Analysis of Heart Rate Variability and Clinical Implications

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1. INTRODUCTION

Continuous electrocardiographic monitoring of heart rate in the perioperative period, in the setting of intensive care unit and during labour and some diagnostic procedures, is considered as a basic standard care. The scope of this paper is limited to description of the recently recognized parameters derived from analysis of different duration of the intervals between consecutive heart contractions, which is named heart rate variability (HRV) and clinical implications (1).

Inherent automaticity of the depolarization of specialized cells in sino-atrial node determines heart rate, but it is the complex interplay of autonomic sympathetic and vagal parasympathetic activity that modulates frequency of the sino-atrial node depolarization. Vagal stimulation produce hyperpolarization of the cardiac pacemaker cells and reduced rate of depolarisation, on the contrary sympathetic stimulation causes increasing of rate of depolarization (2). With every beat of the heart, information about the state of the circulation, are sent to the neurons within the medulla oblongata and processed in the milieu of integrative modulating influences from hypothalamus and higher centers. Efferent signals are sent to output regions of the central nervous system and ensure maintenance of the functioning of the cardiovascular system at the most appropriate level. Sympathetic preganglionic neurons give major contribution in the control of heart rate and blood pressure at the level of spinal cord. Figure 1 represents simplified scheme of the neural components that influence heart activity. Interactions between sympathetic and parasympathetic efferent projections involve different modulation of adenylate cyclase via G-protein-coupled receptor systems. Catecholamines, released from sympathetic efferent projections or from circulation, influence myocardial tissue by binding to $\beta_1$ and $\beta_2$ adrenoreceptors, which are coupled to and stimulate adenylate cyclase via stimulatory guanine nucleotide-binding protein(Gs). Acetylcholine, released from parasympathetic efferent postganglionic neurons, binds to cardiomyocyte $M_2$ muscarinic receptors, which inhibit adenylate cyclase via inhibitory guanine nucleotide-binding protein (Gi). Interactions between these two receptor-coupled systems at the adenylate cyclase level determine the formation of cAMP and influence the function of second messengers in myocyte and subsequently modulate the cell functions (2).

Complex neuronal, reflex and local control of the frequency of heart rate is manifested in different length of cardiac cycle in physiological and it is quite changed in pathological conditions. Acceleration of heart rate is a result of increase in sympathetic activity or decrease in vagal activity with shortening of cardiac cycles and most effect on diastole duration, while bradycardia is a result of predominant parasympathetic activation.

The clinical importance of HRV was recognized by Hon and Lee, who observed that fetal distress was associated with significant changes in HRV before any change in heart rate itself (3).

An important observation was made by Wolf et al. in 1977, who found that a reduced HRV was related to a higher risk of post-infarction mortality. About ten years later Kleiger et al. published a paper on the results of the Multi-Center Post-Infarction Project (MIPPI), what started a more serious interest in HRV among cardiologists (4).

Since then a lot of studies have been performed on the issue of low measures of HRV which have been linked with different diseases and conditions.

In 1996 Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology developed standards of measurements and physiological correlates of HRV and clinical applications. According to the guidelines measurement of heart rate variability (HRV) may provide quantitative information on the modulation of cardiac sympathetic and parasympathetic nerve activities. The two main applications that could be clinically useful are the risk stratification after myocardial infarction and the assessment of diabetic neuropathy (5). Impaired autonomic nervous activity has been recognized as an important symptom and is strongly associated with an increased risk of overall mortality in patients with heart disease.

2. MEASUREMENT OF HRV

The most commonly used methods of HRV analysis can be categorised into four groups: time domain measures, frequency domain measures, rhythm analysis and non-linear methods (3).

Two main methods that are used for evaluation of HRV in clinical practice are time domain methods and frequency domain methods.

2.1. Time Domain Method

QRS detection is necessary for the
determination of the periods between adjacent QRS complexes which are named the N-N (normal-normal) intervals (9).

The simplest calculated measures are: the mean interval length (meanNN) and the standard deviation (SDNN). SDANN is the standard deviation of intervals averaged over 5min sections. The parameter pNN50 is the proportion of interval differences of less than 50 ms. It is a marker for vagal activity. Geometrical measures are based on the density distribution of NN intervals. The shape of the histogram can be approximated by a geometrical shape, such as a triangle, and a measure of that shape can be used in further assessment (5).

Different calculated variables of time domain measures are used for analysis of HRV and they are listed in the Table 1.

### 2.2. Frequency Domain Method

In the spectral analysis of the tachogram, ECG signal is differentiated into the frequencies using a mathematical algorithm (fast Fourier transformation), that can be represented on a graph, and area under the curve is designated as a spectral power (5).

The frequency domain is divided into bands, which isolate typical peaks, as shown in Figure 2. For short-term recordings, the high band (HF) is in range between 0.15 Hz and 0.4 Hz, the low band (LF) from 0.04 Hz to 0.15 Hz and the very low band (VLF) of frequencies below 0.04 Hz. The measurement of VLF, LF and HF power components is mostly in absolute values of power (milliseconds squared–msec⁻²).

Frequency domain methods are appropriate for analysis of short-term recordings and time domain methods are ideal for the analysis of long-term recordings. Several frequency domain measures are listed in the Table 2.

### 3. PHYSIOLOGICAL CHANGES OF HRV PARAMETERS

In the complex interaction of parasympathetic and sympathetic influences, under resting conditions parasympathetic tone exceeds sympathetic effects in healthy subjects. The efferent vagal activity is a major contributor to the HF component. Sympathetic activation is related to spectral power in the LF band, but it can also be influenced by vagal activation (5).

The sympatho-vagal balance is expressed in the relation of LF/HF. Spectral analysis of 24-h recordings shows in normal subjects a circadian pattern with higher values of LF in the daytime and higher HF at night. An increase in LF is observed during 90°-tilt, standing, mental stress, and moderate exercise in healthy subjects (6).

Increased LF power and decreased HF power reflect the normal response to upright tilt movement (5).

Increase in HF components is induced by controlled respiration, cold stimulation of the face and rotational stimuli (7).

### 4. CHANGES OF HRV PARAMETERS IN DISEASE

#### 4.1. Cardiovascular diseases

Numerous experimental and clinical studies have shown significant relationship between the autonomic nervous system disorders and cardiovascular diseases.

In the first hours after the myocardial infarction there is a significant reduction of SDNN. The vagal stimulation is decreased and sympathetic influences predominate. The shift in sympatho-vagal balance is expressed in a predominant LF and a reduced HF, with high LF/HF ratio. Reduced circadian variations of RR intervals and LF and HF components are also present (8).

In the days after the infarction there is a depression in the time and frequency domain parameters of HRV with predominance of sympathetic components. In the later period, after weeks and months, the HRV could be partially recovered (5). The aim of risk stratification is to identify the patients with a high risk of post-infarct mortality. These patients could have benefit from further treatment, as it was shown in a clinical trial by Moss and coworkers (9). On the contrary to their findings, the investigators of DINAMIT trial did not show beneficial effects of implantable cardiac defibrillator in patients with high risk after acute myocardial infarction (10). The HRV is independent from other predictors, like depressed left ventricular ejection fraction, increased ventricular ectopic activity.

There is a general consensus that HRV should be measured a week after myocardial infarction, as a high proportion of complications may occur in that period (5). Some recent studies did not show strong predictive power of HRV in risk stratification after myocardial infarction, what could be explained with the use of thrombolysis, early revascularisation and medications like beta blockers and inhibitors of angiotensin-converting enzyme (11).

It was also shown that HRV could be an independent prognostic factor in patients with stable angina (12).

Data from meta-analyses indicated that within the initial two years after myocardial infarction, patients with lower HRV demonstrated great increase in major arrhythmic events like ventricular fibrillation, ventricular tachycardia or sudden cardiac death (13).

There have been many clinical multicenter trials on the possible beneficial effects of risk stratification, after myocardial infarction (5).
cardiac infarction. Bigger et al. analysed HRV spectral parameters from ECG recordings in 715 participants in the Multicenter Post Infarction Program (MPIP) during the period of four years and found strong association between mortality and total, ULF, and VLF power. They found that adding measures of heart period variability to previously known predictors of risk after myocardial infarction could identify small subgroups with two and a half year mortality risk of approximately 50% (14).

In the prospective study Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI), in which 55% of deaths were sudden, it was shown that within the group of patients after myocardial infarction who had a depressed left ventricular ejection fraction, an increased risk of death was associated with the presence of autonomic imbalance (15). In the trial named AzimiLide PostInfarct SurVival Evaluation (ALIVE) a novel class III antiarrhythmic drug, azimilide, was investigated for its effects on mortality in patients after myocardial infarction, and results showed that azimilide did not improve or worsen the mortality of patients after myocardial infarction, while low HRV independently identified a subpopulation at high risk of mortality, what is presented in the Fig. 3 (16). In the European Myocardial Infarct Amiodarone Trial (EMIAT) it was investigated if the patients with depressed heart rate variability could have benefit from amiodarone treatment. Results showed that patients with left ventricular ejection fraction of more than 40% and depressed HRV could benefit from prophylactic antiarrhythmic treatment with amiodarone, but the need for further studies in an independent data set before further recommendations was emphasized (17). The population of patients with chronic heart failure is growing and there is evidence that autonomic nervous imbalance plays important role in the progression of the disease. In the initial stages of disease increases of LF and a decrease of HF are detected. In the advanced stages of heart failure both LF and HF bands are decreased (18).

4.2. Respiratory Diseases
Obstructive sleep apnea syndrome is characterized by repetitive episodes of upper airway collapse during sleep. The obstruction of the airway produces vigorous efforts to breathe, leading to transient arousal and restoration of the patency of the upper airway. Many data support the hypothesis that long-term exposure to episodic apnea and arousal constitutes an independent risk factor for systemic hypertension, heart failure, myocardial infarction, and stroke (19). Several studies have shown the usefulness of measuring HRV as a powerful tool for obstructive sleep apnea syndrome diagnosis and follow up of therapeutic procedures (19). In patients with mild chronic obstructive pulmonary disease, cardiac disorders are the leading causes of hospitalization, accounting for 42 to 48% of all hospitalizations. Monitoring of HRV changes in the patients with COPD have been shown as a possible marker of cardiac comorbidities (20).

4.3. Endocrine diseases
Cardiovascular autonomic neuropathy is one of the most common and most investigated complications in patients with diabetes mellitus. The earliest sign, that can be detected in asymptomatic patients is a depression of heart rate variability. Primary damage is of the branches of vagus nerve, with resultant resting tachycardia. After latency of some years, damage of sympathetic nerve fibers changes the sympathovagal balance, but tachycardia remains. Later symptoms such as exercise intolerance, orthostatic hypotension and further decrease of HRV are the manifestations of progressive damage to the autonomic balance (21). Investigations of HRV in patients with hyperthyroidism have suggested that thyroid hormone excess may reduce parasympathetic activity (22). Patients with clinical hypothyroidism have a sympatho-vagal imbalance, and the changes of repolarization times may predispose to the potentially life-threatening arrhythmias. The assessment of HRV in patients with clinical hypothyroidism may be a useful tool in monitoring of the cardiovascular complications (23).

4.4. Renal diseases
Autonomic nervous system dysfunction is a prominent characteristic of the uremic state and analysis of HRV has demonstrated striking changes of cardiac autonomic nervous system in patients with chronic renal failure. It has also been associated with sudden death in patients undergoing hemodialysis, especially in those with coronary stenosis and nocturnal myocardial ischemia (24).

4.5. Psychiatric diseases
Depression has significant adverse effects on the course and outcome of coronary heart disease and it has been suggested to be associated with about a three fold increase in cardiac mortality (25). Physiological studies have demonstrated compromised modulation of the sympathetic and parasympathetic nervous system in psychosis. The fact that many antipsychotics could have potentially dangerous cardiac side effects led to investigations with atypical antipsychotics, which have been demonstrated to have beneficial side effects profile (26).

Power spectrum analysis demonstrated significant reduction of HRV, vagal tone activity and augmented sympathetic activity in the patients with post-traumatic stress disorder (PTSD) who had no medications in comparison to healthy subjects. Significant autonomic dysregulation of patients with PTSD at rest, could be corrected with administration of selective serotonin reuptake inhibitors (27).

5. CHANGES OF HRV PARAMETERS UNDER MEDICATION
Heart rate variability could be significantly changed by different groups of drugs, and it could also be used as a parameter to quantify the effects of the drugs in some diseases. Beta-blockers, calcium channel blockers and different antiarrhythmics have been studied in the patients with CVS diseases (16,17). Beta-adrenergic blockers prevent

<table>
<thead>
<tr>
<th>Variable</th>
<th>Units</th>
<th>Description</th>
<th>Frequency range</th>
</tr>
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<tbody>
<tr>
<td>Total power</td>
<td>ms²</td>
<td>Variance of all NN intervals</td>
<td>&lt; 0.4 Hz</td>
</tr>
<tr>
<td>ULF</td>
<td>ms²</td>
<td>Power in ULF range</td>
<td>&lt; 0.003 Hz</td>
</tr>
<tr>
<td>VLF</td>
<td>ms²</td>
<td>Power in VLF range</td>
<td>0.003-0.04 Hz</td>
</tr>
<tr>
<td>LF</td>
<td>ms²</td>
<td>Power in LF range</td>
<td>0.04 -0.15 Hz</td>
</tr>
<tr>
<td>HF</td>
<td>ms²</td>
<td>Power in HF range</td>
<td>0.15 – 0.4 Hz</td>
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Table 2. Selected Frequency Domain Measures of HRV (5)
the rise in the LF component observed in the morning hours. Carvedilol thera-
py in patients with chronic heart fail-
ure significantly increased HRV with beneficial effects on hemodynamics (28). The trials with antihypertensive agents have shown better effects of angiotensin II receptors antagonists in regard to an-
gitensin converting enzyme inhibitors (29). Among other medications, antiep-
ileptics are known to impair cardiac au-
tonomic function, and it is known that carbamazepine increases sympathetic and parasympathetic tone, which could be very important in the overall mor-
bidity and mortality (30,31). Most anti-
psychotic drugs have cardiac effects as a consequence of their pharmacological actions, and it was shown that HRV was reduced. Studies with olanzapine and amisulpride also showed that amisul-
pride had a more vagotonic effect, sug-
istering greater cardiovascular safety in comparison to olanzapine (32).

6. HRV CHANGES IN PERIOPERATIVE PERIOD

General anesthesia and surgery produce significant changes in autonomic nervous system function. Most studies that investigated the effects of different anesthetics were performed during in-
duction of anesthesia, with findings that all most common used induction agents reduce total HRV, with different effects on sympathetic and parasympa-
thetic related components. Clinical tri-
als with inhalational agents have shown reductions in total power of HRV. Most trials revealed that all anesthetic agents produced significant changes of heart rate variability, but further large studies are needed for getting more informa-
tion and evidence on the effects of different anesthetic agents in perioperative period and in different patients popula-
tions (1). Very important issues of risk stratification before surgery and moni-
toring of sympathetic-vagal balance during induction and maintaining of anesthesia are in focus of many current trials of HRV in perioper-
ative period (33).

7. CONCLUSION

Heart rate variability reflects the response of the heart to a va-
riety of influences. Substantial re-
ductions of HRV are seen in the setting after acute cardiac events, like acute myocardial infarction, and it was shown as an indepen-
dent predictive factor of mortality in the patients after acute coronary event. Reduced HRV is an early finding in pa-
tients with cardiac diabetic autonomic neuropathy before development of clini-
cal symptoms. In many other endocrine disorders, neurological and psychiatric diseases, monitoring of changes in HRV enables following of the effects of ther-
apy and the state of the disease.

Perioperative period is another im-
portant issue, as monitoring of preop-
erative HRV could be of great impor-
tance for the risk stratification of the patients with cardiovascular diseases and predicting possible complications. Large prospective and standardized tri-
als could give more information on rele-
vance of this noninvasive monitoring of autonomic nervous system function in the perioperative period. Development of the technique of monitoring, analy-
sis and standardization of procedures of measurement of the heart rate variability (HRV) could give a useful tool in eval-
uating of autonomic changes and auto-
nomic imbalances in the specific disease states and perioperative period.

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