.0599	1.6	30.6	6.5	61.8	38.2
14	33	10	34	146	0.201	0.173	0.028	6.2	34.3	11.9	86.1	5.0
15	34	11	35	153	0.147	0.138	0.009	15.3	42.2	30.6	93.9	3.4
16	33	12	35	146	0.318	0.315	0.0028	112.5	52.2	26.6	99.1	0.9
17	31	13	33	149	0.783	0.679	0.104	6.5	21.8	18.4	86.7	6.9
18	32	14	34	154	0.160	0.158	0.00257	61.4	53.0	25.8	98.4	1.6
19	31	16	33	158	0.088	0.084	0.00336	25.1	54.2	16.4	96.2	3.8
20	31	18	34	148	0.246	0.242	0.00359	67.4	33.9	14.9	98.5	1.5
21	30	19	33	150	0.181	0.168	0.0131	12.8	48.5	15.8	92.8	7.2
22	32	21	35	161	0.738	0.706	0.03233	21.8	37.7	17.4	95.6	4.4
23	32	21	35	147	0.726	0.614	0.112	5.5	14.2	13.9	84.6	21.1
24	31	22	34	167	0.187	0.186	0.0012	154.8	49.3	16.8	99.4	0.6
25	31	23	34	166	0.188	0.181	0.0067	27.0	46.8	18.8	96.4	3.6
26	30	25	34	152	0.503	0.452	0.0508	8.9	39.7	24.4	89.9	10.1
27	30	25	34	153	0.446	0.196	0.25	0.8	15.9	10.8	43.9	43.0
28	31	25	35	148	0.727	0.705	0.0214	32.9	51.2	27.5	97.1	2.9
29	29	27	33	181	0.943	0.475	0.468	1.0	17.4	12.6	50.4	42.7
30	31	28	35	165	0.277	0.267	0.0104	25.7	43.7	23.1	96.2	3.8
31	31	28	35	153	2.030	1.639	0.3912	4.2	27.3	30.7	80.7	19.3
32	29	30	33	152	0.158	0.063	0.095	0.7	7.9	8.9	39.9	60.1
33	28	31	33	159	0.583	0.578	0.0041	141.1	64.7	9.7	99.3	0.7
34	30	32	35	177	0.556	0.307	0.2489	1.2	19.5	9.5	55.2	44.8
35	27	49	34	167	0.278	0.262	0.0163	16.1	50.0	19.8	94.1	5.9
Mean	31.2	19.7	34.0	156.2	0.43	0.36	0.07	34.4	37.2	18.4	86.0	12.5
SEM	0.3	1.8	0.2	1.8	0.07	0.06	0.02	8.4	2.8	1.4	3.3	3.1
Group C												
36	39	1	39	137	0.161	0.151	0.0102	14.8	37.5	15.6	93.7	6.3
37–	40	1	40	138	1.151	1.137	0.0148	76.8	50.2	24.6	98.7	1.3
38	40	1	40	121	0.106	0.102	0.00388	26.4	59.7	19.0	96.3	3.7
39	40	1	40	112	0.763	0.694	0.0684	10.1	30.5	28.9	91.0	9.0
40	40	1	40	134	0.172	0.164	0.00822	19.9	32.7	28.7	95.2	4.8
41	41	1	41	116	0.580	0.527	0.0525	10.0	33.4	26.2	90.9	9.1
42–	41	1	41	96	0.570	0.389	0.1809	2.2	35.9	16.2	68.3	31.7
Mean	40.0	1.0	40.0	124.0	0.36	0.33	0.03	16.3	38.8	23.7	93.4	6.6
SEM	0.3	0.0	0.3	4.4	0.12	0.11	0.01	2.8	4.8	2.4	1.0	1.0
Group D												
43–	34	35	39	150	0.297	0.147	0.15	1.0	23.0	10.0	49.5	50.5
44	34	42	40	169	0.114	0.108	0.0061	17.7	15.1	18.8	94.7	5.3
45	32	49	39	164	0.245	0.234	0.01104	21.2	48.0	19.8	95.5	4.5
46	27	94	39	137	0.918	0.839	0.0783	10.7	24.9	33.1	91.5	8.5
47	27	94	39	127	0.364	0.344	0.02	17.2	35.0	25.3	94.5	5.5
48	27	97	40	135	2.054	1.949	0.105	18.6	28.4	22.3	94.9	5.1
Mean	29.4	75.2	39.4	146.4	0.74	0.69	0.04	17.1	30.3	23.9	94.2	5.8
SEM	1.3	10.9	0.2	7.5	0.32	0.30	0.02	1.5	4.9	2.3	0.6	0.6

Combining age groups A and B (CA = 33 – 35 wk) and C and D (CA = 39 – 41 wk), the new mean values obtained for the low to high band ratio are 44 ± 9 for the AB group, whereas the ratio for the combined CD group is 17 ± 1 . Thus a significant $p < 0.01$ is achieved for the low to high ratio comparison between groups AB and CD. Figure 4A displays the trend observed in the form of a bar graph.

Taking the largest age group, B (CA = 33 – 35), and plotting (Fig. 4B) the low- to high-power ratio as a function of PA within the group, we obtain a statistically nonsignificant

Figure 4. A, Mean LFB to HFB power ratio for the four age groups and the combined age groups; their SEM are indicated in Table 2. Groups AB and CD display a significant difference ($p < 0.01$). B, Upper panel, The low to high ratio (linear scale) of group B preterm infants, displayed as a function of PA, together with its respective regression line. Lower panel, the HFB power spectrum (logarithmic scale) of group B preterm infants, displayed as a function of PA, together with its respective regression line.

negative coefficient (-0.57) for the linear fit (SEM = 1.08 and $r^2 = 0.01$). The second graph, shown in Figure 4B, displays the HFB power as a function of PA. The coefficient of this linear regression is 0.0063 (SEM = 0.0026, $r^2 = 0.18$, and $p < 0.05$), indicating a slight and gradual increase in the HFB or in parasympathetic activity as PA progresses. Note that the HFB power in Figure 4B is plotted on a logarithmic scale because of the wide range of values.

Respiratory influence on HRV. Important additional information was obtained from the respiratory signal when recorded with the ECG and analyzed simultaneously with HR. Inspecting the respiratory time series and respiratory power spectra, we found two main types: 1) a single peak in the spectrum centered around the respiratory frequency, and 2) two separate peaks, the first centered around the respiratory frequency (RSA) and the second around the frequency of the breath amplitude modulation (BASA) (12).

The first type seems similar to an adult (mature) respiratory power spectrum except for the tendency of the respiratory peak to be wider in neonates, especially in premature infants. Figure 5B shows such a single-peak respiratory spectrum. Figure 5A shows the corresponding HR power spectrum for this neonate: it displays a wide respiratory peak in the HFB. The corresponding respiratory spectrum (Fig. 5B) shows a fairly sharp peak at

Figure 5. A, An HR power spectrum displaying a wide respiratory peak of the dispersive type. B, Corresponding respiratory power spectrum displaying a sharp peak at approximately 0.5 Hz.

0.5–0.6 Hz, meaning that the dispersion of the peak observed in the HRV spectrum is not necessarily caused by an unstable respiratory rhythm.

The second type of respiratory power spectra found in our study, the two-peak type, is also the one we found most commonly in premature neonates. Inspecting Figure 6B, we can easily define two frequency bands that contain most of the power in the respiratory power spectrum. The corresponding respiratory time series is shown in Figure 6A. The lower frequency band of respiratory activity is associated with the breathing bursts (13), or amplitude oscillations, and the higher one with the main breathing rate. The burst frequency is approximately an unstable 0.07 Hz ($1/T$), and the respiration frequency is at 0.9 Hz, each with its own harmonics. The maximal peak in the respiratory power spectrum occurs at the respiration frequency (f). Other peaks occur at $f \pm (n/T)$, where n is an integer and T is the period of the breathing bursts, estimated at 10–15 s from Figure 6B. The peak at the lowest frequency occurs at $1/T$, in this case approximately 0.07 Hz. Many additional peaks occur at multiples of this frequency, in addition to the peaks centered around $f = 0.9$ Hz and occurring at 0.07-Hz intervals around f .

In both breathing modes, for all the neonates investigated in this study (breathing spontaneously), the HR fluctuations series (256 s long) displayed a dispersed pattern of high-frequency power. However, because we did not have respiratory recordings for all the neonates, we were unable to correlate between neonatal age and the occurrence of either of the respiratory modes.

Figure 6. A, A respiratory time series displaying breathing bursts. B, Corresponding respiratory power spectrum displaying power primarily at two frequencies: the amplitude oscillation frequency at 0.07 Hz and the respiratory rate at 0.9 Hz.

The power within the respiratory peak in HR power spectra in adults reflects the level of vagal tone, and its shape is usually a faithful replication of the respiratory peak in the respiration power spectrum. If respiration is regular, it appears as a narrow peak in the HR power spectrum; if it is irregular, it appears as a wide peak. What we observe in the neonates is that, even when the respiration is regular and the peak is narrow in the respiratory power spectrum, it may yet express itself in the HR power spectrum as a wide, dispersed respiratory peak. This could be one of the basic expressions of the difference between immature and mature autonomic control systems.

However, whatever the shape of the respiratory peak, its integral over the relevant frequency band in the HR power spectra still reflects the vagal tone. In particular, if the mean respiratory rate remains similar and only the width varies, then the value of the HFB integral still reflects the amount of vagal activity or maturation of vagal control.

DISCUSSION

During the last decade there has been an increasing interest in the beat-by-beat variation of HR generated by the ANS. Studies investigating the spectral content of HRV power in adults indicated the influence and interaction of three primary physiologic oscillations arising from respiration, blood pressure control or baroreceptor activity, and the vasomotor activity associated with temperature regulation (3–8). Although data from either preterm or full-term neonates are available, there still are many open questions regarding normal patterns for the HRV power spectrum (12–14). Total HRV power and its distribution as a function of frequency, as well as its evolution with neonatal maturation, require further investigation and have thus been approached in recent studies (11–13).

Dykes *et al.* (12) studied HRV and respiration in full-term infants and defined three spectral bands: 0–0.02 Hz, 0.02–0.2 Hz, and 0.2–2.0 Hz. Our results confirm the adequacy of this band definition for neonatal HRV spectral analysis. In our study we discard the very low frequency band, 0–0.02 Hz, to avoid possible inclusion of slow drift artifacts. The LFB, 0.02–0.2 Hz, was subdivided into several narrow subranges, some of which are presented in Table 2.

The power distribution of HRV within the different frequency bands discloses two main features: first, the power spectra of HRV in neonates display considerable variation both within a given subject and across the population; and secondly, the ratio of the power in the LFB to that in the HFB seems to decrease with GA and thus in correlation with ANS maturation in infancy. The power ratio of these frequency bands has been assumed to reflect the sympathovagal balance (8).

Assuming that both increasing GA and increasing PA are accompanied by maturation of the newborn and its ANS, we observed a decrease in the values of the low- to high-power ratio with maturation. Figure 4A displays the mean value of the low to high ratios taken from Table 2, showing a decreasing trend as a function of GA and PA. Comparing the mean low to high ratio of group A (24 h after birth) with group B (1–7 wk PA), both 33–35 wk CA, we notice a decline from a high ratio of 71 to a lower ratio of 34 as PA increases. This comparison

was found to be statistically nonsignificant primarily because of the large SEM within the groups. Figure 4B shows a similar trend found within group B in the decreasing low to high ratio (as well as increasing high-frequency power and thus increasing parasympathetic predominance) as a function of PA.

Another comparison can be made between the combined CD group (CA = 39–41 wk) and AB group (CA = 33–35 wk). Here we observed a significant ($p < 0.01$) decrease in both the low to high ratio and the mean HR as CA advanced. This result, again, probably reflects a developmental, relative increase in the parasympathetic contribution to HR control. This decrease in low to high ratio as a function of CA (Fig. 4A) is contributed by both the GA (comparing groups A and C) and the PA (comparing groups A and B). These findings agree with previous reports showing that vagal tone increases as GA increases (15, 16). Our results are also consistent with studies on neonatal lambs (9, 10), which showed predominance of sympathetic over the parasympathetic activity in the fetus and in prematurity (if computed, these results would probably be expressed by a high low to high band power ratio in the HRV spectrum during the premature stage, as found in our study), with a pronounced increase of parasympathetic tone after birth.

The two independent respiratory modes (17, 18) found in the neonatal recordings in the present study point toward a major difference when compared with the single mode observed in the adult or mature respiratory recording. As mentioned, in all cases, the HR power spectrum did not show a clear and defined respiratory peak at the respiratory frequency but rather a wide, dispersive peak that probably resulted from an immaturity in the neural pathways (mainly parasympathetic) responsible for the translation of the respiratory activity into a nervous modulation of the instantaneous HR (or an immature transfer function from respiration to HR modulation) (19). As noted in the study by Giddens and Kitney (20) on full-term neonates, a strong association is found between HRV and BASA (breath amplitude variability). It seems that in the young preterm neonates the respiratory control system is based on a low-frequency amplitude modulation mechanism system with repeated unordered switchovers to the mature type system, defined by a steady respiratory activity (20, 21). These switchovers are reminiscent of the sudden rises in autonomic activity related to the onset of breathing movements that we observed in the human fetus, when measuring fetal HR from an abdominal ECG signal and detecting respiratory movements by ultrasound imaging (22, 23).

In previous studies, the sleep state of the recorded neonates was found to affect both the respiratory and HR power spectra. Signorini *et al.* (14) reported a predominance of sympathetic activity during active sleep and vagal activation during quiet sleep. This group noted that the full-term newborn is found in active sleep 70% of the time. DeHaan *et al.* (24) found that quiet sleep is usually not observed in newborn infants before 35 wk GA and that the percentage of time during which quiet sleep occurs in newborn infants increases with GA. This observation may also, at least partly, explain or somewhat contribute to the significant difference in the low to high power ratio when comparing groups AB (33–35 CA) and CD (full-term infants). It is interesting to note that both the enhancement

in vagal tone and the ability to experience quiet sleep may be reflections (dependent or independent) of autonomic maturation.

Kitney (25) proposed that an elevated low to high ratio might indicate increased risk for the infant. Baldzer *et al.* (11) observed that a difference in breathing rate affects both HRV and the low to high ratio; they divided the 20 full-term infants in their study into two groups according to the low to high ratio. They suggested that PA should be taken into consideration when defining risk factors as a function of low to high power. Because the low to high ratio is generally elevated in premature infants, our work emphasizes the need to account for the GA and PA of the neonate and preferably also to classify the respiratory mode and sleep state (quiet or active) of the infant before reliable risk factors can be determined (20–25).

Finally, we speculate that healthy maturation of the infant is reflected when the respiratory power spectrum in the preterm infant shows a decreasing amount of power at low frequency (breath amplitude modulation), a more narrow peak at mean breathing rate, or both and when the HR power spectrum displays a decrease in the low to high ratio. These conclusions are based on the assumption that a transition from a burst-like onset of breathing movements in the fetus to an irregular (amplitude- and frequency-modulated) respiration in the neonate to a regular, narrow-band breathing in a slightly older child reflects maturation. The observation of a decrease in mean HR and low to high ratio of power of HR fluctuations with progression of GA is another sign of development. Furthermore, our study suggests that parameters such as mean HR, and patterns of the HR power spectrum (in particular the low to high ratio) and of respiratory power spectrum (mainly width of respiratory peak and existence of low-frequency component) can all be used to provide insight into maturation and autonomic development of preterm and full-term neonates.

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