The amplitude of heart rate oscillations is dependent on metabolic status of sinoatrial node cells

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Abstract

Introduction

Current approaches to the interpretation of the heart rate variability (HRV) primarily consider it as the method for the evaluation of the activity of sympathetic and parasympathetic branches of the autonomic nervous system. However this widely spread and accepted view ignores the evidence of the role of intrinsic biochemical and electrophysiological properties of the cells of sinoatrial node (SAN) in responsiveness to external neural and humoral impacts.

The Hypothesis

It is hypothesized that the amplitude of HR oscillations could be critically dependent on the current metabolic status of the organism and the sensitivity of SAN cells in particular. Sufficiently high level of adenosine triphosphate (ATP) together with balanced redox status of SAN cells provide the elongation of diastole, better left ventricle filling and increases stroke volume. It happens similarly as in case of pendulum. If it is provided with high potential energy, the amplitude of oscillations is increasing, if there exists favourable metabolic condition in SAN cells – the amplitude of HR oscillations will be high. In other words – the same power of sympathetic/parasympathetic neural regulation (serves like gravity in case of pendulum) could exert different amplitude of heart rhythm oscillations, depending on metabolic status of SAN cells. The amplitude of heart rhythm oscillations will be higher in case of higher ATP concentration in the cells, more profound hyperpolarization of SAN cell membrane and consequently lower in conditions of metabolic problems such as low ATP supply, derangements of redox potential or genetic variability of the synthesis of proteins responsible for energy metabolism and ion channels functioning.

Evaluation of Hypothesis

There are many observations confirming the validity of the hypothesis. Higher HRV is usually observed in athletes, children and healthy adults, while low parameters are typical for patients with severe diseases like coronary artery disease, hypertension, diabetes etc. Moreover, some medical conditions may cause dramatic decrease in HRV which is reversible and amplitude of HR oscillations recovers to initial levels as soon as the problem is resolved.

Conclusion

The hypothesis explains high individual diversity of HRV parameters, even in relatively homogenous groups participated in numerous studies. Relatively simple explanation is provided for the evidence that in advanced stages of chronic diseases HRV is severely impaired. Severe acute impairment of heart rhythm oscillations especially in patients with previously normal HRV indicates serious risk and may require more precise medical examination of the patient.

Introduction

The regulation of heart rhythm is complex and is realized on several hierarchic levels with the involvement of sympathetic and parasympathetic branches of autonomic nervous system (ANS), humoral and metabolic interactions. Heart contraction is initiated by the activation of specialized cells of its conductive tissue. In physiological conditions cells of sinoatrial node (SAN) serve as a cardiac pacemaker and provide its fundamental property – automaticity¹.

In humans as well as in other mammals parasympathetic nervous system (PNS) acts as a “brake”. Decrease in heart rate (HR) from initial 90-100 (without neural influence) to 60bpm is predominantly caused by PNS activity. Accelerations within the range 60-90bpm are mostly related to parasympathetic tone withdrawal and only in part by sympathetic activation. Relatively fast parasympathetic effects are mediated by myelinated vagal nerve fibres. Its withdrawal is also fast due high activity of cholinesterase, which provides virtually immediate hydrolysis and deactivation of acetylcholine (AC).

Activation of PNS is often associated with high levels of ATP in the cells. Synergism of AC and ATP seems to be not accidental since powerful energy metabolism provide sufficient amount of ATP which subsequently decreases oxygen and substrates demand creating background for the relaxation, recovery and supercompensation that may appear in response to previous activation. This condition provide high level of diastolic hyperpolarization and low activity of f-channels, which in turn lead to significant elongation of cardiac cycle by increased duration of diastole.

Na⁺/K⁺ ATPase dependent currents (Iₚ) provide maintenance of ion concentration gradient on cell membrane. This current is very sensitive to the concentration of Na⁺ ions in the cytoplasm. Iₚ is characterized by cyclic changes of its rate mainly due to changes of in Na⁺ concentration in the cell, membrane potential and ATP concentration reduction¹(Figure 1).

The wide evidence confirms that in case of many disorders associated with...

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oxidative stress, in particular diabetes, cardiovascular disease and other, there is increase in HR, decrease in PNS activity and decrease in heart rate variability (HRV). In contrast, in healthy conditions especially in trained subjects PNS activation is associated with higher HRV values and low HR. Most of the publications concerning HRV consider the heart rhythm oscillations as solely ANS mediated phenomenon but the “sensitivity” of pacemaker cells to external regulatory inputs is generally not considered despite numerous indications of its importance.

The Hypothesis

It is hypothesized that the amplitude of HR oscillations could be critically dependent on current metabolic status of the organism and SAN cells in particular (their sensitivity). The term “sensitivity” concerns mainly PNS activity since in case of favourable energetic conditions at rest there exist significant hyperpolarization of cell membrane and even relatively low intensity vagal influences could result in marked delay of action potential. High intensity impact needed for electric excitation of cells of SAN in such conditions is followed by delayed heart contraction and activation of basic reflexes involved in regulation of cardiovascular system, which lead to increases the amplitude of HR oscillations. Sufficiently high level of ATP accompanied by the balanced redox status of SAN cells, and accompanying elongation of diastole provide better left ventricle filling and increases stroke volume. Increased duration of given heart cycle (RR or more correctly in this case PP interval on electrocardiogram) will lead to rapid parasympathetic withdrawal and recovery of HR to previous condition following with some excessive turn to increased HR (effect of pendulum). Similarly as it happens in case of pendulum provided with high potential energy, the amplitude of HR oscillations will increase. Modulatory function of ANS (balance of sympathetic and parasympathetic activities) in this regard serves as rather timing determinant, while amplitude, at least in large part, is provided by functional and metabolic status of SAN cells.

In other words – the same power of sympathetic/parasympathetic neural regulation could exert different amplitude of heart rhythm oscillations, depending on metabolic status of SAN cells. The amplitude of the heart rhythm oscillations will be higher in case of higher ATP concentration in the cells, more profound hyperpolarization of cell membrane and consequently lower in conditions of metabolic problems such as low ATP supply, derangements of redox potential and regulation etc. Higher amplitude of HR changes (sinus arrhythmia) could provide better adaptation to the changing environment since it could serve as self-training mechanism keeping the regulation of cardiovascular system in “awaked” state without unnecessary activation of higher regulatory centres in the nervous system. This condition could provide some biological advantages and could be important factor supporting organism’s optimal performance.

Evaluation of Hypothesis

The authors have referenced some of their own studies in this hypothesis. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

The following observations support this hypothesis:

1- High amplitude of normal RR-interval oscillations is typical for healthy individuals, highly trained athletes, and teenagers in rest conditions, who have apparently no problems with energetic metabolism. Moreover healthy ageing is usually associated with higher amplitude of HR oscillations.

2- Conditions that affect metabolic status (general inflammation, toxicities, overtraining in athletes, and exhaustion of other origin) in generally healthy subjects decrease amplitude of HR oscillations. In case of alcohol consumption effect depend on the amount of alcohol consumed and the individual responsiveness of the organism. We could speculate that mild consumption could provide an increase in ATP production due to involvement of ethanol in energetic metabolism, however massive consumption could be toxic for both the heart and nervous system.

3- Most chronic diseases and ageing lead to decreased HRV (mainly high frequency (HF) waves are decreased, which are usually associated with PNS activity while share of low frequency waves (LF) in total spectral power increases. Many investigators in this case indicate “activation of sympathetic activity” while it is rather decrease in parasympathetic tone and growing energetic deficit in SAN cells. This is particularly typical for the conditions which are associated with oxidative stress and problems with maintaining redox balance (diabetes, cardiovascular, liver cirrhosis, peptic ulcer, cancer etc.). Moreover pharmacological intervention aimed in decrease of heart rate by reducing f-currents (administration of Ivabradine) lead to reduction of oxidative stress in mice models.

4- The evidence of correlations of HRV parameters with metabolic, inflammatory and other general parameters confirms this hypothesis. Important molecular mechanisms potentially responsible for the relationships of heart rate (and potentially HRV) and oxidative stress are described in a recent paper.

5- It was proved that decreased HRV in patients with myocardial infarction leads to high mortality due to significantly increased risk of fatal ventricular tachyarrhythmia. In fact low ATP supply in cardiocytes may trigger dysrhythmia, while HRV appears to be low. Eventually well-known antiarrhythmic effect of adenosine-
derivatives could also serve as supporting evidence.

**Discussion**

Despite the fact that currently HRV is considered as the instrumental method for ANS evaluation and is frequently used for stress evaluation, the main attention is paid to sympathetic activation as the manifestation of stress, but not to the metabolic background of stress. We do not consider that concept as wrong as at least relative sympathetic prevalence accompanied with suppressed parasympathetic activity is evident; however it is important to mention the importance of intrinsic mechanisms of automatism which may suppress HR oscillations due to occurring health problems. Highly individual qualitative and quantitative diversity of HRV characteristics could be explained by complexity of underlying mechanisms, involvement of regulatory mechanisms on different hierarchic levels and numerous genetic polymorphisms related to ion channels function, energy metabolism, neuronal interactions etc., which was elegantly demonstrated in various mice models. This could also explain individual difference in HRV and responses to the interventions which are often observed in recent studies.

Day-to-day differences of HRV especially in healthy individuals may be also related to changing conditions and high flexibility of HR regulatory system responses to changing environmental conditions.

Considering the fact that the regulation of heart rhythm is based on the multiple feedback mechanism this assumption seems to be realistic.

Wider application of HRV in general clinical practice, being technically simple and widely accessible method, could provide health professionals with additional important information to the evaluation of activity of ANS and balance of its branches. Currently the main limitation of application of HRV recordings in clinical practice is complexity of interpretation of its results. Consideration of HRV as not only reflection of purely neural impacts on heart rate regulation but also the metabolic phenomenon could promote further research which may provide additional supporting evidence for the hypothesis which could potentially promote application of the method for wider cohorts.

The hypothesis explains high individual diversity of HRV parameters, even in relatively homogenous study groups. In addition relatively simple explanation is provided for the evidence that in advanced stages of chronic diseases HRV is severely impaired. Severe acute impairment of heart rhythm oscillations, especially in patients with previously normal HRV, indicates serious risk and may require more precise medical examination of the patient. Worsening of metabolic status is associated with the decrease of HRV, mainly HF-pattern leading to increase of LF/HF ratio, however this parameter, being in the most cases valuable, should be very carefully evaluated in case of low and extremely low values of HRV, since it does not consider the metabolic nature of low amplitude of HR oscillations and this could significantly distort obtained results.

In sports medicine application of HRV for estimation of functional and metabolic status of the athlete could be supported with more precise interpretation and update recent advances in diagnostics of overtraining. In other words, knowing the baseline level of HRV in athlete and evaluating apparently observed its decrease; physician may conclude underrecovery (overtraining) and consequently recommend some additional rest, lower
intensity training or other measures enhancing recovery. In contrast, in case of unusually high HRV – athlete may be recommended to follow his/her training plan or even increase the intensity or duration of the exercise sets.

Conclusion
The hypothesis suggests that the same power of sympathetic/parasympathetic neural regulation could exert different amplitude of heart rhythm oscillations, depending on metabolic status of SAN cells. The amplitude of heart rhythm oscillations will be higher in case of higher ATP concentration in the cells, more profound hyperpolarization of cell membrane and consequently lower in conditions of metabolic problems such as low ATP supply, affected maintaining of redox potential and other metabolic problems.

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References