Heart rate variability – clinical significance

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Summary

Heart rate variability (HRV) is a statistical evaluation of ECG Holter analysis used for non-invasive assessment of autonomic nervous system activity. The autonomic nervous system plays a major role in human homeostasis. Autonomic dysfunction and altered HRV are observed in many life-threatening conditions, like myocardial infarction, multiple organ dysfunction syndrome, sepsis and severe brain injuries. Analysis of HRV uses two major techniques for assessing ECG intervals – time and frequency analysis. Additionally, there is an alternative non-linear method of assessing HRV called fractal analysis. Clinical evaluation of HRV has been performed in medicine for more than three decades. Recent studies show that heart rate variability is a strong predictor of cardiovascular risk and mortality. It has also become common practice in everyday medicine, especially in family medicine, cardiology, neurology and psychiatry. There are some variables affecting HRV analysis: age, gender, physical activity and body mass index. Age and body mass index have negative correlation with HRV. Correlation of gender with HRV is not clearly specified in literature. Recent studies show that young males have increased HRV, and this diminishes faster during aging. Young women present decreased values of HRV, but these differences become indistinguishable after 50. Physical activity may enhance HRV by increasing vagal tone and decreasing sympathetic activity.

Key words: heart rate, autonomic dysfunction, cardiovascular risk.

Definition of HRV

Heart rate variability (HRV) is a statistical evaluation of ECG Holter analysis used for non-invasive assessment of autonomic nervous system activity. HRV determines consecutive NN (or RR) intervals of the sinus rhythm on time pre-defined ECG strips, ranging from a few minutes to 24 hours, and presents its results in the form of a mathematical table. The parameters used in HRV analysis proved to be non-invasive markers of the activity of the autonomic nervous system and have showed to have prognostic value in evaluation of cardiovascular risk [1]. Assessment of HRV requires accurate detection of sinus rhythm, and thus has some limitations, e. g. arrhythmias, premature atrial and ventricular beats, atrial fibrillation provide false results of the analysis and must be removed from the NN sequences. Furthermore, HRV parameters can be compared from different recordings but of the same time intervals [2].

The clinical relevance of heart rate variability has been published in many scientific reports; the first were noted in 1965 by Hon and Lee. They found that fetal distress was preceded by alterations of beat to beat intervals of the ECG analysis, even before any visible heart rate changes occurred [3]. Further research on combined HRV analysis proved to have a prognostic value in diabetic patients. Finally, in 1970–1980, many studies proved the clinical advantage of HRV as a strong and independent predictor of mortality after acute myocardial infarction. This correlation was first disclosed by Wolf et al. in 1978 [4].

Methods of analysis

Heart rate variability uses two major techniques for assessing ECG intervals – time and frequency analysis. Time domain parameters are used to evaluate beat to beat intervals, and frequency domain measures present a spectral analysis of heart-beat patterns [5].

Time analysis of 24-hour ECG recording uses the following parameters:

- mNN – mean NN interval;
- SDNN – standard deviation of all normal NN intervals. There can be two variants of SDNN: SDANN and SDNN index. SDANN is the standard deviation of all 5-minute NN intervals and the SDNN index is the mean of all the 5-minute standard deviations of NN;
- r-MSSD and pNN50. The r-MSSD (root-mean-square successive difference) calculates the square root of the mean squared differences between consecutive NN intervals. The pNN50 estimates the percentage differences of successive NN intervals which are greater than 50 milliseconds.

SDNN is a measure of total heart rate variability, SDANN measures the long-term variation and SDNN index, while r-MSSD and pNN50 measure the short-term variation [6]. All time domain indices, except pNN50, have units of time in milliseconds.

Frequency analysis is based on power spectral density (PSD). The calculations require a computer algorithm, called the fast Fourier transform (FFT). PSD presents the distribution of power (variance) as a function of the frequency. The following frequency domain parameters are analyzed:

- HF (high frequency) – from 0.15 to 0.4 Hz, reflects parasympathetic activity and respiratory sinus arrhythmia, which correlates with r-MSSD and pNN50;
- LF (low frequency) – from 0.04 to 0.15 Hz, reflects both sympathetic and parasympathetic activity [6]. LF is associated with the peripheral baroreceptor system and is considered as an indicator of sympathetic activation [7];
- VLF (very low frequency) – from 0.003 to 0.04 Hz, and ULF (ultralow frequency) – below 0.003 Hz. VLF and ULF reflect long-term variability and correlate with SDANN. VLF is modulated by neurohormonal activity, including the renin–angiotensin–aldosterone system and thermoregulation [8];
A strong negative correlation between HRV and the degree of central nervous system injury was first demonstrated in the 1990s in pediatric populations. HRV analysis may be helpful in predicting [23] and confirming brain death [24]. At the onset of the 21st century, autonomic dysregulation was found to be a significant marker in stroke patients. Studies revealed that the nonlinear parameters of HRV are reliable when assessing the outcome of cerebral ischemia and can predict Stroke-In-Evolution (SIE) in acute ischemic patients. Chen et al. assessed HRV on a non-linear analysis of 90 patients with non-atrial fibrillation acute ischemic stroke. They found that fractal analysis HRV multiscale entropy (MSE) was significantly decreased in patient suffering from SIE and presented MSE as a potential post-stroke predictor of SIE [25]. Epilepsy is another neurological disorder with sympathovagal imbalance [26] and is often accompanied by lower HF, SDNN and RMSSD values when compared to controls [27]. This implies an association with fatal arrhythmias and sudden unexpected death in epilepsy (SUDEP), which is partly the result of parasympathetic predominance [28]. Reduced HRV can also be observed in many studies regarding psychiatric disorders, depression, schizophrenia, anxiety and substance addiction. The greatest effect of reduced HRV is observed in individuals with psychotic disorders [29].

Variables affecting HRV analysis

Clinical evaluation of HRV has been performed in medicine for more than three decades. Although it has proven to be a good marker of autonomic nervous system activity and cardiovascular risk, there are still no complete guidelines on determining the norms of its parameters. Commonly used documents were published by NASPE and ESC in 1996 [6] but have some major limitations. They do not include variabilities, like the influence of age and gender. Recent studies show that age, gender, physical activity and body mass index affect heart rate variability.

The influence of age is quite visible in the time domain parameters of HRV analysis. The most sensitive changes affect the pNN50 index, which starts to drop even in 20–30-year-old subjects and consequently decreases, reaching a 76% drop in the baseline value (estimated as the mean values of 20-year-old subjects) by the end of sixth decade. For comparison, rmSSD by the age of 60 reaches approx. 50%. HRV determined by SDNN and SDANN decreases at a slower rate, mostly between the second and the third decade [30]. However, there are also some studies that show the limitations of time domain indexes. Jokinen et al. conducted a follow-up study which included a fractal analysis. In the 32 months of follow up Holter recordings, they found no significant correlation between traditional time and frequency domain measures and heart rate variability. Furthermore, the fractal analysis turned out to be more sensitive than traditional methods in evaluating age-related HRV alterations [31].

The data in literature concerning gender is inconsistent. Some studies show that females are considered to have higher HRV parameters, due to parasympathetic system predominance [32]. This approach would explain the burden of the high cardiovascular risk in men. Others conclude that there are no major differences after a certain age. The HRV spread between sexes gradually decrease at an age of > 30 years to finally disappear at an age > 50 years [30, 33]. Young females (10–29 years) have significantly lower HRV parameters than the same age-matched males, but the rate of decrease with aging is much faster in males [30].

Physical activity and body mass index can contribute to healthy longevity via parasympathetic activation [34]. Exercise training may enhance HRV by increasing vagal tone and decreasing sympathetic activity. This also affects the reduction of heart rate.
rate, which leads to oxygen consumption decline [35]; hence, the greatest benefit from exercise therapy was demonstrated in patients with myocardial infarction [36], chronic heart failure and in patients after revascularization. Body mass index has an inverse correlation between HRV and body weight [37–39].

The role of HRV in family medicine

Stratification of cardiovascular risk plays a major role in family medicine, especially in the daily care of diabetic and cardiac patients [11]. Heart rate variability, as a strong predictor of cardiovascular risk and mortality, allows the general practitioner to obtain an introduction to optimal medical treatment. Patients after myocardial infarction and those with heart failure or diabetes appear to have double the risk of mortality when autonomic dysfunction is found [40]. HRV is a better tool for the general practitioner to seek out such patients and introduce proper prophylaxis or guide them towards specialist care.

There are many useful tools to evaluate cardiovascular risk in the daily practice of family medicine, e.g. score charts, risk calculators, surveys. They allow one to increase compliance with patients undergoing cardiovascular treatment. HRV can be used as an additional method to graphically present the current risk to patients. The more narrowed the HRV graph, the greater the cardiovascular risk present [6].

Conclusions

Heart rate variability proved to be a strong predictor of cardiovascular risk and mortality. It is also a great tool to estimate autonomic nervous system activity. It is commonly practiced in everyday medicine, especially in cardiology and neurology. However, there are many other diseases affected by autonomic dysregulations, where HRV is still under investigations, such as: sleep apnea, chronic kidney disease, irritable bowel syndrome, muscular dystrophy, Guillain–Barre syndrome and Parkinson disease.

Source of funding: This work was funded by the authors’ own resources.
Conflict of interest: The authors declare no conflict of interests.

References