REVIEW

The use of heart rate variability in cardiology

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Abstract

Heart rate variability is the marker of the heart's response to the autonomic nervous system activity. The decrease in HRV is a clinical predictive factor of overall cardiac mortality, and especially that of arrhythmia complications in the population after infarction. The parameters most significantly used in practice include SDNN and HRV index. Twenty-four-hour measurements are of higher predictive value, and an increase in the positive predictive value can be accomplished by multifactorial stratification. HRV is most frequently combined with ejection fraction and baroreflex sensitivity. The possibilities of HRV assessment are interesting also in coincidence with heart failure, arterial hypertension and atrial fibrillation also after heart transplantation. ***(Tab. 2, Ref. 63.)***

Key words: hear rate variability, myocardial infarction, atrial fibrillation, heart failure, arterial hypertension.

The assessment of heart rate variability (HRV) has been used for several decades as a marker of the autonomic tone. The quantification of HRV serves as a marker of the particular degree of diabetic neuropathy (Yamasaki et al, 1991). Foetal HRV is used in investigation of physiologic birth (Krebs et al, 1982). The absence of HRV after atropine was presented as one of the diagnostic signs of brain death (Siemens et al, 1989). Later, HRV started to be used in clinical cardiology. In 1978, the observation that the patients who survived the first phase of MI with no respiratory sinus arrhythmia had a significantly higher mortality during hospitalisation (Wolf et al, 1978) was published for the first time. Since then many physiologic studies have been published confirming this phenomenon and indicating that there are also other clinical uses of HRV assessment in cardiology.

The assessment of HRV

The quantitative assessment of HRV is far from being as simple as the assessment of other clinical values as e.g. blood pressure (BP) or heart rate (HR), and differs by depending on the fact as to whether short or long-term recordings are used. Quite long ago, an opinion was accepted, namely that in some clinical disorders it was more convenient to assess HRV by means of long-term monitoring of heart activity, i.e. by use of Holter monitoring. Based on this opinion, studies have been initiated investigating the methods of Holter signal processing. However, a majority of these approaches are equally applicable in short ECG records. In patients after heart transplantation also short intracardial recording is used.

In general, we can divide the methods of HRV measurements into three categories. Simple methods involving short-term recordings of ECG and its sudden changes in response to short stimuli profound breathing, Valsalva manoeuvre. Very simple methods of HRV assessment belong herein and can be expressed as a ratio of min. RR int/max. RR int, an absolute difference of max RR minus min RR, or in fraction *maximum – minimum.*

Physiologic sinus rhythm variations responding to relatively fast changes caused by respiration change in a slower manner caused by the sympathovagal system and are in turn affected, or followed by even slower changes in heart rhythm (HR) diurnal variations. The spectral methods are to distinguish these individual componets of sinus rhythm variation and to quantify each compoment independently. There are several methods of HRV spectrum calculation that can be generally divided into non-parametric and parametric methods. Non-parametric methods most

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frequently use the so-called Fourier transformation (FT) that expresses the analysed data as a sum of sinus functions with different periods and the degree of contribution of each sinus function to the overall signal for the assessment of spectral components to the respective periods. It disintegrates the input signal to the sum of sinus functions with various frequencies and amplitudes. Each frequency component in the range of 0–0.5 Hz has its amplitude share in the overall signal variability. In this way, a relatively fast periodicity is extracted, given by respiration, and low-frequency signal components. *In this way a relatively great periodicity given by respiration is extracted, and low-frequency signal components.* The other way of how to gain spectral evaluation is founded on so-called autocorrelation (parametric) methods that are, simply speaking, based on the comparison of the actual signal value and periodically delayed values. The energy of individual spectral components can be expressed in absolute values s^2 or in so-called standard units n.u. that represent a percentage of the overall spectral energy.

The advantage of non-parametric methods resides on the simplicity of the used algorithm (FT) and faster data processing. Parametric methods provide more fluent and smooth graphs of individual spectra, simpler calculations of the values of spectrum parts and a more precise assessment of the overall spectral energy even in coincidence with short-term monitoring.

The advantage of both spectral methods resides in the detail character of the results they provide. They can be used either in the investigation of physiologic variation of the autonomic tone or they are able to determine the particular disturbed component of physiologic variation. By use of spectral methods, e.g. the selective decrease in vagal tone can be assessed while preserving the impact of the sympathetic nervous system on the heart. In 1981, Akselrod described individual spectral HRV components in dogs. On the basis of his findings, he came to the conclusion that the parasympaticus affects HRV in frequencies responding to medium and high frequency peaks of HRV whereas both systems, sympathetic and parasympathetic influence the low frequency HRV component. Even the impacts of the blockade of renin-angiotensin system or that of thermoregulation disturbance on the low frequency component were recorded (Kitney et al, 1977). These facts were confirmed later also by other authors, eg by Zwiener et al (1990) who has observed a similar effect of mutual vagal and beta-adrenergic blockade in rabbits. Many other studies performed on experimental animals were dealing with the relationship of individual diseases disturbing the autonomic nervous system as eg the rat model of diabetic neuropathy (McEwen et al, 1987). Akselrod's observations in animals were later confirmed in humans by Pomeranz et al (1985) By use of atropine and propranolol as well as by combination of both, he proved that high HRV frequency component responding to respiration is fully intermediated by the parasympathetic nervous system having no relation to the sympathetic system, while low and medium HRV frequency components are under strong control of the sympathetic nervous system, however at the same time under that of the vagus nerve. Pomeranz, however, analysed only 256--second records, and therefore did not describe the very low HRV frequency components. The combined effect of the parasympathetic and sympathetic nervous systems on low and medium frequency components of HRV led already long time ago to the assessment of the following concepts assessed for the designation of sympathetic and parasympathetic effects on HRV. High-frequency components are conceived as an indicator of the parasympathetic activity whereas the ratio of low frequency and high frequency components is conceived as an indicator of the sympathetic activity.

However, this ratio in coincidence with very low frequency component leads to false and distorted evaluation of the sympathetic activity, and therefore some authors use the absolute value of low-frequency component of the spectrum in order to describe the sympathetic activity.

Due to a relatively large number of spectral methods of HRV assessment, the European Cardiologic Society and the North-American Society for Stimulation and Electrophysiology came to an agreement to determine the so-called standard parameters for the description of HRV spectrum.

In short-term monitoring (lasting 2-minutes), three main components are distinguished:

— Very low frequency component (VLF),
— Low frequency component (LF)
— High frequency component.

The physiologic essence of the very low frequency component is not defined precisely, and therefore its assessment in records shorter than 5 minutes are considered to be dubious. The energy values of individual components are expressed mostly in ms^2, while LF and HF can be expressed also in n.u. (after deduction of the VLF component). The assessment of LF and HF in n.u. points up the manifestations of fluctuations of the activity of parasympathetic and sympathetic branches of the vegetative nervous system. Despite this, the expression of LF and HF in n.u. should always contain also absolute values.

The spectral methods of HRV assessment can be used also for the purpose of 24-hour record analyses. In addition to the already described components of the spectrum, 24-hour records contain also the ultra-low frequency component of the spectrum.

However, the accuracy is problematic even in spectral methods. The results are dependent to high extent on the accuracy and quality of the analysed data. The use of these methods in analysing Holter monitoring when not all QRS complexes are accurately identified and classified can lead to results that are significantly misleading. When spectral analysis is used, it is also necessary to exclude the effect of ectopic contractions or short runs of ventricular tachycardia. Even after the filtration, the analysis of records with a great number of ectopic contractions (eg in coincidence with bigeminy) is very difficult and can lead to inaccurate values. Regarding the above technical problems in addition to the development of the most accurate technology of recording, alternative approaches to this method have been recommended. These do not include the analysis of the whole spectrum, but enable the assessment of mere specific parts of the spectrum, e.g. low, medium and high frequency components of HRV.

Tab. 1. Selected non-spectral methods ("time domain").

Parameter	Units	Normal values
		Statistical methods
SDNN	ms	Standard deviation of all NN intervals
SDANN	ms	Standard deviation of average NN intervals during 5-minute monitoring
RMSSD	ms	Root mean square value of square differences between neighbouring NN intervals.
SDNN index	ms	Mean standard deviation of all NN intervals from 5-minute segments
SDSD ms		Standard deviation of neighbouring NN intervals differences
NN 50		Count of coupled neighbouring NN intervals differing more than 50 ms in length
p NN 50	%	NN 50 divided by the total count of NN intervals
		Geometrical methods
HRV index		Total count of NN intervals divided by the histogram height
TINN		Triangle base length gained by triangular interpolation of histogram on the principle of smallest squares method

In patients after heart transplantation, HRV is monitored also by use of intracardiac records performed during the endomyocardial biopsy. Bipolar electrodes record the activity of the former sinus node as well as the frequency of the transplanted heart (Ramaekers et al, 1998).

Statistical and geometrical methods

Individual selected non-spectral methods are given in Table 1.

The methods using standard deviations analyse RR intervals independently from their consecutive order. They use simple statistical measurements in order to express RR interval variations. Out of these measurements, the most common assessment of standard deviation of all RR interval durations (the QRS complexes of which have sinus origin), so-called NN intervals (normal to normal interval). Other methods include the standard deviation of differences between the consecutive NN intervals during short periods (most frequently 5-minute periods) of long-term monitoring. These methods combine all spectral components of HRV during monitoring. Should they be assessed during 24-hour monitoring, they include both short-term high frequency changes as well as the lowest frequency components present only in 24-hour records. Short-term monitoring, eg SDNN gradually assess shorter and shorter cycles, while the overall HRV increases together with the duration of monitoring (Saul et al, 1988), Further methods using the standard deviations assess some spectrum components individually. In order to assess the decrease in SF caused by vagus activity, the so-called pNN 50 method has been assessed for HRV measurement. It counts only with a particular amount of NN intervals, namely those that are at least 50 ms longer than the preceding NN interval. Similarly as the former, also these methods depend on the accuracy of the analysed NN intervals. They are influenced significantly by artefacts e.g QRS complexes that are unrecognised due to their low voltage, or premature contractions or artefacts interpreted as normal QRS complexes.

In order to overcome these drawbacks, non-statistical (geometric) methods were suggested appearing to be less influenced by artefacts. These methods are based on the evaluation of histograms of NN intervals duration. The simplest method (called index HRV) expresses HRV as a relative count of NN intervals with the most frequently occurring length. Mathematically speaking, the integral of density is involved (i.e. the count of all NN intervals divided by the maximum density). The more difficult method approximates the histogram of all NN intervals by use of triangular interpolation based on the principle of the smallest squares. Hence, the base of the triangle gained in this way is considered to represent the variability index.

The main advantage of geometric methods resides in their independence from the quality of analysed NN intervals. Disadvantage resides in the necessity of a greater number of NN intervals from monitoring lasting at least 20 minutes, however a 24-hour record is used in practice. In practice, these methods are not appropriate for short-term monitoring analyses.

The literature presents a relatively great number of various non-spectral parameters. In practice however, the already mentioned agreement recommends the preference of only four out of them:

- SDNN and HRV index — expressing the overall HRV
- SDANN — a marker of spectral components with a long period,
- RMSSD — a marker of components with a short period.

These methods do not substitute each other, however supplement each other mutually. The selection of individual parameters must respond to the targets of the particular study. It is not recommended to correlate the values gained from records with different durations of monitoring. Short-term records evaluation should be preferably based on spectral methods. However, twenty-four-hour records provide close correlations between spectral and non-spectral parameters.

Normal values of most frequently used parameters are given in Table 2.

Tab. 1. Selected non-spectral methods ("time domain").

Parameter	Units	Normal values
Statistical and geometric methods in 24-hour monitoring ("time domain")		
SDNN	ms	141±39
SDANN	ms	127±35
RMSSD	ms	27±12
HRV index	ms	37±15
Spectral analysis in 5-minute monitoring in supine position and at rest		
Overall energy (TP)	ms^2	3466±1018
LF	ms^2	1170±416
HF	ms^2	957±203
LF	n.u.	54±4
HF	n.u.	29±3

HRV in clinical practice

In clinical practice, a decrease in HRV means a decrease in the protecting power of vagal reflexes or a permanent increase in the sympathetic tone. It occurs in patients with ischemic heart disease, cardiomyopathies, heart failures, ventricular as well as symptomatic ventricular arrhythmias inducible by programmed stimulation of the ventricles, in patients after cardiopulmocerebral resuscitations, in patients suffering from severe arterial hypertension and autonomic, most frequently diabetic neuropathies. The mortality in people with low HRV is 5-fold higher because their vagal protection is weakened with the risk of sudden death (SD). The clinical use of HRV in a particular subpopulation of patients is to a significant extent given by its predictive informational value in relation to sudden death, progression of disease, re-hospitalisations or overall mortality. The decrease in HRV per se in general population is of no clinical significance.

In his prospective 10-year study, Mäkikallio et al (1998) investigated 347 people older than 65 years. A decrease in HRV was less significant in the prediction of sudden death than age, male sex, case-history of angina pectoris, myocardial infarction, heart failure and NYHA classification. The extent of practical use of HRV in clinical cardiology differs in coincidence with each nosologic unit.

Ischemic heart disease

The most frequent application of HRV in clinical practice resides in its use in stratification of patients after MI. Wolf et al (1978) was the first author to describe higher hospital mortality in patients after MI having no respiration arrhythmia. Later, this fact was proved also by other centres, and not merely in coincidence with hospital mortality, but also in patients after being dismissed from hospital. Some latest studies not only confirmed Wolf‚s results, but also indicated to the fact that HRV, when examined in the acute phase of MI, has a significant relation to the significance markers of MI as CPK?, LVEF and Killip‚s classification (Casolo et al, 1992). A coercive evidence that HRV is a significant predictive factor of MI was given by the Multicentric Postinfarction Research group. Already in his first results, Kleiger (1987) has proved a close relation between the decreased HRV (measured by 24-hour Holter monitoring as standard deviations of NN intervals) and the increased mortality in the first four years after MI. In coincidence with the division of 808 patients according to the average HR, EF, VES count, presence of couplets or VES runs, the authors found out that the low HRV is an independent predictive factor of sudden death. In the subsequent study of Bigger et al (1988) who investigated individual sympathetic and parasympathetic components of the spectrum, proved that the patients at an increased risk of sudden death after MI yielded a marked reduction in the parasympathetic the activity. These findings were confirmed also by the study of professor Malik (Postinfarction Survey Program, St. George's Hospital Medical School, London). This study indicated to the fact that the decrease in HRV in not only a predictor of sudden death after IM, but also that of the occurrence of persisting ventricular tachycardia in patients after MI (Cripps et al, 1991; Bigger et al, 1989).

HRV changes significantly also during the primary PTCA. The work of Bonnemeir et al investigated the course of HRV evaluated prior to, during and after successful re-canalisation of the artery inflicted by infarction by means of primary angioplasty in 89 patients with acute myocardial infarction. The reperfusion of the coronary artery after a transient decrease in investigated parameters of HRV led to a subsequent increase in spectral as well as non-spectral HRV values. At the same time the average heart rate and LF/HF ratio decreased significantly, thus marking the sypathovagal unbalance. On the basis of this bi-phase course of HRV values, it is possible to judge that after a transient deterioration and after reperfusion, a significant increase in vagal tone takes place, the fact of which can contribute to the cardioprotective effect of the primary PTCA in coincidence with acute myocardial infarction (Bonnemeier et al, 1998). The Angina Prognosis Study in Stockholm analysed the prognostic impact of the catecholamine level and HRV in patients with stable angina pectoris. A decreased HRV (TP, LF, HF) was a risk factor of cardiovascular mortality, however not that of the occurrence of non-fatal MI. No prognostic significance was ascribed either to the ratio of low and high frequency components (LF/HF), or the levels of catecholamines in the serum and urine. The authors suggest that the parasympathetic activity in patients with stable angina pectoris is probably of greater prognostic significance than the sympathetic activity (Fourstund et al, 2000).

Malik et al (1990) dedicated themselves to the problem as to whether the assessment of HRV after MI based merely on short records has the same informational value as that based on a 24-hour record (Malik and Camm, 1990; Hikuri et al, 1992). The short record had a low specificity in the prediction of arrhythmias and it was only the evaluation of a 24-hour whole day integrated circadian variation of the activity of the autonomic nervous system that had an acceptable sensitivity and specificity. In clinical practice this means that all commercial systems of HRV measurement that are based on short records (2–5 minutes) or based on the average spectrum of 2–5 minute segments are less appropriate for the prediction of sudden death after MI. The assessment of HRV during 5 minutes of monitoring can be used in practice as a simple screening method (Fei and Malik, 1995), The patients with low SDNN during 5-minute monitoring should be subdued to 24-hour monitoring analyses. The most frequently presented risk values in coincidence with 24-hour monitoring are as follows: SDNN <50 ms, HRV index <15 for a significant decrease in HRV, and SDNN <100 ms and HRV index <20 as a moderately decreased HRV. The assessment of HRV after MI requires also the consideration of the dynamics in changes in HRV values in the acute phase of MI. The lowest values of HRV can be detected in the first 24 hours after the coronary attack and the gradual improvement takes place during the subsequent 24 hours. These changes do not depend on the medication and are important also in the comparison of results gained in various studies (Doulalas et al, 1999).

Odemuyira et al (1991) investigated whether the post-infarction HRV is a better predictor of the overall mortality due to cardiac reasons, arrhythmic complications (i.e. sudden death and persisting KT) or only that of sudden death. When comparing the prognostic value, EF and HRV were identically significant in the prediction of the overall mortality in the population after MI, whereas HRV was more significant in the prediction of sudden death and the symptomatic KT. These conclusions respond to our picture of the pathophysiology of the decrease in HRV after MI. The decreased EF reflects the left ventricular failure, thus its decrease means rather that the patient is at risk of heart failure and sudden death. On the other hand, the decrease in HRV reflects the absence of autonomic protection against VF and thus it marks rather the patients at risk of sudden death.

The predictive value of HRV reflects the relation between the autonomic control of HR and the reflexive response to the acute myocardial ischemia. The lower the HRV, the greater the probability that the current myocardial ischemia will lead to the prevalence of sympathetic tone and subsequently a higher risk of lethal arrhythmia. The decrease in the afferent sympathetic activity is probably the particular mechanism contributing to the decrease in HRV after MI. Normal HRV values after MI prove the vagal protection from VF. A decrease in HRV therefore has to have a lesser predictive value in the development of heart failure than the EF and to identify rather the patients at risk of arrhythmic complications. However under cinical conditions, HRV has a greater prognostic significance in the estimations of the development of left ventricular remodelling, This fact proves to be valid especially in smaller and medium myocardial infarctions (Bugiardini et al, 1999).

Also the circadian changes in the variability of heart frequency are interesting. The study of Bonnemeier et al (1998) based on 185 patients after infarction indicated to the fact that the patients with EF <40 % had not only significantly lower HRV values during both day and night, but also a more significant decrease in HRV values in the morning hours, during which the risk of cardiovascular attacks (NSS, AIM) is the greatest.

Despite the fact that much information from this field has been already published, it seems obvious that in coincidence with the stratification of patients after MI, individual risk factors must be combined with HRV. We assume that HRV can be successfully combined with the examination of late ventricular potentials and the examination of ventricular ectopic activity (Camm and Fei, 1995). Late ventricular potentials enable to reveal the anatomic substrate for the re-entry tachyarrhythmia, high VES count proves the triggering of arrhythmia and the decreased HRV represents a decrease in the parasympathetic protection from KF.

An increase in the positive predictive value was successfully described in combination of HRV with the average HR and EF (Camm and Fei, 1995; Cripps et al, 1991).

The combination of HRV and the sensitivity of baroreflex (BRS) represent the subsequent possibility. It has also been described as an important predictor of arrhythmias after MI. Despite the fact that both these methods relate to the function of the autonomic nerves, there is a weak correlation between them. This is probably caused by the fact that HRV reflects the physiological level of the autonomic nervous system, whereas the baroreflex sensitivity represents the response of the heart to extreme parasympathetic stimulation. Hence, both these factors represent an independent predictor of arrhythmia after MI. The prospective multicentric Post-Infarct Risk Stratification Study investigated 1-year mortality after acute transmural MI, while the risk factors were defined as follows:

1) EF <40 %,
2) positive Holter monitoring (>10 ventricular extrasystols per hour, >4 KES couplets per 24 hours, >1 KES salva per 24 hours),
3) positive late ventricular potentials,
4) HRV (SDNN <75 msec),
5) baroreflex sensitivity (<3 msec/Torr).

Both acute and long-term therapies were individually optimised. 1029 patients were included into the study, and HRV as well as baroreflex sensitivity as markers of disturbed sympatovagal balance were evaluated as independent mortality risk factors in patients after transmural MI. It was only in combination with EF that it was possible to gain a positive predictive value acceptable in practice (PPV). The highest PPV (43 %) and 99 % specificity were gained in combination of EF with the occurrence of atrial fibrillation, however on the expense of the sensitivity being only 5 %. The best combination in this study was by EF+BRS with PPV of 29 %, sensitivity being 31 %, and specificity 96 % (Seidl et al, 2000).

The accomplishment of the generally accepted agreement in this field requires further studies to be performed dealing systematically with multifactorial analyses of post-infarction methods, as well those of their combinations. The limit values of individual parameters needed for their inclusion into the multifactorial analysis resulting in optimal ratio of positive value and sensitivity, have still not been clearly assessed.

Heart failure

HRV is decreased also in patients with heart failure (Casolo et al, 1989; Coumel et al, 1991; Coast et al, 1992). In comparison with the healthy population, the spectral, as well as non-spectral HRV parameters in patients with heart failure are decreased. In severe forms of heart failure, the circadian HRV variation can withdraw. It is expressed by the LF/HF ratio during day and night. Healthy people are able to react by changing their heart rate to the needed extent. The patients with heart failure are not able to modify their heart rate to such an extent and as fast as in healthy individuals.

All investigated non-spectral parameters of HRV in 24-hour monitoring were decreased in cases with heart failure when compared to healthy controls (Casolo et al, 1989). The high and low frequency components were almost absent in spectral measurements monitored during the day. When compared with healthy controls, these values were 10-fold decreased (Casolo et al, 1991).

It is also known that the activity of the sympathetic nervous system increases in coincidence with heart failure. This is proved by the increased level of circulating catecholamines in failing patients at rest and after exercise. (Thomas and Marks, 1978; Colucci et al, 1989; Cohn et al, 1993). Hence, an increase in the low-frequency component of HRV spectrum was expected to take place as a marker of the sympathetic regulation. On the other hand, this increased activity leads to a depletion of stored catecholamines, and decreases the density of B1 receptors within the myocardium. The heart decreases its response to the sympathetic stimulation. Therefore, it is the absence of low-frequency component that identifies the failing patients at high risk of re-hospitalisations and death. Scalvini et al (1998) investigated patients with heart failure who had had no frequency components during the two past years. The mortality in these patients was 50 % in comparison with 14.5 % in the group of patients with a detectable LF. Also the frequency of re-hospitalisations in these two groups of patients differed significantly (39.2 % in 20 %). Hence, HRV reflects a complex of disorders in the autonomic control over the failing myocardium, not only in the parasympathetic components but also in the sympathetic components of the spectrum of HRV. Several studies dealt with the correlation of HRV and the progression of heart failure. The degree of the decrease in HRV was proportional to the degree of failure evaluated by NYHA classification. This relation was proved for both spectral and non-spectral methods of HRV assessment (Stefeneli et al, 1992; Casolo et al, 1993; Binkley et al, 1993; Flapan et al, 1992). In the prospective study UK-HEART investigating the relation of HRV to mortality in the failing patients with sinus rhythm, HRV was evaluated as an independent predictive factor of mortality in chronic heart failure. Galinier et al (1999) investigated the relation of HRV and sudden death in 190 patients with heart failure with sinus rhythm. In addition to the ischemic disease, which is the etiology of failure, cardiothoracic index >60 % and ejection fraction <30 %, also the spectral parameters of HRV were of predictive value. The SDANN values <50 msec, RMSSD <2.4 ms and LF >3.3 ms assessed from 24-hour Holter records proved that the risk of sudden heart death increased in coincidence with heart failure (Galinier et al, 1999).

The possibility to investigate the degree of autonomic regulation disorder in a clinically asymptomatic heart failure, the relation of HRV and mean heart rate, or HRV response to the therapy of heart failure are just as well interesting. The hypothesis that in severe degrees of failure, the sympathetic activation and the suppression of the vagus nerve lead to a closer correlation between the mean heart rate and HRV has been proved. The severer the degree of heart failure, the closer the relation between the increase in heart rate and the values of HRV (Hedman et al, 1999).

Coats et al (1992) performed a prospective study based on 17 patients with NYHA stage ranging from II to IV, and assessed SDNN (19 %, $p<0.05$) prior to and after 8 weeks of exercise. They recorded a significant increase in high frequency components of the spectrum (HF +53 %, $p<0.05$) and a decrease in low frequency (LF -21.2 %, $p<0.07$) after 8 weeks of exercise.

The results of further studies indicate that beta-blockers in heart failure not only recover the autonomic balance, but also improve the ability of the reflexive increase in the vagal activity, the fact of which contributes to the comprehension of their favourable impact on the prognosis in heart failure. The ability to improve the neurohumoral state in the failing patients was proved also in digoxin (Georghiade and Ferguson, 1991) by proving the increase in HF (Krum et al, 1993; Brouwer et al, 1993) p NN 50, RMSSD as well as in SDNN parameters. The blockage of aldosterone by spironolactone similarly improves the HRV parameters in heart failure, while this effect culminated during morning hours when ACTH-induced secretion of aldosterone is the greatest. By increasing the parasympathetic activity, the therapy by means of antagonists of aldosterone and ACE-inhibitors can thus contribute to a decrease in the frequency of arrhythmic complications and sudden heart death during heart failure.

HRV after heart transplantation

Since the transplanted heart remains denervated to a great extent (Mason and Harrison, 1979), however not absolutely (Burke er al, 1995), it can be expected to yield a decreased HRV. This fact was proved by Sandsom et al (1989) who investigated HRV in patients with orthotopic heart transplantation. They investigated not only the overall reduction in their spectrum energy in comparison with healthy people, but also the HRV spectrum with no peaks. Therefore, it seems that the presence of clear low and high frequency peaks is more important than the overall energy of HRV spectrum. Up to 52 months after transplantation, no vagal effect on HRV was detected, while in addition to HRV, individual studies investigated also baroreflex mechanisms. Between the 12th and 20th months after the transplantation, some patients yielded spectral peaks as well as baroreflexes responding to the sympathetic re-innervation. In patients after transplantation, the high-frequency component of HRV responding to respiration assumingly does not dependent on autonomic re-innervation, and its basis is formed by non-autonomic mechanisms such as atrial stretch.

Also Zbiluta et al (1988) came to a clinically important finding, namely that the peak energy of high-frequency component was a sensitive, however non-specific predictor of graft rejection. Sands et al (1989) described an increase in overall energy of HRV spectrum in patients after heart transplantation, who developed rejection in comparison to patients in whom no rejection was proved by endomyocardial biopsy. The increased HRV in these patients was however caused by overall, or even chaotic, irregularity of the heart rhythm without any detectable components of HRV spectrum. The spectra of these patients resembled wide-band white noise. They assumed that these findings were caused by an affliction of the sinus atrial node, or that of the supraventricular conduction system during the rejection process. Despite the fact that the spectra of patients after heart transplantation differ significantly in dependence on the presence of rejection, these changes in a part of patients only followed the signs of rejection in endomyocardial biopsy. Therefore, further studies must be performed on the possibility of using HRV as a rejection predictor.

The investigation of the renewal of the autonomic tonus in the transplanted heart can be performed by a new method, namely by short intracardial records. Ramekers et al (1998) investigated 39 patients with the average period of 14 months after the transplantation. In these patients, they performed 170 intracardial 10-minute records. The HRV spectrum of the graft was relatively flat, however they recorded a gradual increase in LF as well as HF in the HRV spectrum of the former sinus node, while its frequency was significantly lower than that of the transplanted heart (Ramaekers et al, 1998).

In patients after heart transplantation, in addition to baroreflex, the assessment of HRV contributes to the comprehension of autonomic and non-autonomic mechanisms influencing the heart rate in these patients.

HRV in essential hypertension

Several studies have already assumed that the patients with essential hypertension have an increased sympathetic activity. Its impact on HRV was studied by Guzzetti et al (1988). When comparing the patients with high blood pressure to people with physiologic blood pressure, the former subjects had higher low-frequency components and lower high-frequency HRV components. In a passive position, smaller changes in low and high-frequency components take place in hypertensive patients than in the normotensive control group. Moreover, both values (low-frequency component + the degree of the decrease in response to the position) correlated closely with the increase in blood pressure. The chronic therapy by means of beta-blockers that decreased the pressure in these patients, recovered HRV toward normal values. Regarding this Guzzetti study, it can be assumed that the assessment of HRV in essential hypertension can help in the estimation of damage incurred to sympatovagal balance. 24--hour records of pressure and heart rate enabled to follow the details of changes in these parameters during day and night. In healthy people as well as in patients with mild or moderate hypertension, the circadian changes in pressure and frequency are parallel (Mancia et al, 1983; Zanchetti, 1986; Mancia et al, 1993). To a substantial extent, these changes are assessed not only by the mutual relations of pressure and heart rate, but also by the central nervous system.

Left ventricular hypertrophy is an unbiased predictive factor of sudden death. When HRV in hypertensive patients with left ventricular hypertrophy is compared with that in hypertensive patients with normal left ventricular wall thickness, parasympathetic parameters decreased constantly in both groups, and the values of sympathetic components of the spectrum decreased in the group with hypertrophy. In all 244 hypertensive patients included into the study, the ratio of low and high frequency components of the spectrum (LF/HF) appeared to be a good prognostic marker of cardiovascular attacks (Pathak et al, 2000), Decreased values of HRV are indirectly proportional to pressure, body mass index and insulinemia in young (average age 34±11 years) and obese patients (BMI 40.6±4.3) without clinical symptoms of cardiovascular disease, diabetes or damage of target organs. In this study of Ravagli et al (1998), the pressure values correlated closely also with the insulin level. Even further studies have proved the negative impact of chronic hyperinsulinemia on HRV in obese hypertensive patients, especially that on the parameters expressing the increased sympathetic acitivity, while this relation did not depend on the pressure value and BMI (Galinier et al, 1998).

In diabetics, HRV is prevalently used in the assessment of the degree of cardiovascular autonomic neuropathy that leads to the increase in mortality. The HRV values in diabetics however coincide also with the diastolic left ventricular dysfunction. May et al, found out that there was a close relation between the decreased HRV parameters and the diastolic relaxation of the left ventricular disorder expressed by E/A ratio of filling velocities measured by pulsation Doppler. The HRV values correlated also with the value of the systolic pressure and the degree of proteinuria in diabetics. Their relation to ejection fraction has not been found (May et al, 1998).

HRV and atrial fibrillation

The assessment of HRV in patients with paroxysmal atrial fibrillation (AF) reflects the relation between the sympathovagal balance disorder and paroxysms of atrial fibrillation. The vagal form of atrial fibrillation typically occurs in young men, more frequently during night or at rest, and often is preceded by bradycardia. Atrial fibrillation is less frequent. It is intermediated by the sympathetic nervous system and linked with day hours. It occurs after exercise or stress, and prior to the attack the sinus tachycardia and supraventricular extrasystoles are occur. The assessment of HRV in these patients could possibly clarify the impact of the autonomic nervous system on the sinus. The night paroxysms of atrial fibrillation should be preceded by an increase in the high-frequency component of spectrum. The heart rate of atrial fibrillation trigerred by the sympathetic nervous system is, prior to and during the attack, higher in comparison with the vagal type (Andresen and Bruggemann, 1998).

Despite the fact that "pure", vagal or sympathetic types of patients would be rare, the analysis of case-histories together with the assessment of HRV could enable to estimate better the selection of the appropriate anti-arrhythmic drug for the prevention of recurrence. BB could be the drug of choice in prevalently sympathetic types of AF. The proportion of HRV in the determination of therapy must be however tested by means of controlled studies.

In coincidence with the clinical decision, we know how to use HRV rather in the identification of patients at higher risk of recurrent atrial fibrillation after electroimpulsotherapy (Lombardi et al, 1998; Vardas et al, 2000). The patients with higher percentage of recurrent atrial fibrillations have higher values of low-frequency component, by means of which also the ratio of the low and high frequency components of HRV spectrum (LF/HF) changes. In practice, patients with this ratio greater than 2 are at higher risk of recurrent fibrillation after cardioversion, while the patients with the value of LF/HF ratio smaller than 2 are considered as being at lower risk (Lombardi et al, 1998). HRV in patients with paroxysmal AF relates to their quality of life. The evaluation of life quality in the study of von den Berg et al (2000) included physical output, emotional functions, vitality and the overall sense of health in 73 patients with paroxysmal AF caused by various etiologic factors. The frequency of attacks had it's predictive value only in relation to physical output, the basic heart disease that led to AF had no significant relation to any of the evaluated modalities. On the other hand the methods evaluating the disturbed autonomic state of the patient (baroreflex sensitivity and HRV) correlated with all four evaluated aspects of life quality. When judging the results gained in this work, the disorders in autonomic regulation, especially the decrease in vagal activity are of prognostic value for life quality in patients with paroxysmal AP regardless of the etiology. Also the findings of disturbed parameters of vitality in patients taking beta-blockers were interesting, as well as the fact that the patients with the vagal type of AF accomplished better results in the evaluation of vitality (von der Berg et al, 2000).

The investigation of changes in the autonomic tonus within the atrium by means of double cavity cardiostimulator with memory functions has led to the finding that imminently prior to atrial fibrillation, SDAA (standard deviation of atrial intervals) and rMSSD (square mean sum of square differences of neighbouring atrial intervals) are decreased significantly. This means that prior to the onsand of paroxysm, a measurable change in autonomic regulation takes place. This fact could be used in patients with double-cavity stimulation and paroxysmal atrial fibrillation in the developments of preventive anti-tachycardia algorithms of stimulation (Bonnemeier et al, 2000). Similar changes were recorded in the sympathovagal balance prior to the onsand of AF paroxysms, also during the 24-hour Holter monitoring (Fera et al, 2000)

HRV is a marker of cardiac response to the sympathetic and parasympathetic activities. The sympathetic nervous system is one of the crucial neurohumoral axes in cardiology. An increased activity of the sympathetic system links with several important risk factors of the ischemic heart disease – hypertension, insulin resistance, diabetes mellitus as well as atherosclerosis. The effect of the increased sympathetic activity on evoking the arrhythmia as well as its relation to the development of left ventricular hypertrophy lead to an increase in the risk of sudden heart death. The development of arteriolar hypertrophy inclines to spasms of coronary arteries. Therefore, should HRV be able to express the disorder of sympathovagal balance, the correlation of its values with the risk of sudden cardiac death is not surprising.

It has been proved that by several ways of HRV measurement, relevant information can be gained. In current clinical practice, HRV, particularly its decrease is an independent predictor of the overall cardiac mortality, but especially that of arrhythmic complications in patients who have survived the acute phase of MI. Out of the currently used methods, the risk can be assessed most accurately from a complete 24-hour Holter record.

It is possible to state definitively, that HRV is and independent predictor of mortality and complications of arrhythmia. The optimal time of the assessment is one week after acute MI. Short term recordings are also of prognostic value, however 24-hour records are of higher predictive value. Short-term recordings should performed as screening of all patients after MI. The most significant non-spectral parameters are as follows: SDNN smaller than 50 ms (sensitivity 46 %, positive predictive value 34 % in the prediction of two-year cardiac mortality) and HRV index smaller than 15 (sensitivity 40 %, positive predictive value 33–60 %).

A wider use of this method however encounters a relatively low positive predictive value, specificity and sensitivity of the HRV assessment per se. Therefore it is used in practice as a supplement to the multifactorial stratification of patients after coronary attack. The monitoring of HRV in essential hypertension, either alone or together with pressure and baroreflex sensitivity, provide information on cardiovascular regulatory mechanisms in hypertensive patients. In the background of the relation of systolic pressure, proteinuria and autonomic neuropathy to HRV values in diabetic patients, there can be microangiopathy as well as the failing heart, peripheral nervous system and the kidneys. Also chronic hyperinsulinemia seems to represent an independent factor having an impact on HRV, chiefly in the spectrum expressing the sympathetic activity.

HRV in other clinical applications can provide the same important information, however this fact has not been definitely proved so as in patients after MI. The monitoring of patients with paroxysmal atrial fibrillation seems to represent a promising method that could possibly help in clarifying the autonomic nervous system activity closely prior to the onsand of atrial fibrillation with a potential impact on the therapeutic considerations of physicians. Its significance resides in the possible the future development of preventive anti-tachycardiac systems as well as in its relation to life quality of these patients is significant too.

It is difficult to evaluate the current practical and prognostic value of these clinical applications. However, it is possible to assume that sophisticated HRV-measuring systems that will be based on the theory of chaos are going to be developed. Their merit will have to be confirmed in practice.

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Received August 8, 2002.
Accepted September 20, 2002.