DOPPLER STANDARD ULTRASOUND ASSESSMENT OF IVABRADINE EFFECT COMPARED TO METOPROLOL ON THE DIASTOLIC FUNCTION OF THE LEFT VENTRICLE

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Keywords: *ivabradine, metoprolol, diastolic function, Doppler*

Abstract: *Purpose: The study evaluated the opportunity of replacing the therapy with metoprolol in the diabetic patients with left ventricular dysfunction with ivabradine, a specific inhibitor of the If current in the sinoatrial node, indicated in reducing the sinus rhythm, ischemic heart and left ventricular dysfunction. Methods: A therapeutic controlled study was performed on a sample of 90 diabetic patients with metoprolol therapy. The experimental group, n=50 subjects, replaced metoprolol with equivalent doses of ivabradine. The reference group, n=40 subjects, continued the therapy with metoprolol. Evaluation: Doppler ultrasound parameters were assessed at the beginning of the study and after 3 months of follow-up. Conclusions: Ivabradine proved to be at least similar to the effect of metoprolol on Doppler parameters of the diastolic function and may represent a therapeutic alternative in the patients with side effects or contraindication to metoprolol.*

Cuvinte cheie: *ivabradină, metoprolol, funcție diastolică, ecografie Doppler*

Rezumat: *Scopul: Studiul a evaluat oportunitatea înlocuirii tratamentului cu metoprolol, la pacienți diabetici cu disfuncție diastolică a ventriculului stâng, cu ivabradină, un inhibitor specific al curentului If la nivelul nodului sinoatrial, al cărui efect este exclusiv rărirea ritmului sinusal, cu indicație în cardiopatia ischemică și în disfuncția sistolică a venticulului stâng, neevaluat până în prezent pentru disfuncția diastolică. Metodologie: S-a efectuat un studiu teraputic controlat pe un eșantion de 90 pacienți diabetici aflați inițial sub terapie cu metoprolol. La lotul experimental, n= 50 pacienți, s-a înlocuit metoprololul cu ivabradină. Lotul mator, n=30 pacienți, a continuat tratamentul cu metoprolol. Evaluare: Au fost evaluați parametrii ecografici Doppler standard în momentul inițial și după 3 luni de tratament. Concluzii: Ivabradina s-a dovedit a fi cel puțin similară cu metoprololul ca efect asupra parametrilor ecografici Doppler ai funcției diastolice, putând reprezenta o alternativă terapeutică la pacienții cu reacții adverse sau contraindicații la metoprolol.*

INTRODUCTION

Starting from the epidemic proportions of diabetes mellitus and the fact that 30-50% of diabetics have diastolic dysfunction with preserved LV ejection fraction, potentially lethal pathology, initially asymptomatic, there is the need to combat its impact by primary and secondary actions. There is no specific treatment for the diastolic dysfunction, the pathophysiological mechanisms involved not being fully elucidated. None of the drugs recommended by the European and American guidelines for heart failure with preserved ejection fraction has clearly proven its effectiveness in large studies, regarding the improvement of the quality of life or the survival of these patients. The Doppler technique has the ability to assess heart rate adaptation to the hemodynamic conditions and the physiological development of the proto-, meso-and telediastole. By analyzing the standard Doppler ultrasound parameters we can determine the diastolic function in relation to heart rate and the possible therapeutic benefits of sinus rhythm thinning therapy.

WORKING HYPOTHESIS

Ivabradine is a specific inhibitor of the If current in the sinoatrial node, exclusively determining the reduction of the sinus rhythm frequency, with an indication in the treatment of stable angina in the patients with sinus rhythm, with intolerance or contraindication to beta-blockers and in the treatment of chronic heart failure with systolic dysfunction, class II-IV NYHA, with systolic dysfunction in the patients with sinus rhythm, with heart rate above 75/min, in association to the standard therapy. Overall efficiency for lowering the sinus frequency is similar for ivabradine (15mg/day) and metoprolol (50mg/day), as was shown previously. Probably, there is an important subgroup of patients who either have side effects to metoprolol, or this one hides the symptoms of hypoglycemia and who would benefit from replacing metoprolol by ivabradine, especially if it is proven that this one has benefic effects at least similar to metoprolol on LV diastolic dysfunction with preserved ejection fraction.

PURPOSE

The study evaluated the opportunity for replacing the therapy with metoprolol in the diabetic patients with left ventricular dysfunction with ivabradine, a specific inhibitor of the If current in the sinoatrial node, indicated in reducing the sinus rhythm, ischemic heart and left ventricular dysfunction, unassessed for the diastolic dysfunction until now.

METHODS

The research was conducted based on a design of a *randomized clinical trial.*

The reference population was represented by 90 diabetic patients of the Outpatient Diabetes and Nutrition Clinic within the County Clinical Emergency Hospital of Sibiu,

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undergoing therapy with metoprolol. 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, with a resting heart rate between 60 and 70-minutes, with no clinical signs of right heart failure. The patients were not examined from the cardiology point of view in the past. The patients were divided into 2 groups randomly. *The experimental group* consisted of 50 subjects who replaced metoprolol by ivabradine, in equivalent doses. *The control group* consisted of 40 subjects who continued the therapy with metoprolol as standard therapy. The two groups had a homogeneous structure in terms of average age ($p = 0.687$), sex ratio ($p = 0.665$), initial Doppler ultrasound examination and regarding the morbid associations ($p = 0.817$). The analysis of drug combinations showed that the two groups had a similar therapy, which influenced the development of the diastolic dysfunction in similar proportions, allowing making comparisons.

The inclusion criteria were: the 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 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.

The followed parameters were: clinical aspect, electrocardiographic and standard Doppler ultrasound aspect and Tissue Doppler, especially the parameters of the LV diastolic function.

Frequency of measurements. The patients were examined when entering the study and three months later. Upon entering the study, the patients were examined clinically, with NYHA class assessment, identifying the current medication, heart rate, laboratory checking made in ambulatory last month, sent by the diabetologist (blood glucose, serum urea, serum creatinine, cholesterol, triglyceride, blood count, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase), blood pressure, 12-lead electrocardiogram and ultrasound examination, M, 2D, Doppler standard. The acquisition protocol was identical for all patients. We used an Acuson Sequoia C256 ultrasound Doppler, with 3V2c phased array transducer. The same examination, except for the biochemical tests, was repeated after 3 months of treatment. Upon the initial examination, all patients registered left ventricular ejection fraction of 50% and were within the normal LV relaxation type, or in the impaired relaxation type, none registering other types of severe diastolic dysfunction prognosis. The improvement of the left ventricular diastolic function was assessed by increasing the Vmax E/Vmax A ratio, the increase of the VmaxE/VmaxEa ratio, nearing the normal values of IVRT, MDT and Adur extension. The patients were examined weekly by family doctors and communicated by phone the heart rates below 50 or above 65 beats/minute, adverse symptoms related to bradycardia, extreme values of blood pressure (over 180/110 mmHg, systolic blood pressure less than 85mmHg) angina pectoris, dyspnea, palpitations, visual disorders.

Administered treatment. The subjects *in the experimental group* were treated with ivabradine, administered in an equivalent dose in order to obtain a similar reduction in heart rate, respectively 25mg/day metoprolol replaced by 10mg/day ivabradine, divided into two doses, 50mg/day metorolol, replaced by 15 mg/day ivabradine in two doses. All patients have been asked for their written consent in order to participate in the study. Reporting an inappropriate heart rate led to the adjustment of ivabradine dose, from 2x5mg/day to 2x7, 2x2 5, respectively to2x2, 5mg/day to achieve the target heart rate. If the dose adjustments did not allow this, the patient would be excluded. Reporting a significant degree of the symptoms mentioned in the study also determined the exclusion from the study. The subjects in the *control group* continued the treatment with metoprolol in a dose to ensure a heart rate between 50 and 65/minute respectively 25mg/day metoprolol, divided into two doses, 50mg/day metorolol in two doses.

The *statistical analysis* of the data was performed by using the statistical package SPSS v. 10. For the comparison of the qualitative variables, the Crosstabs association table was used, as well as the Independent T test for the quantitative variables.

RESULTS AND DISCUSSIONS

A. Analysis of the initial ultrasound parameters

In the experimental group, upon the initial examination, the maximum velocity of the early diastolic wave of the transmitral flow (VmaxE) had an average of 0.82 m/s, with a standard deviation of 0.7 m/s. This parameter was normal, exceeding 1 m/s only in 9 patients (18%), the remaining 41 patients (82%) showing subnormal values. The control group had a mean VmaxE of 0.80 m/s, with a standard deviation of 0.18 and exceeded 1 m/s in 4 patients (10%), the remaining patients having subnormal values. The two groups registered statistically significant differences ($p = 0.581$), regarding this parameter of diastolic function, at baseline.

On the initial examination, in the experimental group, the relation between the VmaxE and maximum velocity of the late diastolic wave of the transmitral flow A (VmaxE/VmaxA) was subunitary in 25 patients (50%), and supraunitary or unitary in 25 patients (50%), while in the control group, it was subunitary in 24 patients (60%) and supraunitary in 16 patients (40%). The two groups recorded proportions that did not differ significantly from the statistics point of view ($p = 0.343$) from the patients with this pathologic relation, with impaired relaxation significance (when VmaxE is less than 1m/s), respectively normal, expected result, considering the homogeneous distribution of the other qualitative and quantitative variables analyzed so far. In the experimental group, on the initial moment, the velocity of the E wave on the onset of A wave (VElaA) had an average value of 0.31 m/s, with a standard deviation of 0.11 m/s, and in the control group of 0.30 m/s with a standard deviation of 0.11 m/s, with no statistically significant differences between the two groups ($p = 0.703$). In the experimental group, VElaA values were below 0.20 m/s, so normal only in 7 patients (14%), while in the remaining 43 patients (86%) were high, indicating a delayed ventricular relaxation and the transition from the predominantly protodiastolic ventricular filling to the telediastolic one, while in the control group, they were normal in 8 patients (18%) and increased in 32 patients (80%).

Izovolumetric relaxation time (IVRT) recorded initially in the experimental group a mean value of 143.74 ms, with a standard deviation of 35.63 ms, and in the control group, a mean value of 144.55 ms, with a standard deviation of 35, 19ms; the groups did not differ significantly from the statistics point of view (p = 0.914). In the experimental group, IVRT was between 60 and 100ms, so normal only in 6 patients (12%) and over 100 ms, meaning delayed relaxation in 44 patients (88%). In the control group, 3 patients (7.5%) had normal IVRT and the remaining 37 patients (92.5%) had prolonged IVRT, so delayed ventricular relaxation. In the experimental group, mitral deceleration time (MDT) had an initial average value of 251.58 ms, with a standard deviation de100, 69ms, and in the control group, it had a mean value of 253.60 ms, with a standard deviation of 100.78 ms, the groups being similar (p = 0.925). In the control group, MDT had a normal value (between 140 and 200ms) in 16 patients (32%) and it was extended over 200ms, signifying impaired relaxation in 12 patients (30%) and prolonged in 28 patients (70%). A wave duration (Adur) in the experimental group had an average initial value of 143, 68ms, with a standard deviation of 47.22 ms, and in the control group, a mean initial value of 141.03 with a standard deviation of 47.02 ms, with no significant differences between the two groups. Adur in the experimental group recorded pathological values below 120ms in 19 patients (38%) and normal values in the remaining 31 patients (62%). In the control group, Adur was shortened initially in 14 patients (35%) and normal in the remaining 26 patients (65%). This parameter showed diastolic dysfunction in the two groups less frequently than other parameters. No partial fusions were observed of the E and A waves, or cardiac arrhythmia, atrioventricular block grade II or III, or short PR, making difficult to interpret Adur.

B. Analysis of ultrasound parameters 3 months later

VmaxE had a final average value of 0.94 m/s, with a standard deviation of 0.21 m/s for the experimental group and of 1.03 m/s, with a standard deviation of 1.46 m/s for the control group. There is no significant difference between the two groups after the treatment with ivabradine, respectively with metoprolol (p = 0.672 not taken into account). *VmaxA* had the final average value in the experimental group of 0.84 m/s, with a standard deviation of 0.19 m/s and in the control group, it was of 1.08 m/s, with a standard deviation of 1.28 m/s, with no significant differences between the two groups after the treatment with ivabradine, respectively with metoprolol. VmaxE/VmaxA final value was supraunitary in 25 patients (50%) of the experimental group and in 24 patients (60%) in the control group, the same situation as on the initial moment and without statistically significant differences between the groups (p = 0.343). VElA had a final average value of 0.29 m/s, with a standard deviation of 0.14 m/s in the experimental group and of 0.29 m/s, with a standard deviation of 0.09 m/s in the control group. There were no significant differences between the groups (p = 0.934) after the treatment with ivabradine, respectively with metoprolol. IVRT had a final average value of 142.12 ms, with a standard deviation of 41.29 ms in the experimental group and of 149.32 ms, with a standard deviation of 37.03 ms in the control group. The two groups did not differ significantly in terms of mean values (p = 0.597) after the treatment with ivabradine or metoprolol respectively; their average values were not improved over time, but the group treated with ivabradine registered a rate of 20% (10 patients) in which IVRT values were between 60 and 100ms, so normal, up significantly from baseline, while the group treated with metoprolol registered a rate of 5% (2 patients) with normal values, which were down to baseline. This result could partly explain the evolution of Adur.

MDT had a final average value of 262.68 ms in the experimental group, with a standard deviation of 92.83 ms and 251.65 ms in the control group, with a standard deviation of 103.91 ms, no statistically significant in the final moment, in terms of average values. The percentage of the patients with normal levels of MDT was constant, as against the initial registration: 32% (16 patients) in the experimental group and 30% (12 patients) in the control group, noticing no difference between the patients treated with ivabradine, respectively with metoprolol. Adur had a final average value of 177.78 ms, with a standard deviation of 54.96 ms for the experimental group and of 146.53 ms, with a standard deviation of 44.94 ms for the control group, p = 0.04, so it can be concluded that ivabradine significantly statistically extended this parameter, compared to metoprolol, after 3 months of treatment; there were no baseline differences between the two groups in this regard. The percentage of the patients with normal Adur increased in the experimental group from 62% (31 patients) at baseline to 74% (37 patients) at the end, under ivabradine treatment.

CONCLUSIONS

- The only ultrasound parameter of the left ventricular diastolic function that was significantly influenced is the length of the late diastolic wave A, which was extended, showing an additional beneficial effect of ivabradine on the left ventricular diastolic function compared to metoprolol.
- Although the average IVRT in the two groups did not differ statistically significantly, namely those who had less drastic extension of IVRT were treated with ivabradine, whereas those with extreme extension of the IVRT, who probably had more severe myocardial structural changes, not benefited from it.
- Following the systematic review of the literature shows that the variation of the flow transmitral A wave duration under treatment may appreciate the improvement of the diastolic function.
- The analysis of the evolution of the main Doppler standard parameters indicates that ivabradine has effects at least similar to metoprolol on the left ventricular diastolic function in diabetics, Adur parametre being even further improved.

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