

## HEART RATE VARIABILITY (HRV) - ANALYSIS AND CLINICAL SIGNIFICANCE

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### ABSTRACT

Heart rate variability (HRV) is a significant measure indicating how much variation exists in one's heartbeats within a specific timeframe. Two important models- the polyvagal theory and neurovisceral integration models and correlation among vagally assessed high-frequency heart-rate variability (HF-HRV) with neurovisceral integration describe the heart rate variability. The neurovisceral integration model explains the role of prefrontal cortex in regulating the limbic structures suppressing parasympathetic and activating sympathetic activities leading to HRV and modulation of HRV. Major methods for analyzing HRV are: a): Time-domain measurement; b): Geometric-measurement methods; c): Frequency-domain methods; and d): Non-linear measurement methods. Increase in vagal functional activity has indeed quite potential involvement. However, there is no clear clue indicating the extent of increase that might be beneficial. There are various cardiac diseases and non-cardiological diseases where decrease in HRV occurs. However, increase in HRV for well-being and normal health can be produced by several factors/ conditions for protective measures. Conclusively, the factors increasing the HRV may provide protection against cardiac disease, mortality and sudden death. However, it seems also important to keep in mind that there might not be always true to assume that too much high modification of HRV may bring cardiac protection.

**Key-words:** Heart rate variability (HRV), HRV analysis, significance of HRV, cardiac and non-cardiac diseases, modification of HRV, protective measures

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### INTRODUCTION

Heart rate variability (HRV) is a measure indicating how much variation exists in one's heartbeats within a specific timeframe (Vesterinen *et al.*, 2016). It is also termed as "RR variability" (variability in terms of interval between successive Rs; term 'NN' in place of 'RR' is used to indicate normal beats). Electrocardiography (ECG) is considered superior to other methods for directly detecting the inter-beat interval (IBI) and hence, HRV, since it detects clear waveforms that help excluding heartbeats not arising from sinoatrial node (Mateo *et al.*, 2011). However, other methods include blood pressure, BCG (ballistocardiogram) (Bruser *et al.*, 2011) and PPG (photoplethysmogram) that can be used for detecting heart beats. Sampling rate of the data acquisition system determines the accuracy of HRV (Kuusela, 2013). The rMSSD (root mean-square of successive-differences) is most commonly employed HRV formula (Hautala *et al.*, 2006; Vesterinen *et al.*, 2013).

The SA node receiving various RR interval forming inputs mainly from the SN (sympathetic nervous-system), PN (parasympathetic nervous-system) and humoral factors are affected by a variety of factors. Under normal circumstances, SA node generates heartbeat regulated by the autonomic nervous system (ANS) efferent neurons and hormonal control. Hence, an intricate balanced activity of sympathetic & parasympathetic systems occur. Change in HRV is produced by a variety of factors including intrinsic neurocardiac system, baroreceptor reflex, metabolism, circadian oscillations, renin-angiotensin system, regulation of HR by respiration, stress, cytokines, hormones, meals, physical activity, sleep-wake cycle, thermoregulation, training, emotional self-regulation etc. We found correlation among HRV, BMI and leptin levels (Serafi *et al.*, 2016) and suggested the role of leptin and other adipocytokines in hypertension (Serafi *et al.*, 2016; Serafi, 2018) and other conditions (Alshehri *et al.*, 2018). Four primary frequency bands are the high-frequency(HF), low-frequency(LF), very low-frequency(VLF) and ultra low-frequency (ULF) bands that are recorded for 5-minutes segments and have substantial effects on HRV-frequency as well as time-domain evaluations as described in Task Force report (1996).

The HF activity in the range of 0.15-0.40 Hz associated with respiratory sinus arrhythmia (RSA), is linked with parasympathetic activity. However, very little information is available about the physiological LF(0.04-0.15 Hz) input. It is essential to record approximately 1 minute for assessing HF components of HRV whereas more than 4 minutes are required for LF component. The SNS activity is involved in forming HRV. However, it is now suggested that both SNS and PSNS are involved with a mixed input (Billman, 2013) for their contribution. The major variations are respiratory arrhythmia or RSA (Respiratory sinus arrhythmia), and low frequency oscillations (usually 10second period/or 0.1Hz) frequency; associated with Mayer waves of blood pressure) (Sayers, 1973).

## REGULATION OF HRV

Two important models- the polyvagal theory (Haselton *et al.*, 1992; Gatti *et al.*, 1996; Porges, 2003; Porges, 2007; Porges, 2011) and neurovisceral integration models (Heart rate variability, 1996; Thayer and Sternberg, 2006; Napadow *et al.*, 2008; Thayer *et al.*, 2012); and correlation among vagally assessed HF-HRV to neurovisceral integration (Richard Jennings *et al.*, 2015) describe the heart rate variability. There is structural and functional involvement of polyvagal regulation of the heart and HRV (Haselton *et al.*, 1992; Gatti *et al.*, 1996). Polyvagal theory model is based on RSA (respiratory sinus-arrhythmia) and its conduction via a neuronal communication quite different from the other HRV-components (Porges, 2007; Porges, 2011).

Interesting information was obtained for the association existing for fitness (aerobic), SN/PN cardiac-control utilizing HF HRV PEP (pre-ejection-period), and performance of variable cognitively controlled task (Alderman and Olson, 2014). It was found that affective emotion causes increase in HRV and stimulates left dorsolateral prefrontal cortex in the post-traumatic growth. (Wei *et al.*, 2017). The neurovisceral integration model explains the role of prefrontal cortex in regulating the limbic involvement that decreases the PS activities and increase the sympathetic activation. Furthermore, the changes in sympathetic and parasympathetic output can produce HRV (Heart rate variability, 1996; Thayer and Sternberg, 2006; Napadow *et al.*, 2008; Thayer *et al.*, 2012).

## ANALYSIS OF HRV

Major methods for analyzing HRV are: a): Time-domain measurement (Mietus *et al.*, 2002; DeGiorgio *et al.*, 2010; Tarvainen *et al.*, 2017); b): Geometric methods (Vanderlei *et al.*, 2010; Parameter aus dem Lorenz-Plot, 2016; Lorenz curve command, 2016); c): Frequency domain methods (Kleiger *et al.*, 2005; Isler and Kuntalp, 2007; Kuusela, 2013; Shaffer *et al.*, 2014); and d): non linear (Costa *et al.*, 2002; Stein and Reddy, 2005; Voss *et al.*, 2009; Bailly *et al.*, 2011; Ebadi *et al.*, 2011; Shirazi *et al.*, 2013; De Souza *et al.*, 2015) methods. The intervals and variables in the mentioned methods are given in Table 1.

Table 1. Methods of analyzing HRV.

Methods	Intervals	Variables	References
Time-domain measurement	Mean normal to normal (NN) intervals	Time-domain indices (original or natural logarithm (Ln) units), SDNN, SDANN, SDNN-index, RMSSD, SDSD, NN-50 count, pNN-50, EBC, NN20, pNN20, HRMax-HRMin, HRV-triangular-index,	Heart rate variability, 1996; Umetani <i>et al.</i> , 1998; Mietus <i>et al.</i> , 2002; DeGiorgio <i>et al.</i> , 2010; Tarvainen <i>et al.</i> , 2017
Geometric methods	Series of (N-N) intervals converted into geometric pattern	Geometric indexes, SDD (sample-density distribution) of N-N interval durations/differences, geometric patterns for Poincaré plot or Lorenz plot	Heart rate variability, 1996; Vanderlei <i>et al.</i> , 2010; Parameter aus dem Lorenz-Plot, 2016; Lorenz curve command, 2016
Frequency-domain measurement methods	Assigning frequency* bands & counting number of band matching normal to normal intervals	Peaks and power distributions across frequencies; PSD; DFT; FFT; WEM, 5min total-power, VLF, LF, LF-norm, HF, HF-norm, LF/HF, entire 24 hrs-analysis, ULF, LF, VLE, HF	Heart rate variability, 1996; Task Force Report, 1996; Kleiger <i>et al.</i> , 2005; Isler and Kuntalp, 2007; Kuusela, 2013; Shaffer <i>et al.</i> , 2014
Non linear methods	Geometric shapes of the data	S, SD1, SD2, SD1/SD2, ApEn, SampEn, DFA $\alpha_1$ , DFA $\alpha_2$ , D2; Pair of successive beats by Poincaré plot, nonlinear predictability, correlation dimension, pointwise correlation dimension, symbolic-dynamics, sample-entropy, approximate-entropy, detrended-fluctuation-analysis, multiscale entropy analysis, long range correlations geometrically, memory length, sample asymmetry	Kanters <i>et al.</i> , 1994; Peng <i>et al.</i> , 1995; HRV, 1996; Storella <i>et al.</i> , 1998; Richman and Moorma, 2000; Brennan <i>et al.</i> , 2001; Kantelhardt <i>et al.</i> , 2001; Costa <i>et al.</i> , 2002; Stein and Reddy, 2005; Voss <i>et al.</i> , 2009; Bailly <i>et al.</i> , 2011; Ebadi <i>et al.</i> , 2011; Shirazi <i>et al.</i> , 2013; De Souza <i>et al.</i> , 2015

SDANN:SD of the average N-N intervals;RMSSD:root-mean-square of successive-differences;SDSD:SD of successive-differences;NN-50: number of pairs of successive-NNs differing by more than 50-ms;pNN-50:proportion of NN-50 divided by total number of NNs;EBC: estimated breath cycle; NN20: number of pairs of successive-NNs differing by more than 20ms; pNN-20: proportion of NN-20 divided by total number of NNs; \*high frequency-(HF):0.15-0.4 Hz;low frequency-(LF):0.04-0.15 Hz, very low frequency(VLF):0.0033-0.04 Hz;PSD: power-spectral distribution;DFT:discrete Fourier-transform;FFT:fast Fourier-transform;WEM:wavelet entropy measures;ULF: ultra-low frequency bands;S:Area of the ellipse or total HRV;SD1:Poincaré plot SD perpendicular of identity-line;SD2: Poincaré plot SD along identity-line; SD1/SD2,Ap-En:Approximate-entropy;SampEn:Sample-entropy;DFA  $\alpha_1$ :Detrended-fluctuation for shortterm change;DFA- $\alpha_2$ :Detrended-fluctuation for longterm change;D2:Correlation dimension

Table 2. HRV changes in cardiac and non-cardiac diseases.

Diseases	HRV changes
Myocardial infarction	Reduced HRV indicating decreased vagal activity (Sessa <i>et al.</i> , 2018)
Autonomic dysfunction (depression, anxiety, asthma, SID etc)	Low HRV than healthy subjects (Giardino <i>et al.</i> , 2004; Cohen and Benjamin, 2006)
Cardiac transplantation	Quite reduced HRV (Havlicekova and Jurko, 2005)
Congestive heart failure	Reduced HRV (Mahajan <i>et al.</i> , 2017)
Myocardial dysfunction	Decreased HRV with sympathetic activation (Wiggers <i>et al.</i> , 2002)
Hypertension	Decreased HRV (Schroeder <i>et al.</i> , 2003)
Fetal distress	Low HRV (Hon and Lee, 1963)
Diabetic neuropathy	Reduction of time domain parameters of HRV (Ewing <i>et al.</i> , 1976)
Tetraplegia	LF component detection in HRV and arterial pressure variabilities (La Fountaine <i>et al.</i> , 2010)
Sepsis	Decreased HRV (Barnaby <i>et al.</i> , 2018)
Liver cirrhosis	Decreased HRV (Abrahamovychet <i>et al.</i> , 2017)
All-cause mortality	HRV may decrease (Tsuji <i>et al.</i> , 1994; Dekker <i>et al.</i> , 1997).

SID: Sudden infant death

Table 3. Factors modifying HRV and protection measures.

HRV modifying factors	Modification and protection measures
Antiarrhythmic drugs; flecainide , propafenone	Some effect of antiarrhythmic therapy associated with stabilization of cardiac rhythm and HRV; some of these drugs modify HRV by decreasing time domain measures of HRV, or decrease LF much more than HF; a significant change occurred in patients treated with flecainide or propafenone (Zuanetti ; Khaspekova <i>et al.</i> , 2005)
$\beta$ -adrenergic blockers, selective beta-adrenergic blocker, metoprolol	Little human data describing HRV modification. Indirect studies show modification (Bloom <i>et al.</i> , 2014)
Resonant breathing biofeedback training	Effective for controlling involuntary HRV; Resonant frequency biofeedback training increases cardiac variability (Lehrer <i>et al.</i> , 2000)
Regular physical exercise	Shows higher HRV than sedentary subjects (Dietz <i>et al.</i> , 2016).
Thrombolysis in patients with acute myocardial infarction (AMI).	May cause increase in HRV in acute-MI patients (Larosa <i>et al.</i> , 2005)
Atropine	May cause increase in HRV though varies widely (Picard <i>et al.</i> , 2009)
Scopolamine	Modifies HRV (Katoh <i>et al.</i> , 2003)
Acupuncture	Modifies HRV (Wang <i>et al.</i> , 2013)

### HRV IN CARDIAC/NON-CARDIAC DISEASES

The HRV is reduced in MI (Kleiger *et al.*, 1987; Bigger *et al.*, 1992; Sessa *et al.*, 2018), myocardial dysfunction (Wiggers *et al.*, 2002) usually in congestive heart-failure (Mahajan *et al.*, 2017), post-cardiac transplant (Havlicekova and Jurko, 2005), depression (Giardino *et al.*, 2004; Cohen and Benjamin, 2006) , fetal distress (Hon and Lee, 1963), hypertension (Schroeder *et al.*, 2003), diabetic neuropathy (Ewing *et al.*, 1976), autonomic

dysfunction (anxiety, asthma etc) (Giardino *et al.*, 2004; Cohen and Benjamin, 2006), tetraplegia (La Fountaine *et al.*, 2010), sepsis (Barnaby *et al.*, 2018), liver cirrhosis (Abrahamovych *et al.*, 2017), in relation to premature babies and Sudden infant death syndrome (SIDS) (Giardino *et al.*, 2004; Cohen and Benjamin, 2006), and all cause-mortality (Tsuji *et al.*, 1994; Dekker *et al.*, 1997).

The HRV decreases in high-pressure, emotionally strained conditions, elevated anxiety (Nickel and Nachreiner, 2003; Jönsson, 2007; Paniccia *et al.*, 2017), in individuals showing much worry, and PTSD (post-traumatic stress disorder) (Brosschot *et al.*, 2009; Meyer *et al.*, 2016). Various cardiac and non-cardiac diseases and HRV changes are mentioned in Table 2.

## MODIFICATION OF HRV AND PROTECTION MEASURES

There are a variety of manipulations (e.g. antiarrhythmic drugs,  $\beta$ -adrenergic blockers, selective beta-adrenergic blocker, metoprolol, resonant breathing biofeedback training, regular physical exercise, thrombolysis in patients with acute myocardial infarction (AMI), atropine, scopolamine, acupuncture etc) for modifying the HRV for protection measures. Table-3 summarizes the factors/ conditions modifying HRV and protection measures.

## CONCLUSIONS

Increase in vagal activity is indeed important but it is not clearly known how much increase might be beneficial. There exists a complex interaction/relationship between the sympathetic nervous system component and parasympathetic nervous system component and respiratory and baroreceptor-reflexes resulting to the short term and ultra short HRVs.

There is an intricate balance for sympathetic and parasympathetic activity in healthy individuals. Since it is evident that slower regulatory mechanisms take part in HRV-metrics taken in measurements with longer periods, it is important to understand that the values at 24 hour/short term/ultra short term period are not inter-changeable with each other. There are various cardiological and non-cardiological diseases where decrease in HRV occurs. However, modification in HRV for well being and normal health can be produced by several factors including intrinsic neurocardiac system, baroreceptor reflex, metabolism, circadian oscillations, renin-angiotensin system, regulation of HR by respiration, hormones, meals, physical activity, sleep-wake cycle, thermoregulation, training, emotional self-regulation etc.

Conclusively, the factors increasing the HRV may provide protection against cardiac disease, mortality and sudden death. However, it seems also important to keep in mind that there might not always be true to assume that too much high modification of HRV may bring cardiac protection.

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