Childs Nerv Syst (2017) 33:1053–1063
DOI 10.1007/s00381-017-3436-8

REVIEW PAPER

Autonomic nervous system in newborns: a review based on heart rate variability

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Received: 26 March 2017 / Accepted: 26 April 2017 / Published online: 13 May 2017

Abstract
Purpose Heart rate variability (HRV) has been a relevant tool in the assessment of the autonomic nervous system (ANS). How autonomic control normally develops in newborns and how it is affected by gestational age (GA) is not fully understood. We aimed to review the current evidence on HRV in preterm (PT) and term neonates (TN) and investigate the relation between GA and the maturation of ANS.
Methods Electronic databases (Pubmed, World of Science, and Scopus) were searched for studies from 1997 to 2017 examining HRV (time and frequency domain) in PT and TN who followed to the Task Force (1996) guidelines. Ten studies met our inclusion criteria and were analyzed.
Results An increasing postnatal age was related to a significant rise of HRV parameters. Several significant differences were established between PT and TN (lower values on PTN), also found when PTN are evaluated at their theoretical term age. In general, there were no relevant results on LF/HF (low frequency/high frequency) ratio, as being an adequate marker of sympathovagal balance, but this was not a universal finding of this review. Frequency parameters that were more often used to evaluate newborns and HF showed the most relevant increase with GA.
Conclusions HRV is an important tool to assess the maturation of ANS in newborns and there is a progressive increasing on cardiac parasympathetic activity, according to GA. HF appears as a relevant parameter in measurements of vagal maturation. HRV is higher in TN when compared with PTN and is more studied in newborns in terms of frequency domain. Standard recommendations in newborns remain to be fully defined.

Keywords Heart rate variability · Autonomic nervous system · Newborns · Infants · Neonates · Preterm · Term

Introduction

Heart rate variability (HRV) refers to beat-to-beat fluctuations in either heart rate or the duration of the RR interval and has become a relevant clinical and investigational non-invasive tool [1, 2].

The heart rate (HR) is modulated by the cardiac sinoatrial node located in the heart, that receives nerve impulses from the autonomic nervous system (ANS), including both sympathetic and parasympathetic branches [2]. Therefore, HRV is widely used to efficiently monitor the human body and, more precisely, to assess the ANS by its sympathetic and parasympathetic components [3]. Generally, increased HRV is linked to good health and decreased level of stress [2].

The impaired function of ANS is a consequence from the inbalance of the parasympathetic and the sympathetic systems. This can be applied to newborns, especially preterm neonates (PTN), whose ANS is not yet fully developed [4, 5].

The maturation of ANS needs at least 37 weeks of intrauterine development to reach a threshold value [6], in which newborns delivered before the 37th week are defined as PTN [7].

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The maturation of ANS in PTN is accompanied by an increase of HRV indices [8, 9]. In the matter of maturational stages, it is important to consider the increasing importance of the development of the parasympathetic branch of ANS in PTN [10].

Since the 1970s several measures have been developed to quantify the beat-by-beat fluctuations in HR and according to Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophisiology there are different methods to measure HRV [1].

In contrast to data concerning the autonomic control of the heart in adult population, much less work has been conducted in newborns, due to difficulties on standardization of the different methods.

Given this background, one of the aims of this review was to examine if there is a relevant evidence that the gestational age (GA) influences the autonomic control and to find how maturation of SNA occurs in newborns, including preterm (PT) and term neonates (TN), by assessing HRV parameters. Another purpose of this review was to determine which parameters have more evidence and significant results in newborns' assessments.

Methods

Literature research strategy and inclusion criteria

A systematic research of the literature was performed in January 2017, based on three databases (PubMed, Web of Science, and Scopus) with the following terms: (heart rate variability) and (autonomic nervous system) and ((newborns) or (infants), or (neonates)) and ((preterm) or (term)). One hundred five articles from PubMed, 120 from Web of Science and 104 from Scopus were found. After withdrawing duplicates, abstracts were screened, according to following criteria: articles from 1997 to 2017, findings on human PT or TN, with no congenital diseases or other comorbidities, from empirical investigations (excluding meta-analysis, reviews and single-case reports), using the HRV assessment with at least one index of HRV measurement in accordance with the guidelines provided by the Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology (1996), and available as full-text written in Portuguese or English. According to inclusion criteria and abstracts' information, ten articles were included. Full texts of articles matching pre-defined criteria were screened.

Data extraction

Data extraction records were performed for each of the ten studies eligible for inclusion. The aim/study design, author/year, participant characteristics, parameters used for the measurement of HRV analysis (time and frequency domain), experimental conditions, and key findings were extracted.

Results

Based on Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophisiology [1] and several studies [11–13] about HRV measurements on neonatal period, there is a list of parameters that can be evaluated by both time and frequency domain, summarized on Tables 1 and 2.

Given the parameters summarized above, we gathered the data available on each study and proceeded to expose them on Tables 3, 4 and 5.

Primarily, we verified that there were variations between frequency bandwidths reference values from the included studies and the values suggested by the Task Force [1] (Table 2). The majority of groups utilize 0.2 HZ as the cut-off point between LF and HF bands. Most studies excluding a VLF band start LF at 0.02 Hz and those including VLF band use 0.04 Hz as the point dividing the two (Table 3).

Longin E et al. [14] analyzed a population of healthy TN and tried to establish normative data of HRV components in terms of time and frequency domains (Table 3). It is important to notice that in this study, they used a different definition on frequency parameters and determined a medium frequency (MF) between 0.05 and 0.2 Hz, differently of what it is found on Task Force Guidelines (Table 2). Both components were found with a significant correlation with increasing postnatal age. RMSDD, HF, MF, LF, and TP were higher in advanced postnatal age. Therefore, it is possible to assume that an increasing postnatal age is related to a significant rise of HRV parameters.

Considering the inclusion criteria of this review, there were more evidences about PTN than TN. In fact, several studies assessed HRV parameters on PTN (Table 3). One of them [15] clearly demonstrated HRV time domain anticorrelation between HF and LF components in PTN, meaning that the maximum of one curve matches with the minimum of the other curve. So, they found that an

Table 1 Selected time domain measures of HRV [1]

Variable	Units	Description	Interpretation
SDNN	ms	Standard deviation of all RR intervals	Estimates overall HRV
SDANN	ms	Standard deviation of the averages of RR intervals in all 5 min segments of entire recording	Estimates long-term components of HRV
RMSSD	ms	The square root of the mean of the sum of the squares of differences between adjacent RR intervals	Estimates short-term components of HRV

ms milliseconds

increase of the LF is correlated with a decrease of HF on PTN (Table 3).

Still respectively, the population of PTN, Nakamura T et al. [16] investigated how some time and frequency domain parameters change with age. The SDNN increased with age. In terms of the main power components (HF and LF), both of them tended to decrease and LF/HF ratio to increase with age (Table 3).

Moreover, when assessed HRV time domain indices on PTN, Lucchni et al. [17] discovered an increasing of SDNN and RMSSD with age.

According to the comparison between PTN born before 32 weeks with those born after 32 weeks, considering the frequency parameters of HRV [18] were found significant differences on Ptot, LF, MF, and HF (higher in the second group). Therewithal, attending to the relative changes, the greatest variations were measurable for HF and MF. There were no significant differences on MF/LF ratio. Overall, with these findings, it is possible to accept that there are significant differences for most of HRV frequency parameters, according to gestational age of PTN, except for MF/LF ratio. As previously referred, although MF is not found as a frequency parameter according to Task Force, the authors applied this definition also on this study (Table 3).

According to Table 4, with regard to the comparison between HRV between PT and TN, several significant differences are found. In general, PTN showed significant lower HRV parameters than TN. Selig F et al. [4] analyzed HRV parameters and characterized time and frequency domains. The variables SDNN and RMSSD were significantly different in PTN and TN groups. Both of them were found higher in the last group. The evaluations regarding the frequency domain included the data of HF, LF, and VLF. The comparisons between PTN and TN with statistically significant differences revealed higher values in TN group. LF/HF ratio was found higher in PTN.

In a second assessment on a previously mentioned study [18], the authors compared all PT (born before 32 weeks and after 32 weeks) with TN. The frequency parameters (Ptot, HF, MF, LF, and MF/HF ratio) revealed significant differences: Ptot, HF, MF, and LF were higher in PTN and MF/HF ratio lower in the same population. According to relative changes in these variables, HF and LF revealed the most relevant increase.

Table 2 Selected frequency domain measures of HRV [1]

Variable	Units	Description	Frequency range	Interpretation
HF	ms^2	Power in high frequency range	0.15–0.4 Hz	Major contributor for efferent vagal activity
HF norm	n.u.	HF power in normalized units		
LF	ms^2	Power in low frequency range	0.04–0.15 Hz	Represents both sympathetic and parasympathetic activity
LF norm	n.u.	LF power in normalized units		
VLF	ms^2	Power in very low frequency range	≤ 0.04 Hz	
LF/HF		Ratio LF [ms^2]/HF [ms^2]		Possible markers of sympathetic-parasympathetic balance
TP[a]	ms^2	Total Power: variance of all NN intervals	Approximately ≤0.04 Hz	

ms^2 milliseconds^2 , *Hz* Hertz, *n.u.* normalized units

[a] Some studies apply the *Ptot* abbreviation, representing TP

There are some prospective evaluations on ANS maturity in PTN at their theoretical term age and in TN, in order to investigate a possible deficit in ANS in PTN, at theoretical term, when compared with TN (Table 5).

In general, PTN had a reduced ANS activity when compared with TN [19]. The most significant differences were found in terms of HF parameter, which increased with gestational age (from less than 27 weeks to more than 38). According to PTN group, HF values were lower than TN. The PTN showed a linear correlation between theoretical age and HF. However, when PTN were compared considering gestational age and divided in three different groups such as: (1) <27 weeks, (2) 28–31 weeks, and (3) 32–37 weeks, there were no significant differences. HF was only found after 38th week, so none of PTN reached the HF value. Furthermore, considering other frequency parameters (LF, VLF, and HF/LF ratio), no significant differences were presented.

Following a similar analysis [20], PTN (evaluated at the time of the theoretical term) had statistically lower values of Ptot, HF, LF, and VLF when compared with TN (at birth), but LF/HF ratio was not significantly different between these two groups. Beyond that, significant differences were found on LFnu and HFnu (Table 5).

According to a follow-up of ANS activity in PTN during 7 weeks after birth [21], all PTN groups (regardless the degree of prematurity) presented extremely low HF values measured in the first week of life, when compared with TN control group. Besides the fact that HF was significant lower, there were also found significant differences for Ptot, LF, and VLF, in contrast with LF/HF ratio, LFnu, and HFnu.

In contrast, when PTN were longitudinally analyzed from 28 to 34-week-old, no significant differences were evident on TP, HF, and LF/HF ratio values during the 7 weeks analysis after birth [22].

Discussion

Explanation of findings

Currently, the importance of autonomic control by HRV has been evaluated in several studies concerning newborns' populations. Nevertheless, the Task Force [1] about HRV measurement represents the background knowledge about this topic and it is well established among adults' assessments. The lack of standardization on the earliest stages of human development leads to the adaptation of some measurement parameters, considering neonatal physiology. Thus, frequency bandwidths are frequently adjusted in concordance to the literature [12, 13], as it is noticed on Tables 3, 4, and 5 different values for frequency domain parameters. Some authors [14, 18] defined different variables that are not included on Task Force [1], as MF and MF/HF ratio. MF is defined in both studies between 0.05 and 0.2 Hz, approximately, the frequency range associated with LF on Task Force [1] (Table 2).

The major findings of this literature review were based on the concept that at term cardiovascular system is not yet fully mature, and development continues for several weeks after birth, and it is essentially controlled by the ANS [23].

In terms of HRV in TN, it was found a significant increasing of time and frequency domains parameters, according to postnatal age.

Among PTN, it is more consensual that HRV increases with gestational age, showing the increasing of parasympathetic system influence on autonomic control. These results are in conformity with literature previous to 1997 [8, 24, 25].

Despite the differences on frequency values referred on results analysis, it is possible to conclude about the role of HF, since all the studies analyzed used frequencies higher than 0.15 Hz, reflecting a relevant uniformity at high frequencies. Therefore, HF seems to have an important role, showing the most marked increase, a curious fact, also described in the past for Clairambault et al. [9] Thus, as HF suggests a parasympathetic influence on cardiac control, that can reflect a greater maturation of vagal activity during ANS development in PTN.

There are some evidence of a decreasing tendency of HF and LF in PTN, also found in the literature [26] and reflecting that parasympathetic activity can decrease after birth.

A comparison between PT and TN seems relevant, because it has been demonstrated the role of age on the maturation of ANS, but there are few studies comparing the two populations.

TN were found with significant higher values of time and frequency parameters than PTN. The findings on time domain can be explained by the fact that TN have higher heart rate fluctuations in comparison to their average.

Concerning to frequency domain, HF seems to experiment the most marked increasing between PTN and TN, as demonstrated before when PTN were evaluated.

Another interesting comparison done in several longitudinal studies with PTN at their theoretical term age and TN can also evaluate ANS maturation. It was only found a marked increase of parasympathetic activity in TN. Considering frequency domain parameters, HRV is commonly elevated in TN in comparison with PTN at theoretical age. This can mean that prematurity has impact on the parasympathetic activity. The variable that seems to be more associated with that is HF, with more solid results in several studies. An interesting finding was in PTN, in which none of them reached a HF level before the 38th week of theoretical GA, that can be justified by a delay on parasympathetic maturation due to prematurity, even after the theoretical birth age.

In other hand, the sympathetic predominance that could be illustrated by an elevation of LF/HF ratio is not well characterized on this review. In general, there are no significant results considering the LF/HF ratio. Besides, the relevance of LF/HF ratio was found on one study [15], justified by the anticorrelation between LF and HF that can be interpreted as the sympathovagal balance. Considering that, there are several studies prior to 1997 about sympathovagal balance in newborns based on LF/HF ratio analysis [25, 27, 28]. However, according to the most recent literature, the role HF/LF ratio is not well defined, so it is not evident that it can be used for evaluate sympathetic-parasympathetic balance [3, 29].

Limitations and future studies

The most relevant limitation of this review consists on lack of standardization of the Task Force recommendations for neonatal population. Standard values described may not be applicable for newborns so, guidelines have been constantly adapted from adult population. In consequence, different authors use different ranges of frequency parameters. To establish the comparison between studies becomes more difficult and inaccurate.

Besides that, there are few studies concerning newborns HRV assessment, and each study uses small samples. Furthermore, obtaining a basal ECG recording with no artifacts in newborns is difficult and it can influence the HRV assessment.

Despite the present review taking a rigorous methodology and including only those studies based on published guidelines for assessing HRV [1], a considerable heterogeneity in the approaches utilized was evident (e.g., HRV indices reported, body position used, inclusion/exclusion criteria, and period of recordings). Moreover, diversified sampling rates lead to difficulties on the comparison between studies, due to more or less acuity of the results, and considering higher or lower rates, respectively.

According to that, it is mandatory to determine solid guidelines concerning newborns, to better guide future studies and better interpret the results found. More than encourage new studies about this topic, we firstly suggest a creation of a Task Force of the European Society of Cardiology, European Society of Neonatology, and the North American Society of Pacing and Electrophysiology about standards of measurement, physiological interpretation and clinical use of HRV on newborns' population. As it is known, the neonates heart rate differs from that from the adults; so, the frequency ranges recommended by the Task Force [1] may not be appropriate for newborn infants due to the shift of the spectrum for high frequencies. Some authors suggest a higher HF range for newborns, for example. This lack of standardization leads to different methods being used which makes interpretation of results much more difficult.

The recognition and standardization of the relevant differences between newborns and adults is very important to solve this problem. One of the first steps is to determine the appropriate cut-off points of frequency ranges for newborns. A second step could be the analysis of normative data on HRV measured from a large sample of healthy newborns, applying the standardized methods that would facilitate the evaluation and application of this modality in a variety of clinical settings.

Conclusions

The available evidence indicates a marked and progressive increase in cardiac parasympathetic activity relative to sympathetic activity in newborns. Advanced GA is correlated with an increasing of HRV, an important tool to assess the maturation of ANS. Frequency domain are more commonly used on the studies included on this review, and HF shows a relevant role in measurements of vagal maturation. Despite this, universal guidelines in this population remain to be fully defined.

Compliance with ethical standards

Conflicts of interests On behalf of all authors, the corresponding author states that there is no conflict of interest.

Appendix

Table 3 HRV in TN and PTN

Aim design	Authors (year)	Participants	HRV measurement	Experimental conditions	Key findings
HRV in TN (transversal study)	Longin E et al. (2005) [14]	TN (n = 88) Mean GA 39 weeks Age 1–7 days Mean birth weight 3448 g Mean length 52 cm Mean Apgar (5 min) 10 Mean umbilical cord pH 7.24	VAGUS 2100 Sampling rate 256 Hz Duration of recording 10 min TD: RMSSD FD: TP (<1 Hz), HF (0.2–1.0 Hz), MF (0.05–0.2 Hz) LF (0.01–0.05 Hz) and MF/HF ratio	Reliability/validity: Excessive restlessness and crying led to interruption of the recording Elimination of amplitude artifacts Arrhythmia and ectopic beats eliminated All ECG recordings reviewed by a physician Inclusion criteria: Weight at least 2400 g Exclusion criteria: Cardiological and neurological abnormalities, Apgar score 1 min <5 or 5 min <8, any medication and mothers who had used medication during pregnancy, with chronic diseases and drug abuse and smoking Recording: Room temperature in the morning, 30–60 min after feeding, 10 min recording; position: resting/lying	TD: RMSSD increased with increasing postnatal age (p = 0.04) FD: Ptot (p = 0.0002), HF (p = 0.0012), MF (p = 0.0013) and LF (p = 0.05) increased with postnatal age
HRV in PTN (transversal studies)	Rassi D et al. (2005) [15]	PTN (n = 9) GA 26–29weeks + 3days Birth weight 720–1350 g	HP Viridia CMS2000 monitors Sampling rate 500 Hz Average duration of recording 45 min FD: HF (0.2–2.0 Hz), LF (0.05–0.2 Hz)	Reliability/validity: Digital filtering applied to extract HF and LF components Oscillations of HR separated according to their characteristic timescales Inclusion criteria: All PTN: caffeine and antibiotics administered, on respiratory support (2 different types of ventilation: synchronized intermittent mandatory ventilation (n = 5) and high frequency oscillatory ventilation (n = 4))	FD: Persistent anticorrelation of HF and LF (the maximum of one curve coincides with the minimum of the other curve) in all data sets
	Nakamura T el a. (2005) [16]	PTN (n = 11) GA 26–34weeks Birth weight 467–2108 g Apgar 1°, 5°, 10° min 1/2/4–9/10/10	Nihon Kohden BSM-8800 Sampling rate 1000 Hz Duration of recording 2.5 h 20,000 beats 121 RR intervals TD: SDNN FD: HF (0.15–0.4 Hz), LF (0.04–0.15 Hz) and LF/HF ratio	Reliability/validity: Abnormal RR intervals caused by body movements or arrhythmia correct Data including deficit value more than 1% excluded Inclusion criteria: No adrenergic, anticholinergic and some medicines that affect ANA and circulatory system Exclusion criteria: Congenital anomalies, intraventricular hemorrhage, cardiac disease, perinatal asphyxia or evidence of maternal ilicit drug use Recording: All the time in the incubator	TD: SDNN increased with age (p < 0.05) FD: HF and LF decreased (p < 0.001) and LF/HF ratio increased with age (p < 0.01)
HRV in PTN (longitudinal study)	Lucchini M et al. (2016) [17]	PTN (n = 35) Mean GA 28.7 weeks	ECG recordings Duration of recording: First study protocol 6 h	Recording prior to discharge from hospital (n = 35) and 2 months after (n = 24)	TD: SDNN and RMSSD increased with age (p < 0.01)

Table 3 (continued)

Aim design	Authors (year)	Participants	HRV measurement	Experimental conditions	Key findings
			Follow-up study 1 h Sampling rate 500 Hz TD: SDNN and RMSSD	First study protocol 3 h sleeping in supine position and 3 h prone position, feeding right before the start Follow-up study protocol 30 min in each position Reliability/validity: Experienced clinicians coded sleep states Visual inspection of the series to remove peaks due to arrhythmic beats or erroneous automated identification of RR waves Inclusion criteria: First study: At least three segments of good quality RR series of 3 min with continuous sleep state Follow-up: at least one segment of 3 min good quality RR series with continuous sleep state	
HRV in PTN (case-control study)	Longin E et al. (2006) [18]	PTN (n = 39) Mean GA 33 ± 1weeks Mean age1–7 days Mean birth weight 1935 ± 388 g Mean length 44 ± 3 cm Apgar 5 from 8 to 10 Mean umbilical cord pH 7.27 ± 0.07 Na pH Group 1 (n = 9) GA <32weeks Group 2 (n = 30) GA >32weeks TN (n = 80)	VAGUS 2010 Sampling rate 256 Hz Period of recording 10 min FD: TP (<1 Hz), HF (0.2–1 Hz), MF (0.05–0.2 Hz), LF (0.01–0.05 Hz) and MF/HF ratio	Reliability/validity: Excessive restlessness and/or crying, episodes of apnea and/or bradycardia led to interruption of recording Inclusion criteria: No medication, except antibiotics (ampiciline and gentamycine-prophylatic measures to all infants <1500 g; n = 13) Exclusion criteria: Cardiological and neurological diseases, cerebral hemorrhage, mechanical ventilation and Apgar 5 <8 Recording conditions: Breathing spontaneous, room temperature, 0.5–1 h after feeding, at bedside; position: supine First comparison between group 1 (<32 weeks) and group 2 (>32 weeks) second comparison between PTN and TN	First comparison: FD: significant differences on TP, HF, MF, and LF ($p < 0.05$)–higher on group 2 (>32weeks) Strongest changes in HF (+229%) and MF (+141%) MF/HF ratio with no significant differences ($p = 0.83$)

w weeks, *TD* time domain, FD frequency domain, *ECG* electrocardiogram, *min* minutes, *d* days, *g* grams, *cm* centimeters, *MD* medium frequency

Table 4 Comparison of HRV between PTN and TN

Aim design	Authors (year)	Participants	HRV measurement	Experimental conditions	Key findings
Comparison between PTN and TN (case control studies)	Selig F et al. (2011) [4]	PTN (n = 48 in 27 PTN) GA <37weeks Mean birth weight: 1476 g TN (n = 78) GA >37weeks, between 0 and 3 days of life Mean birth weight 3085 g	POLAR ADVANCED S810i device 1000 consecutive RR intervals Period of recording: PTN mean 26.0 min TN mean 11.0 min TD: SDNN, RMSSD FD: HF (>0.15 Hz), LF, VLF, and LF/HF ratio	Reliability/validity: Consecutive RR intervals Intervals digitally filtered to eliminate premature beats and artifacts and manually to remove residual artifacts Only time séries with <10% of artifacts included Inclusion criteria: Absence of comorbidities	TD: SDNN and RMSSD higher in TN ($p < 0.0001$) FD: HF, LF, and VLF higher in TN ($p < 0.0001$) LF/HF ratio lower in TN ($p = 0.0149$)
	Longin E et al. (2006) [18]	PTN (n = 39) Mean GA 33 ± 1weeks Mean age 1–7days Mean birth weight 1935 ± 388 g Mean length 44 ± 3 cm Apgar 5 from 8 to 10 Mean umbilical cord pH 7.27 ± 0.07 Na pH Group 1 (n = 9) GA <32weeks Group 2 (n = 30) GA >32weeks TN (n = 80)	VAGUS 2010 Sampling rate 256 Hz Period of recording 10 min FD TP (<1 Hz), HF (0.2–1 Hz), MF (0.05–0.2 Hz), LF (0.01–0.05 Hz) and MF/HF ratio	Reliability/validity: Excessive restlessness and/or crying, episodes of apnea and/or bradycardia led to interruption of recording Inclusion criteria: No medication, except antibiotics (ampiciline and gentamycine-prophylatic measures to all infants <1500 g; n = 13) Exclusion criteria: Cardiological and neurological diseases, cerebral hemorrhage, mechanical ventilation and Apgar 5 <8 Recording conditions: Breathing spontaneous, room temperature, 0.5–1 h after feeding, at bedside; position**:** supine First comparison between group 1 (<32 weeks) and group 2 (>32 weeks) Second comparison between PTN and TN	Second comparison: FD: Significant differences on TP, HF, MF, LF and MF/HF ratio ($p < 0.05$): TP, HF, MF and LF higher in TN; MF/HF ratio lower in TN Strongest changes in HF (+59%) and LF (+56%)

w weeks, *TD* time domain, *FD* frequency domain, *ECG* electrocardiogram, *min* minutes, *d* days, *g* grams, *cm* centimeters, *MD* medium frequency

Table 5 Follow-up of HRV in PTN at their theoretical age or 7 weeks after birth

Aim design	Authors (year)	Participants	HRV measurement	Experimental conditions	Key findings
HRV in PTN at theoretical term age and comparison with TN (longitudinal studies)	Patural H et al. (2004) [19]	PTN (n = 23) GA 25–37 weeks Group 1 <28 weeks (n = 4) Group 2 28–31weeks (n = 5) Group 3 32–37 weeks (n = 14) TN (n = 8) GA >37 weeks Group 4 ≥38weeks All birth weights appropriate for GA (ranged from 890 to 3150 g)	ECG Holter System DuoSoft RR interval precision 0.004 s Duration of recording: At least 5 min PTN recordings: At theoretical full term age (38–41 weeks), whatever their GA at birth TN recordings: During their first week of life FD: HF (>0.15 Hz), LF, VLF, LF/HF ratio	Reliability/validity: Long enough recordings to include prolonged quiet sleep periods Assessment by simultaneous EEG monitoring and visual clinical control Selected only quiet sleep periods Inclusion criteria: Apgar 5 ≥7 No cardiac or respiratory drug therapy at the time of recording Exclusion criteria: Congenital diseases and acute cardiac or respiratory diseases Recording conditions: PTN free of incubator support	FD: PTN with lower ANS activity than TN ($p < 0.0001$) HF with significant differences between groups–HF lower in 3 groups of PTN than TN ($p < 0.05$) Linear relationship between PTN at theoretical age and HF ($p < 0.05$) HF only found after 38th week (none of PTN reached the HF value) No significant differences on LF, VLF and HF/LF ratio between PTN and TN
HRV in PTN at theoretical term age and comparison with TN (longitudinal study)	Landrot I et al. (2007) [20]	PTN (n = 30) GA 25–37 weeks TN (n = 19) Caucasian population All birth weights according with GA	ECG Holter System Duolter RR intervals precision 2 ms Duration of recording: At 40 min PTN recordings: At their theoretical term at 40 weeks (n = 30), at age 2–3 years (n = 25) or 6–7 years (n = 5) TN recordings: At birth (n = 19), at age 2–3 years (n = 5) or at age 6–7 years (n = 9) FD Ptot (≤0.04 Hz), HF (0.15–1.40 Hz), HFnu, LF (0.04–0.15 Hz), LFnu, VLF (≤0.04 Hz) and LF/HF ratio	Reliability/validity: ECG monitor with EEG or visual monitoring to assess quiet sleep periods All RR intervals manually validated Missing intervals and ectopic beats corrected prior to analysis Inclusion criteria: All infants able to drink maternal milk of formula without continuous gastric tube feeding Exclusion criteria: Arrhythmias, diabetes, any current cardiologic or pulmonar drug treatment and unstable presentation with cardiopulmonary or neurological pathology; neonatal period: mothers smokers, drug-addicted of taking any medication during pregnancy Recording: Control of incubator and ambient temperatures and child position	FD: At theoretical term, Ptot (p = 0.0003), HF, LF, and VLF ($p < 0.0001$) lower in PTN than in TN LF/HF ratio not significantly different between PTN and TN (p = 0.31) LFnu and HFnu lower in PTN ($p < 0.005$)
	Patural H et al. (2008) [21]	PTN (n = 39) GA 25–31 weeks Mean GA 28 weeks Mean birth weight 1032 g Mean height 36.1 cm Mean head circumference 25.3 cm Mean Apgar (5 min) 8 Mean Apgar (10 min) 10 TN (n = 19)	IntelliVue MP40 patient monitor Range of 1500 RR intervals RR interval precision 1 ms Sampling frequency 512 Hz FD Ptot (0.0–1.4 Hz), HF (0.15–1.40 Hz), HFnu, LF (0.03–0.15 Hz), LFnu, VLF (<0.03 Hz), and LF/HF ratio	Reliability/validity: Quiet sleep periods identified by physiological and behavior monitoring RR intervals manually validated Correction of missing intervals or ectopic beats Inclusion criteria: To prevent apneas, all PTN received a daily caffeine citrate dose	FD: HF extremely lower in PTN at the first week of life, compared with control TN ($p < 0.0001$) Significant differences between PTN and TN for Ptot, LF and VLF values ($p < 0.0001$) lower values in PTN

Table 5 (continued)

Aim design	Authors (year)	Participants	HRV measurement	Experimental conditions	Key findings
		Mean GA 40 weeks Mean birth weight 3012 g Mean height 49.1 cm Mean head circumference 35.6 cm Mean Apgar (5 min) 9 Mean Apgar (10 min) 10		None received morphine during hospitalization Exclusion criteria: Neurological or cardiac congenital defects, cardiac arrhythmias or absence of sinus rhythm, need for prolonged resuscitation at birth and/or Apgar score <5 at 5 min, and any maternal nicotine use during pregnancy Recording: All in quiet sleep periods, 30 min after a morning-time feeding period; position: supine; environmental conditions controlled for incubator and ambient temperatures	No significant differences for LF/HF ratio ($p < 0.31$), LFnu and HFnu ($p < 0.06$)
HRV in PTN during 7 weeks (longitudinal study)	Krueger C et al. (2010) [22]	Low-risk PTN ($n = 31$) GA 28–34 w Mean birth weight: 1120 g Mean IA 1° 5°: 6/8	Agilent Neonatal monitor ECG signal sampled at equal intervals for 300 s Sampling rate 500 Hz FD Ptot (0.04–2.0 Hz), HF (0.30–1.30 Hz), LF/HF ratio (0.04–0.2/0.30–1.30 Hz)	Reliability/validity: Matlab program to filter, or smooth, the signal by removing noise components and baseline wander. ECG recordings at the same time of the day for each infant Exclusion criteria: Abnormal head ultrasound, sensorineural hearing loss, confirmed prenatally transmitted viral/bacterial infections and cardiac abnormalities State: active sleep	FD: No significant effect on Ptot, HF, and LF/HF ratio during the 7 weeks after birth

w weeks, *TD* time domain, *FD* frequency domain, *ECG* electrocardiogram, *min* minutes *d* days, *g* grams, *cm* centimeters

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