Early Human Development, 28 (1992) 169–183
Elsevier Scientific Publishers Ireland Ltd.

EHD 01223

Heart rate variability in normal sleeping full-term and preterm neonates

Jean Clairambault[a], Lilia Curzi-Dascalova[b], François Kauffmann[a,c], Claire Médigue[a] and Christopher Leffler[a,b,c]

[a]*INRIA Rocquencourt, France* [b]*INSERM CJF8909 Hospital Antoine-Béclère, Clamart,* [c]*Department of Mathematics University of Caen (France)*

(Received 17 April 1991; revision received 15 November 1991; accepted 21 January 1992)

Summary

To assess maturation of the Autonomic Nervous System (ANS) and sleep states, Heart Rate Variability (HRV) was studied in 24 healthy sleeping newborns, aged from 31 to 41 weeks, conceptional age (CA). Spectral analysis of the interbeat interval (RR) signal, was performed by Short-Time Fourier Transform, in three frequency bands: high (HF), of purely vagal origin, mid (MF), and low (LF), vagal and sympathetic, thus allowing evaluation of both branches of the ANS, observed in Active Sleep (AS = REM Sleep) and in Quiet Sleep (QS = nREM Sleep). Principal Component Analysis, Discriminant Analysis, and hypothesis tests were used to investigate the evolution of spectral variables and their relation with sleep states. HF, MF, LF, and mean RR all increased with age; the differences from the premature to the full-term group, were more marked, as a whole, in AS than in QS. HF showed the highest increase from the premature (31–36 weeks CA) to the intermediate (37–38) group, whereas LF showed equal differences from the premature to the intermediate, and from the intermediate to the full-term (39–41) groups. These results suggest a steep increase in vagal tone at 37–38 weeks CA, with stability afterwards, and a more regular increase in sympathetic tone from 31 to 41 weeks CA

Key words: heart rate variability; spectral analysis; data analysis; sleep; newborn infant; premature.

Correspondence to: J. Clairambault, INRIA, Bâtiment 12, F78153 Rocquencourt, France

0378-3782/92/$05.00
Printed and Published in Ireland

Introduction

The variations of heart rate have long been used as a mean of investigating the Autonomic Nervous System (ANS) [30]. Short-term (or high frequency, HF) variations have been reported to reflect only parasympathetic control of heart rate, and long-term (or low frequency, LF) variations both sympathetic and parasympathetic control [3,12,29,32]. These differences in the frequency domain between the two branches of the ANS (fast vagal and slow sympathetic) may be explained by different response delays in the vagal (about 1 heartbeat duration) and sympathetic (2 to 3 s in adults) pathways [3,38].

HF variations are related to the respiratory cycle (period: 1–3 s, in newborn infants), and carry the part of Heart Rate Variability (HRV) which is referred to as Respiratory Sinus Arrhythmia (RSA) [19,20,29] It is identified, on an adult cardiorespiratory tracing, as an increase in heart rate during inspiration, and a decrease during expiration; it has been classically described as the effect on the centres of a reflex input from lung, atrium, or aortic stretch sensors, but it also might be due to a coupling of respiratory and cardiac vagal medullary motoneurones [17,39].

Various origins (variations in blood pressure due to the baroreflex, thermoregulation, renin/angiotensin system adaptation) have been attributed to LF variations, the period of which ranges from 4 to 30 s in infants [34]. A distinction has been established by numerous authors between low (or mid, MF, period around 10 s) frequency, reported to reflect baroreflex activity, and very low (LF, period usually beyond 20 s) frequency, the origin of which is less clear [3,7,12,32].

In infants from 1 week to 6 months, HF variations have been reported to be higher in quiet sleep (QS) than in active sleep (AS) [15,16,17]; the opposite is true for LF variations [16–18] According to Harper et al, sleep states in infants may be discriminated by HRV variables, on these grounds, with a high degree of accuracy [16].

The physiological importance of these questions is certainly not negligible for a better understanding of early human ontogenesis; furthermore, physiopathological implications are of great interest. This is particularly true for Sudden Infant Death Syndrome, for which a possible role of the ANS has been reported, and in which different studies have analyzed possible differences from controls in heart rate or HRV [2,13,14,24,31,35,36,40].

Regarding normal human ontogenesis, no study so far, to our knowledge, has analyzed by spectral analysis of HRV, maturation of the ANS according to sleep states in healthy premature and full-term newborn infants.

Our aim in this study was to analyze: (1) the age-related modifications of variables quantifying HRV in different frequency bands (and thus parasympathetic and sympathetic tones), in each sleep state and (2) the discrimination between sleep states, as measured by HRV variables, and the evolution of this discrimination with age

Materials and Methods

Subjects

Twenty-four neonates, all clinically and neurologically healthy (in particular,

Apgar score was at least 8 at 1 s, and always 10 at 5 s), were studied between the 2nd and 11th day of extrauterine life (in order to exclude influence of drugs possibly given during labour, or conditions of labour itself, as well as postnatal adaptation of heart rate) by polygraphic sleep recordings (ECG, EEG, eye movements)

They had been divided according to conceptional age (CA) at the time of the recording in three different age groups:

- 8 Full-term; $39 \leq CA \leq 41$ weeks
- 8 Intermediate; $37 \leq CA \leq 38$ weeks
- 8 Premature; $31 \leq CA \leq 36$ weeks.

Recordings

Paper and analog tape recordings were performed in the morning, during a sleep between two meals All neonates were lying supine, either in their beds, at ambient temperature (25–26°C) for full-term and intermediate newborns, or in incubator (30–36°C) for prematures, in order to ensure a normal body temperature for each subject

Recordings were performed until awakening of the subject All recordings contained at least one complete sleep cycle, yielding at least one 512 heartbeat epoch (statistical observation unit) of Active Sleep (AS = REM Sleep) and one of Quiet Sleep (QS = nREM Sleep), coded on paper tracings by using REM and EEG patterns [9,11].

ECG signal processing

ECG recordings were digitized at 282 Hz and processed by a signal-to-noise ratio algorithm [22,23] to obtain the RR series. Every raw RR series (not resampled) was processed by Short-Time Fourier Transform, a non-stationary spectral analysis procedure which uses complex demodulation [28,37], and provides an 'instantaneous' evaluation of spectral amplitude in given frequency bands, one time series for each chosen band.

The estimation of spectral amplitude A_{f_0} of the RR signal in the band $[f_0 - \epsilon, f_0 + \epsilon]$ is given by:

$$A_{f_0}(n) = \left| \sum_{k=0}^{n} RR(k)\omega_\epsilon(n-k) \exp(-2\pi i f_0 k) \right|$$

where (ω_ϵ) is a low-pass elliptic iir filter, with $[0, \epsilon]$ passband If RR(n) is in miltiseconds, so is $A_{f_0}(n)$

In this study, we focused our attention on three types of HRV: High Frequency (HF) variations (with period in heartbeats: 3–8, ranging from 1 to 4 equivalent seconds; (conversion from heartbeats to 'equivalent seconds' is performed by multiplying number of beats by mean RR in a given 512-heartbeat epoch), and two sub-types of low frequency variations mid frequency: (MF) variations (with period in heartbeats: 10 to 25, ranging from 4 to 12 equivalent seconds), and (very) Low Frequency (LF) variations (with period in heartbeats: 30 to 100, ranging from 12 to 50 equivalent seconds).

An illustration of these signals is presented on Fig 1, which shows a rather strik-

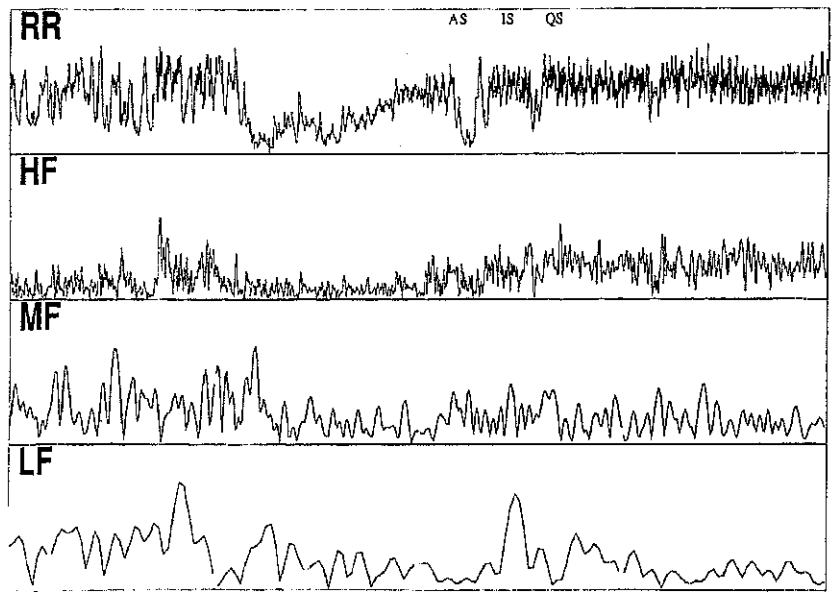

Fig. 1 Raw RR signal and Short-Time Fourier Transform in the three frequency bands: high (HF), mid (MF), and low (LF), from top to bottom, for a series of 2048 consecutive heartbeats, in a full-term newborn (39 weeks, 2 days of life), during about 16 min, and showing a striking transition (middle of page) from Active Sleep (AS) to Quiet Sleep (QS); *y*-scales are from 350 to 650 ms for RR and from 0 to 100 ms for the other signals. Notice the changes in HF (increase from AS to QS) and in LF (decrease from AS to QS)

ing example of what may be seen during the transition from AS to QS, when vagal tone is high enough (here, in a full-term newborn, 39 weeks CA, 2 days of life)

We measured in each epoch of 512 beats the mean amplitude of the raw RR and of the 3 extracted (HF, MF, LF) time signals. These means (338 for each signal) were used as material for subsequent statistical analysis.

Statistical processing

Statistical processing was performed at two levels.

(a) To assess the influence of age and sleep state on each variable separately, and ascertain independence of observations, hypothesis tests were performed on the set of 24 within-individual means, averaged over all 512-heartbeat epochs belonging to the same subject (48 within-individual-and-sleep-state means, for 2-way ANOVA on age and sleep state): *F*-test in analysis of variance, paired and unpaired 2-tailed *t*-tests for the comparison of means between age groups or sleep states

(b) To take into account possible combinations between variables, on the one hand, and within-individual variance for each variable, on the other hand, we performed multivariate data analysis on the set of all 338 epochs, considered as points in the (HF, MF, LF) 3d-space: Principal Component Analysis and Linear Discrimi-

nant Analysis [5,6,26], with cross-validation [27], between age groups or sleep states. Subsequent analysis of the respective parts played by each variable in discrimination was carried through by studying the correlation coefficients of each variable with the discriminant linear function which provides the discrimination rule. RR was not used for these multidimensional analyses, since HF, MF, and LF had been extracted from it.

By using these two complementary classes of methods, we wanted to answer two questions:

(1) Are HRV variables relevant, separately or combined together, to distinguish between age groups, in one given sleep state, or whatever the sleep state? And if it is so, what is the part played by each variable in age group distinction?

(2) Are HRV variables relevant, separately or combined together, to distinguish between sleep states, in one given age group, or whatever the age group? And if it is so, what is the part played by each variable in sleep state distinction ?

Results

Firstly, to examine each variable separately, a two-way analysis of variance was performed on age group and sleep state, by using the 48 within-subject-and-sleep-state means, for HF, MF, LF, and RR.

It may be seen on Table I that RR and all HRV variables are relevant for age distinction, whereas only HF, LF, and, to a lesser extent, RR provide significant between-sleep-state differences. No interaction between age and sleep state has been found.

Then, to go further in the analysis of variance, a normed Principal Component Analysis was performed to analyze, in relation to age (Figs. 2 and 3) and sleep state (Fig. 4) the contribution of each HRV variable to the global variance of the 'statistical cloud' constituted by all 338 epochs of 512 heartbeats, considered as points in the (HF, MF, LF) 3d-space. Equations for the 'principal factor plane':

$$x = 0.69\mathrm{HF} + 0.93\mathrm{MF} + 0.82\mathrm{LF}$$

$$y = 0.71\mathrm{HF} - 0.07\mathrm{MF} - 0.51\mathrm{LF}$$

TABLE I

2-way ANOVA (three ages, two sleep states) on RR and HRV variables.

$n = 48$	F^2_{42} (age group)	F^1_{42} (sleep state)	F^2_{42} (interaction)
HF	9.92**	11.26*	1.08 (NS)
MF	12.37***	0.67 (NS)	0.04 (NS)
LF	11.13**	13.08**	0.87 (NS)
RR	10.56**	6.97*	0.33 (NS)

*$P \leq 0.01$.
**$P \leq 0.001$.
***$P \leq 0.0001$
NS, non-significant.

where numbers are correlation coefficients between variables (HF, MF, LF) and factors (x, y), show that the first factor, x, roughly represents total HRV, and the second one, y, represents a HF/LF opposition; x and y, respectively represent 67% and 26% of the total variance of the statistical cloud

Figure 2 shows the projection of all 338 epochs onto the (x,y) plane. Full-term neonate (39–41 weeks CA) epochs occupy the right part of this figure, and premature (31–36 weeks CA) epochs the left part of it. Intermediate neonate (37–38 weeks CA) epochs are homogeneously displayed along the x-axis. One can therefore see the first factor, x, as a 'maturity factor'

Figure 3 shows a view of all 24 subjects (averages of epochs within each subject, disregarding sleep state) and centres of gravity (mean points) of age groups

Figure 4 shows the same projection as Fig. 2 onto the (x, y) plane, but emphasizes sleep state distinction. AS epochs are predominantly found in the lower part of this figure, and QS epochs in the upper part of it; the second factor, y, thus might be seen as a 'sleep state factor'; but the same HF/LF opposition for y, with a negligible coefficient for MF, was found when performing the same analyses in each sleep state, so that this factor may not be directly related to sleep state

In order to better analyze these general results and answer more precisely the two questions mentioned above about age and sleep state distinction, we performed comparison between groups, first by hypothesis tests for each variable separately, and then by mutivariate discriminant analyses on all HRV variables.

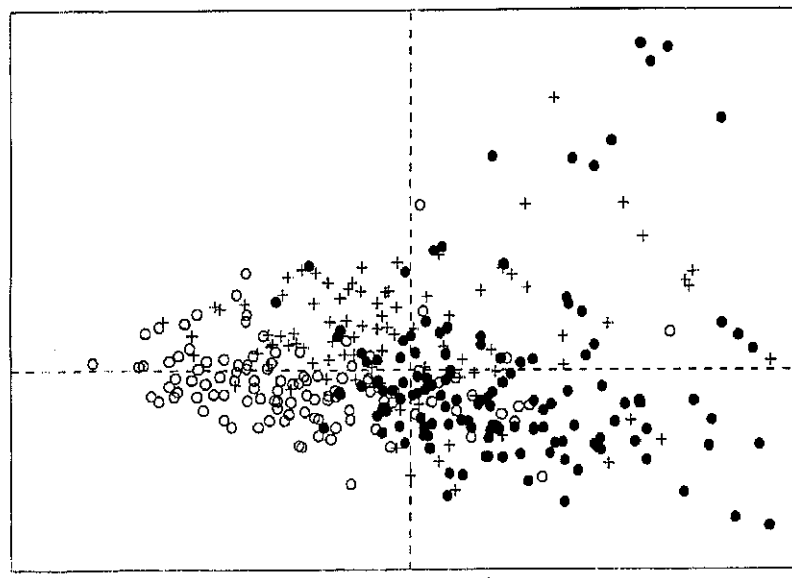

Fig 2 Age group distinction by Principal Component Analysis: projection of all 338 512-heartbeat epochs (corresponding to all 24 newborns studied) onto the principal factor plane: $x = 0.69HF + 0.93MF + 0.82LF$, $y = 0.71HF - 0.07MF - 0.51LF$. Full dots (●) represent full-term neonate epochs, crosses (+) intermediate ones, and empty dots (○) premature ones

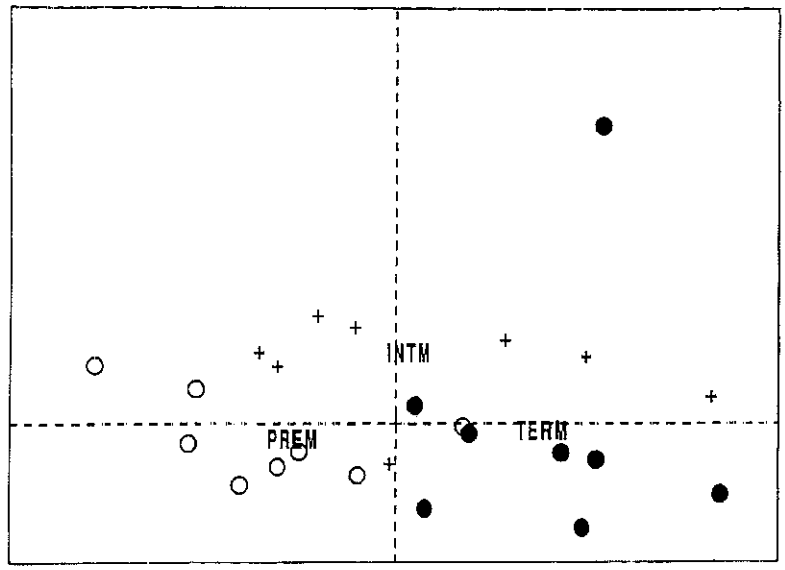

Fig 3 Age group distinction by Principal Component Analysis: projection of all 24 newborns and centres of gravity (mean points) of each age group (TERM for full-term, INTM for intermediate, PREM for premature) onto the principal factor plane: x = 0.69HF + 0.93MF + 0.82LF, y = 0.71HF − 0.07MF − 0.51LF Full dots (●) represent full-term neonate epochs, crosses (+) intermediate ones, and empty dots (○) premature ones; here, the x-axis may clearly be seen as a 'maturity axis'

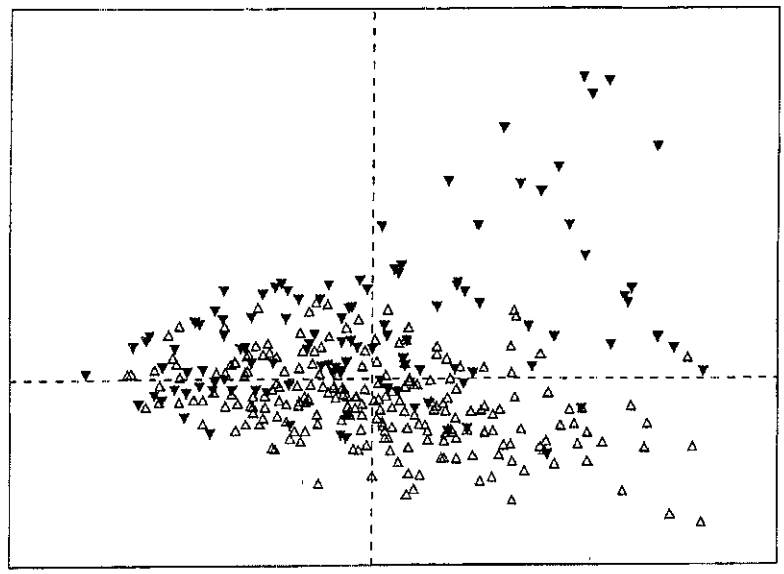

Fig 4 Sleep state distinction by Principal Component Analysis: projection of all 338 512-heartbeat epochs (corresponding to all 24 newborns studied) onto the principal factor plane; Active Sleep epochs are indicated by empty triangles (△), Quiet Sleep epochs by full triangles (▼)

Evolution of HRV variables with age

Trends between age groups, in AS and in QS, are presented on Fig. 5. This figure shows that all HRV variables and mean RR increase with age, but not all with the same regularity. At the two levels of statistical analysis described earlier:

(a) Table II shows the evolution of RR, HF, MF, and LF with age in the 24 neonates, first without consideration of sleep state (top), and then in AS (middle), and in QS (bottom), studied by Student's *t*-test for the comparison of means between couples of age groups. All variables show significant between-age-group differences, and these differences are most emphasized in AS. Studying each variable separately, in contiguous age groups, one can observe that for HF, the strongest changes (on the increase with CA) occur between the premature and intermediate groups; for MF this remains true, but only in AS; as regards LF, differences are nearly significant ($P = 0.06$) between the premature and intermediate groups, and between the intermediate and full-term groups, equally in each case, but only in AS.

(b) Table III assesses the parts played by each variable in multivariate age group discrimination: Linear Discriminant Analysis was performed on the set of 338 512-heartbeat epochs, using HF, MF, and LF, providing percentages of well-classified epochs, Mahalanobis Distance scores, and the correlation coefficients r_{HF}, r_{MF}, r_{LF} of each of these variables with the discriminant linear function, (Mahalanobis Distance between the centres of gravity of groups is a complementary measure of the quality of discrimination [5,6]).

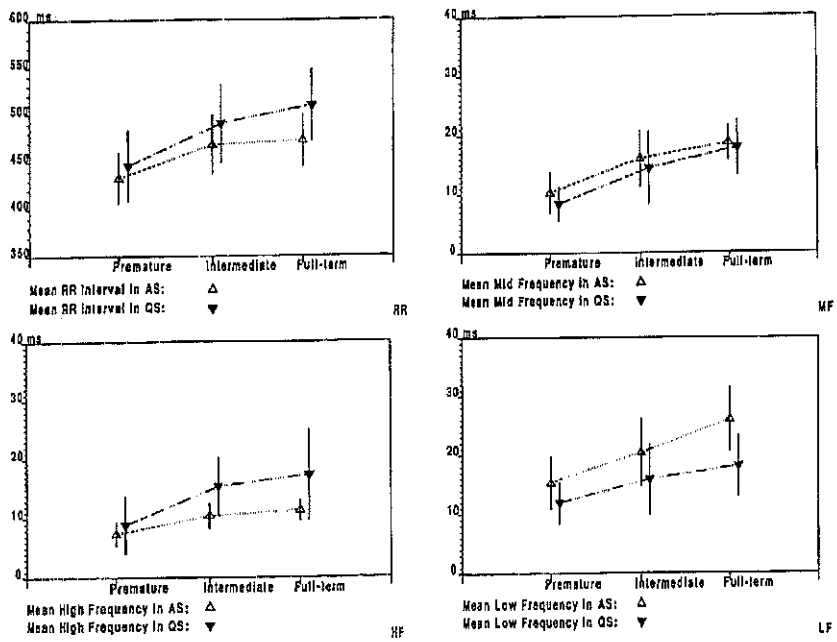

Fig. 5. Trends between age groups, for RR, HF, MF, and LF: mean values in AS (Δ) and in QS (▼); vertical bars indicate ± 1 S.D. around mean values.

TABLE II

Evolution of HRV and RR with age: Student's unpaired *t*-test for the comparison of means between 2 age groups: full-term versus premature (8t/8p), premature versus intermediate (8p/8i), and intermediate versus full-term (8i/8t). From top to bottom: all states mixed, in Active Sleep and in Quiet Sleep.

	8t/8p	8p/8i	8i/8t
All states			
HF	3.41**	4.69***	0.27 (NS)
MF	4.02**	1.66 (NS)	1.71 (NS)
LF	4.47***	1.50 (NS)	2.32*
RR	3.04**	2.54*	0.35 (NS)
Active sleep			
HF	4.98**	3.51**	0.94 (NS)
MF	4.86***	2.51*	1.35 (NS)
LF	4.34***	2.03 ($P = 0.06$)	2.02 ($P = 0.06$)
RR	3.13**	2.59*	0.31 (NS)
Quiet sleep			
HF	2.74*	2.85*	0.60 (NS)
MF	3.41**	1.65 (NS)	1.26 (NS)
LF	2.82*	1.63 (NS)	0.79 (NS)
RR	3.31**	2.19*	0.97 (NS)

(t = full-term newborns (39–41 weeks CA); i = intermediate newborns (37–38 week CA); p = prematures (31–36 weeks CA)
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.
NS, non-significant.

A preliminary attempt to discriminate all 338 epochs in three age groups (full-term, intermediate and premature) had given poor results (less than 50% well-classified epochs), as might have been suspected from the overlapping of groups in Fig. 2. We thus decided to discriminate between all possible pairs of age groups.

Firstly, to distinguish premature from full-term epochs (intermediate ones were temporarily discarded), for all sleep states, and in each sleep state separately, discriminant analyses were performed on the set of 247 non-intermediate epochs. As may be seen on Table III, these analyses yield rather satisfying percentages of well-classified epochs, especially in AS (87%). As may be inferred from the analysis of the correlation coefficients, all HRV variables are relevant and contribute in the same way to age group discrimination.

Secondly, to distinguish premature from intermediate epochs, the same processing was applied to the set of 207 non-full-term epochs. Table III shows satisfying percentages of well-classified epochs, especially in QS (86%); the predominance of HF in discrimination is overwhelming here (r_{HF} as compared to r_{MF}, r_{LF}) which is in favour of a strong enhancement in HF from the premature to the intermediate group.

Thirdly, to distinguish intermediate from full-term epochs, this processing was applied to the set of 222 non-premature epochs. Table III shows results which are a little poorer in AS, but drastically diminished in QS, and a negligible contribution of HF to discrimination. This is in favour of a relative stability of HF, and a moderate increase in MF and LF from the intermediate to the full-term group.

Evolution of sleep state distinction with age

In the same way, to study between-sleep-state differences on each variable separately, paired *t*-tests for the comparison of means within each age group were performed and are presented on Table IV.

The results obtained by 2-way ANOVA are confirmed here: MF is not relevant for sleep state discrimination, whatever the age. HF, and most of all LF, show significant between-state differences among full-term newborns. In the intermediate group, differences in HF and in LF are still significant, but in the premature group, only LF shows significant between-state differences.

In order to assess the parts played by each HRV variable in global (multivariate) discrimination between sleep states, discriminant analyses were also performed on the set of all 338 epochs, for all ages, and in each age group independently.

Table V shows that these analyses yield satisfying percentages of well-classified epochs in the full-term group, but poorer ones in the other groups. The evolution of Mahalanobis distance between the centres of gravity of sleep states shows a constant progression from the premature group to the full-term group.

TABLE III

Between-2-age-group discrimination: Between full-term and premature (131 + 116 = 247 epochs, top), between premature and intermediate (116 + 91 = 207 epochs, middle) and between intermediate and full-term (91 + 131 = 222 epochs, bottom)

	Linear Discr.	Mahalanobis Distance	r_{HF}	r_{MF}	r_{LF}
Full-term/prem.					
All states	85%	3.41	0.75	0.89	0.82
Active Sleep	87%	3.56	0.87	0.94	0.89
Quiet Sleep	77%	3.46	0.90	0.79	0.67
Prem./intermed.					
All states	81%	2.21	0.97	0.42	0.29
Active Sleep	74%	1.91	0.99	0.42	0.27
Quiet Sleep	86%	4.46	0.91	0.39	0.37
Intermed./full-term					
All states	74%	1.17	0.02	0.88	0.91
Active Sleep	79%	1.79	0.18	0.88	0.91
Quiet Sleep	54%	0.40	0.45	0.99	0.69

(Linear Discr : percentages of well-classified epochs, globally or within one given age group; Mahalanobis Distance (between the centres of gravity of groups), a complementary measure of the quality of discrimination; r_{HF}, r_{MF} r_{LF} correlation coefficients of Discriminant Linear Function with HRV variables)

TABLE IV

Evolution of between-state distinction. Means of differences between Active Sleep (As) and Quiet Sleep (QS): paired *t*-test.

t(AS – QS)	Premature (8)	Intermediate (8)	Full-term (8)
HF	−0 80 (NS)	−2 96*	−2 44*
MF	0 39 (NS)	0.79 (NS)	0.94 (NS)
LF	3 63*	2 84*	6 15***
RR	−2.78*	−3.00*	−4 19**

*$P \leq 0.05$.
**$P \leq 0.01$
***$P \leq 0.001$.
NS, non significant.

The analysis of the contribution of each variable (r_{HF}, r_{MF}, r_{LF}) to this discrimination confirms that an opposition between HF and LF is an important feature in sleep state distinction. As a matter of fact, we also performed the same analyses with only HF and LF: the results proved slightly better, which suggests that MF, which is important in age group discrimination, brings no contribution to sleep state discrimination.

Discussion

In this study, we asked the question of the relevance of HRV variables to age or sleep state distinction in premature and full-term newborns, and interpreted the influence of each variable in this distinction. At the two statistical levels considered (within-individual means and all epochs of 512 heartbeats), our results demonstrate two main physiological points.

Firstly, HRV parameters are highly discriminant for age, between premature and full-term newborns. All HRV variables are on the increase from the premature group

TABLE V

Evolution of between-state discrimination: discriminant analyses, using HF, MF, and LF, performed on all 338 epochs of 512 heartbeats (All ages), 116 premature epochs (Premature), 91 intermediate epochs (Intermediate), and 131 full-term epochs (Full-term).

Age group	Linear Discr.	Mahalanobis Distance	r_{HF}	r_{MF}	r_{LF}
All ages	77%	1 90	−0 66	0 16	0 57
Premature	71%	0 84	−0 33	0 24	0 76
Intermediate	76%	2.73	−0.86	−0 05	0 26
Full-term	82%	3 32	−0 80	0 16	0.68

(Linear Discr.: percentages of well-classified epochs globally or within one given age group; Mahalanobis Distance (between the centres of gravity of groups), a complementary measure of the quality of discrimination; r_{HF}, r_{MF}, r_{LF}, correlation coefficients of Discriminant Linear Function with HRV variables)

(31–36 weeks CA) to the full-term group (39–41 weeks CA), but HF undergoes a rather steep increase from the premature to the intermediate group, remaining relatively stable afterwards, whereas LF grows more regularly from 31 to 41 weeks CA. Since HF reflects only vagal tone, and LF both vagal and sympathetic tones, this is in favour of an important increase of vagal tone at 37 and 38 weeks, with a slower growth afterwards, and of a more constant increase of sympathetic tone from 31 to 41 weeks.

Secondly, concerning sleep organization, we found that according to HRV parameters, sleep states may be discriminated better and better as CA increases, to reach satisfying levels of discrimination (over 80% well-classified epochs) in the full-term group. Between-age differences at hypothesis tests are higher in AS than in QS. This suggests an earlier differentiation of AS, as compared to QS, which is in agreement with previous findings [8,10]. But since significant differences between sleep states in prematures are found only in LF, (higher in AS than in QS), this also suggests earlier maturation of sympathetic heart rate control during AS, HF (lower in AS than in QS) becoming more discriminant later, from 37 weeks on.

This second point is coherent with the first one, developed above, and also with previous findings by Baldzer et al. [4], who used the opposition between LF and Respiratory Sinus Arrhythmia (which is carried by HF) as a parameter for separation in two groups of healthy neonates, and speculated on a later postnatal development of the parasympathetic system as compared to the sympathetic system. From this point of view, we can also suggest an interpretation for the second factor of our Principal Component Analysis, roughly speaking 'HF–LF', higher in full-term newborns than in prematures, and higher in QS than in AS: it may be closely related to vagal tone.

Our results should be compared very cautiously with previous studies on the same subject, since our subjects are healthy premature and full-term neonates recorded in the first days of life, whereas in previous studies, infants were investigated at different postnatal ages [4], QS only being taken into account [1,4], or total HRV only studied [21]. Especially, comparison with interesting results of Harper, Schechtman et al., whose frequency bands are comparable with ours [16,34], may be partially inadequate because of differences in the ages investigated: they studied infants between 1 week and 6 months of age, and while our results may be compared with theirs for 1 week old newborns, this comparison is no more valid in older infants, because of probable fast modifications of autonomic control during the first weeks of postnatal age.

Regarding statistical analysis:

- The relatively small number of subjects in each group (8) is due to the difficulty to find completely healthy newborn babies in the premature group, and we did not want to unbalance our age groups.
- We confirmed the validity of results obtained at parametric tests by performing equivalent non-parametric tests on the same data (Mann-Whitney and Wilcoxon for *t*-test, Kruskal-Wallis for ANOVA): the levels of significance were the same.
- Linear discriminant analysis, which theoretically assumes normality, is robust enough to tolerate violations of the normality assumption [25,26].

- The two levels of statistical processing presented in this study are complementary, and, to our meaning, not interchangeable: apparently good results which would be obtained from hypothesis tests on the set of all epochs, or from discriminant analyses on the set of within-individual means, would be delusive, either forgetting possible non-independence of observations, or considering too few statistical individuals
- To examine a possible dependence of some of the HRV variables upon heart rate, we adjusted them for RR [24], performing Principal Component Analysis and 2-way ANOVA on the same data, but using quotients HF/RR, MF/RR, and LF/RR. The distribution of age and sleep state groups within the statistical cloud was not considerably changed, and levels of significance at Fisher's test were only slightly modified (NS remaining NS, and the other ones remaining at $P \leq 0.01$)

Conclusions

Different statistical approaches converge to sketch the same description of early ANS maturation: a strong enhancement in vagal tone at 37–38 weeks CA, with a relative stability afterwards, and a more constant increase in sympathetic tone from 31 to 41 weeks. These approaches rest mainly on HF and LF, which are the most significant HRV variables and are sufficient to describe maturation of the ANS in normal neonates, premature and full-term

The method of analysis presented here has shown appropriate for studying normal maturation of the ANS, and we purpose to use it now to study heart rate control by the ANS in at-risk and pathological newborns and infants

Acknowledgements

L.C.-D. was supported by grants RGR62 INSERM-CNAMTS and INSERM CJF8909, and C.L. was a visiting student during summer 1990 from the Harvard-MIT Division of Health Sciences and Technology, Cambridge, MA, U.S.A. We are gratefully indebted to Prof. Cl. Gaultier for helping revising the manuscript

References

1 Äärimaa, T., Oja, R., Antila K. and Välimäki, I. (1988): Interaction of heart rate and respiration in newborn babies. Pediatr. Res., 24, 745–750.

2 Antila, K.J., Välimäki, I.A.T., Mäkelä, M., Tuominen, J., Wilson, A.J. and Southall, D.P. (1990): Heart rate variability in infants subsequently suffering sudden infant death syndrome (SIDS). Early Hum. Dev., 22: 57–72.

3 Akselrod, S., Gordon, D., Ubel, F.A., Shannon, D.C., Barger, A.C. and Cohen, R.J. (1981): Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat to beat cardiovascular control. Science, 213: 220–222.

4 Baldzer, K., Dykes, F.D., Jones, S.A., Brogan, M., Carrigan, T.A. and Giddens, D.P. (1989): Heart rate variability analysis in full-term infants: spectral indices for study of neonatal cardiorespiratory control. Pediatr. Res., 26, 188–195.

5 Celeux, G., Diday, E., Govaert, G., Lechevallier, Y. and Ralambondrainy, H. (1989): L'analyse, discriminante. In: Classification Automatique des Données, Ch. 4, pp. 237–275. Dunod, Paris.

6 Celeux, G. (1990): Règles statistiques de décision In: Analyse Discriminante sur Variables Continues, pp. 15–36. Editor: G Celeux INRIA, Rocquencourt, France

7 Chess G.F., Tam, R M.K. and Calaresu F R (1975): Influence of cardiac neural inputs on rhythmic variations of heart period in the cat Am. J. Physiol., 228, 775–780

8 Curzi-Dascalova, L., Peirano, P and Morel-Kahn, F. (1988): Development of sleep states in normal premature and full-term newborns Dev Psychobiol., 21. 431–444.

9 Curzi-Dascalova, L., (1990): Sleep and respiratory control development during the first months of life Ergebn. Exp Med., 53, 137–152

10 Curzi-Dascalova, L., Clairambault, J Kauffmann P., Médigue, C. and Peirano, P. (1991): Cardiorespiratory variability and development of sleep state organization In: Sleep and Cardiorespiratory Control, pp. 155–163. Editors: C Gaultier., P Escourrou, L Curzi-Dascalova. John Libbey, London.

11 Dreyfus-Brisac, C (1979): Ontogenesis of the brain bioelectrical activity and sleep organization in neonates and infants. In: Human Growth, a Comprehensive Treatise, pp 157–182 Editors: F Falkner, J.M. Tanner Plenum Press, New York

12 Giddens, D.P. and Kitney, R.I. (1985): Neonatal heart rate variability and its relation to respiration J. Theor Biol., 113, 759–780.

13 Gordon, D., Cohen, R J., Kelly, D., Akselrod, S and Shannon, D C (1984): Sudden infant death syndrome: abnormalities in short term fluctuations in heart rate and respiratory activity Pediatr Res., 18: 921–926.

14 Gordon, D., Southall, D P., Kelly D H., Wilson, A., Akselrod, S., Richards, J., Kenet, B., Kenet, R., Cohen, R J. and Shannon, D C. (1986): Analysis of heart rate and respiratory patterns in sudden infant death syndrome victims and control infants. Pediatr. Res., 20: 680–684

15 Harper, R.M., Walter, D.O., Leake, B., Hoffmann, H J., Sieck, G.C., Sterman, M.B., Hoppenbrouwers, T. and Hodgman, J (1978): Development of sinus arrhythmia during sleeping and waking states in normal infants Sleep, 1 33–48

16 Harper, R.M., Schechtman, V L. and Kluge, K A (1987): Machine classification of infant sleep state using cardiorespiratory measures. Electroencephalogr. Clin Neurophysiol., 67, 379–387.

17 Hathorn, M K S. (1987): Respiratory sinus arrhythmia in newborn infants J Physiol (London) 385, 1–12

18 Hathorn M.K.S. (1989): Respiratory modulation of heart rate in newborn infants Early Hum Dev., 20, 81–99.

19 Hirsch, J A. and Bishop, B (1981): Respiratory sinus arrhythmia in humans: how breathing pattern modulates heart rate Am. J. Physiol., 241. H620–H629.

20 Katona, P G and Jih, F. (1975): Respiratory sinus arrhythmia: non invasive measure of parasympathetic control. J Appl Physiol., 39, 801–805.

21 Katona, P.G., Frasz, A. and Egbert, J. (1980): Maturation of cardiac control in full-term and preterm infants during sleep Early Hum Dev., 4, 145–159.

22 Kauffmann, F., Clairambault, J and Médigue, C (1991): Un système d'analyse des signaux biomédicaux. Bull. Liaison Rech. Inf. Autom., (INRIA), 131, 38–41

23 Kauffmann, F and Cauchemez, B (1991): Extraction of cardiorespiratory parameters In: Sleep and Cardiorespiratory Control, pp 105–112. Editors: C Gaultier, P Escourrou and L Curzi-Dascalova. John Libbey, London

24 Kluge, K A., Harper, R.M., Schechtman, V L., Wilson, A J., Hoffman, H J and Southall, D P (1988): Spectral Analysis assessment of respiratory sinus arrhythmia in normal infants and infants who subsequently died of sudden infant death syndrome. Pediatr. Res., 24, 677–682

25 Krzanowski, W.J. (1977): The performance of Fisher's linear discriminant function under non-optimal conditions Technometrics, 19 191–200

26 Lachenbruch, P.A. (1975): Discriminant Analysis, Ch 7, Hafner Press, MacMillan Publishing Co

27 McLachlan, G J (1986): Assessing the performance of an allocation rule Comput Math Appl 12A, 261–272

28 Nawab, S H. and Quatieri, T.F. (1988): Short-Time Fourier Transform. In: Advanced topics in signal processing, pp. 289–337. Editors: J S. Lim, A.V Oppenheim. Prentice-Hall, Englewood Cliffs, New Jersey

29 Pomeranz, B , Macaulay, R.J B., Caudill, M A., Kutz, I., Adam, D., Gordon, D., Kilborn, K.M., Barger, A C., Shannon, D C , Cohen, R J. and Benson, H (1985): Assessment of autonomic function in humans by heart rate spectral analysis. Am. J. Physiol , 248, H151–H153.

30 Rosenblueth, A and Simeone, F.A. (1934): The interrelations of vagal and accelerator effects on the cardiac rate. Am J. Physiol , 110, 42–55.

31 Rother, M , Zwiener, U , Eiselt, M , Witte, H , Zwacka, G and Frenzel J. (1987): Differentiation of healthy newborns and newborns-at-risk by spectral analysis of heart rate fluctuations and respiratory movements. Early Hum. Dev., 15 349–363.

32 Sayers, B McA (1973): Analysis of heart rate variability. Ergonomics, 16. 85–97.

33 Schechtman, V L.,Kluge, K A. and Harper, R.M (1988): Time-domain system for assessing variation in heart rate Med. Biol. Eng. Comput , 26 367–373.

34 Schechtman, V L , Harper, R M and Kluge, K A. (1989): Development of heart rate variation over the first 6 months of life in normal infants Pediatr. Res., 26, 343–346.

35 Schechtman, V L., Harper, R.M., Kluge, K A , Wilson, A J., Hoffman, H.J. and Southall, D P. (1989): Heart rate variation in normal infants and victims of the sudden infant death syndrome. Early Hum. Dev., 19, 167–181.

36 Schechtman V L., Harper, R M , Kluge, K.A., Wilson A J and Southall, D.P. (1990): Correlations between cardiorespiratory measures in normal infants and victims of sudden infant death syndrome. Sleep, 13, 304–317.

37 Shaw-Jyh Shin (1989): Assessment of autonomic regulation of heart rate variability by the method of complex demodulation. IEEE Trans Biomed. Eng , 36, 274–283

38 Siimes, A.S.I., Välimäki., I A I. Antila, K J , Julkunen, M.K A , Metsala, T H , Halkola, L T. and Sarajas, H.S.S. (1990): Regulation of Heart Rate Variation by the Autonomic Nervous System in Neonatal Lambs. Pediatr Res , 27 383–391.

39 Spyer, K M (1991): Functional organization of cardiorespiratory control. In: Sleep and Cardiorespiratory Control, pp. 3–8 Editors: C Gaultier, P Escourrou and L Curzi-Dascalova John Libbey., London.

40 Wilson, A J , Stevens, V , Franks, C I , Alexander, J. and Southall D P (1985): Respiratory and heart rate patterns in infants destined to be victims of sudden infant death syndrome: average rates and their variability measured over 24 h. Br. Med. J , 290, 497–501