BETA BLOCKERS IN CARDIOPROTECTION AFTER ACUTE MYOCARDIAL INFARCTION

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Summary. *In post myocardial infarction patients beta blockers have shown a reduction of total mortality (23%), sudden cardiac death (25%) and non fatal reinfarction (30%). Beside beta blockers, only a few agents have shown reduction of mortality and sudden cardiac death in post myocardial infarction patients. Beta blockers have showed more favorable effects In patients with Q wave myocardial infarction than in patients with non-Q wave myocardial infarction. Patients with the left ventricular dysfunction and complex ventricular arrhythmias after myocardial infarction have increased risk of mortality and morbidity, and these patients have benefited the most from the beta blockers. ACE inhibitors have shown efficacy in the secondary prevention of postinfarct patients with left ventricle dysfunction and beta blockers have demonstrated a synergic effect in risk reduction. Various beta blockers can be given with exception of agents with partial agonist activity (ISA). All patients with Q wave myocardial infarction should receive beta blocker treatment (in absence of contraindications). Beta blockers are contraindicated in decompensated heart failure, in hypotension and atrioventricular conduction disorders, as well as in severe obstructive lung disease.*

Key words: *Beta blockers, myocardial infarction, sudden cardiac death*

Introduction

In developed western countries there is a trend of a steadily declining mortality from coronary artery disease which lasts more than twenty years (1). In developing countries there is an opposite tendency of continuous mortality increasing from coronary artery disease. Favorable declining tendency of mortality in developed countries probably results from a combination of factors including aggressive primary prevention of atherosclerotic disease and better management of patients with known coronary artery disease. Beta blockers, angiotensin-converting enzyme (ACE) inhibitors, aspirin and statins are medicaments that have shown favorable effect on survival in post myocardial infarction patients. Beta blockers have shown a considerable reduction in total mortality and sudden cardiac death rate in post infarction patients, and also a reduction of the post infarction angina pectoris and nonfatal myocardial infarction (2,3,4).

Cardiovascular effects of beta blockade

Beta blockers are antiischemic agents and they decrease myocardial oxygen consumption by reducing heart rate, blood pressure and myocardial contractility. Heart rate is reduced at rest and more importantly during exercise and excitement, when sympathetic tone is increased. Maximal double product of heart rate and systolic blood pressure during exercise, measure of myocardial oxygen consumption, may be reduced up to 20% under influence of the beta blockers. By decreasing surges of the systolic arterial pressure, beta blockers may prevent the rupture of the coronary atherosclerotic plaque and the development of the acute coronary syndrome (5). Prolonged diastole due to reduced heart rate, which is caused by beta blockers, enables better perfusion of the jeopardized subendocardial myocardium.

Beta blockers manifest antiarrhythmic effects, decrease automatism of sinus node and ectopic focus and suppress calcium influenced afterdepolarizations. These agents represent a treatment of choice for sympathetic mediated rhythm disorders such as arrhythmias during exercise or an emotional excitement (5).

The effects of beta blockers in patients after acute myocardial infarction

Randomized double blind, placebo controlled studies of patients after an acute myocardial infarction have shown favorable effects on mortality and morbidity of the beta blockers. Well known BHAT study (Beta blockers in Heart Attack Trial) has shown that post myocardial infarction patients with chronic Propranolol

(60 – 80 mg three times per day) treatment had lower degree of the total mortality and lower sudden cardiac death frequency (1). Beta blockers have shown better effects in improving survival in patients with Q wave myocardial infarction than in patients with non-Q infarction. Also, patients with more extensive myocardial infarction and lower left ventricular ejection fraction have achieved better results while treated wirh beta blockers in improving prognosis (13). Norwegian multicenter Study have shown a reduction of 26% in sudden cardiac death and nonfatal reinfarction in post infarction patients who had received timolol (7). This study has also shown better effects of beta blocker in Q wave myocardial infarction patients in relation to patients with non Q wave infarction.

Meta analysis of 17 trials with 20 000 patients has shown a 20% reduction of mortality in the first year after myocardial infarction in patients treated with beta blockers. Another meta analysis of 25 studies with 24 000 post myocardial infarction patients has shown a 23% reduction of mortality in the first year after infarction in patients treated with beta blockers (2,3,4). Favorable effects of beta blockers in post infarction patients can be expressed as 30 patient years of treatment for one extra year of life. Meta analysis of studies with different beta blockers has found correlation between the degree of reduction of the rest heart rate by beta blockers and the efficacy of the mortality reduction. Patients who have manifested greater reduction of the rest heart rate under the influence of the beta blocker, showed better survival results. It was suggested that the degree of the heart rate reduction under the influence of beta blocker is a measure of efficacy of medication in improving survival (8,9,10).

Ventricular premature contractions can be considered as a major predictor of both sudden death and long term mortality in patients after myocardial infarction. In post myocardial infarction patients, a complex premature ventricular contraction can be efficiently suppressed by beta blockers, and these agents are also known to reduce the proarrhythmic effect of the Ic antiarrhythmic agents (11,12,13,14). Beta blockers are an optimal medication for premature ventricular contraction in post myocardial infarction patients who have not a severely depressed left ventricle contractile function. Beta blocker treatment has resulted in a greater decrease of mortality in patients with complex ventricular ectopy than in patients without complex ventricular premature beats. The importance of complex premature ventricular contractions as an indicator of a sudden cardiac death risk is increased in postinfract patients with left ventricular dysfunction and in these patients beta blockers have shown greater degree of efficiency in reducing mortality. Beta blockade has been shown to improve heart rate variability in patients with coronary artery disease and previous infarction and the restoration of the autonomic balance is one of the possible mechanisms by which these agents provide protection against arrhythmic events. Beside beta blockers, only a few agents

have shown reduction of mortality and sudden cardiac death in post myocardial infarction patients (15).

In post infarct patients with the left ventricular dysfunction angiotensin-converting enzyme (ACE) inhibitors and beta blockers have shown additional favorable effects. The benefits of beta blockers are the most prominent in the firs year postinfract, while the benefits of ACE inhibitors are most evident in the second or third year, due to an improved ventricular remodeling with less dilatation.

It has been recently demonstrated that an excessive neurohumoral stimulation in heart failure has deleterious effect on cardiovascular function. Excessive chronic sympathetic stimulation in heart failure, above compensatory needs, induces myocardial necrosis, deterioration of the myocardial contractile function and increases sudden cardiac death rate. Beneficial effects of beta blockers in patients with dilated and ischemic cardiomyopathy have been demonstrated. It has been shown that in patients with coronary artery disease and ischemic cardiomyopathy, chronic treatment with beta blockers carvedilol, metoprolol or bisoprolol improves the ejection fraction and reduces symptoms of heart failure. It must be stressed that beta blockers do not replace standard heart failure treatment with diuretics, vasodilators and inotropic agents but represent an adjunctive medication in selected patients. Ischemic cardiomyopathy represents relatively new indication for beta blocker treatment.

Which post myocardial infarction patients benefit most from beta blockers?

Beta blockers have showed more favorable effects In patients with Q wave myocardial infarction than in patients with non-Q wave myocardial infarction. Patients with more extensive myocardial infarct, more reduced systolic pump function and lower ejection fraction have received more benefits from beta blockers than patients without left ventricular dysfunction. It is important to stress that in patient with severely depressed left ventricular dysfunction and signs of overt pulmonary congestion, beta blockers are contraindicated until patients become compensated. Ideal candidates for beta blocker treatment are patients with angina pectoris related to exercise and coexistent arterial hypertension. Indications for beta blockers are also supraventricular or ventricular arrhythmias and prominent anxiety states (13,14,15). Beta blockers are contraindicated in patients with bradycardia, atrio-ventricular block, hypotension and obstructive pulmonary disease.

Which beta blocker to choose, when to administer and for how long?

Beta blockers with documented efficacy in large trials are recommended for cardioprotection after myocardial infarction. Favorable effects of atenolol, metoprolol and propranolol have been documented, while beta blockers with positive intrinsic agonist activity (ISA) are not recommended for cardioprotection after myo-

cardial infarction. In acute phase of the myocardial infarction beta blockers are indicated in the presence of the hypercinetic syndrome. Beta blockers may be given as cardioprotective agents as early as stabile hemodynamic condition are achieved after onset of myocardial infarction at third day or later, but before discharge from hospital. Favorable effects of beta blockers are documented in first two years after myocardial infarction in majority trials, but there are studies which have demonstrated sustained benefits lasting beyond six years (16, 17, 18, 19). Today's policy is to prescribe a beta blocker continuously for indefinite duration.

Conclusion

Chronic beta blockers treatment markedly reduce total mortality, sudden cardiac death and nonfatal myocardial reinfarction in patients after acute an myocardial infarction. All patients with Q wave myocardial infarction should receive beta blocker treatment (in absence of contraindications) (17). Patients should also take aspirin and angiotensin-converting enzyme (ACE) inhibitors in the case of the left ventricle dysfunction.

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BETA BLOKATORI U KARDIOPROTEKCIJI
POSLE AKUTNOG INFARKTA MIOKARDA

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Kratak sadržaj: *U sekundarnoj profilaksi, posle infarkta miokarda, beta blokatori su doveli do smanjenja ukupnog mortaliteta (23%), nagle srčane smrti (25%) i nefatalnog infarkta miokarda (30%). Bolesnici sa postinfarktnom disfunkcijom leve komore i kompleksnim komorskim ekstrasistolama imaju povećan morbiditet i mortalitet i ovi bolesnici i imaju najviše koristi od beta blokatora. ACE inhibitori su pokazali efikasnost u popravljanju prognoze bolesnika sa disfunkcijom leve komore posle infarkta miokarda, a beta blokatori su imali sinergistički efekat u redukciji rizika. Različiti beta blokatori se mogu dati bolesnicima sa izuzetkom agenasa koji poseduju pozitivnu ISA*

aktivnost. Beta blokatori su kontraindikovani u dekompenzovanoj srčanoj insuficijenciji, hipotenziji, kod poremećaja atrioventrikularnog provođenja, i u obstruktivnoj bolesti pluća.