Chapter

Heart Rate Variability as a Marker of Homeostatic Level

Moacir Fernandes de Godoy and Michele Lima Gregório

Abstract

Many variables have been used as homeostatic level markers. Heart Rate Variability (HRV) has been frequently cited as an indicator of homeostatic status. Low levels of HRV are associated with aging, disease, or increased risk of death. We present a study based on more than 10.5 million data collected from the literature, associating the degree of global clinical impairment of individuals, with their respective HRV data, seeking to establish a classification of Homeostatic Levels. Three specific variables were evaluated: heart rate (HR), the root-mean-square of successive differences between adjacent normal RR intervals in a time interval (RMSSD) and the HF band (HF ms^2). It was possible to detect significant differences between the 83,927 data from healthy individuals and the 382,039 data from individuals with significant homeostatic impairment. It was demonstrated that the RMSSD is very sensitive to the worst homeostatic state, presenting a behavior independent of age and that the values found in the general population do not match the values of apparently healthy individuals. An alphanumeric classification of the homeostatic level in a three-level architecture was proposed, with three stages for each level, which may be extremely useful in prognostic assessment and decision-making about individual people.

Keywords: autonomic nervous system, heart rate variability, homeostatic level

1. Introduction

The human organism is a dynamic, deterministic, non-linear system that shows a sensitive dependence on initial conditions. The amount of cells in the human body is extraordinarily large. A study carried out by Eva Bianconi with collaborators from Italy, Greece and Spain, concluded with the number of $3.72 \pm 0.81 \times 10^{13}$, or approximately 37 trillion cells. There is already an estimate of the amount of cells that need to be removed daily in a healthy human adult, seeking to maintain the body's stability. That number reaches the extraordinary value of 150 billion cells a day! If we remember that the total amount of cells is approximately 37.2 trillion, we conclude that, per day, a healthy human individual loses 0.4% of its cell mass [1].

It is inferred, then, that for the maintenance of life through the proper, harmonious and stable functioning of these cells, in addition to the restoration of lost elements, it is mandatory to spend energy. The clinical concept that refers to this condition of maintenance of conditions of stability is Alostasia. Through Alostasia, Homeostasis is maintained.

The name Homeostasis was created by Walter B. Cannon, in 1932. Literally translated, homeostasis means "staying the same", but this is not entirely accurate. In reality, homeostasis is not a static state; rather, it is a dynamic state.

In biology, homeostasis is classical, the state of steady internal, physical, and chemical conditions maintained by living systems. This is the condition of optimal functioning for the organism and includes many variables, such as body temperature and fluid balance, being kept within certain pre-set limits, and which we will call from now on, as the Homeostatic Level.

One of the fundamental elements for the control of the Homeostatic Level is the Autonomic Nervous System (ANS), with its different components, the sympathetic nervous system, the parasympathetic nervous system and the enteric nervous system [2].

The effects of aging on the autonomic nervous system are multiple and vary between and within both sympathetic and parasympathetic portions. Normal human aging is associated with changes in autonomic control of several bodily functions, particularly those served by cardiovascular and thermoregulatory systems [3].

The assessment of the autonomic nervous system has been possible through the quantification of a biological marker called Heart Rate Variability (HRV). The literature is extremely rich in studies on HRV, and its high applicability in terms of diagnosis and prognosis is a consensus.

It is possible to study HRV in different domains, namely time, frequency and non-linear. In these domains, different variables have already been described, each with its greater or lesser sensitivity.

Briefly, however, we can highlight three of them among those with the greatest clinical applicability: heart rate (HR), the root-mean-square of successive differences between adjacent normal RR intervals in a time interval (RMSSD) and the HF band representing the power in the frequency range between 0.15 and 0.4 Hz (HFms2) [4].

2. Heart rate

Resting heart rate has ceased to be just another vital sign and has become a relevant cardiovascular risk marker. It has long been known that life span is inversely related to resting heart rate in most organisms. The classic article by Levine [5], shows the existence of an inverse semilogarithmic relation between heart rate and life expectancy among mammals, suggesting a predetermined number of heart -beats in a lifetime, with a magic average number of $7.3 \pm 5.6 \times 10^8$ heart-beats/lifetime.

Boudoulas KD et al. [6], make an excellent review relating heart rate, life expectancy and the cardiovascular system. They conclude that many factors regulate heart rate, and it may be these factors, rather than the heart rate itself, which determine survival, but heart rate has multiple direct effects on the cardiovascular system, regardless of the regulatory mechanisms. These effects directly affect the cardiovascular system in multiple ways that, in turn, may affect survival.

From a pathophysiological point of view, the main finding is that resting heart rate is associated with shear and endothelial function in humans [7].

The impact of increased resting heart rate on prognosis is validated in the general population in patients with hypertension, coronary artery disease, or heart failure and irrespective of age, cardiovascular risk factors, or comorbidities, although there is still no definitive confirmation of the prognostic effect of heart rate reduction with the use of drugs such as ivabradine, on primary combined events [8].

3. RMSSD

RMSSD is the root-mean-square of successive differences between adjacent normal RR intervals in a time interval, expressed in millisseconds, and is the primary time domain measure used to assess parasympathetic sources of HRV [4].

Several studies have shown a reduction in RMSSD values in the presence of disease or aging, reflecting a reduction in heart rate variability. Maurer CW et al., in 2016 [9], evaluated the behavior of the autonomic nervous system in 35 patients with functional movement disorders (FMD) compared to 38 healthy controls. They found a significant reduction in RMSSD in patients with FMD ($P = 0.02$), as well as an increased mean heart rate ($P = 0.03$), concluding that decreased vagal tone may reflect increased stress vulnerability in patients with FMD.

DeGiorgio, CM et al. [10], studied 19 subjects with intractable partial seizures, at least three per month, in a randomized clinical trial of omega-3 fatty acids in epilepsy. They looked for whether or not there was a correlation between heart rate variability and the estimated risk of Sudden Unexplained Death in Epilepsy, quantified by the SUDEP-7 Inventory. They found that the RMSSD was inversely correlated with the SUDEP-7 score, $r = -0.64$, $p = 0.004$. Subjects with higher SUDEP-7 scores had reduced levels of HRV (RMSSD). Other time-dependent measures of HRV (SDNN, SDANN) were not significantly correlated with SUDEP risk scores.

In another study, Maheshwari A et al. [11] evaluated a large group of 12,543 individuals from the general population, participating in The Atherosclerosis Risk in Communities Study. They were looking for a relationship between low HRV and sudden cardiac death (SCD). During a median follow-up of 13 years, 215 SCDs were identified. In the group in which sudden deaths occurred, there was a statistically significant difference in heart rate (70.3 ± 13.8 bpm versus 67.7 ± 10.3 bpm; $P = 0.008$) and in HF power ms2 (1.6 ± 1.5 Ln versus 2.1 ± 1.3 Ln; $P < 0.0001$). As for the RMSSD, there was no statistically significant difference between the groups, but in both conditions, the values were below the ideal values for normality (27.3 ± 28.3 ms versus 29.2 ± 23.3 ms; $P = 0.25$).

Based on the knowledge that sepsis is associated with marked alterations in hemodynamic responses, autonomic dysfunction and impaired vascular function, Bongiorno Junior et al. [12], explored the prognostic utility of cardiac output (CO), stroke volume (SV), indices of vagal modulation (RMSSD and SD1), total heart rate variability (HRV) and flow-mediated dilation (FMD) of the brachial artery (%FMD) in 60 patients recruited at an intensive care unit. They found that in the group of 39 patients who did not survive, HR was higher (105 ± 27 bpm versus 84 ± 15 bpm; $P = 0.02$) and it was observed that the RMSSD and SD1 indices could be predictors of endothelial function and RMSSD could predict the risk of death in these patients.

The ROC Curve of RMSSD was useful in predicting 28-day mortality in patients with sepsis. The area under the curve was 0.784 (0.656–0.881). The value of 10.8 ms was chosen as the cut-off point for RMSSD (sensitivity of 77.1%, specificity of 73.9%, the positive likelihood ratio of 2.96 and negative likelihood ratio of 0.31. With RMSSD ≤10.8 ms, the mean survival time was 23.1 days and with RMSSD>10.8 ms, the mean survival time was 23.1 days).

4. HF ms^2

There are three main spectral components in an HRV spectrum named as high frequency (HF), low frequency (LF), and very low frequency (VLF) bands. The HF band represents the power in the frequency range between 0.15 and 0.4 Hz. HF power is generally believed to represent respiration-linked changes in heart rate and is generally accepted as a measure of respiratory sinus arrhythmia (RSA), or the parasympathetic contribution to HRV. RSA refers to the acceleration in heart rate that occurs during inspiration (due to the cardiovascular control center's inhibition of vagal outflow) and the subsequent heart rate deceleration that occurs during expiration, due to vagal restoration [13, 14].

Doheny et al. in 2015 [15], evaluated the possibility of using a non-invasive biomarker that allows early detection of patients at risk of necrotizing enterocolitis (NEC), that is an acute neonatal inflammatory disease that may lead to intestinal necrosis, multi-system failure and death. For that, they used the high frequency (HF) component of heart rate variability. They studied 70 stable preterm infants (gestational age 28-35 week). HF ms^2 was 21.5 ± 2.7 ms^2 in infants that remained healthy and 3.9 ± 0.81 ms^2 in those that later developed stage 2 + NEC ($P < 0.001$). The cut-off value in the ROC curve was 4.68ms^2, predictive for developing NEC with sensitivity and specificity of 89% and 87%, and positive and negative predictive values of 50% and 98%, respectively. They concluded that HF ms^2 may serve as a potential, non-invasive predictive biomarker of NEC-risk in infants.

In 2004, Abramkin et al. [16], studied 188 patients to compare the prognostic value of different noninvasive reflex tests on days 4-11 of myocardial infarction. The age varied from 34 to 75 years, 68% were men, and 93.6% were on beta-blockers, all without heart failure NYHA IV on the day of tests. HF power < 65 ms2 during active standing (OR 28.8, 95% CI 4.1-104.2; p = 0.001, positive predictive value 29.4%) was an independent predictor of sudden cardiac death.

In a meta-analytic study carried out in 2021 by Heimrich et al. [17], the objective was to verify whether the analysis of heart rate variability could indicate decreased parasympathetic tone in patients with Parkinson's disease. A total of 47 studies were evaluated, including 2772 individuals, 1566 of which had Parkinson's Disease (65.0 ± 0.6 years) and 1206 were healthy controls (62.6 ± 1.0 years). Based on 24 studies, it was possible to detect that the FH ms2 was significantly lower in the group of patients with the disease (145.2 ± 41.1 versus 219.4 ± 48.8 ms2; P = 0.002; heterogeneity 91%).

5. Objective

Considering that the heart rate (HR), the root-mean-square of successive differences between adjacent normal RR intervals (RMSSD) and the HF band power in the frequency range between 0.15 and 0.4 Hz (HFms2), can help to differentiate the homeostatic level between individuals with severe impairment and high risk, and healthy individuals, we performed an intensive review of the literature by collecting published data involving the aforementioned variables, in search of a cutoff value for defining homeostatic reference levels and creating an individualized diagnostic coding.

6. Method

Based on research projects linked to FAPESP - Brazil (2017/12529-7) and CNPq -Brazil (308,555/2018-0), studies involving the use of one or more of the

three variables mentioned above were evaluated. In total, it was possible to analyze 164 studies involving the heart rate of individuals with importantly compromised homeostatic level (HL_ic), 181 studies involving the heart rate of apparently healthy individuals (HL_ah), 179 studies involving the RMSSD of individuals with HL_ic, 221 studies involving the RMSSD from HL_ah subjects, 125 studies involving the HF ms2 of subjects with HL_ic and 155 studies involving the HF ms2 of HL_ah subjects. Obviously, there were concurrent studies in certain situations. Due to a large number of references, they are cited separately and available in a *supplementary file*.

7. Statistical analysis

Data were presented as mean and standard deviation, weighted mean, quantities, percentages and correlation coefficients. Comparisons between groups were made by analysis of variance or the Kruskal-Wallis test and its post-tests, according to the indication. Correlation graphs were constructed and Box-Whisker graphs were used for illustration. An alpha error of 5% was accepted, with P values less than or equal to 0.05 being considered significant. The statistical software used was StatsDirect version 3.3.5 (03/22/2021).

8. Results

The total amount of data analyzed was extremely high. **Table 1** below indicates the amounts for each variable under conditions of significantly compromised and apparently healthy homeostasis, as well as the mean and standard deviation values for the age of the group, the mean and standard deviation of the variable, and the weighted mean of the variable.

	N References	N Data	Age [Mean ± SD]	Variable [Mean ± SD]	Variable [weighted mean]	*P*-value
HR HL_ic bpm	164	365,195	48.7 ± 20.7	97.6 ± 20.1	85.7	
HR HL_ah bpm	181	22,443	32.9 ± 21.7	75.9 ± 18.9	69.7	P < 0.0001
RMSSD HL_ic ms	179	10,014	54.4 ± 16.5	22.8 ± 19.9	27.4	
RMSSD HL_ah ms	221	35,531	30.1 ± 19.3	45.6 ± 18.8	32.5	P < 0.0001
HF ms^2 HL_ic ms^2	125	6830	54.2 ± 15.2	173.7 ± 181.4	155.9	
HF ms^2 HL_ah ms^2	155	25,953	32.7 ± 19.7	565.2 ± 459.1	468.1	P < 0.0001

Table 1.
Distribution of the number of studies included, amount of data per variable, according to homeostatic level (importantly compromised [HL_ic] or apparently healthy [HL_ah].

As the behavior of heart rate variability is related to age, linear correlation calculations were made between age (predictor) and the variable to be predicted (HR, RMSSD or HFms^2) in the HL_ic and HL_ah groups (**Table 2**; **Figures 1–6**).

Variable	Simple linear regression	Correlation coefficient (r)	Correlation coefficient (r^2)	Two sided P-values
HR HL_ic	−0.493334 age + 121.57553	−0.532497	0.283553	< 0.0001
HR HL_ah	−0.444059 Age + 90.500925	−0.510337	0.260444	< 0.0001
RMSSD HL_ic	−0.159605 Age + 31.493563	−0.131765	0.017362	0.0787#
RMSSD HL_ah	−0.520603 Age + 61.235545	−0.534807	0.286018	< 0.0001
HFms2 HL_ic	−2.572467 Age + 313.130404	−0.215726	0.046538	0.0157
HFms2 HL_ah	−11.218318 Age + 932.609833	−0.480536	0.230915	< 0.0001

#Correlation coefficient is not significantly different from zero.

Table 2.
Distribution of simple linear regression, correlation coefficients (r and r^2) and two-sided P-values, by homeostatic condition.

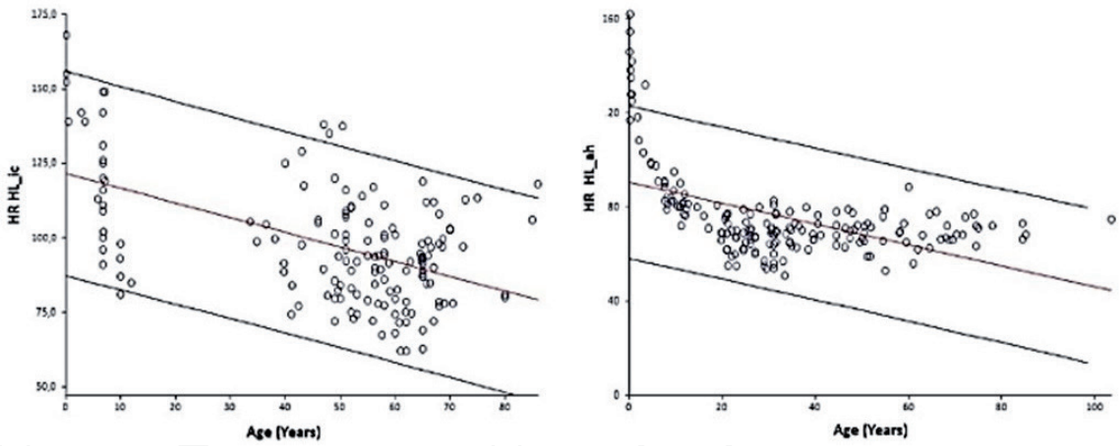

Figure 1.
Correlation graphs (age x heart rate) in the groups of individuals with importantly compromised homeostatic level (HL-ic) and apparently healthy (HL_ah).

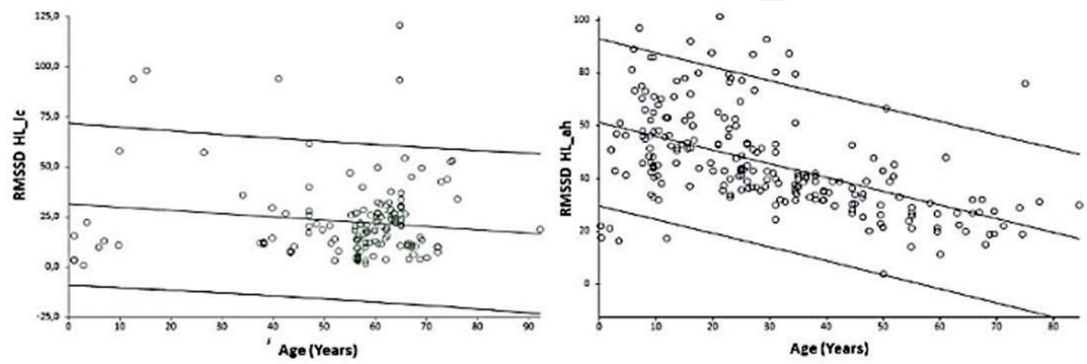

Figure 2.
Correlation graphs (age x RMSSD) in the groups of individuals with importantly compromised homeostatic level (HL-ic) and apparently healthy (HL_ah).

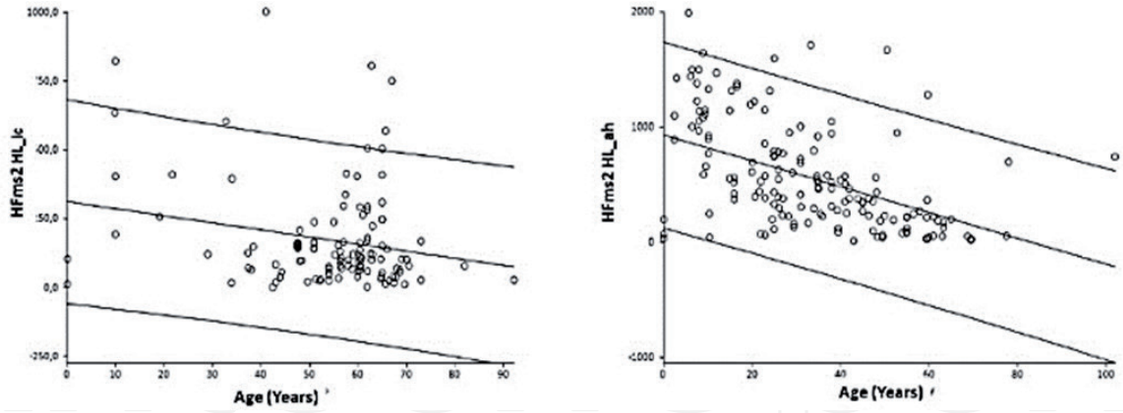

Figure 3.
Correlation graphs (age x HF ms^2) in the groups of individuals with importantly compromised homeostatic level (HL-ic) and apparently healthy (HL_ah).

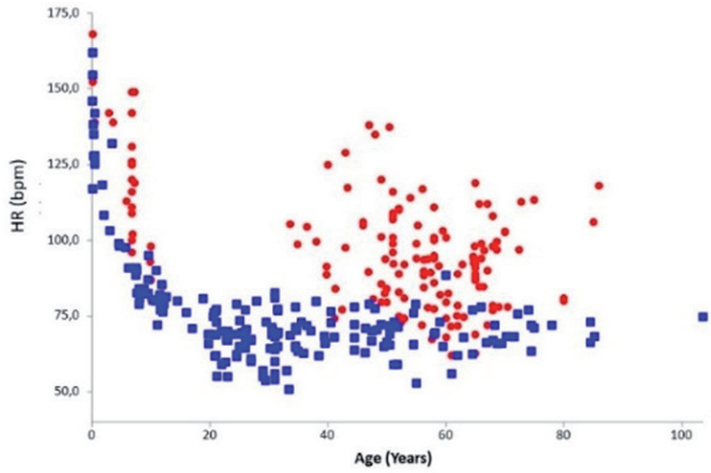

Figure 4.
Scattergram (HR in bpm) for the groups of individuals with importantly compromised homeostatic level (HL- ic; red circles) and apparently healthy (HL_ah; blue squares).

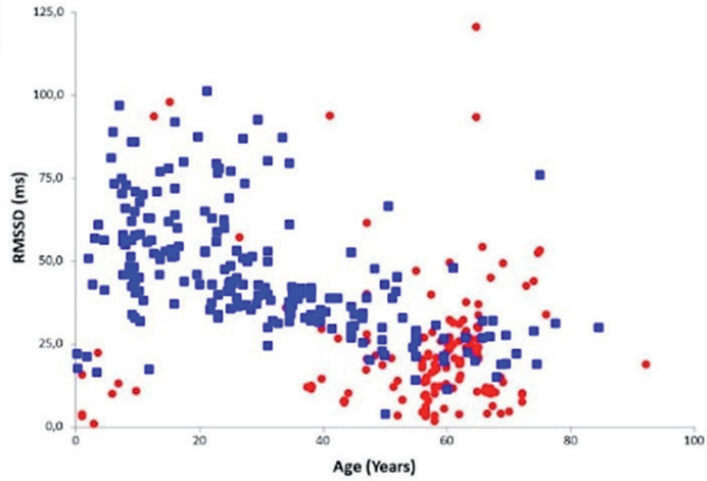

Figure 5.
Scattergram (RMSSD in ms) for the groups of individuals with importantly compromised homeostatic level (HL-ic; red circles) and apparently healthy (HL_ah; blue squares).

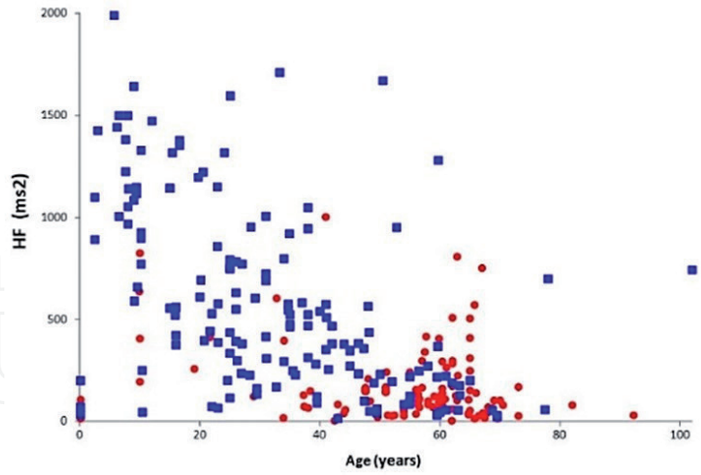

Figure 6.
Scattergram (HF in ms²) for the groups of individuals with importantly compromised homeostatic level (HL- ic; red circles) and apparently healthy (HL_ah; blue squares).

A moderate negative correlation was found between heart rate and age, both in cases with significant homeostatic impairment and in apparently healthy cases. There was also a moderate negative correlation between RMSSD and age, and between HFms^2 and age in the apparently healthy group. The fact that there was only a weak negative correlation between HFms2 and age in the group with significant homeostatic impairment and also the absence of correlation between RMSSD and age in this impaired group, was noteworthy. This may suggest that RMSSD is a more effective or sensitive biological marker of homeostasis, revealing changes regardless of age.

It became also relevant to evaluate the data of the three selected variables, in the group composed of individuals named as being from the general population (HL_gp). Thus, from the global data survey carried out, a number of 10,121,910 were obtained from individuals from the general population, in different age groups. The values of mean, standard deviation, weighted mean, mean age ± standard deviation and number of articles consulted are found in **Table 3** and **Figure 7**.

Comparative statistical analysis between the 3 groups (HL_ah, HL_ic and HL_gp) for the three selected variables, using the Kruskal-Wallis test with post-test Dwass-Steel-Chritchlow-Fligner, showed a non-significant difference between HR HL_ah versus HR HL_gp ($P = 0.6228$); the statistically significant difference between HR HL_ah versus HR HL_ic ($P < 0.0001$); the statistically significant difference between HR HL_gp versus HR HL_ic ($P < 0.0001$).

	Heart rate	RMSSD	HF ms^2
Data (N)	144,817	5,098,117	4,878,976
Mean	71.1	30.3	273.1
Standard Deviation	5.8	12.5	266.2
Weighted mean	68.3	43.2	569.2
Age (mean ± SD)	51.0 ± 15.3	48.9 ± 16.8	50.9 ± 13.8
References	110	138	118

Table 3.
Data and values were obtained in the assessment of the general population (HL_gp).

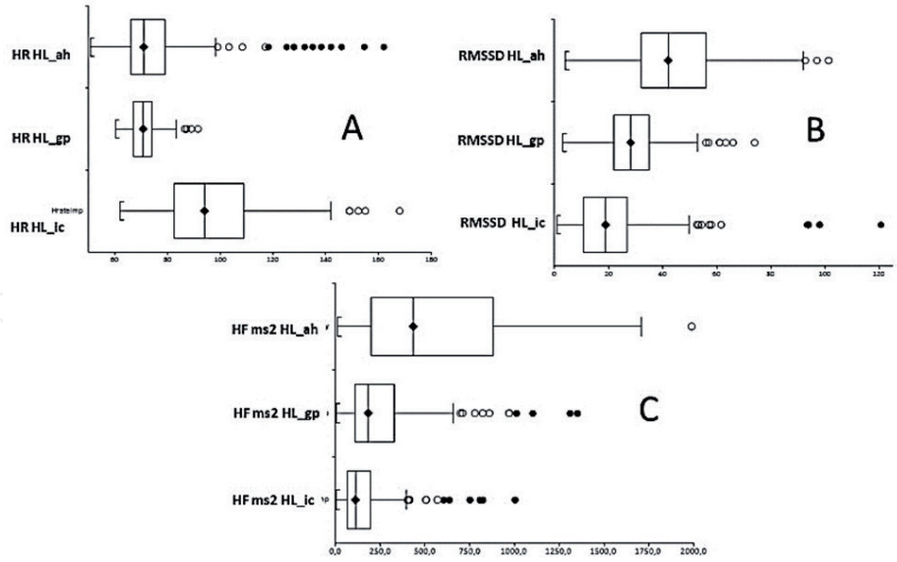

Figure 7.
Box-whisker graphs of the distributions of values for heart rate (A), RMSSD (B) and HF ms2 (C) variables, by the homeostatic level group.

Regarding the variable RMSSD, there was a statistically significant difference between RMSSD HL_ah versus RMSSD HL_gp ($P < 0.0001$); the statistically significant difference between RMSSD HL_ah versus RMSSD HL_ic ($P < 0.0001$); the statistically significant difference between RMSSD HL_gp versus RMSSD HL_ic ($P < 0.0001$).

In the comparative analysis of the variable HF ms2, there was a statistically significant difference between RMSSD HL_ah versus RMSSD HL_gp ($P < 0.0001$); statistically significant difference between RMSSD HL_ah versus RMSSD HL_ic ($P < 0.0001$); statistically significant difference between RMSSD HL_gp versus RMSSD HL_ic ($P = 0.0002$).

Therefore, it is concluded that data from the so-called general population are not suitable to be considered as a normal condition and this must be taken into account when this group is used as a control group.

Finally, based on the weighted average of the results in **Table 1**, on the scatter plots involving the group of individuals with significant homeostatic impairment and the group of apparently healthy individuals, we propose a classification model for the individual homeostatic level. This classificatory model is a three-level, three-stage alphanumeric coding, designed as follows:

Level A: Heart Rate (bpm)
- Stage A1: Heart Rate less than 70 bpm
- Stage A2: Heart Rate between 70 and 85 bpm
- Stage A3: Heart Rate above 85 bpm

Level B: RMSSD (ms)
- Stage B1: RMSSD above 32 milliseconds.
- Stage B2: RMSSD between 32 and 28 milliseconds.
- Stage B3: RMSSD less than 28 milliseconds.

Level C: HF ms^2
- Stage C1: HF ms^2 above 468 ms^2
- Stage C2: HF ms^2 between 468 and 156 ms^2.
- Stage C3: HF ms^2 less than 156 ms^2.

Thus, a totally healthy individual, with an excellent Homeostatic Level and, therefore, with very low risk, would receive the A1B1C1 classification. An individual with a

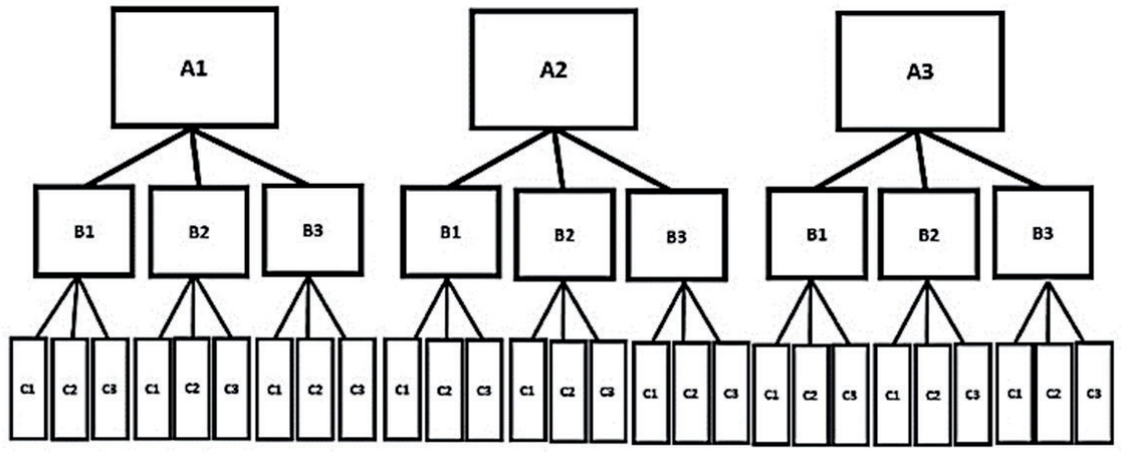

Figure 8.
Set of possibilities in the alphanumeric classification of the individual homeostatic level (Created by the authors).

high basal heart rate, a very low RMSSD value and a very low HF power value would be classified as A3B3C3 indicating high severity, low homeostatic level and, therefore, at high risk. Several intermediate combinations would be possible characterizing the current state of each case. The figure below illustrates the full set of possibilities (**Figure 8**).

In conclusion, the present analytical study, based on an extensive amount of data published in the literature (more than 10.5 million values), referring to three recognized variables of heart rate variability markers of the level of homeostasis, allowed us to define cut-off levels indicative of apparently healthy or with important homeostatic compromise. It was possible to conclude that values obtained in the general population are not equivalent to normal values, a fact that must be considered when this group is used as a control. It was also possible, to elaborate a very simple alphanumeric classification with practical applicability in the characterization of the individual homeostatic level.

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