Chapter

Root Mean Square of the Successive Differences as Marker of the Parasympathetic System and Difference in the Outcome after ANS Stimulation

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Abstract

The autonomic nervous system has a huge impact on the cardiac regulatory mechanism, and many markers exist for evaluating it. In this chapter we are going to focus on the RMSSD (Root mean square of successive differences), considered the most precise marker for the parasympathetic effector on the heart. Before is necessary to learn what the Heart Rate Variability is and how it works, which type of range of HRV exists and how we can measure it. Finally, there will be a presentation of how the RMSSD can be used in different field, and how and why the outcome can change and what does it mean.

Keywords: autonomic nervous system, sympathetic nervous system, parasympathetic nervous system, root mean square of successive differences, heart, cardiac mechanism, ANS influence

1. Introduction

Homeostasis can be defined as the result of the stability of physiological systems that maintain life; it applies strictly to a limited number of systems such as regulation of pH, concentration of different ions in the extracellular fluid, osmolality of extracellular fluid, glucose levels and arterial oxygen tension, which are truly essential for life and are therefore maintained within a narrow range for the current life history stage [1]. The homeostatic balance is considered as a change of state compatible with the actual environmental situations [2]. The temporary variations between the "set point" of the homeostatic control system during adaptation to internal (i.e. digestion) or external (i.e. climatic condition) perturbations are called *allostasis* [1]. Thus, allostasis is the reaching of physiological stability through a change of homeostatic state [1, 3].

The allostatic adaptations during environmental changes are temporary processes; if not turned off when not needed, if they occur too frequently or fail to occur at all, there may be development of systemic disease(s) such as cardiovascular disease, type II diabetes, obesity, etc. [4–6]. Allostatic and homeostatic control are ruled by the autonomic nervous system (ANS) integrated within the central

nervous system (CNS) [1]. A disorder of the ANS can affect the homeostatic and allostatic processes, leading to a risk of developing systemic disorder such as hypertension [7] baroreflex failure for blood pressure regulation [8], type II diabetes or affect the immune system and the inflammatory process [9]. Moreover, this has been demonstrated how the ANS is strictly correlated to the modulation of pain perceived by the subject.

One of the most common markers of the ANS is the rMSSD, square root of the mean squared differences of successive NN intervals. It is evaluated through the Heart Rate Variability (HRV) and the distance between the peaks of the R values in the echocardiogram. The rMSSD allowed the researcher to monitor the alteration in the parasympathetic activity with good precision. In this chapter will be explained how the rMSDD is related to parasympathetic nervous system, what could modulate the outcome and what a different result mean.

2. Heart rate variability

Heart rate variability consists of changes in the time intervals between consecutive heartbeats called interbeat intervals (IBIs) [10]. A healthy heart is not a metronome. The oscillations of a healthy heart are complex and constantly changing, which allow the cardiovascular system to rapidly adjust to sudden physical and psychological challenges to homeostasis.

The HRV is the fluctuation in time intervals between adjacent heartbeats, it indexes neurocardiac function and is generated by heart-brain interactions and dynamic non-linear autonomic nervous system (ANS) processes. HRV is an emergent property of interdependent regulatory systems which operate on different time scales to help us adapt to environmental and psychological challenges by stimulating and regulating some vascular component of the allostasis: HRV reflects regulation of autonomic balance, blood pressure (BP), gas exchange, gut, heart, and vascular tone, which refers to the diameter of the blood vessels that regulate BP, and possibly facial muscles [11].

Higher HRV is not always associated to better state of health of the subjects, numerous diseases affect the HRV and has the potential to increase this value. When cardiac conduction abnormalities cause an increase in the HRV, this is strongly linked to increased risk of mortality, particularly among the elderly (e.g. causing atrial fibrillation) [12].

Despite that has been demonstrated how optimal level of HRV are associated to health and self-regulatory capacity, adaptability and resilience [13, 14]. This is due to the vagal modulation of the HRV: heart rate (HR) estimated at any given time represents the net effect of the neural output of the parasympathetic (vagus) nerves, which slow HR, and the sympathetic nerves, which accelerate it. Opthof published a study on the normal range and the determinants of intrinsic heart rate in man, following the main research done before on the subject by Jose an Collins in 1970: he found that a denervated human heart, with no connections to the ANS, the intrinsic rate generated by the pacemaker, the Senoatrial Node (SA), is near to 100 beats per minute [15]. Whenever the rate decrease below this level, it means that a parasympathetic outflow is predominating in the balance between sympathetic and parasympathetic activity. This happens usually during normal daily activities, at rest and when we sleep. On the contrary, if the ratio raises over 100 beats the shift is toward the sympathetic system. The average 24 h HR in healthy people is approximately 73 bpm. Higher HRs are independent markers of mortality in a wide spectrum of conditions [16].

2.1 Sympathetic and parasympathetic pathways on the heart

Sinus node pacemaker cells activity is continuously under regulation by specific neural mechanism.

The SA node is targeted by the descending efferent sympathetic nerves via the intrinsic cardiac nervous system and the bulk of the myocardium. Norepinephrine and epinephrine release, which increases HR and strengthens the contractility of the atria and ventricles, is triggered by these motor neurons action potentials. Subsequent the onset of sympathetic stimulus, there is a delay of up to 5 seconds before the stimulation induces a progressive rise in HR, which reaches a stable level in 20–30 seconds if the stimulus is continuous [17]. A sympathetic stimulus, even if brief, can easily affect the HRV rhythm for 5–10 seconds. This is in contrast with the vagal stimulation, which is almost instantaneous, due to the acetylcholine degradation mechanism [17, 18], we will see that later on this chapter. What does that mean? That any sudden changes in the HR, up or down, or between the beat, is primarily mediated by the parasympathetic nervous system.

The vagus nerves innervate the intrinsic cardiac nervous system. Inside the intrinsic cardiac nervous systems are present some synapse between vagus nerve and motor neurons that directly project to the sinoatrial node and a portion of the surrounding tissue. They trigger acetylcholine release to slow HR. [19] However, more than 80% of the efferent preganglionic vagal neurons has connection to local circuitry neurons in the intrinsic cardiac nervous system where motor information is integrated with inputs from T.

The single efferent vagal stimulation on the SA node is very short, resulting in an immediate response that typically occurs within the cardiac circle in which it occurs, affecting only 1 or 2 heartbeats after its onset [17]. After cessation of vagal stimulation, HR rapidly increases to its previous level. An increase in heart rate can also be achieved by reduced vagal activity, or vagal withdrawal. Hence, any sudden increase or decrease HR, between 1 beat and the next, are primarily parasympathetically mediated [17, 18].

The medulla oblongata is the major structure integrating incoming afferent information from the heart, lungs and face with inputs from cortical and subcortical structures and is the source of the respiratory modulation of the activity patterns in sympathetic and parasympathetic outflow. The intrinsic cardiac nervous system integrates mechanosensitive and chemosensitive neuron inputs with efferent information from both the sympathetic and parasympathetic inputs from the brain. As a complete system, it affects HRV, vasoconstriction, venoconstriction, and cardiac contractility in order to regulate HR and BP [17].

2.2 Heart rate variability frequency band

The European Society of Cardiology and the North American Society of Pacing and Electrophysiology Task Force Report on HRV divided heart rhythm oscillations into 4 primary frequency bands: high-frequency (HF), low-frequency (LF), very-low-frequency (VLF), and ultra-low-frequency (ULF) [20]. Most HRV analysis is done in 5-min segments (of a 24 h recording), although other recording periods are often used. When other recording lengths are analyzed, the length of the recording should be reported since this has large effects on both HRV frequency and time domain values.

2.2.1 High-frequency band

The HF range is from 0.15 to 0.4 Hz, which correspond to a rhythm period between 2.5 and 7 seconds. This band is called the "respiratory band" because

correspond to the HR variations related to the respiratory cycle, known also as "respiratory sinus arrhythmia". Is conventionally recorded over a minimum 1 min period. For infants and children, who breathe faster than adults, the resting range can be adjusted to 0.24–1.04 Hz [21]. A complex regulatory mechanism involving both central and reflex interaction is the main organizer of this system. During inhalation there is an acceleration in the heart rate due to an inhibition of the vagal/outflow from the cardio-respiratory center. On the opposite, while exhaling, the vagal outflow is restored to a normal level resulting in slowing the HR.

The HF modulation has also psychological involvement: reduced vagally mediated HRV has been related to a reduced self-regulatory capacity and cognitive functions that involve the executive centers of the prefrontal cortex. This is consistent with the finding that lower HF power is associated with stress, panic, anxiety, or worry. It has to be noted how this reaction is due a reduction of the parasympathetic activity, and not to an increase in sympathetic ones. This has been shown by numerous studies, where a total vagal blockade obtained pharmacologically eliminates the HF oscillations and reduces power in the LF range, resulting in a strong reduction of the HRV, including LF and VLF bands. Thus, they concluded that HRV is a resultant of the parasympathetic mechanism.

High-frequency power is highly correlated with the pNN50 and RMSSD time-domain measures [22]. HF band power may increase at night and decrease during the day [10].

2.2.2 Low-frequency band

LF range is between 0.04 and 0.15 Hz, which equates to rhythms or modulations periods between 7 and 25 seconds. Is typically recorded over a minimum 2 min period [23]. This range of action was called the "baroreceptor range" or "mid-frequency band", due to its strong correlation with baroreceptor activity at rest [10, 24]. Baroreceptors are stretch-sensitive mechanoreceptors located in vena cavae, carotid sinuses, aortic arch and heart chambers. The ones found in the carotid are the most sensitive. Baroreflex is transported to the brain by the vagus nerve and represent the beat-to-beat change in HR per unit of change in systolic blood pressure [25]. A decreased baroreflex is related to aging and weakened regulatory capacity [26].

There is a different influence of the sympathetic and parasympathetic system inside this band, due to the rhythms: above 0.1 Hz the SNS seems to be lesser influent, whilst the parasympathetic affect heart rhythms down to 0.05 Hz [27, 28]. There rhythms are obtained during slow respiration rates, where a vagal activity easily generates oscillations in the heart rhythms crossing into the LF band [29, 30]. Therefore, when the respiratory rates are below 8.5 per minutes, or 1 in 7 seconds, or when a subject take a deep breath there is a vagal mediation influence.

Despite has been generally accepted the LF band has a marker for the sympathetic activity, and the LF/HF ratio is used to assess the balance between SNS and PNS, is still not totally clear if in resting condition the Low Frequency band reflect the baroreflex activity instead of the cardiac sympathetic innervation [31–33].

2.2.3 Very-low-frequency band

The VLF is the power in the range between 0.0033 and 0.04 Hz, which equates to rhythms or modulations with periods that occur between 25 and 300 seconds. Although all 24 h clinical measures of HRV reflecting low HRV are linked with increased risk of adverse outcomes, the VLF band has stronger associations with all-cause mortality than the LF and HF bands [34–37]. Low VLF power has been shown

to be associated with arrhythmic death [38] and posttraumatic stress disorder (PTSD) [39]. Moreover, low power expression in this band has been associated with high inflammation [40, 41] and has been correlated with low levels of testosterone. In contrast, other biochemical markers, such as those mediated by the hypothalamic–pituitary–adrenal (HPA) *Axis axis* (e.g., cortisol), did not [42]. Longer time periods using 24 h HRV recordings should be obtained to provide comprehensive assessment of VLF and ULF fluctuations [22].

Historically, is still not well defined the physiological explanation and mechanisms involved in the generation of the VLF component, compared to the LF and HF components. Despite the accuracy and the most predictive outcomes, this area has been largely ignored even. Long-term regulatory mechanisms and ANS activity related to thermoregulation, the renin-angiotensin system, and other hormonal factors appear to contribute to this band [43, 44].

Very-low-frequency power is strongly correlated with the SDNNI time-domain measure, which averages 5 min standard deviations for all NN intervals over a 24 h period. There is uncertainty regarding the physiological mechanisms responsible for activity within this band [14]. The heart's intrinsic nervous system appears to contribute to the VLF rhythm and the SNS influences the amplitude and frequency of its oscillations [20].

Based on work by Armor [45] and Kember et al. [32, 46], the VLF rhythm appears to be generated by the stimulation of afferent sensory neurons in the heart. This, in turn, activates various levels of the feedback and feed-forward loops in the heart's intrinsic cardiac nervous system, as well as between the heart, the extrinsic cardiac ganglia, and spinal column. This experimental evidence suggests that the heart intrinsically generates the VLF rhythm and efferent SNS activity due to physical activity and stress responses modulates its amplitude and frequency.

2.2.4 Ultra-low-frequency band

The ultra-low-frequency band (ULF) falls below 0.0033 Hz (333 seconds or 5.6 minutes). Oscillations or events in the heart rhythm with a period of 5 minutes or greater are reflected in this band and it can only be assessed with 24 h and longer recordings [22]. The circadian oscillation in HR is the primary source of the ULF power, although other very slow-acting regulatory processes, such as core body temperature regulation, metabolism, and the renin-angiotensin system likely add to the power in this band [20]. The Task Force Report on HRV suggests that 24 h recordings should be divided into 5-min segments and that HRV analysis should be performed on the individual segments prior to the calculation of mean values. This effectively filters out any oscillations with periods longer than 5 minutes. However, when spectral analysis is applied to entire 24 h records, several lower frequency rhythms are easily detected in healthy individuals [23].

There is disagreement about the contribution by the PNS and SNS to this band. Different psychiatric disorders show distinct circadian patterns in 24 h HRs, particularly during sleep [25, 47].

2.3 Heart rate variability measurement

Three types of measurement exist for the HRV, time-domain index, frequency-domain index and non-linear measurements. Time-domain indices quantify the amount of HRV observed during monitoring periods that may range from ~2 min to 24 h. Frequency-domain values calculate the absolute or relative amount of signal energy within component bands. N*on-linear measurements* allow us to quantify the unpredictability of a time series.

2.3.1 Time domain measurements of heart rate variability

Time domain measures are the simplest to calculate. Time domain measures do not provide a means to adequately quantify autonomic dynamics or determine the rhythmic or oscillatory activity generated by the different physiological control systems. However, since they are always calculated the same way, data collected by different researchers are comparable but only if the recordings are exactly the same length of time and the data are collected under the same conditions. Time domain indices quantify the amount of variance in the inter-beat-intervals (IBI) using statistical measures. The three most important and commonly reported time domain measures are the standard deviation of normal-to-normal (SDNN), the SDNN index, and the root mean square of successive differences (RMSSD) are the most commonly reported metrics.

2.3.2 The standard deviation of the normal-to-normal

The SDNN is the standard deviation of the normal-to-normal (NN) sinus-initiated IBIs measured in milliseconds. This measure reflects the ebb and flow of all the factors that contribute to HRV. In 24 h recordings, the SDNN is highly correlated with ULF and total power [48]. In short-term resting recordings, the primary source of the variation is parasympathetically mediated, especially with slow, deep breathing protocols. However, in ambulatory and longer term recordings the SDNN values are highly correlated with lower frequency rhythms [23]. Thus, low age-adjusted values predict morbidity and mortality. For example, patients with moderate SDNN values (50–100 milliseconds) have a 400% lower risk of mortality than those with low values (0–50 milliseconds) in 24 h recordings [49, 50].

2.3.3 Standard deviation of the normal-to-normal index

The SDNN index is the mean of the standard deviations of all the NN intervals for each 5 min segment. Therefore, this measurement only estimates variability due to the factors affecting HRV within a 5 min period. In 24 h HRV recordings, it is calculated by first dividing the 24 h record into 288 five-minute segments and then calculating the standard deviation of all NN intervals contained within each segment. The SDNN index is the average of these 288 values [20]. The SDNN index is believed to primarily measure autonomic influence on HRV. This measure tends to correlate with VLF power over a 24 h period [23].

2.3.4 The root mean square of successive differences

The RMSSD is the root mean square of successive differences between normal heartbeats. This value is obtained by first calculating each successive time difference between heartbeats in milliseconds. Each of the values is then squared and the result is averaged before the square root of the total is obtained. The RMSSD reflects the beat-to-beat variance in HR and is the primary time domain measure used to estimate the vagally mediated changes reflected in HRV [20]. The RMSSD is correlated with HF power and therefore also reflects self-regulatory capacity as discussed earlier [23].

3. Root mean square of successive differences as PNS marker

As aforementioned, the RMSSD reflects the vagally mediated changes in the relation that occur between two peaks in the R value of an echocardiogram, thus give to the researcher an overview of the PNS activity.

The parasympathetic modification evaluation is one of the most used parameters and find its utility in different research [51, 52]. Accordingly, to Zygmunt and Stanczyk [53], the rMSSD *"describes short-term variations, and thus reflects parasympathetic activities"*. Although the HRV and rMSSD does not reflect perfectly the tonic activity of parasympathetic and sympathetic, but rather the resultant on the effector, that are sinus cells node receptors; the vagal activity is predominant compared to sympathetic one. Influence of parasympathetic is fast and transient, due to acetylcholine degradation by acetylesterase. These physiological redundancies cause parasympathetic activities to be visible in the cycle that follows the stimulus, whilst the sympathetic stimulation develop more slowly, and their effects are visible only after 2–3 s, causing slower oscillation with higher amplitude [54]. One concern regarding this issue is that HRV studies are quite sensitive to a number of factors as eloquently pointed out by Piché and Descarreaux [55], which can make data interpretation challenging.

Due to the ambiguity in physiological meaning in low frequency (LF) variations during short recording periods [20] the Time Domain Indices (rMSSD) has revealed itself more reliable than frequency domain [56], and considered as PNS modulation indices [20]. R-R intervals is a time domain measure of HRV calculated by the equation of Kim et al. [57]. According to Hayward et al. [58], the rMSSD time domain measurement has high sensitivity to identify ANS modification in temporal window of 1–2 minutes, concordant to Thong et al. [59] who found how rMSSD is a valuable measurement for ultra-short-term records (1–5 minutes) due to its ability to be improved by combining disjoint records; e.g. combining 6 rMSSD records of 10 seconds each to obtain the equivalent of a 60 seconds length rMMSD registration. Moreover, Esco and Flat [60] showed and almost perfect relationship between ultra-short-term and criterion measures (5 minutes) by recording rMSSD in 23 athletes pre- and post-exercises.

3.1 RMSSD modulation with physical activity

RMSSD is often used for professional athletes in order to monitor cardiac activity and modulation of the HRV subsequentially to physical performance. Acute decreases in HRV have been reported to occur following intense endurance training [61], resistance training [62], and competition [63]. Therefore, low HRV is commonly thought to provide a reflection of acute fatigue from training or competing.

But despite what has been accepted for the last years, recent discovery shows how not always an increase in this value is a positive result.

In the context of monitoring fatigue or training status in athletes, a common belief is that high HRV is good and low HRV is bad. Or, in terms of observing the overall trend, increasing HRV trends are good, indicative of positive adaptation or increases in fitness. Decreasing trends are bad, indicative of fatigue accumulation or "overtraining" and performance decrements.

Unfortunately, an increasing HRV trend throughout training is not always a good thing and thus should not always be interpreted as such. In fact, several studies have reported increasing HRV trends in overtrained athletes predominately involved in endurance sports. For example, Le Meur et al. [64] showed decreased maximal incremental exercise performance and increased weekly HRV mean values in elite endurance athletes following a 3 week overload period, compared to a control group who saw no changes. Following a taper, performance supercompensation was observed along with a return of HRV toward baseline.

He most common response to overload training is a progressive decrease in HRV. This is your typical alarm response to a stressor, where the sympathetic arm of the autonomic nervous system is activated. In this situation, resting HR is elevated

and HRV decreases. With insufficient recovery time, HRV may not fully recover to baseline before the next training stimulus and thus will result in a downward trend when this cycle is perpetuated. An intense day of training can result in suppressed HRV for up to 72 hours post-exercise [65]. With the higher training frequencies and training volumes often associated with overload periods, it makes sense that HRV will show a decreasing trend. Typically, HRV will respond first with a decreasing trend and performance decrements will follow if the overload period is sustained.

A study by Pichot et al. [66] provides a good example of a decreasing HRV trend in response to overload training. They showed that middle distance runners saw a progressive downward HRV trend (up to −43%) during a 3 week overload period. In week 4, training loads were reduced and HRV recovered and exceeded baseline values.

These aspects demonstrate a new aspect of the RMSSD modulation due to a physical stimulus, and the complexity of the cardiac regulation mechanism.

3.2 RMSSD application inside the psychological field

Altered cardiac autonomic functions in form of reduced Heart Rate Variability (HRV) have been found to be associated with increased cardiovascular morbidity and mortality in depressive patients.

Most studies have now identified depression as a strong and independent risk factor for cardiovascular disease even in physically healthy individuals [67] and also for adverse cardiovascular outcomes such as mortality [68]. Although the underlying pathophysiological mechanism is yet to be elucidated, autonomic imbalance has been projected as one of the underlying mechanisms [69]. Heart Rate Variability (HRV) is a useful non-invasive measure for assessing cardiac autonomic modulations.

Reduced HRV has been reported in several studies done in depressed patients both with and without cardiovascular diseases compared to non-depressed subjects [70, 71]. Although negative studies have been reported as well, which were unable to prove an association [72]. Most of the researches carried out to observe the association between HRV and depression have been done in individuals who were already either having Cardiovascular Disease (CVD) besides depression or were on medications [73].

A meta-analysis done by Kemp et al., in depression patients without cardiovascular diseases also reported the association between reduced HRV and depression and was found to be more in severely depressed individuals [74].

In addition, Agelink et al., showed the inverse correlation of parasympathetic HRV values with the severity of depression [75]. In a recent study Wang et al., also observed higher LF, LF:HF Ratio and lower SDNN, RMSSD and HF values in depression group compared to control group [52].

4. Conclusion

The rMSSD can be a very useful tool for many relevant findings: from the parasympathetic activation to a marker for cardiac dysfunction. Despite the findings and the large are of application, it is still an unknown area.

The correlation between the psychological issues and the rMSSD value add a deeper meaning on how the body is strictly correlated to the mind, and the interrelation between the thought and its physical response. Many research has been done regarding the heart and its physiology and mechanism, but only now we are starting to really understand how this tissue really works, and for better comprehend how

this organ is connected to the body and how it respond to the numerous different stimuli throughout the day, is necessary to delineate a clear structure of evaluation capable of considering also these new aspect, like the psychological impact and the psychological response.

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