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Heart-rate variability in low-risk prematurely born infants reaching normal term: a comparison with full-term newborns

M. Eiselt[a], L. Curzi-Dascalova[b], J. Clairambault[c], F. Kauffmann[d], C. Médigue[c] and P. Peirano[e]

[a]*Institute of Pathological Physiology, Friedrich Schiller University, Jena (Germany),* [b]*INSERM, CJF89-09, Laboratoire Physiologie, Hôpital A. Béclère, Clamart,* [c]*INRIA, Rocquencourt,* [d]*University of Caen, Department of Mathematics, Caen (France) and* [e]*INTA, Santiago (Chile)*

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Summary

To investigate the influence of prematurity and postnatal age on the maturation of the autonomic nervous system function, we analysed heart-rate and heart-rate variability in twelve prematurely born infants (< 37 weeks gestational age) reaching the conceptional age of 37–41 weeks. These neonates were compared with sixteen 37–41 week conceptional age newborns (< 10 days postnatal age). Heart-rate variability was analysed by spectral analysis of interbeat intervals using Short-Time Fourier Transform. We found that during both active and quiet sleep, the durations of RR-intervals were shorter and the amplitude of heart-rate variability in different frequency bands was lower in prematures reaching term than in newborns of the same conceptional age ($P < 0.001$). Between-state comparison showed differences in both groups. In both groups, low-frequency heart-rate variability was higher in active sleep than in quiet sleep. Between-state differences of RR-intervals and high-frequency heart-rate variability were present only in newborns ($P < 0.01$). Discrimination between newborns and prematures reaching term, based on RR-intervals and heart-rate variability, was correct in both sleep states with errors between 7 to 16%. However, in both newborns and prematures reaching term, between-state discrimination showed less reliable results, especially for quiet sleep discrimination with 24% (in PRT) and 20% (in NB) of errors. Our results, especially information given by factor analysis, suggest that the differences between newborns and prematures reaching term, concerning RR-interval and heart-rate variability, may be

Correspondence to: M. Eiselt, Institute of Pathological Physiology, Löbderstrasse 3, 0-6900 Jena, Germany.

related to a changed balance between the sympathetic and parasympathetic nervous systems with a diminished parasympathetic component of heart rate control in prematures reaching term, as compared to newborns.

Key words: prematurity; heart-rate; heart-rate variability; sleep states

Introduction

The progress in neonatal care increases the number of surviving preterm infants. This raises the question of the effect of prematurity and extrauterine life on central nervous system maturation. The comparison of preterm infants near their expected date of birth and of full-term infants at the same conceptional age may provide information on this question. However, the results from literature are controversial. Similarities have been found concerning the EEG [15], behaviour and sleep state organisation [2,11,28], or the thoraco-abdominal relationship during respiration [8]. On the contrary, in several other studies, small differences appeared concerning latency and amplitude of visually evoked potentials [14,31], respiratory frequency, respiratory pauses and periodic breathing [1,5,9,10], arousal state [25], and body motility [4,27].

Heart-rate and total heart-rate variability of prematures reaching normal term have been investigated by Katona et al. [19]. It could be found that in prematures reaching the 41-week conceptional age, mean RR-duration was shorter, in comparison with full-term newborns. Total heart-rate variability, studied by pulse interval variability, was not different.

The present study was performed to investigate the influence of prematurity and postnatal age on heart-rate and heart-rate variability in different frequency bands. We expected to obtain new information about the effect of prematurity and of postnatal life on autonomic nervous system maturation.

Materials and Method

Subjects

The investigation was carried out in two groups: (a) prematurely born (< 37 weeks gestational age) infants, recorded when they reached 37–41 weeks conceptional age, below named prematures reaching term (PRT) and (b) full-term newborns (37–41 weeks conceptional age) recorded during the first 2–10 days of life, below named newborns (NB). Characteristics of the population studied are given on Table I.

Data from the literature show differences between newborns of 37–38 and 39–41 weeks conceptional age [10]. Thus, we subdivided the group of prematures reaching term and newborns in two subgroups of 37–38 weeks conceptional age and 39–41 weeks conceptional age (Table I).

All infants were clinically and neurologically normal. None of them presented any respiratory or heart-rate abnormalities from birth until the day of recording. Criteria

TABLE I

Characteristics of newborns (NB) and prematures reaching term (PRT) investigated (CA, conceptional age; *N*, number of infants per group; CP, cranial perimeter, mean ± S.D.).

CA (weeks)	*N*	Sex ratio m:f	Postnatal age (days)	Birth weight (g)	Length (cm)	CP (cm)	5 min. Apgar-Score
NB 39–41	8	2:6	3.3 + 1.0	3398 + 386	50 + 1.5	35.5 + 1.4	10
NB 37–38	8	3:5	4.8 + 2.1	2884 + 316	48 + 1.8	33.9 + 1.1	10
PRT 39–41	5	3:2	31.4 + 6.8	2108 + 625	46 + 1.8	31.3 + 0.7	≥8
PRT 37–38	7	5:2	28.9 + 15.8	1883 + 333	45 + 4.1	30.8 + 1.6	≥7

of normality and conceptional age correspond to those described in earlier publications [9].

Recordings

Recordings were performed in the morning, during sleep, and between two meals. All neonates were lying in supine position in their own crib, at ambient temperature (25–26°C).

Polygraphic tracings lasted a mean of 157 ± 60 min (range 92–330 min) and included: EEG, ECG, eye movements (recorded with piezo-electrical quartz accelerometer), thoracic and abdominal respiratory movements, nasal air flow recordings, and a binary clock signal. Details of the polygraphic method have been previously described [8]. All data were simultaneously recorded on analog tape.

Sleep states were defined according to EEG-patterns and the presence or absence of rapid eye movements [11].

The recording of each infant included at least one complete sleep cycle, yielding at least one active sleep (AS) and one quiet sleep (QS). Analyses have been performed on total tracing duration.

ECG signal processing

The ECG signal was digitised at 282 Hz. R-wave detection was performed using a signal-to-noise ratio algorithm [20,21]. Then the time (ms) between the preceding R-wave and the current one was associated to each heart beat (RR-signal). The sequential RR-signal was cut in epochs of 512 heartbeats. These epochs were the observation units in which heart-rate variability was quantified.

Artefact treatment used the detection and correction of aberrant RR-intervals. This method evaluated a mean RR-interval series and compared the current values with the estimated mean. If this difference was greater than a threshold, or if the current value was outside a normal interval, the RR-label was set to false and corrected with the previous correct RR-value [21].

Every epoch containing more than 10% artefacts was rejected. Every RR-interval series was analysed by Short-Time Fourier Transform, a non-stationary spectral

analysis procedure [26,32], which provides an 'instantaneous' evaluation of spectral amplitude in given frequency bands. For the frequency band $[f_0 - \epsilon, f_0 + \epsilon]$, measured in cycles/beat, the complex demodulation formula runs as follows:

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

where $(\omega_{f_0,\epsilon})$ is a low-pass IIR filter with $[0,\epsilon]$ passband, and RR_{f_0} has been prefiltered with a linear filter bank (cascaded high-pass and low-pass elliptic filter, resulting in band pass filtering) from RR in the band $[f_0, -\epsilon, f_0 + \epsilon]$, RR has been decimated by 4 for MF demodulation, and by 12 for LF demodulation.

In the present study, the amplitude of heart-rate variability was calculated in three bands according to the following wavelengths: high-frequency (HF) with three to eight RR-intervals, mid-frequency (MF) 10 to 25 RR-intervals, and low-frequency (LF) of 30 to 100 RR-intervals.

Statistical methods

Data were statistically tested: (a) non-parametric hypothesis tests (Wilcoxon and Whitney-Mann) were performed on averaged values per infant and sleep states. To eliminate the possible dependence between HF, MF, LF, and mean RR, non-parametric hypothesis tests were also performed on HF/RR, MF/RR and LF/RR [22]. (b) Factor analysis and linear discriminant analysis were performed on the total number of epochs measured.

Results

We investigated 400 epochs each of 512 heartbeats, 237 in AS and 163 in QS; for more details on the distribution of these epochs between groups and sleep states, see

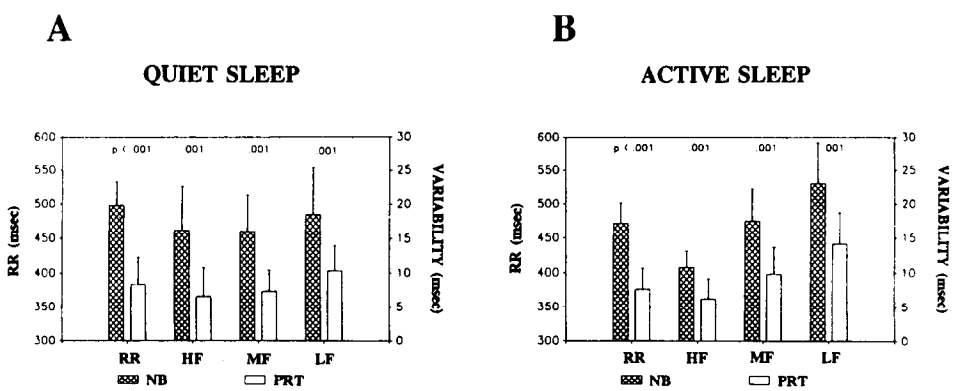

Fig. 1. Mean (± S.D.) RR-interval (left ordinate) and amplitude of heart-rate variability (right ordinate) in three frequency bands in newborns of 37–41 weeks conceptional age (NB) and prematures reaching the same conceptional age (PRT). (A) In quiet sleep; (B) in active sleep; $P <$, for comparison between NB and PRT; RR, RR-intervals; frequency bands (for definition see text), (high-frequency, HF; mid-frequency, MF; low-frequency, LF)

the appendix. There were no significant differences between the groups concerning the number of investigated epochs and the percentage of eliminated artefacts.

In both NB and PRT, no significant differences were found when RR-intervals and heart-rate variability of 37- to 38-week conceptional age subgroups were compared with 39- to 41-week subgroups. In both NB and PRT, we did not find correlations between postnatal age and heart-rate or postnatal age and heart-rate variability in the three frequency bands. Thus, all further studies were performed on two groups: NB and PRT.

Comparison between groups

In both QS and AS, PRT were significantly different from NB by a shorter duration of RR-intervals ($P < 0.001$) and lower amplitude of heart-rate variability in the three frequency bands ($P < 0.001$, for every comparison; see Fig. 1). This finding was confirmed by comparing heart-rate variability variables divided by RR ($P < 0.01$), which takes into account a possible dependence of them upon RR.

Factor analysis was used for the extraction of factors explaining the variance observed. In QS and AS, two factors could be extracted, by which 90.6% (for QS) and 90.4% (for AS) of variance between the recorded epochs could be explained.

In QS and AS, factor 1 (75.4% of variance in QS and 79.7% of variance in AS) was mainly determined by RR and HF. Factor 2 (15.1% of variance in QS and 10.8% of variance in AS) was principally determined by LF (see appendix for further information concerning the factor load of parameters RR, HF, MF, and LF). In both sleep states, the distances between the centres of gravity of NB and PRT were mainly determined by factor 1 (Fig. 2).

Comparison between states

The comparison of sleep states in the given groups yielded the following results. In NB, QS was significantly different from AS by longer RR-intervals, higher

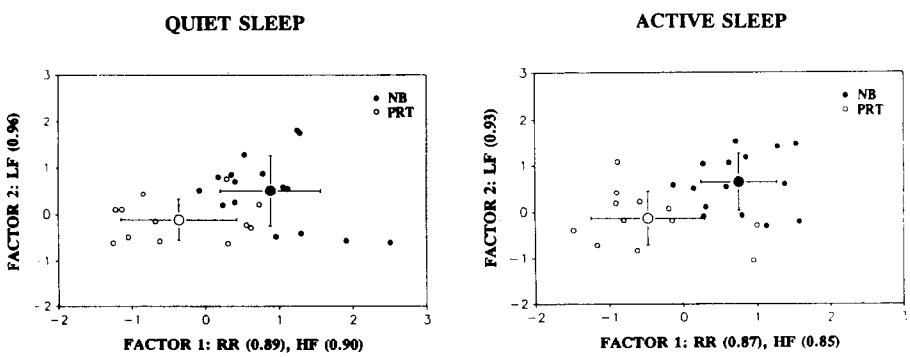

Fig. 2. Factor analysis of variance determined by RR-interval, HF, MF and LF heart-rate variability between newborns (NB) and prematures reaching term (PRT), in quiet sleep and in active sleep. The calculation of the factors were based on the total of recorded epochs. The large points correspond to means per group with standard deviation. Every small point corresponds to the mean per infant. Note, that in both states, between-group variance is mainly determined by factor 1. Together with the factors, parameters mainly determining the corresponding factors are given (the calculation of the parameters is based on the recorded epochs).

TABLE II

Duration of RR intervals and amplitude of heart-rate variability in three frequency bands during quiet sleep (QS) and active sleep (AS) in newborns (37–41 weeks conceptional age) and in prematures reaching term (37–41 weeks conceptional age). (QS-AS, significance of differences between both sleep states; mean ± S.D.).

Sleep states	R-R interval (ms)	High frequency (ms)	Mid frequency (ms)	Low frequency (ms)
Newborns				
Quiet sleep	498.0 ± 35.2	16.2 ± 6.4	16.0 ± 5.3	18.4 ± 6.9
Active sleep	471.9 ± 29.9	10.8 ± 2.4	17.5 ± 4.7	23.1 ± 6.1
QS-AS	0.001	0.01	NS	0.001
Prematures reaching term				
Quiet sleep	383.3 ± 39.2	6.5 ± 4.2	7.3 ± 3.1	10.3 ± 3.7
Active sleep	376.8 ± 30.0	6.2 ± 3.0	9.8 ± 3.9	14.1 ± 4.6
QS-AS	NS	NS	0.01	0.02

amplitude of HF, and lower amplitude of LF ($P < 0.01$). This between-state difference remained significant when heart-rate variability variables divided by RR were compared ($P < 0.05$). In PRT, differences reached the degree of significance due to lower amplitude of MF and LF during QS as compared to AS ($P < 0.02$; Table II). When comparing heart-rate variability variables divided by RR, only the difference of MF/RR between AS and QS reached the level of significance ($P < 0.05$).

Factor analysis allowed extracting in both NB and PRT two factors by which 78.9% (NB) and 91.6% (PRT) of variance between the recorded epochs could be explained.

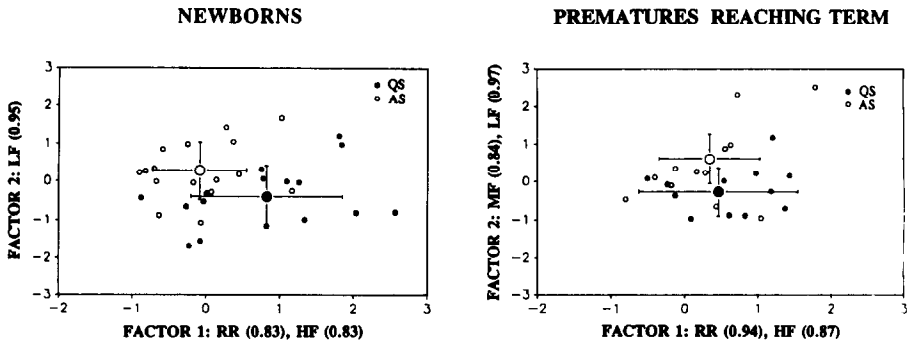

Fig. 3. Factor analysis of variance in quiet (QS) and active (AS) sleep. Left: newborns, right: prematures reaching term. Note that in newborns between-state variance is mainly determined by factor 1, while in prematures reaching term, it is determined by factor 2. For legend, see Fig. 2.

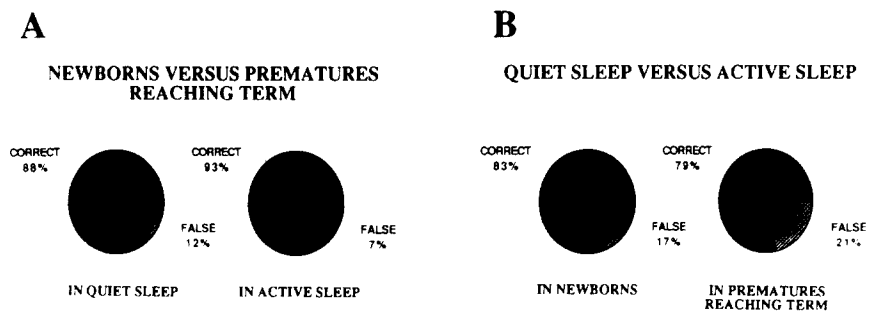

Fig. 4. Data of discriminant analysis (percentage of correct and false classification of epochs): (A) newborns versus PRT in quiet and active sleep; (B) active sleep versus quiet sleep in newborns versus prematures reaching term. For percentage of errors see Table III.

In the group of NB, factor 1 (51.7% of variance) was mainly determined by RR and HF and factor 2 (27.2% of variance) was determined by LF.

In the group of PRT, factor 1 (68.8% of variance) was mainly determined by RR and HF and factor 2 (22.8% of variance) by MF and LF.

In the group of NB, the distance between the centres of gravity of QS and AS was mainly determined by factor 1 corresponding to the parameters RR and HF. In the group of PRT, the distance was mainly determined by factor 2 corresponding to the parameters MF and LF (Fig. 3).

Discrimination between groups and sleep states

Discriminant analysis between NB and PRT showed 88% of correctly classified

TABLE III

Number of periods classified according to the actual (a) group and the predicted (p) by discriminant analysis with percentage of errors (%FC). **A:** Newborns (NB) versus prematures reaching term (PRT) in quiet and active sleep. **B:** Quiet sleep (QS) versus active sleep (AS) in newborns and prematures reaching term.

A	In quiet sleep			In active sleep		
	NB (p)	PRT (p)	%FC	NB (p)	PRT (p)	%FC
NB (a)	70	5	6.7	128	8	7.9
PRT (a)	14	74	15.9	8	93	5.9
B	In newborns			In prematures reaching term		
	QS (p)	AS (p)	%FC	QS (p)	AS (p)	%FC
QS (a)	60	15	20.0	67	21	23.9
AS (a)	22	114	16.2	18	83	17.8

epochs for QS and 93% for AS (Fig. 4A). Detailed information concerning actual and predicted classification resulting from discriminant analysis and the percentage of errors, are given in Table III. Differences in correctly classified epochs in both sleep states did not reach statistically significant levels. The percentage of correctly classified epochs of AS and QS in NB and PRT was 79% in PRT and 83% in NB (Fig. 4B). In both groups, AS was more frequently correctly classified than QS (Table III).

Discussion

The present study shows that PRT are characterised by shorter RR-intervals, i.e. higher heart-rate, and lower amplitude of heart-rate variability in the high-, mid-, and low-frequency bands, as compared to newborns of the same conceptional age. The results of factor analysis show that the distinction between PRT and NB relies mainly on diminished RR-intervals and high-frequency heart-rate variability (factor 1 explains more than 75% of total variance), much more than on diminished mid and low frequency heart-rate variability (factor 2 explains not more than 15% of total variance).

The differences between groups may result from retardation or acceleration of the maturational course in PRT. Investigations in fetuses and premature newborns showed that, with increasing maturity, the RR-intervals become longer and the amplitude of heart-rate variability higher [7,12,16,35]. These changes of vegetative parameters are accompanied by maturation of sympathetic and parasympathetic function of varying rates. The sympathetic nervous system develops and becomes functional earlier than the parasympathetic system, which becomes more important near term and thereafter [3]. Preliminary results of the comparison of heart-rate variability of PRT with premature newborns of less than 37 weeks conceptional age yielded no significant differences between the amplitudes of heart-rate variability in the three frequency bands. However in PRT, RR-intervals are shorter (QS: 383 ± 39 ms; AS: 377 ± 30 ms), as compared with premature newborns (QS: 445 ± 35 ms; AS: 432 ± 27 ms) [13].

During the normal development, as compared with 40 weeks conceptional age newborns, heart-rate first increases with at maximum of about 1–2 months of life [17]. Thereafter, heart-rate progressively decreases up to the 6th month of life. Thus, there is a transient increase of heart-rate during the normal development, but the heart-rate was lower (QS: 133 beats/min ; AS: 135 beats/min) [17] than the heart-rate measured in PRT (QS: 157 beats/min ; AS: 160 beats/min). Similar changes like those found for heart-rate were described by Schechtman et al. [30], concerning the developmental changes of the amplitude of heart-rate variability in the three frequency bands. During the first month of life, the amplitude first decreases and then increases. Thus, neither the available data from literature nor our present results allow us to decide whether higher heart-rate and lower amplitude of heart-rate variability in PRT are related to immaturity or to an accelerated development of neurovegetative control mechanisms.

Because in PRT heart-rate is higher, in comparison with prematures of 31–36 weeks conceptional age or infants at 1 month of life, some other influences should

be suspected. The adaptation to the extrauterine environment appears to be an additional factor affecting the development of prematurely born infants. In PRT, faster respiratory frequency was found, as compared to newborns of the same conceptional age [9]. Furthermore, a result of a prolonged postnatal increase of the standard metabolic rate [6] in prematurely born infants, as compared to term newborns, may be a sign of increased metabolic-rate in PRT, as compared to NB. This is supported by results of a prolonged increase of cold induced heat production, higher standard metabolic rate corrected by the high amount of extracellular fluid in prematurely born infants, as compared to full-term newborns [34], and higher threshold of the lower limit of the thermoneutral zone [24].

The dependence of the heart-rate on postnatal age rather than on conceptional age [19,36] could not be confirmed by our results. Thus, factors acting during the postnatal period may only modify the developmental course.

Our results show that in both groups, AS can be distinguished from QS by a higher amplitude of low-frequency variability. RR-intervals and high-frequency variability only showed differences between sleep states in NB, but not in PRT.

With regard to the control of mean heart-rate, vagal effects start to dominate over the sympathetic effects during the period of development investigated [23]. Furthermore, according to pharmacological investigations in neonatal lambs, the vagal component has been shown to have a stronger influence on heart-rate variability than the sympathetic component, particularly effecting rapid changes in heart-rate. The beta-adrenergic system shows effects on the slow changes of heart-rate represented by variability in the low-frequency band [33].

Our results provide evidence that the between-sleep state differences in sympathetic tone (related to factor 2 of factor analysis), are similar in NB and PRT. This agrees with results of investigations in animals and human prematures that the sympathetic nervous system develops and becomes functional early [3,7]. On the contrary, it seems that between-state differences in the vagal component are lower in PRT, because the differences between QS and AS, related to RR and HF (factor 1), are strongly reduced as compared to NB.

Our data show significant between-group (NB versus PRT) and between-sleep-state (QS versus AS) differences. This raises the question of the possibility of using RR-intervals and heart-rate variability in different frequency bands for the discrimination between NB and PRT on the one hand, and for between-state differentiation on the other hand.

In the case of the discrimination between NB and PRT it was possible to distinguish the two groups with errors less than 12% in QS and AS.

Between-state discrimination showed lower reliability, as compared to between-group discrimination. In both groups, the percentage of errors was lower for AS periods, but remained high (between 20 and 24% of errors) for QS periods. Slightly lower values of errors, shown by Harper et al. (15.2–20.0%) [18] and Rother et al. (16.6%) [29], may result from using different parameters. Thus, Harper et al. [18] studied heart-rate, respiratory rate and variability of heart-rate, and respiratory rate, cardiac interbeat intervals variability at respiratory rate, and lower frequencies. Rother et al. [29] studied mean coherence between heart-rate variability and respiration within the 0.26–0.97 Hz band.

In conclusion, our study demonstrates that PRT are different from NB concerning heart-rate and heart-rate variability in both QS and AS. The analysis of data suggests that this may be caused by a changed balance between the two parts of the vegetative nervous system with the diminished parasympathetic component of heart-rate control shortly after birth.

Finally, our data show that, if heart-rate and heart-rate variability allow correct discrimination between normal newborns and PRT, between-state discrimination using these parameters does not remain on the same level of accuracy in the two groups.

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Appendix

1. Load of factor on the parameters RR-interval, HF, MF and LF

Comparison	Factor 1	Factor 2
Between group comparison during QS		
RR	0.889	0.262
HF	0.903	0.226
MF	0.761	0.577
LF	0.258	0.958
Between group comparison during AS		
RR	0.868	0.332
HF	0.854	0.366
MF	0.655	0.697
LF	0.327	0.931
Between sleep state comparison in the group of NB		
RR	0.829	0.111
HF	0.828	0.085
MF	0.476	0.792
LF	−0.053	0.954
Between sleep state comparison in the group of PRT		
RR	0.940	0.125
HF	0.872	0.344
MF	0.476	0.840
LF	0.104	0.971

2. Standardised discriminant function

Discrimination between NB and PRT during QS:
$y = -0.785$ RR + 0.052 HF−0.001 MF + 0.032 LF
Discrimination between NB and PRT during AS:
$y = 1.112$ RR + 0.022 HF−0.46 MF + 0.337 LF
Discrimination between QS and AS in NB:
$y = 0.645$ RR + 0.956 HF-0.995 MF + 0.023 LF
Discrimination between QS and AS in PRT:
$y = -0.818$RR −0.518 HF + 1.438 MF −0.031 LF

3. Distribution of the recorded 512 RR-interval epochs between the groups

Group	Quiet sleep	Active sleep
NB 39–41	35	84
NB 37–38	40	52
PRT 39–41	29	40
PRT 37–38	59	61
Total	163	237