Chapter

Evolution of Parasympathetic Modulation throughout the Life Cycle

Moacir Fernandes de Godoy and Michele Lima Gregório

Abstract

Based on the largest data set ever available for analysis of heart rate variability (HRV) variables, in healthy individuals, it was possible to determine the evolutionary behavior of three representative components of parasympathetic nervous system function (RMSSD, PNN50, and HF ms^2), in different age groups of the life cycle: newborns, children and adolescents, young adults, and, finally, middle-aged adults. A near-parabolic and nonsynchronous behavior was observed among the different variables evaluated, with low values at first, then progressive elevation, and later fall, approximating the values of the newborns to the values of middle-aged adults and suggesting that the autonomic nervous system, at least relatively to its parasympathetic component, undergoes a growing maturation that is completed in the young adult and later suffers a progressive degeneration, completing the life cycle. This fact should be considered when comparing the analysis between healthy individuals and those with different states of pathological impairment.

Keywords: autonomic nervous system, parasympathetic nervous system, heart rate variability, homeostasis, life cycle

1. Introduction

The autonomic nervous system (ANS) is a division of the peripheral nervous system and, based on anatomy and physiology, has three subdivisions: sympathetic nervous system (SNS), parasympathetic nervous system (PNS), and enteric nervous system (ENS). SNS has thoracolumbar distribution, and PNS has a craniosacral distribution, while ENS is the major part of the peripheral nervous system being found throughout the gastrointestinal tract, extending from the esophagus to the rectum, and is also present in the pancreas and in the gallbladder [1–4].

ANS has the responsibility to ensure that homeostasis be maintained in the face of disturbances produced by both the external and internal environment [5]. In the heart of rats, ANS begins its development on the embryonic 18.5 day until the twenty-first postnatal day (P21) [6].

Sympathetic neurons are located in the paravertebral ganglia, have long axonal projections to the organs, and produce excitatory effects mediated by the noradrenergic transmitter norepinephrine (NE). Conversely, parasympathetic neurons are located in ganglia near or on the surface of organs, have shorter axonal projections, and produce inhibitory effects mediated by the cholinergic transmitter

acetylcholine (ACh). The enteric nervous system provides the intrinsic innervation of the gut, controlling different aspects of the gut function, such as motility [4].

Although ANS can actually function autonomously, the central nervous system can contribute to a significant regulatory effect [3].

Heart rate variability (HRV) analysis is a practical, noninvasive, reproducible, and cost-effective resource that has been widely applied to study the autonomic behavior of the human organism, being particularly useful for the evaluation of sympathetic and parasympathetic components, although with regard to sympathetic behavior, there is still controversy about the mechanisms involved [7].

Higher vagally mediated heart rate variability is associated with better autonomic balance, better health outcomes, and flexible physiological responses. In contrast, lower HRV is associated with disease and all-cause mortality [8].

In [9], some reference values for normality of HRV variables are suggested, although highlighting that "As no comprehensive investigations of all HRV indices in large normal populations have yet been performed, some of the normal values [...] were obtained from studies involving small number of subjects."

The reference values for normality cited and recommended in the Task Force were taken from the work of Bigger et al. (1995). The authors were based on only 274 individuals considered healthy and restricted to be 40–69 years old [10].

The aim of this chapter is restricted to the parasympathetic division of ANS. For the evaluation of this component, there is a well-established consensus that some variables, such as the root mean square of the successive RR interval differences (RMSSD), the percent of normal RR intervals that differed by more than 50 ms (PNN50) both in the time domain, and the absolute power of the high-frequency band component (HF ms^2), in the frequency domain, specifically represent vagal modulation, presenting both diagnostic and prognostic properties [11–12].

Generally speaking, heart rate variability analysis has become the most used noninvasive tool to evaluate autonomic control mechanisms and to predict mortality risk in several clinical conditions, including coronary artery disease, heart failure, diabetes, and hypertension [13].

According to Goldberger et al. [14], there was some evidence that age influenced the responsiveness of the HRV parameters with changing parasympathetic effect. They studied 29 normal volunteers (15 women; mean age 39 $\pm$ 12 years) after β-adrenergic blockade with intravenous propranolol. Five-minute ECG recordings were made during graded infusions of phenylephrine and nitroprusside to achieve baroreflex-mediated increases and decreases in parasympathetic effect, respectively. There was some evidence that age influenced the responsiveness of the HRV parameters with changing parasympathetic effect, with significant association for RMSSD and PNN50.

Despite the significant amount of studies in the literature dealing with the HRV and autonomic regulation subject, there is a lack of studies with large series, addressing several variables in different age ranges, from birth to the elderly adult. So, we will evaluate the contribution of these three variables in the study of parasympathetic autonomic behavior throughout the life cycle based on the evaluation of a significant amount of data (835,902 in total) extracted from the literature regarding heart rate variability variables and admittedly related to the parasympathetic nervous system being 53,882 results from healthy individuals.

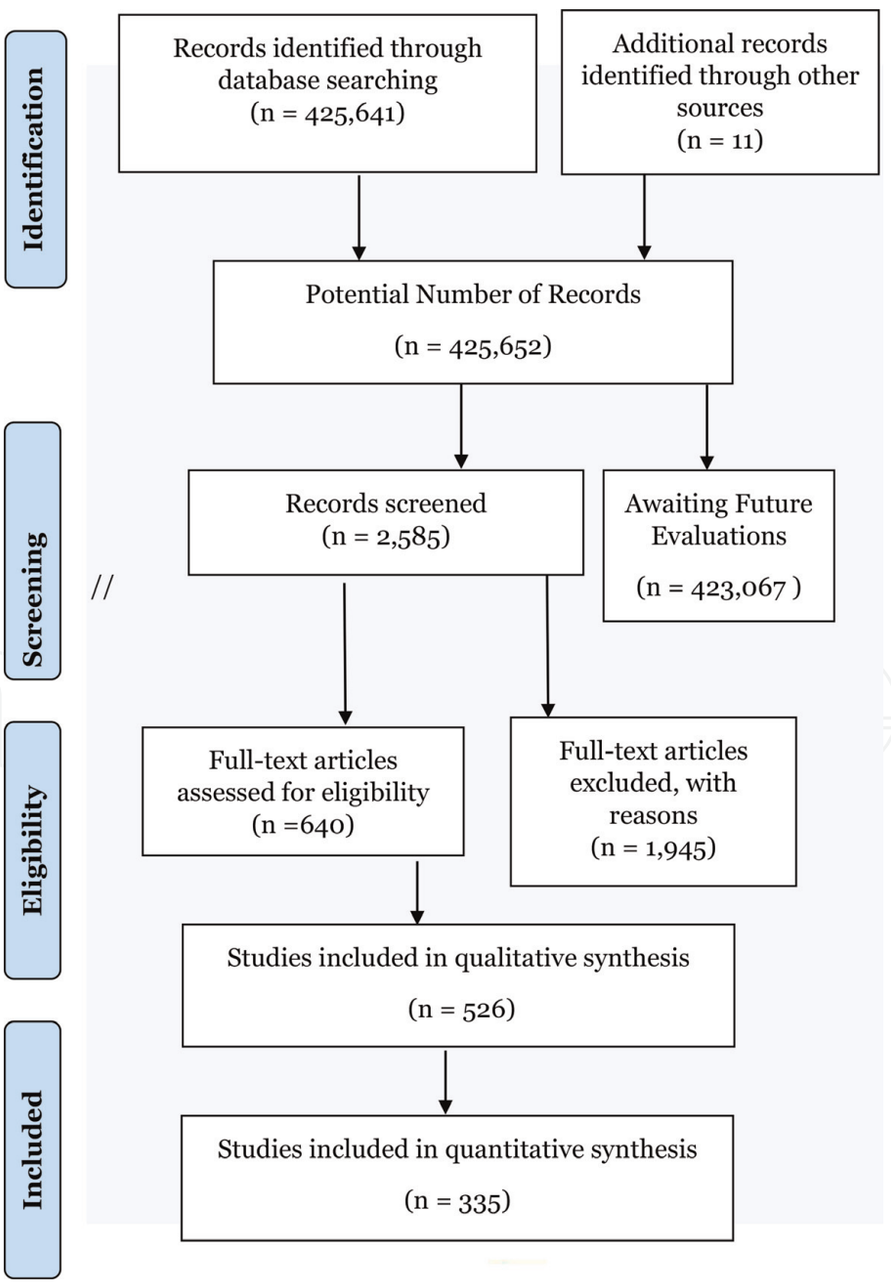
2. Method

The inclusion criterion was quite broad in view of the proposed objective, which was to establish reference values, based on the largest amount of information

possible. Thus, by searching the available databases (PubMed, Google Scholar, Cochrane Library, ScienceDirect, Wiley Online Library, SciELO, LILACS, and Thesis Banks of Brazilian Universities, among others) and following the PRISMA 2009 flow diagram [15], articles evaluating the values of heart rate variability (**Flow Diagram**) were included, and after, those directly related to the parasympathetic component of ANS, in the time domains (RMSSD and PNN50) and in the frequency domain (HF ms^2), in humans, regardless of age and gender and also regardless of the length of the time series, patient position, and analysis equipment, were selected but provided that the data were always collected from individuals specifically considered to be healthy. Based on this criterion, it is noteworthy that the individuals, who in the original work were cataloged as being from the general population, were not considered to be healthy because there are known comorbidities in this type of sample, and so, they were not included.

Values with evident evidence of extreme outliers (three or more standard deviations below the first quartile or above the third quartile, from the set of values collected for a given variable) were excluded.

Flow diagram



Domain	Variable	Total group	General population + diseased	Healthy
Time	RMSSD ms	208,657	183,155	25,502
Time	PNN50	49,400	35,043	14,357
Frequency	HF ms2	159,894	145,871	14,023

Table 1.
Distribution of the literature data evaluated, in terms of the variable studied, highlighting the sample of interest (healthy individuals) and its size in relation to the total amount obtained.

Age range (years)	Age mean ± SD	RMSSD (ms)	PNN50 (%)	HF(ms^2)
Newborns	[0 a 3 days]	234	78	272
Up to 20	13.29 ± 4.64	4,419	2,790	4,346
20–40	25.21 ± 4.88	8,459	1,031	5,721
40–70	52.74 ± 7.56	12,390	10,468	3,684
Totals		25,502	14,357	14,023

Table 2.
Mean and standard deviation of the analyzed age groups and respective amounts of data analyzed, by studied variable..

Table 1 informs the studied variable, its domain, and the amount of values collected in the literature.

RMSSD (root mean square of the successive RR intervals differences, in ms; PNN50 (percent of normal RR intervals that differed by more than 50 ms in %); HF (absolute power of the high-frequency band; 0.15–0.40 Hz, in ms^2).

Groupings were made by age range to precisely characterize the evolutionary behavior of the parasympathetic system throughout the life cycle. The amounts of data evaluated for each group and their average ages and standard deviations are shown in **Table 2**.

From all included studies, the mean and the standard deviation values of each variable of interest were extracted. The overall mean value was obtained by weighted average. The global standard deviation was obtained from the individual mean set of each study. As the collected values were the means and standard deviations, the existence of normality was assumed. The values from the different age groups were compared with the aid of the unpaired t-test assuming that the standard deviations of each group were not similar to each other (Welch correction). GraphPad InStat version 3.00 software was used to obtain P-values. A PDF file containing all the 335 references used to mounting the database can be solicited to the correspondent author. The large number of references would make it impossible to include them directly in the present text.

3. Results

Table 3 summarizes the results obtained.

RMSSD (root mean square of the successive RR intervals differences in ms; PNN50 (percent of normal RR intervals that differed by more than 50 ms), HF (absolute power of the high-frequency band; 0.15–0.40 Hz); SD, standard deviation.

Group	Age range	RMSSD	PNN50	HF
		Mean ± SD	**Mean ± SD**	**Mean ± SD**
1	Newborns	11.6 ± 0.9	1.4 ± 3.7	66.7 ± 85.5
2	Up to 20	52.0 ± 18.0	25.7 ± 11.6	1124.0 ± 710.8
3	20–40	53.1 ± 22.2	19.9 ± 12.9	2067.2 ± 1144.7
4	40–70	28.2 ± 11.8	6.9 ± 0.3	236.3 ± 248.5

Table 3.
Mean and standard deviation of the variables studied according to the different age groups.

The statistical analysis (p-values, t-test unpaired, two-tailed, Welch correction) comparing the mean values for each variable along the age ranges is showed below.

Group	RMSSD	PNN50	HF
1 versus 2	P < 0.0001	P < 0.0001	P < 0.0001
1 versus 3	P < 0.0001	P < 0.0001	P < 0.0001
1 versus 4	P < 0.0001	P < 0.0001	P < 0.0001
2 versus 3	P = 0.0024	P < 0.0001	P < 0.0001
2 versus 4	P < 0.0001	P < 0.0001	P < 0.0001
3 versus 4	P < 0.0001	P < 0.0001	P < 0.0001

As can be observed, the P-values were extremely robust indicating significant extreme differences for all comparisons.

Figures were constructed showing the behavior of each variable along the progressive increase in chronological age, from the healthy newborn group (subgroup 1) to children and adolescents (subgroup 2) and young adults (subgroup 3), until reaching the middle-aged adults (subgroup 4).

F**igures 1–3** graphically demonstrate this behavior.

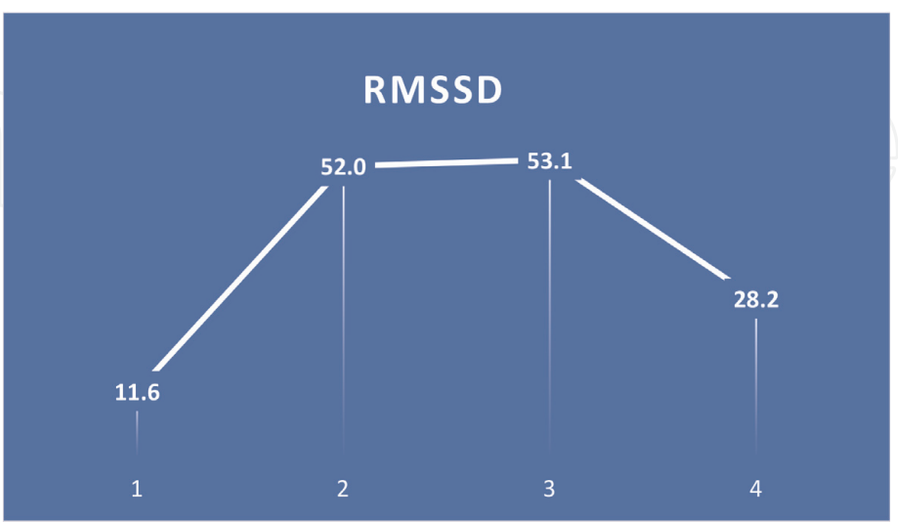


Figure 1.
Mean evolutionary behavior of RMSSS values for the different age groups studied. RMSSD (root mean square of the successive RR interval differences in ms; 1, healthy newborns subgroup; 2, children and adolescents (up to 20 years) subgroup; 3, young adults (20–40 years) subgroup; 4, middle-aged adults (40–70 years) subgroup.

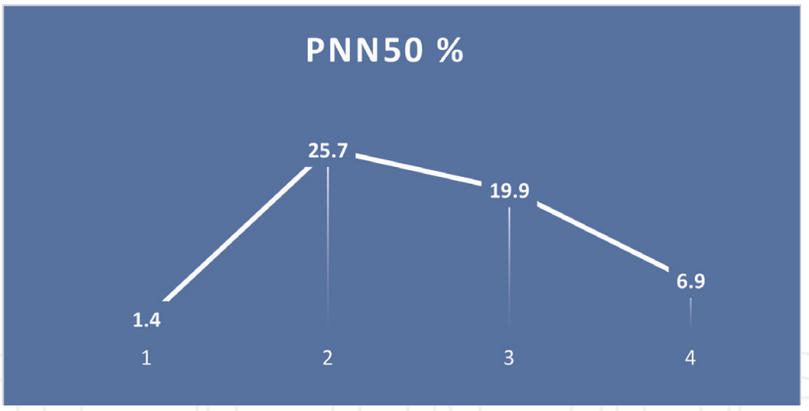


Figure 2.
Mean evolutionary behavior of PNN50 values for the different age groups studied.PNN50% ((percent of normal R-R intervals that differed by more than 50 ms); 1, healthy newborns subgroup; 2, children and adolescents (up to 20 years) subgroup; 3, young adults (20–40 years) subgroup; 4, middle-aged adults (40–70 years) subgroup.

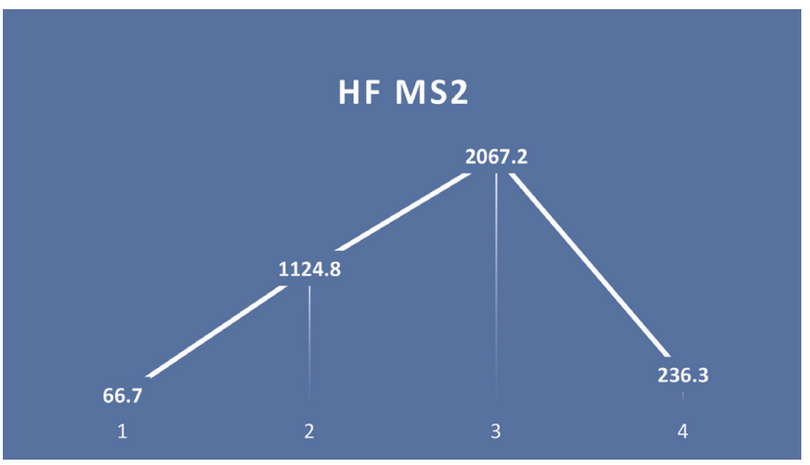


Figure 3.
Mean evolutionary behavior of HF ms² values for the different age groups studied. HF ms² (absolute power of the high-frequency band; 0.15–0.40 Hz); 1, healthy newborns subgroup; 2, children and adolescents (up to 20 years) subgroup; 3: Young adults (20–40 years) subgroup; 4, middle-aged adults (40–70 years) subgroup.

4. Discussion

It is well known that the heart rate variability declines with age. Bonnemeier et al. (2003) [16] obtained 24 h recordings from 166 healthy volunteers (85 men and 81 women) aged 20–70 years. They found the most dramatic HRV parameter decrease between the second and third decades. Almeida-Santos et al. (2016) [17] obtained 24 h ECG recordings of 1743 subjects of 40–100 years of age. They found a linear decline in SDNN, SDANN, and SDNN index. Curiously, they described U-shaped pattern for RMSSD and pNN50 with aging, decreasing from 40 to 60 and then increasing after age 70.

The present study adds new information about this evolutionary behavior. It was quite clear that parasympathetic autonomic development in healthy individuals is peculiar, being reduced at birth, presenting a progressive elevation up to about 20 years of age (for the three variables studied), and typically, after that initial elevation, two different patterns of behavior occur. The RMSSD variable arises a little more until around 40 years of age when it then begins to decline progressively (**Figure 1**), which we might call as a "'negatively skewed tent' behavior." The PNN50 variable, once reaching its maximum levels around the age of 20, begins to

decline progressively until the age of 70 (**Figure 2**), which would graphically be a "positively skewed tent" behavior. Finally, the HF variable rises from birth to about 40 years, when it begins to decline until 70 years of age being graphically a "negatively skewed tent" behavior (**Figure 3**).

We did not find significant studies on heart rate variability in healthy individuals over 70s, probably because above that age, the vast majority of the individuals already have some pathological impairment. Yes, it would exist for the general population, but that was not the focus at this moment. Therefore, a complete definition of HRV behavior in that older group, based on a significant sample like that used here for the other age groups, was not yet possible.

The significant amount of data obtained, together with the extremely significant difference between the values in the different age groups, strongly indicates that this was not a casual finding but a true expression of parasympathetic autonomic behavior.

This is a relevant finding as it sheds new light on the knowledge of normal values in different age groups, since the current gold standard is still established by the Task Force data, based on only 274 cases and exclusively on the age range of 40–69 years.

5. Conclusion

Like every other complex system, in accordance with Chaos Theory, ANS, at least in its parasympathetic component, exhibits a near-parabolic and nonsynchronous behavior for the main variables that evaluates it using heart rate variability, and this fact should be considered in the comparative analysis between healthy individuals and those with different grades of pathological impairment.

Based on the largest data set ever available for healthy individuals, the found values can be proposed as reference standards for future studies about heart rate variability.

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Conflict of interest

The authors declare no conflict of interest.

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