MYOCARDIAL INFARCTION AND THE BETA-BLOCKERS TREATMENT

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Abstract: *The medical use of beta-blockers in their variant shapes and names was possible due to some elaborate clinical studies that took a full swing in the last decades: the so-called population studies on large representative groups whose results grant us the handling of these precious medical substances in the medical practice. Beta-blockings have properties that intervene in the myocardial ischemia treatment by adjusting the prejudices made by hypoxia or by preventing other local damages. Beta 1 stimulating hemodynamic effects are antagonized, such as: the blood pressure decrease rate leads to the ventricular contractility decrease rate, and the ventricular wall pressure increases due to the ventricular volume lift. The major effect is that of reducing the increase of oxygen requirement with 20-30% and the contraction in the ischemia area which is improved.*

Keywords: *myocardial infraction, beta-blockers treatment*

Rezumat: *Utilizarea beta-blocanţilor în practica medicală, în variatele lor forme şi denumiri, a fost posibilă datorită unor studii clinice asidue, care în ultimele decenii, au luat o extensie deosebită, aşa numitele studii populaţionale pe loturi mari reprezentative, ale căror rezultate ne oferă garanţia manevrării acestor deosebit de valoroase substanţe medicamentoase în practica medicală. Beta-blocanţii posedă proprietăţi care intervin în tratamentul ischemiei miocardice, corectând prejudiciile produse de hipoxie sau prevenind alte deteriorări locale, efectele hemodinamice beta 1 stimulatoare sunt antagonizate, ca spre exemplu, rata de scădere a presiunii sangvine duce la scăderea ratei contractilităţii ventriculare, iar tensiunea peretelui ventricular creşte datorită măririi de volum a ventriculului. Efectul major este însă acela de scădere a cererii de oxigen cu 20-30% şi a contracţiei din zona ischemiată care se îmbunătăţeşte.*

Cuvinte cheie: *infarctul miocardic, tratament, beta-blocante*

General description

Coronary-cardiac diseases are the main and the most frequent causes of death in the developed countries. For survivors that make it to the hospital the quantity of spur myocardium after the necrosis process is vital for the determination of mortality as well as short and long term morbidity. The patients showing extended infarct areas of up to 40% or more of the left ventricle suffer a marked decrease of the left ventricle function and very frequently develop life threatening ventricular arrhythmia or cardiogen shock, especially those patients with coronary antecedents.(1)

During the infarction process of the cardiac muscle by occlusion of a number of coronary arteries the blood and oxygen supply drops proportionally with the value of stems interested in the occlusion process. The autonomic sympathetic system responds to this aspect of local damage by increasing the frequency of the ventricular contractions and, on the other hand, the low coronary flow engages the myocardium in a metabolic disorder caused by the decrease of the energetic substrata for the increased hemodynamic needs and thus appears a set of mechanism that seriously damage the cardiac beat, (the demand-supply balance is affected by a decrease in supply).

Oxygen supply decrease alters the balance and the supply between the two major energetic pathways of the myocardium, meaning: oxidative pathway to glucose and free fatty acids pathway altering glucose use and resulting in a production decrease of macro-energetic compounds in Krebbs cycle implicitly altering the membrane ATP-dependent functions and, on the other hand, resulting in excessive cellular acidosis by accumulation of pyruvate derived lactic acid. The phenomena in the ischemic waterfall are linked as follows: as a result of the myocardial ischemic process in the specific area the heterogenic coronary flow leads to local metabolic disorder that causes diastolic dysfunction with regional disynergy, causes functional disorder of the ion channels and their transfers, causes the development of the sympathetic dysfunction, and consequently to this activity increase appears the injury and necrosis process.

Ischemia and infarct may augment by decrease of the oxygen supply and of the coronary inflow or by increase of the oxygen demand that may appear as a result of:

1. Some hemodynamic changes such as:
   - Increase of the cardiac frequency
   - Increase of the myocardium contractility
   - Increase of the systolic pressure of the left

ventricle and of the left ventricle pressure rate (increase of the ventricular wall pressure)

2. Metabolic changes such as the level increase of the free fatty acids in plasma due to beta 1 stimulants that lead to the increase of myocardial oxygen consumption.
3. Beta-blockings have properties that intervene in the myocardial ischemia treatment by adjusting the prejudices made by hypoxia or by preventing other local damages. Beta 1 stimulating hemodynamic effects are antagonized, such as: the blood pressure decrease rate leads to the ventricular contractility decrease rate, and the ventricular wall pressure increases due to the ventricular volume lift. The major effect though is that of increase in oxygen requirement with 20-30% and the contraction in the ischemia area which improves.

Beta-blockings cause the decrease of the free fatty acids leading to an improvement in the usage of carbon-hydrates in myocardial metabolism, and the oxygen supply decreases accordingly. ATP concentration increases in ischemic areas, pH decreases and carbon dioxide pressure increases in ischemic areas treated with beta-blockings.(2)

Beta-blockings cause the decrease of the thickness of the blood plates and intervenes in the thrombotic processes.

Beta-blockings intervene or improve rhythm disorders that also cause the increase of the myocardial oxygen demand, ventricular fibrillation is frequently seen at beta-blocking agents without ISA, and Q-Tc interval at rest is shortened.

Most of the episodes of the 24 hours S-T segment depression come with pain. The silent ischemic events are usually hemodynamically undistinguishable from myocardial events. Such episodes may be followed by an increase in the cardiac frequency, and the beta-blockings are effective in inducing such episodes.

One must notice that the frequency of the episodes of S-T segment depression is higher in the morning and coincides with the incidence peak of the myocardial infract and beta-blockings may eliminate this phenomenon.(3)

Treatment of acute infarction with beta-blockings; Clinical studies

During acute infarction beta-blockings are advised for oral administration at all patients with no contra-indication. I.V. administration must be considered at patients presenting ischemic pains resistant to opoids, recurring ischemia for control of concomitant arterial pressure, tachycardia and arrhythmias.

Beta-blocking substances limit the extension of the myocardial infarct, reduce life threatening arrhythmias, ease the pain and reduce death cases, including sudden death from cardiac arrest.

There were two relevant major studies for the usage of beta-blockings within the first hours from the occurrence of the myocardial infarct. In the former study named “The First International Study of Infarct Survival” (ISIS-1) patients in their first 12 hours of evolution from the occurrence were randomized to be administrated I.V. injection with Atenolol, followed by oral administration for 7 days, respectively 3.7% compared to 4.7% , equalling to six lives saved at 1000 patients treated. The benefit was due first to the limitation of the number of ruptures of the cardiac wall in the necrosis area, as opposed to what was shown after a day, a month, a year of treatment.(4)

In the latter study named ”Metoprolol in Myocardial Infarction” (MIAMI), Metoprolol administrated by I.V. injection and followed by oral administration did not significantly reduce mortality after 15 days, as compared to placebo (4.3% compared to 4.9%).

A meta-analysis of 28 trials with beta-blockings administrated by I.V. injection showed a significant short term reduction of mortality from 4.3% to 3.7%, showing thus seven lives saved at 1000 patients treated.(5)

Other two randomized trials of treatment with beta-blocking agents administered by I.V. injection carried out after myocardial reperfusion started to be widely used in myocardial infarction showed similar results. In the latter trial “Thrombolysis in Myocardial Infarction” (TIMI 2) thrombolysed patients were randomized in order to be administrated Metoprolol first by I.V. injection and then by oral administration, compared to oral administration after day six.

Reinfarction and recurrent ischemia were less frequent in the group that has been timely administrated with beta-blockings, and when treatment was applied during the first two hours from the occurrence of the symptoms there was a reduction of the composite end point of death or reinfarction.

In association with Heparin at a wide number of patients suffering from acute myocardial infarction showed a share of the thrombotic obstructed coronary arteries of 75% at 90 minutes from the beginning of the treatment compared to 53% for streptokinase, 85% after 24-48h and 81% after 1-3 weeks (75% for streptokinase).

We have new information from PAMI trials (primary angioplasty in AMI), Stent-PAMI, AeR PAMI and CADILLAC, that seem to prove a reduction of mortality when beta-blockings are used before primary percutaneous interventions.

In a similar study (1976) with Propanolol injected I.V. (3-10mg), pain was significantly reduced or even eliminated at 9-12 patients. The beta-blockings’ mechanism for decreasing and eliminating the pain is different than the mechanism of analgesics opoids. Pain decrease after I.V. injection with beta-blockings is related to the decrease of the intracardiac pressure, suggesting thus that the demand for myocardial oxygen implicitly drops.

A meta-analysis on 82 random trials, out of which three have been long term monitored, clearly showed the advantage of long term usage of beta-blockings for reduction of mortality and morbidity after acute myocardial infarction, even though they have been

simultaneously administrated with Aspirin, fibrinolytics or angiotensin II converting enzyme inhibitors.

There was a death reduction of 1.2 at 100 patients treated with beta-blockings after myocardial infarction. Similarly, there was a reinfarction reduction of 0.9 events at 100 patients treated, the equivalent of the necessity to treat 107 patients for one year in order to avoid a fatal reinfarction.

In the study "The Beta-blocker Heart Attack Trial" (BHAT) the patients randomized at 5-12 days after acute myocardial infarction in order to receive beta-blockings, mainly Propanolol and placebo, were monitored for two years. After that period mortality dropped by 25%, respectively 7% as compared to 9,5% , representing 25 lives saved out of 1000 patients treated. (5)

Another study, "The Norwegian Trial", in which patients were randomly chosen to receive Timolol or placebo after 7-28 days from acute myocardial infarction; as a result, mortality dropped from 9.8% to 7.2%, meaning that at 26 patients out of 1000 treated mortality dropped after 25 months.

A different study of Boissel & Co. – Acebutalol et Prevention Secondarie de L' infartus (PSI), dealt with high risk patients at 2-22 days from acute myocardial infarction. After Acebutalol treatment, mortality decreased by 48%.

In the study CAPRICORN – (The Carvedilol Post Infarct Suvival Control in Left Ventricular Dysfunction) that included patients after 2 to 21 days from acute myocardial infarction, with reduced left ventricular ejection fraction that have been administrated angiotensin II converting enzyme inhibitors, mortality was lower in the group that has been administered Carvedilol than the mortality registered in the group that has been administrated placebo, meaning 12% deaths in Carvedilol group, and 15% deaths in placebo group. The significant drop of mortality in the case of the cardiac insufficiency observed when using beta-blockings, and the results of the CAPRICORN study, support even more the usage of these substances at high risk patients and with affected or insufficient function of left ventricle after infarction, and prove that the benefits of beta-blockings are also observed at patients that have been treated according to the mandatory current methods envisaged for the particular clinical stage, including reperfusion treatment and angiotensin II converting enzyme inhibitors.(6) Although the advantage of the beta-blockings treatment is seen at all patients having suffered acute myocardial infarction or having suffered from other long term cardiovascular diseases, the most important advantage is registered at high risk patients, such as those having suffered from extended infarction or from inner layer infarction. The opportunity of the treatment is also analyzed for low risk patients, such as young patients, revascularized patients, that have not suffered from inner layer infarction, residual ischemia, ventricular arrhythmias, patients presenting normal ventricular function, because the long term prognosis is favourable, patients suffering from stable chronic ischemic cardiac disease and patients suffering from atherosclerosis could benefit from a combined treatment: statin and beta-blocker treatment.

Table no. 1. Ways to use beta-blockers in myocardial infarction – Com. Eur. Card. 2004

Drug substance	Dose for I.V. injection	Maintenance dose
Atenolol	5 + 5 mg	Oral administration: 50-100 mg per day
Esmolol	0.5 mg⁄kg in 1- 5 min.	0.05-0.3 mg⁄kg⁄min. i.v.
Labetalol	20 mg in 2 min.	2-10 mg i.v.
Metoprolol	2,5 mg i.v. bolus up to 2 min., 2-3 times per dose	Oral administration 25-100 mg for 12 hours
Propanolol	0.15 mg⁄kg	0.10-0.20 mg⁄kg⁄min. Oral administration 80-240 mg⁄day

REFERENCES

1. Chatrath R et. al. Beta-blocker therapy failures in samptomatic probands with 2004 genotyped long QT syndrome. Rediatr Cardiol 2004;25(5):459-65.
2. Baker J. The selectivity of beta-adrenoceptor antagonists at the humanbetai, beta2 and betas adrenoceptors. Br J Pharmacol 2005;144(3):317-22.
3. Gherasim L. Progrese în cardiologie, Ed. Infomedia Bucureşti, 2002:243-310.
4. Belleyer N et al. Effects of Carvedilol on left ventriculary remodelling in chronic 2003 stable heart failure a cardiovascular magnetic resonance study. Heart 2004;90:760-764.
5. Mohamed A et. al. Effects of Nebivolol, Atenolol and Propranolol on Aiway beta-1991 Adrenergic Responsiveness in Normal Subjects. Drug investigation 3 (supp) 1991;196-198.
6. Michael Kindermann Carvedilol but not Metroprolol reduces beta-Adrenergic M.D. 2004 Responsiveness After complete Elimination From in VivoCirculation 2004:109;3182-3190 157.Mickley H. 2004 Incidence and treatment" of sexual dysfunction in heart disease. Ugeskr Leager 2002;164:(41):4760-4.