Heart Rate Variability in Preterm and Term Neonates

Fabio Augusto Selig, Emanuele Renata Tonolli, Érico Vinicius Campos Moreira da Silva, Moacir Fernandes de Godoy
Faculdade de Medicina de São José do Rio Preto, São José do Rio Preto, SP - Brazil

Abstract

Background: Several studies have demonstrated the importance of the autonomic nervous system through sympathetic and parasympathetic components in the management of the interaction between different parts of the body. These studies have applied linear and nonlinear techniques (Chaos Theory) for assessment in different situations, illnesses and age groups, using the heart rate variability (HRV).

Objective: To apply knowledge of linear and nonlinear dynamics in the assessment of preterm neonates (PTN), analyzing their HRV and comparing with healthy term neonates (NT).

Methods: Forty-eight premature neonates with different gestational ages had their heart rates assessed with the aid of a Polar Advanced S810i and HRV obtained by recording RR intervals. HRV was analyzed according to time (SDNN, RMSSD, SD1/SD2), frequency (VLF, LF, HF and LF/HF) and chaos (TAU and its standardization [TAU(n)], Lyapunov Exponent and Enthropy). PTN were compared with a group of 78 healthy NT with no perinatal events using Kruskal-Wallis nonparametric test.

Results: We detected a statistically significant difference between groups for all variables, both in time, frequency and chaos.

Conclusion: Preterm neonates have a less complex heart rate variability behavior than term neonates, which was evident in time, frequency and chaos. The study of heart rate variability in this group can be considered another tool in the evaluation of autonomic maturation and hence the progression to normality. (Arq Bras Cardiol. 2011; [online].ahead print, PP.0-0)

Keywords: Heart rate; infant, newborn; nonlinear dynamics.

Introduction

In the early twentieth century, the American physiologist Walter Bradford Cannon established the concept of homeostasis whose meaning was the self-regulating property of a system or organism to maintain its internal environment in stable condition despite a complex dynamics, in which the interaction of various components and its constant renewal keeps the proper functioning of the body. It is known that biological organisms are complex systems that generally have a nonlinear behavior. Nonlinear complex systems are fitted into a line of thought which came to be called the Chaos Theory.

Chaotic behavior is characteristic of systems in which, despite the seeming randomness, there is a hidden order, being dynamic, deterministic, governed by nonlinear equations and highly sensitive to initial conditions. This nonlinearity is essential for life, because it is what keeps the homeostasis of the organism. One can then infer that the chaotic behavior, when applied to biological systems, indicates proper operation, therefore, related to health, and not vice versa, as the vernacular concept of the term chaos could suggest.

Unlike the concept of equilibrium in which no interactions occur, maintaining homeostasis means maintaining body stability over time, which requires minor changes and adjustments every time, even subtle and unnoticed ones. The younger and healthier the adult individual is, the greater their ability to maintain stability. One of the key elements for this stability to occur is the appropriate sympathetic-parasympathetic balance. Several studies in the literature[1,2] showed that the more inadequate functioning of the autonomic nervous system, the more the human body tends to lose the chaotic behavior tending to linearity. This also seems true for newborns, especially premature infants, once the nervous system is not yet fully mature in this group of individuals[3].

The current concept of homeostasis, therefore, refers to an organism's tendency to maintain a relative regularity in organic functions regulated by the autonomic nervous system via sympathetic and parasympathetic components and under the influence of different systems (endocrinal, cardiovascular, etc.) and the environment. Based on this assumption, any physiological parameter that can be mapped or recorded, such as temperature, blood pressure, breathing pattern or walking, could reflect the higher or lower degree of chaotic behavior of the organism[4]. The parameters commonly used in the literature to analyze the chaotic pattern are the spontaneous

Mailing address: Moacir Fernandes de Godoy •
Rua Garabed Karabashian, 570 - Mansur Daud - 15070-600 - São José do Rio Preto, SP - Brazil
E-mail: moacirgodoy@cardiol.br, mfgodoy@netsite.com.br
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fluctuations that can be observed in heart rate, collectively called heart rate variability (HRV). Since the magnitude of such fluctuations could be measured, HRV could, in addition, be further studied and compared by different approaches. It can be analyzed under three specific foci, called domains - time, frequency and chaos[5,6].

Therefore, the objective of this study was:

1. To characterize the pattern of heart rate variability in the domains of time, frequency and chaos in premature infants, and follow the evolution of this pattern with the maturation of the autonomic nervous system;
2. To characterize the differences in the behavior of heart rate variability of preterm neonates according to gestational age and compared to a group of term neonates.

Methods

The study started in 2005, after its approval by the Ethics Committee on Human Research of the Institution. After explaining the study to parents and/or guardians, who signed an informed consent, and authorization from the department heads responsible for the neonatal intensive care units where data collection was performed, questionnaires were applied, relevant data from medical records was obtained, and physical evaluations were performed to determine the following aspects: identification, gender, type of delivery (vaginal or cesarean), number of maternal pregnancies (individualizing the number of vaginal deliveries, caesarean sections and abortions), gestational age at birth by the Parkin[7] method, weight birth and characterization in normal value percentile according to gestational age, weight at the time of evaluation, APGAR[8] index in the first and fifth minutes, age in days at the time of evaluation, type of ventilation (spontaneous, assisted with positive pressure devices or mechanical), fraction of oxygen delivered and existence and characterization of comorbidities.

According to the diagnostic protocols of potential causes of prematurity in services where data collection was performed, all preterm neonates were subjected to laboratory tests of complete blood count, C reactive protein and arterial blood gases at the time of initial evaluation of heart rate variability. In subsequent evaluations, tests were done in the presence of justifiable clinical criteria. These data were compared to the comorbidities, to obtain numerical parameters of characterization of infectious processes and oxygenation/ventilation. Birth weight was characterized according to sex and intrauterine growth curve[9], being classified according to this percentile.

To assess the presence or absence of active infectious process, we used the complete blood count and C-reactive protein in Rodwell's[10] hematologic score. The degree of lung damage was assessed and compared between patients in the same stage, using the parameters of ventilation mode - spontaneous, inhaled oxygen, noninvasive ventilation with positive pressure [CPAP] or mechanical ventilation - and arterial blood gas - pH, pCO_2, pO_2 and O_2 saturation.

Analysis of heart rate variability

The heart rate variability can be defined as the amount of fluctuations in heart rate or heart rate compared to the average cardiac rhythm, and can be a useful tool in assessing autonomic nervous system by its sympathetic and parasympathetic components and balance, and its reflection in the cardiorespiratory control system. Data collection and analysis of variability are easy to be carried out, are not invasive, and have a good reproducibility under appropriate circumstances.

Electrocardiographic data (1,000 consecutive RR intervals) were captured digitally on a POLAR ADVANCED S810i device already validated for this purpose[11,12] and transferred to a computer for analysis. The technique of capturing the RR intervals in preterm neonates can be facilitated by adapting the capturer to electrodes commonly used in cardiac monitoring as shown in Figure 1. These intervals were digitally filtered to eliminate premature beats and noises, and then manually reviewed to exclude residual artifacts. Only time series with less than 10% of artifacts were included for analysis.

The variables analyzed in the time domain were average RR interval, standard deviation of normal beats (SDNN), square root of mean squared differences between adjacent RR intervals (RMSDD) and the relation between the standard deviations 1 and 2 obtained by Poincaré-Bendixson (SD1/SD2) chart.

For the frequency domain, the variables very low frequency (VLF), low frequency (LF) and high frequency (HF) were used, and the relationship between LF and HF.

The assessment in the Chaos domain used the variables of autocorrelation coefficient (TAU), Lyapunov exponent (LE) and entropy, widely used in the literature for the characterization of chaotic behavior in a wide variety of clinical situations. As the autocorrelation coefficient depends directly on the heart rate, the TAU was corrected according to heart rate, called normalized TAU coefficient ($TAU_{(n)}$).

Statistical analysis

Sequential evaluations in the same patient were considered for statistical purposes, such as new cases. Evolutionary comparison of each individual and within groups was not performed, but between the medians of the group as a whole with the medians of a group of term neonates (TN GROUP) used as control. To calculate the LE variables and Entropy the dimensions 3 and 10 with delay of 1 in both cases were used, respectively. The corrected gestational age was obtained by multiplying the result of the method of Parkin by 7 (days a week), plus the actual number of days postpartum.

Aiming to keep the differentiation between the two groups subjected to statistical comparison, those assessments whose corrected age was greater than or equal to the age of term were excluded from the preterm group (37 weeks, the boundary between preterm and term) minus 7 days (preterm group - PTN).

Data from the term neonates group (NT) were obtained from a specific database belonging to a research group on nonlinear and complex behavior in humans. Individuals in

Figure 1 - Fastening Polar S810i in a preterm neonate using platinum electrodes for cardiac monitoring.

this group were all born after 37 weeks of gestation and were evaluated by their third day of life at the most, before hospital discharge, and none of them had comorbidity.

Statistical calculations were performed on the variables with the aid of the programs CDA_Pro,GraphPad InStat v. 3.06 and HRV analysis software v. 11[13]. The statistical test used for comparison between groups was the nonparametric Kruskal-Wallis test with multiple comparisons. An alpha error of 5% was assumed. $P \leq 0.05$ was considered significant.

Findings

Comparison between the groups PTN and TN was performed in domains of time, frequency and chaos, aiming to examine whether premature birth and hence the immaturity of the sympathetic and parasympathetic systems could directly influence the degree and type of behavior of heart rate variability of these individuals.

The TPN group was composed of 48 assessments in 27 preterm patients, 16 males and 11 females. The first neonate to undergo data collection was -69 (minus 69) days of life, while the nearest neonate of the term had -9 (minus 9) days, an average of -27.4 days of corrected age. Mean birth weight was 1,476 g (770 g to 2380 g), and in subsequent evaluations it was 1,463 g (765 g to 2,380 g). This difference is due to the fact that most assessments have been done with a few days of life, during which PTNs tend to lose weight.

Concerning the data obtained by a Polar device, samples whose error (amount of artifacts) was greater than 10% were discarded, and the final average was equal to 3.53% (0.1% to 9.3%). The RR intervals were obtained in the period between 11.5 and 46.5 minutes (average of 26.0 min.) with an average amount of 3,642 total beats (beats 1,641-6,380). For comparative uniformity, time series of 1,000 RR intervals were analyzed.

During the time of hospitalization, and therefore during the time of collection of samples, two preterm neonates progressed to lethal condition: the first was on spontaneous ventilation, with mild jaundice and died on the fifth day of life, hours after data collection of second sample by aspiration of milk followed by cardiac arrest. The second death occurred in a very low-weight neonate (770 g at birth) and evaluated on the first day of life, dying in the second week of life from sepsis associated with prematurity.

This study included 78 assessments of term neonates (NT) with gestational age greater than 37 weeks, between zero and three days of life (median of one day). These ages have stimulated the establishment of the abovementioned TPN group, in an attempt to further differentiate this with the TN group. The average weight of this group at birth was 3,085 g (1,940-3,985 g).

Just like the assessment of preterm neonates, the data obtained by a Polar device discarded samples whose error (amount of artifacts) was greater than 10%, and the final average was equal to 4.1% (0.6% to 9.1%).

The RR intervals were obtained in the period between 9.0 and 14.0 minutes (average of 11.0 min.) with an average amount of 1,499 beats (1,038-2,084 beats). All variables in different domains as well as their relevant values are shown in Table 1.

Evaluations in the time domain

In the analysis in the time domain, the parameters used were mean RR and standard deviation (known as SDNN); this is variable present in most papers on this subject. The parameter square root of the mean square of RR intervals (RMSSD) was also used to estimate the variability of RR intervals in a short period of time.

The SDNN index represents the sympathetic and parasympathetic activities. The RMSSD index represents only the parasympathetic activity. Finally, the intervals were analyzed using the Poincaré chart, in which two subsequent beats are correlated obtaining thus the standard deviations of short-term variability, SD1 (reflecting the parasympathetic nervous system) and long-term, SD2 (related to sympathetic nervous system). By dividing SD1 by SD2, we obtain the relationship of balance between the two systems (parasympathetic/sympathetic).

The variables mean RR, SDNN and RMSSD showed, through the nonparametric Kruskal-Wallis test, multiple comparisons with statistically significant difference between TN groups against PTN ($p < 0.0001$), the same occurring with the variable SD1/SD2 ($p = 0.04$).

Evaluations in the frequency domain

The Fourier transformer algorithm was applied to decompose sequential series of RR intervals at different frequencies and amplitudes, obtaining thus the data of VLF, LF (especially related to the behavior of the sympathetic system) and HF (basically related to the parasympathetic system).

The calculation of the LF/HF is another way to establish the relationship between the two components of the autonomic nervous system, this time indicating the sympathetic/parasympathetic balance.

The variables VLF, LF and HF presented, through the nonparametric Kruskal-Wallis test, multiple comparisons with statistically significant difference between TN groups against PTN ($p < 0.0001$), as well as the variable LF/HF ($p = 0.0149$).

Evaluations in the chaos domain

The variables studied in the field of chaos were the Autocorrelation Coefficient (TAU) and its Standardization ($TAU_{(n)}$), the Lyapunov exponent (LE) and Entropy.

The variables TAU Coefficient, $TAU_{(n)}$, Lyapunov Exponent and Entropy, presented, through the nonparametric Kruskal-Wallis test with multiple comparisons, a statistically significant difference between groups TN against PTN, respectively, $p = 0.0008$, $p = 0.0008$, $p < 0.001$ and $p = 0.0079$.-

Discussion

Since applicability to the human body was considered, the evaluation of nonlinear dynamics in heart rate variability has been used to assess health in a variety of situations, such as risk stratification in cardiac patients, for example[14]. As these tests

Table 1 - **Variables in the various domains and their values**

		n	Average	SD	Maximum	TQ	Median	LQ	Minimum
RMSSD (ms)	PTN	48	5.9	3.7	17.7	8.1	5.4	2.8	1.1
	RNT	78	11.1	6.8	38.7	14.3	9.5	5.9	2.9
MEAN RR (ms)	PTN	48	411.2	53.3	640	434	402	381	335
	RNT	78	485.3	50.7	600	519.2	486	446.7	390
SDNN (ms)	PTN	48	13.8	6.8	31	17	14	9	2
	RNT	78	22.6	7.9	46	28	20.5	17	10
SD1/SD2	PTN	48	0.15	0.06	0.33	0.19	0.15	0.11	0.03
	RNT	78	0.19	0.09	0.58	0.24	0.18	0.12	0.07
LF (ms^2)	PTN	48	47.9	53.7	256	65.7	35.5	10.7	0
	RNT	78	115.7	87.9	466	162.7	87.5	54.2	7
HF (ms^2)	PTN	48	11.4	12.6	46	20	6.5	1.2	0
	RNT	78	33	34	216	49	19.5	10	2
LF/HF	PTN	48	7.6	6.7	35.5	9.3	5	3.6	1
	RNT	78	4.7	2.3	13.3	5.9	4.1	2.9	1.3
VLF (ms^2)	PTN	48	47.3	50.7	245	63.2	27.5	14.2	1
	RNT	78	129.8	111.1	652	172.5	94.5	53	20
Entropy	PTN	48	0.4	0.1	0.7	0.5	0.5	0.4	0.2
	RNT	78	0.5	0.1	0.8	0.6	0.5	0.4	0.2
LE	PTN	48	0.6	0.1	1	0.7	0.5	0.4	0.2
	RNT	78	0.8	0.1	1	0.9	0.8	0.7	0.4
$TAU_{(n)}$	PTN	48	30.3	27.7	99.5	47	21.9	7.1	2.4
	RNT	78	19.3	21.9	87.6	25.1	10.1	4.6	1.9

SD - standard deviation; TQ - top quartile; LQ - lower quartile; ms - milliseconds.

were being established, the direct relationship between the greater ability to adapt to different situations (variability) with health and disease has been increasingly characterized. The heart rate variability is therefore only a reflex resulting from the various and complex simultaneous organic reactions that occur as a whole, and any situation which alters the natural state of the organism could also change this reflex[15].

Indeed, age has a great influence on the balance of sympathetic and parasympathetic systems, knowing that the older is the age, the lower the heart rate variability; that is, the elderly have much lower variability than young adults. This relationship, however, is inverted when going from young adults toward neonates, those with less variability than young adults probably due to an autonomic nervous system not fully developed yet. This has been demonstrated in the literature, but data reporting comparative evaluations between term neonates and preterm neonates are scarce, especially evaluations in the chaos domain (nonlinear).

Considering the above, it would be correct to assume that term neonates have a more chaotic (or less linear) pattern of behavior than premature neonates, since the latter, who have no well balanced sympathetic-parasympathetic systems, can also be considered "less healthy" within the concept of health-disease. This logic is explained easily because some intrinsic or extrinsic factors must occur to justify delivery before the term, 37 weeks. It is also expected that different age groups and the presence or absence of comorbidities change the results of the variables used in assessing the standard of nonlinear behavior.

This study was intended to clarify whether due to the immaturity of the nervous system resulting from prematurity there would be any significant difference between the chaotic behavior of those two groups: term and preterm neonates.

As the TN group consisted of patients aged 1 to 3 days and because of the limitations of the Parkin method (given in weeks), the PTN group was formed only by cases of corrected gestational age smaller than the term minus 7 days.

The variable of key importance in the time domain is the average of RR intervals, as it is from its comparison with the fluctuations in heart rate that the other statistical calculations are performed. The four variables studied in this domain - mean RR, SDNN, RMSSD and SD1/SD2 - showed statistically significant difference between the groups PTN and TN. The mean RR was significantly higher in the TN compared with the PTN, as well as the SDNN, which compares that average with its fluctuations. The SDNN is more expressive when data collection is performed over a long period of time, usually within 24 hours, but even so, in this study, HRV of term neonates was significantly higher than in preterm neonates. The square root of the mean square of RR intervals (RMSSD) better expresses these fluctuations in a short period of time. This variable, the result of mean and median were also significantly higher in TN. This means that term neonates had higher heart rate fluctuations in relation to their average in all variables in the time domain and therefore had greater variability.

One way of comparing the variability of short and long term is to express these two events graphically on a histogram made up of a heartbeat on the ordinate and its predecessor in the abscissa, called the Poincaré chart. When the points on this chart are dispersed, it means that this sample is random (one beat bears little relation to each other). In the samples that follow a chaotic pattern, the chart is presented in the form of an ellipse or bouquet. This graphic sample derives the values of standard deviations 1 and 2 (SD1 and SD2), which correspond, respectively, to heart rate variability in the short term, reflex of the parasympathetic nervous system, and in the long-term, reflex of the sympathetic nervous system. Then, by dividing SD1 by SD2, we obtain the relationship between these two systems. In absolute numbers, the values of SD1/SD2 were lower for preterm neonates compared with term neonates, meaning a greater influence of the sympathetic nervous system in that group.

The main advantage of studying samples in the frequency domain is that in the stratification of the spectral analysis of RR intervals it is possible to characterize specific oscillations by determining the influence of factors such as blood pressure and ventilation, for example, which can influence heart rate variability. The final value in hertz is obtained by applying the algorithm of Fourier transformer, which decomposes sequential series of RR intervals at different frequencies and amplitudes; this result was divided by the average RR interval.

Within the high frequency band, above 0.15 Hz, we find wave peaks corresponding to respiratory sinus arrhythmia. TN higher HF power values (mean of 33 ms^2) compared with PTN (11.4 ms^2) could then be explained by the type of ventilation of patients, as in the case of the term group all of them were in spontaneous ventilation against 87.5% to 89% in the preterm neonates. The same significant difference occurred in the comparison between TN and PTN in the bands of low and very low frequency, showing that the difference between these groups is greater than that caused solely by intrinsic "noise" (baroreceptors, thermoreceptors etc).

In the chaos domain, the coefficient TAU autocorrelates beat with beat, analyzing the number of beats necessary for the autocorrelation to fall below the limit of 36%; i.e., it quantifies the regularity of heartbeats. If this drop is very fast, the individual has a more random behavior, while if it is too slow, it is more linear. Therefore, in addition to the TAU obtained by statistical programs, we proceeded to a correction of this value by heart rate, starting from the principle that the greater this value, the faster the drop of the exponent occurs.

The values of TAU corrected by the frequency were designated Normalized TAU ($TAU_{(n)}$), and the comparison between the patients studied showed a statistically significant difference between term and preterm neonates. Slowness in the decline of the curve and a smaller difference in the beat to beat comparison of the group of premature neonates were found in relation to those born at term, i.e., more linear pattern in the first compared to the second.

The Lyapunov exponent measures the "Butterfly Effect", or the changes in the final results in relation to changes in initial data, even though these are very small. Mathematically, the more the result is close to 1, the greater the chaotic pattern, and the closer to zero, the greater is the linear pattern. We use the lowest entry value into the program CDA_PRO D3/N1 (size 3 and delay 1), which means a sequential comparison of groups of three consecutive RR with interval of one beating between each group. For the Lyapunov exponent, PTN is significantly different from TN, with $p < 0.0001$. Still, concerning absolute values, the TN group was closer to 1 in the LE than the PTN; this fact is explained by the probable immaturity of the autonomic nervous system of this group, which is more linear than the term in comparative terms.

Entropy is the energy expended to produce work. The more linear is the behavior of the individual, the greater is its positive entropy, because greater is the irrecoverable loss of energy to the universe. Nevertheless, considering the as a concept-entropy rather than a state-entropy, based on the Information Theory (Shannon Entropy), it is extrapolated that in time series, this loss of energy would be equivalent to the progressive loss of adaptability; i.e., the loss of information up to the most linear pattern possible - death -, a moment of maximum positive Entropy. Mathematically, in the calculation of Shannon entropy the signal is negative; that is, the higher the entropy value, the more information and consequently greater adaptability to the environment.

The statistical analysis incorporated the parameters D10N1, which means sequential comparison of groups of 10 consecutive RR with intervals of one beating between each group. Entropy of preterm neonates was small but statistically lower than those at term, showing that the first group, due to lower relative age, has a lower biotic potential.

Regarding the comparison of epidemiological data, it seems obvious to say that, as the preterm birth has occurred, the pregnancy had some type of infection, in contrast to the control group composed exclusively of neonates born at term and healthy. The reasons for preterm delivery may be several, such as maternal infection processes, oligo-hydramnios or cervical incontinence, for example. Therefore, through epidemiological data, we characterized the cause of prematurity and possible postnatal factors that acted as comorbidities. These are the different causes of preterm birth that explain so different weights birth for neonates with the same gestational age, but this variable was not statistically significant when comparing preterm neonates. Other epidemiological data, especially the type of ventilation and the presence of hematologic score of infection could not be further evaluated because they are not evolutionary data like age.

Finally, the collection of data revealed that two patients died. The circumstances surrounding these deaths were quite different. One patient underwent a second evaluation on the fifth day of life outside the incubator heated without infection and with full oral feeding. A few hours after the evaluation, the patient had sudden cardiac arrest after feeding, milk was found in the airway during endotracheal intubation procedure. For this case, the SDNN value was 25, much closer to the average of the TN (22.6) than PTN (13.8). The same pattern occurred for $TAU_{(n)}$, a value of 9.4, which is relatively low and compatible with the TN group that had a mean of 19.3 than with the PTN group with a mean of 30.3. These data may mean that the event that resulted in this patient's death was accidental, because his heart rate variability and chaotic pattern were close to those of term neonates[16].

The second death occurred in the most premature and lightest patient in the sample. The only evaluation was performed on the first day of life, and showed SDNN of 15 and $TAU_{(n)}$ of 31.6. As opposed to the findings described elsewhere in this study, the comparison of these values with those obtained in the averages of the groups TN and PTN draws this case much closer to premature infants and linearity other than to the chaotic pattern. This outcome was unsatisfactory, with the very preterm combined with septicemia, leading to a lethal outcome, suggesting the clinical and diagnostic potential of the evaluation of heart rate variability.

Conclusions

Preterm neonates have a less complex heart rate variability behavior than term neonates, which was evident in time, frequency and chaos. This should be interpreted as indicative of minor neurological development, a fact that was independent of gestational age corrected, since preterm infants showed a significantly smaller variability than the normal neonates. The study of heart rate variability in this group can be considered another tool in the evaluation of autonomic maturation and hence the progression to normality. Further studies may detect from what age premature reach the development found in a neonate at term.

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