

IVABRADINE EFFECT VERSUS METOPROLOL ON THE MAIN TISSUE DOPPLER PARAMETERS IN THE DIABETICS WITH DIASTOLIC DYSFUNCTION WITH PRESERVED EJECTION FRACTION

RODICA MOGA¹, I. MANIȚIU²

¹PhD candidate "Lucian Blaga" University of Sibiu, ²"Lucian Blaga" University of Sibiu

Keywords: ivabradine, metoprolol, Tissue Doppler, diabetics, left ventricular diastolic function

Abstract: Objectives: To check the effects of ivabradine, compared to metoprolol on the main parameters of left ventricular diastolic function with preserved ejection fraction, on a group of diabetic patients in order to determine the opportunity of replacing metoprolol by ivabradine in the patients with side effects or contraindications to metoprolol. Methodology: We have studied the main Tissue Doppler parameters of the left ventricular diastolic function on a group of 90 diabetic patients with preserved ejection fraction, under metoprolol treatment, of which, in 50 patients, it was replaced by ivabradine. Conclusions: Ivabradine has similar effects to metoprolol on the Doppler Tissue main parameters of the left ventricular diastolic function in diabetics.

Cuvinte cheie: ivabradină, metoprolol, diabetici, Tissue Doppler, funcția diastolică a ventriculului stâng

Rezumat: Obiective: Verificarea efectelor ivabradinei, față de metoprolol, asupra principalilor parametri ai funcției diastolice a ventriculului stâng, cu fracție de ejecție păstrată, pe un lot de pacienți diabetici, pentru a aprecia oportunitatea înlocuirii metoprololului cu ivabradină, la pacienții cu reacții adverse sau contraindicații la metoprolol. Metodologie: S-au studiat parametrii principali Tissue Doppler ai funcției diastolice a ventriculului stâng pe un lot de 90 pacienți diabetici cu fracție de ejecție păstrată, aflați sub tratament cu metoprolol, din care, la 50 acesta a fost înlocuit cu ivabradină. Concluzii: Ivabradina are efecte similare cu metoprololul asupra parametrilor principali Tissue Doppler ai funcției diastolice a ventriculului stâng, la diabetici.

INTRODUCTION

Diastolic dysfunction with preserved left ventricular (LV) ejection fraction occurs in diabetics due to the specific cardiomyopathy and due to the association of hypertension, coronary heart disease and cardiovascular diabetic neuropathy, more commonly in diabetics than in non-diabetics.

None of the drugs recommended by the European or American guidelines for heart failure treatment with preserved ejection fraction has clearly proven in large studies its effectiveness in improving the quality of life or the survival rate of these patients.

By analyzing the standard Doppler ultrasound parameters and Tissue Doppler, we can assess the diastolic function in relation to heart rate and the possible therapeutic benefits of sinus rhythm thinning therapy.

OBJECTIVES

We aimed at evaluating the benefits of ivabradine compared to metoprolol on LV diastolic dysfunction with preserved ejection fraction in diabetics. Ivabradine is a specific inhibitor of the If current in the sinoatrial node, producing exclusively the reduction of the frequency of sinus rhythm, with an indication in the treatment of stable angina in the patients in sinus rhythm, with intolerance or contraindication to beta-blockers and in chronic heart failure systolic dysfunction with NYHA class II-IV systolic dysfunction in the patients in sinus rhythm with heart rate above 75/min, in addition to the standard therapy.

METHODS

Design. We conducted a case-control study on two groups of diabetic patients with preserved LV ejection fraction,

from the Outpatient Clinic of Diabetes and Nutrition within the County Clinical Emergency Hospital of Sibiu, unexamined cardiologically in the past, being initially treated with metoprolol, which, in a subgroup, ivabradine has been replaced by metoprolol in equivalent doses, as an effect for lowering the sinus rate, creating two groups: the study group treated with ivabradine, compared with the witness group, which continued the treatment with metoprolol. The two groups were similar in terms of age structure, sex, initial Doppler ultrasound aspect, morbid and drug combinations. These two groups were examined in terms of Tissue Doppler, particularly observing the LV diastolic function parameters in the initial moment, the change of the treatment of one of the groups after 3 months of treatment, in which no changes occurred.

Patients. The inclusion criteria were: presence of type II diabetes mellitus, ejection fraction above 50%, absent diastolic dysfunction, or the "impaired relaxation" type, sinus rhythm, stable clinical condition and unchanged treatment for the last month.

The exclusion criteria were: giving up the treatment started at the beginning of the study due to various reasons, recent myocardial infarction (less than 2 months), hemodynamically significant valvular pathology, pericardial pathology, previous cardiac surgery, coronary revascularization, or resynchronization therapy, atrial or ventricular pacemaker, congenital heart disease, stroke in the last month, active myocarditis, improper ultrasound display, significant calcification of mitral annulus, atrial fibrillation, atrial flutter, sinus node disease, atrioventricular block, severe ventricular arrhythmias, severe hypertension (over 180/110mmHg), drug-uncontrolled, hypotension (below 85mmHg), associating the

¹Corresponding author: Rodica Moga, Bd. C. Coposu, Nr. 2-4, Sibiu, România, E-mail: rodica.moga@yahoo.com, Tel. +40723 396526
Article received on 12.01.2012 and accepted for publication on 23.03.2012
ACTA MEDICA TRANSILVANICA December 2012;2(4):204-205

CLINICAL ASPECTS

treatment with non-dihydropyridine calcium blockers, antiarrhythmic agents of class I and III, or drugs that strongly inhibit the cytochrome P4503A4 (macrolide antibiotics, cyclosporine, antiretroviral drugs, systemic azole antifungals, nefazodone), severe hepatic or renal impairment, known anemia, lack of contraception in fertile women.

90 patients were included in the study, of which 36 women and 54 men, aged between 20 and 80 years old, with type II diabetes. As associated pathology, they presented hypertension, ischemic heart disease (clinically diagnosed: symptoms, electrocardiographic changes), diabetic nephropathy, chronic renal insufficiency up to stage II, lower limb peripheral arterial disease, diabetic neuropathy, chronic obstructive pulmonary disease with a resting heart rate between 60 and 70-minutes. The medication given for this pathology has been established in accordance with the international guidelines, all being treated with metoprolol, which later, in 50 of them was replaced with ivabradine, aiming at achieving a resting heart rate between 50 and 65 beats per minute.

Assessment of the ultrasound parameters evolution

Upon the first examination, all patients had a left ventricular ejection fraction above 50% and were within the normal LV relaxation type, or in the impaired relaxation type; none of them had any types with a more severe diastolic dysfunction prognosis. The improvement of the left ventricular diastolic function was assessed by increasing the $V_{max} E/V_{max} A$ ratio, the increase of the $V_{max} E/V_{max} Ea$ ratio, nearing the normal values of IVRT, MDT and Adur extension.

Administered treatment

In the group treated with ivabradine, this one was administered in an equivalent dose, in order to obtain a similar reduction of the heart rate (metoprolol 25mg/day 10mg/day replaced with ivabradine, divided into two doses, 50mg/day metoprolol, replaced by 15 mg/day ivabradine in two doses). The patients were examined weekly by the family doctors, aiming at maintaining the heart rate between 50 and 65 beats/minute, the side effects or the emergence of exclusion criteria on the way.

Statistical analysis

For the statistical analysis, we used the SPSS v. 10 program. In order to compare the qualitative variables, we used the association Crosstabs table, and for the quantitative variables, testing the equality of the averages of two samples (Independent T Test). The age distribution of the two groups was homogenous, allowing comparison (Crosstabs likelihood ratio $p = 0.687$). Gender distribution of the two groups was also homogeneous, allowing comparison (Crosstabs likelihood ratio $p = 0.665$). The analysis of the prevalence of hypertension, angina pectoris and electrocardiographic changes specific for ischemic heart disease and dyslipidemia association showed that this one had a homogeneous distribution in the two groups. The analysis of drug combination to the treatment with ivabradine or metoprolol showed that the two groups had a similar therapy, which similarly influenced the evolution of the diastolic dysfunction, allowing comparison.

RESULTS

Analysis of the initial ultrasound parameters

Tissue Doppler echocardiographic parameters were similar in the two groups at the time of the initial examination, allowing the comparison of their subsequent evolution. $V_{max} Ea$ had an initial average of 0.08 m/s, with a standard deviation of 0.04 m/s for the experimental group and for the control group, of 0.07 m/s, with a standard deviation of 0.04%. The groups are not significantly different ($p = 0.423$).

The initial percentage of patients with absolute $V_{max} Ea$ below 0.08 m/s in the experimental group was of 88%

(44 patients), detecting the impaired relaxation with greater sensitivity than the E wave of the transmitral flow. In the control group, the percentage of the patients with $V_{max} Ea$ below 0.08 m/s was of 95% (38 patients).

The $V_{max} Ea/V_{max} Aa$ ratio was initially subunitary in the experimental group in 29 patients (58%), diagnosing with greater sensitivity the diastolic dysfunction than the $V_{max} E/V_{max} A$ ratio analysis of the transmitral flow. In the control group, $V_{max} Ea/V_{max} Aa$ was subunitary in 28 patients (70%), significantly increasing the percentage of those with diastolic dysfunction diagnosed by this method.

The $V_{max} E/V_{max} Ea$ ratio had an initial average value of 10.24 with a standard deviation of 1.72 for the experimental group and for the control group, this ratio has an average initial value of 11.42 with a standard deviation of 0.04. There were no statistically significant differences between the groups ($p = 0.699$).

Analysis of ultrasound parameters registered 3 months later

$V_{max} Ea$ had a final average value of 0.94 m/s, with a standard deviation of 0.05 m/s for the experimental group and of 0.08 m/s, with a standard deviation of 0.05 m/s for the control group, the groups being similar in terms of averages, after the treatment with ivabradine, respectively with metoprolol ($p=0.470$). $V_{max} Ea/V_{max} Aa$ had a subunitary value in 29 patients (58%) in the experimental group and 28 patients (70%) in the control group, as in the initial moment, without being influenced by the treatment with ivabradine or by continuing the treatment with metoprolol. $V_{max} E/V_{max} Ea$ final average was 10.44 with a final standard deviation of 1.72 for the experimental group and 12.87 with a standard deviation of 1.13 for the control group. There were no significant differences between the groups in terms of final averages ($p = 0.473$) and no significant variation in time.

CONCLUSIONS

The analysis of main Tissue Doppler parameters allows the conclusion that ivabradine has equivalent effects to metoprolol on the left ventricular diastolic function in diabetics.

BIBLIOGRAPHY

1. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure, *Circulation*. 2002;105:1387-1393.
2. Oghlakan GO, Sipahi I, Fanq JC. Treatment of heart failure with preserved ejection fraction, *Mayo Clinic Proceedings*. 86;531-539.
3. Redfield MM, Jacobsen SJ, et al. Burden of systolic and diastolic dysfunction, *JAMA*. 2003;289:194-202.
4. Fruhwald F, Pieske B. Left ventricular remodelling in systolic heart failure using ivabradine, *European Journal of Heart Failure*. 2011;32:2481-2482.
5. Tardif JC, Meara E, et al. Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: results from the SHIFT echocardiographic substudy. *European Heart Journal*. 2011;32:2507-2515.
6. Heidenreich PA, Sahay A, et al. Divergent trends in survival and readmission following a hospitalization for heart failure, *Journal of American Coll Cardiol*. 2010;56:362-368.
7. Eckman I, Chassany O, et al. Heart rate reduction with ivabradine and health related quality of life in patients with chronic heart failure, *European Heart Journal*. 2011;32:2395-2404.