Heart rate – predictor of cardiovascular risk
Srčana frekvenčija – prediktor rizika od kardiovaskularnih bolesti

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Introduction
A trend of hypertension occurrence in patients with rapid resting heart rate (RHR) was observed more than six decades ago 1. Since then, the role of rapid RHR in cardiovascular and total mortality has been proved in the general population and in the population of patients with cardiovascular diseases 2–9. However, it remains controversial whether RHR could be accepted merely as one of the well-known risk factors of development of cardiovascular diseases (arterial hypertension, hyperlipidemia, smoking, obesity).

Epidemiological data associating RHR and the outcome in the general population and the population of cardiovascular patients
Many clinical or epidemiological studies have shown that RHR is an independent risk factor of total and cardiovascular mortality 2–5. Dyer et al. 2 revealed statistically significant relationships between RHR and both cardiovascular mortality and total mortality in men followed for 15 years in the Chicago People Gas Company study and for 17 and 5 years, in the Chicago Western Electric Company (n = 1,899) and Chicago Heart Association Detection Project (n = 5,784) respectively. RHR was also an independent risk predictor of sudden death, even when other cardiovascular risk factors, such as age, blood pressure, total blood cholesterol, smoking and body weight, were taken into account in a multivariate analysis. A significant relationship was also found in the Framingham study between a high RHR and increased rates of cardiovascular mortality, coronary heart disease and sudden death both in men and women followed for 30 years 3.

Jouven et al. 4 tested the hypothesis that abnormal heart rate profile was associated with the risk of sudden death during stress and recovery phase. The study included 5,713 asymptomatic working men aged 42 to 53 who were followed for 23 years. They found that the risk of sudden death in acute myocardial infarction was increased in patients with RHR higher than 75 beats per minute (bpm) (RR 3.92; 95% CI: 1.91–8.00).

The evidence that rapid RHR is an important predictor of cardiovascular and total mortality in middle-aged people was followed by studies which detected its adverse effect in the group of elderly. Namely, Palatini et al. 5 showed, in a sample of 763 men and 1,165 women older than 65 years of age, during a 12-year follow-up, that the increased RHR was a convincing predictor of cardiovascular mortality in elderly men.

The above mentioned researches showed that RHR and profile of heart rate in stress were the predictors of cardiovascular mortality in men. Some studies excluded women, others obtained inconsistent data, so the relationship between RHR and cardiovascular and cerebrovascular events in women has long been unknown. The dilemma about the relationship between RHR and cardiovascular and total mortality in women was based on two contradictory facts. On one side, there is the fact that the average life expectancy in women is slightly longer and the other fact is that RHR in women, even after adjustment to age, is from 2 to 7 bpm higher than in men. Tverdal et al. 6 in a large cohort study, which included 180,353 men and 199,490 women aged 40 to 45 with no history of cardiovascular disease and diabetes, confirmed the previous findings and resolved the dilemma about the impact of gender on the relationship between RHR and cardiovascular morbidity and mortality. However, they found that the correlation between cardiovascular mortality and RHR was still weaker in women.
A more recent study of Hsia et al. 7 has shown that RHR was a predictor of coronary events in women independently of physical activity and conventional risk factors. They emphasized that the correlation between rapid RHR and coronary events was stronger in women aged between 50 and 64. At the same time they showed that RHR was not a predictor of stroke in women.

Increased RHR is not only a significant predictor of total and cardiovascular mortality in healthy population, but also in patients with suspected or proven coronary artery disease.

Diaz et al. 8 analyzed the influence of heart rate on cardiovascular morbidity and mortality during 15 years in 24,913 patients with suspected or proven coronary artery disease, who were included in the Coronary Artery Surgery Study registry. They found that rehospitalizations due to cardiovascular diseases were more frequent in patients with RHR higher than 77 bpm independently on other risk factors in comparison with patients with a lower heart rate. The RHR was associated with body weight and progression of coronary artery atherosclerosis and it was an independent predictor of plaque rupture.

Hjalmarson et al. 9 followed 1,807 patients from the second day after myocardial infarction on to the end of the first year in order to determine the impact of RHR on total postinfarction mortality. Intra- and extra-hospital mortality correlated with RHR. The total mortality of patients whose heart frequency on admission was between 50 and 60 bpm was 15%, but 41% for those whose frequency was greater than 90 bpm and even 48% in patients with frequency over 110 bpm. They found that cumulative mortality of the patients with heart failure ranged from 60% to 68% depending on the admission heart rate.

The goal of INVEST study was to determine the relationship between RHR and adverse outcomes in patients with coronary artery disease treated for hypertension 10. In contrast to previous studies which revealed a linear relationship between RHR and total cardiovascular mortality, this study found a J-shaped relationship. More precisely, the study noted an increase of risk in patients with relatively low RHR. This relationship was shown in the studies that included high-risk patients with isolated systolic hypertension, unstable angina and men with acute myocardial infarction without ST elevation 11–13.

Framingham Heart study confirmed that RHR was an independent predictor of total and cardiovascular mortality in patients with arterial hypertension 14. The new analysis of the results of the study VALUE identified that most of the risk occurred in patients with arterial hypertension and with heart rates of 79 bpm or more. There was an increase of the primary end point in the highest quintile of heart rate (≥ 79 bpm) compared with the lower four quintiles. The annual incidence of new primary-end-point events in the highest quintile (compared with the lower four) was 30% higher in the first year of the study, 55% higher in the second, 55% higher in the third year, 52% more in the fourth, and 46% greater in the fifth year of the study. A similar trend was seen throughout the trial of the heart failure and sudden death components of the end point 15.

Palatini et al. 11 showed that the rapid RHR was a predictor of mortality in elderly patients with isolated systolic hypertension. This research undoubtedly proved that the clinical method of measurement of heart rate, which was applied in almost all these studies, was equally precise as heart frequency obtained by ambulatory 24-hour Holter monitoring of ECG. In fact they found a similar predictive power of the heart rate obtained by these two modalities.

**Pathophysiologic mechanisms that connect rapid heart rate, atherosclerosis and cardiovascular diseases**

In order to explain the role of rapid RHR in the development of endothelial dysfunction and atherosclerosis, it is important to know to which hemodynamic forces arterial wall is exposed. These forces include flow-generated shear stress which is tangential and produced by the friction of blood flow on the endothelial surface and blood-pressure-induced tensile stress that is circumferential and represents the blood-pressure derived force imposed on the circumference of the arterial wall. Accelerated heart rate increase the magnitude and frequency of tensile stress on arterial walls, which prolongs exposure to oscillatory shear stress 16. Increased tensile stress directly induces endothelial injury and increases permeability for low density lipoprotein (LDL) and inflammatory mediators.

Rapid RHR intensifies pulsatile movement of the heart and periodically changes geometry of the coronary artery, affecting the local hemodynamics. These processes lead to additional structural and functional changes of coronary artery endothelial cells, which leads to atherosclerosis 17.

In addition to small diameter arteries, rapid RHR also affects large elastic arteries. Moderate tachycardia (over 100 bpm) increases blood pressure and tensile stress and can promote endothelial injury and wall stiffness 18. It has been proved that one of the consequences of RHR increase in mice, provoked by electric pacing, was progressive reduction in arterial compliance and distensibility 19.

Accelerated RHR reflects, but also contributes to cardiovascular pathology. 16. Increase in RHR affects the contraction-perfusion matching that determines the myocardial supply and function. In a healthy heart, increased metabolism due to increased contractile function, results in increased myocardial blood flow and increased oxygen consumption. In the presence of coronary artery disease perfusion-contractile discrepancy is reflected in the areas with inadequate blood supply. When coronary flow cannot suffice, contractile and diastolic functions in the affected areas are reduced. Increase in RHR results in not only the increase in oxygen consumption but also in the reduction of diastolic perfusion time and damage of collateral perfusion supply. This imbalance may promote ischemia, ventricular arrhythmias, and ventricular dysfunction, *i.e.* acute coronary artery event, heart failure and sudden death.

Under the circumstances of the previously present changes of shear and pulsatile stress endothelium additionally releases growth hormones (transforming growth factor
beta and insulin-like growth factor 17) and vasoconstrictive peptide (endothelin), which is associated with the increased platelet aggregation and relative deficiency of NO synthesis.

Prolonged rapid RHR causes increase of noradrenaline synthesis in the heart and the circulating level of noradrenaline is on the increase. This increase in sympathetic activity may have a direct cytotoxic effect, increase apoptosis and contribute to ventricular remodeling.

In patients with stable angina pectoris or previous myocardial infarction, the reduced supply of O2 can be also caused by vasoconstriction, which is detected in the experimental conditions of accelerated heart rate.

In patients with stable angina the occurrence of ischemia is affected by RHR and stress duration. Patients with RHR higher than 80 bpm have two times higher prevalence of ischemic episodes than those with RHR lower than 70 bpm. Experimental studies showed that RHR is not only important for the occurrence of ischemia but it also may be a trigger for the occurrence of rhythm disturbances.

The relationship between RHR and the left ventricular dysfunction was indirectly confirmed in the case of an animal model. Surgically caused mitral insufficiency with consequent left ventricular dysfunction in dogs was ameliorated with the use of beta blockers.

**Benefits of pharmacological reduction of heart rate**

Two groups of drugs, based on application over decades, have proved their unequivocal role in the reduction of RHR. These medications are beta blockers and nondihydropiridines.

The influence of beta-blockers on the reduction of RHR and mortality of patients with acute myocardial infarction and heart failure have been previously confirmed. Data analysis of six studies which included 1,427 patients with acute myocardial infarction showed that infarct size reduction in beta-blocker group of patients was in direct relation with the reduction of heart rate. The analysis of 11 placebo-controlled trials showed that there was a significant correlation between the long-term use of beta blockers after acute myocardial infarction and the reduction in RHR and mortality.

A meta-analysis of randomized clinical trials which included patients with previous myocardial infarction suggested that the benefit from the application of these two groups of drugs was proportional to the reduction of RHR. This meta-analysis showed that the reduction for each 10 beats per minute reduced the relative risk of cardiac death by 30%, the risk of sudden death by 30% and the risk of all-cause mortality by 20%.

In patients with stable angina, later appearance of ischemia during the stress test, correlated with the reduction of heart rate during the test.

Numerous studies confirmed the relationship between the reduction of RHR and outcomes in patients with heart failure. A recent meta-analysis of 35 studies which included patients with chronic systolic heart failure (n = 22,926) found a strong correlation between RHR and analyzed all-cause mortality (p = 0.004), and also between the change in RHR and the change in the left ventricular ejection fraction (p < 0.001). As a result, it was suggested that RHR lowering effect of beta-blockers was a major contributor to the clinical benefit associated with these agents. A study of 152 patients with heart failure who were receiving beta-blocker therapy showed that higher beta-blocker doses provided additional clinical benefits among patients with persistently elevated RHR. These results suggest that the magnitude of reduction in RHR may be more important than achieving the target dose of beta-blocker therapy in patients with heart failure.

Whether to use beta-blockers as first-line agents in the treatment of arterial hypertension is a dilemma that has marked the last decade. Opinions about the role of beta-blockers in the reduction of RHR in patients with arterial hypertension are divided. Despite the lack of data about the reduction of RHR in patients with arterial hypertension, Consensus Document of the European Society of Hypertension suggests that, "heart rate reduction by antihypertensive agents may have beneficial effects". However, Bangalore et al. have found quite the opposite effect. Meta-analysis of 60,000 patients included in 9 major clinical trials which determined the effectiveness of beta-blockers in the treatment of arterial hypertension showed that greater RHR reduction increased the risk of cardiovascular events. The benefit of drug-induced bradycardia was less beneficial than bradycardia generated spontaneously because of the dysynchrony of the reflected pulse wave and the outgoing pressure wave. The pulse wave dysynchrony explains the beta-blocker-hypertension paradox. Hypertension paradox and pseudoantihypertensive effect of beta-blockers were examined in patients who were receiving atenolol, so these conclusions could not be unconditionally accepted, especially since we know that beta-blockers with vasodilatative effects equally effectively reduce the brachial and central pressure in the aorta.

The new specific RHR-lowering agent-ivabradine acts directly on the sinoatrial node by inhibiting the I1 current of cardiac pacemaker cells, not affecting other cardiac ionic currents when used in therapeutic concentrations. The study BEAUTIFUL, which included patients with coronary artery disease and the left ventricular systolic dysfunction showed the risk reduction of the coronary heart disease by 22%, of fatal and non-fatal myocardial infarction by 36% and the need for revascularization by 30%. It is also expected that trials which are ongoing or will be conducted will prove cardioprotective efficacy of ivabradine in other cardiovascular diseases.

**Conclusion**

It is evident that RHR represents a strong predictor of mortality in the general population and in patients with arterial hypertension, coronary artery heart disease and heart failure. However, the dilemma whether rapid RHR is just a predictor or a risk factor still remains. In clinical practice, RHR has not been accepted as a classic cardiovascular risk factor. The gap between the epidemiological data and clinical practice can be explained by the fact that the clinical benefit of RHR reduction has not been proved in non-cardiologic patients.
REFERENCES


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