Effects of therapy with trimetazidine in ischemic heart disease

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This graduation paper was made at the Department of Cardiology, KBC Rebro, University of Zagreb School of Medicine under the supervision of Prof. dr.sc. Martina Lovrić-Benčić and it was submitted for evaluation in the academic year 2015/2016.

Abbreviations

IHD – Ischemic heart disease

PCI – Percutaneous intervention

CABG – Coronary artery bypass graft

LV- Left ventricle

MET- Metabolic equivalent of task

VES- Ventricular extrasystole

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Summary

Title: Effect of Trimetazidine in Ischemic Heart Disease

Key words: Ischemic heart disease, trimetazidine

Author: Tena Jukić

In the developed world, IHD is the leading cause of death in both sexes, accounting for 30% of all deaths. Because of that high mortality rate, it becomes a really important topic of not just public health, but also every part of human society including economics, food industry, health industry etc.

Myocardial ischemia refers to inadequate supply of oxygen and metabolic substrate to the heart. The term myocardial ischemia covers a heterogeneous group of clinical syndromes, globally called IHD, which includes chronic stable angina at one end of the spectrum and acute myocardial infarction at the other end.

Clinical approach is an important factor in diagnosing IHD. Diagnosis is suspected if chest discomfort is typical and is worsening by exertion and relieved by rest. Some specific test include ECG, stress test ECG, echocardiography, radionuclide imaging and coronary angiography. Treatment depends on the severity of the angina pain, mostly it is treated with drugs like antiplatelet drugs, beta blockers, long-acting nitrates and calcium channel blockers. In severe cases, i.e. if angina persists despite drug therapy, PCI and CABG will be indicated.

In patients who are not PCI or CABG candidates, or are not responding well on the normal drug treatment, are very good candidates for trimetazidine. Trimetazidine is a drug which acts on mitochondrial level and shifts cardiac metabolism.

Introduction

Nowdays, IHD is an inevitable world wide social and medical problem. In developed countries it is a leading cause of death, although the mortality rate is significantly decreased in past three decades. Therefore prevention of disease is a challenge not just for specialized medical doctors, also for the society.

IHD is presence of clinical symptoms that are present due to myocardial ischemia which is a consequence of changes in coronary circulation and disproportion in myocardial oxygen need and utilization. Diagnosis of IHD includes those who are atherosclerotic and non-atherosclerotic in origin.

IHD is most common cause of death in developed countries and causes more deaths and economic loses then any other known disease. According to Croatian statistics, there is a slight increase in IHD, unlike USA and other developed countries which have a decrease in IHD which is possible due to good public health actions and promotion and implementation of primary and secondary prevention. In any age group there is a higher prevalence in male gender (4:1).

Atherosclerosis of coronary arteries with or without superimposed thrombus is most common cause of IHD. The ground lesion is atherosclerotic plaque which can be stabile, activated and ruptured. Therefore patients will have different clinical picture of IHD. In younger population, some other diseases can cause ischemia like congenital anomalies of coronary arteries. In eldery population, ischemia can be caused by some connective tissue diseases like systemic lupus. Other possible causes are coronary arteries emboli (especially in patients with atrial fibrillation). Spasm of healthy coronary artery

can also be one of the causes of ischemia. Most common noncoronary cause of ishemia are nonregulated arterial hypertension, aortic stenosis and hypertrophic cardiomyopathy (1).

The most common symptom of IHD is angina. Angina can be described as a chest tightness, pressure, aching, burning, squeezing or painful feeling. Sometimes it can be mistaken for heartburn. Angina is usually felt in the chest, but can spread to the left shoulder, arms, neck, back, or jaw. Other symptoms that can occur include: shortness of breath (especially in exertion), palpitations, weakness, dizziness, nausea, sweating (2).

Risk factors include: dyslipidemias; particularly high low density cholesterol (LDL-C) and low high density cholesterol (HDL-C), hypertension, diabetes mellitus, smoking (most important modifiable risk factor), family history of premature coronary artery disease, obesity, male sex and advanced age etc (3, 4).

Numerous primary and secondary prevention trials have shown that aggressive management of modifiable risk factors reduces death rates, myocardial infarction, stroke, and other cardiovascular events, including the need for revascularization. A 1-mm Hg decrease in blood pressure lowers the long-term risk of MI by 2% to 3%, whereas a 10% reduction in LDL cholesterol diminishes cardiovascular death by 10% and cardiovascular events by 25%. Similarly, smoking cessation reduces the attendant cardiovascular risk. Diabetes mellitus and metabolic syndrome elevate the risk of cardiovascular death 2- to 4-fold and reduce life expectancy by 5 to 10 years. The National Cholesterol Education Program Adult Treatment Panel III report has defined and recently refined guidelines for the primary and secondary prevention of atherosclerosis on the basis of risk scales that

account for blood lipids, modifiable and nonmodifiable nonlipid risk factors, and other emerging risk factors (5).

Lifestyle measures must remain the foundation for the primary prevention of cardiovascular disease. However, individuals whose risk of cardiovascular events exceeds 2%/y and patients with CAD or CAD equivalents often also merit drug therapy. The Heart Protection Study showed unambiguous benefit of statin administration in individuals aged 40 to 80 years with total cholesterol >135 mg/dL and at risk because of a previous myocardial infarction or other coronary or noncoronary artery occlusive disease, diabetes mellitus, or treated hypertension (6). The Physicians' Health Study showed that aspirin significantly reduced the rates of myocardial infarction in men aged 40 to 80 years (7). The Heart Outcomes Prevention Evaluation study enrolled patients 55 years of age or older with evidence of vascular disease or diabetes plus 1 other cardiovascular risk factor randomized to the angiotensin-converting enzyme inhibitor ramipril or placebo (8), and the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease studied the effects of perindopril in patients with stable CAD of a lower-risk category (9). Both studies showed that ACE inhibitor administration significantly reduced cardiovascular events. A recent trial in a lower-risk population showed no advantage of ACE inhibitor therapy over contemporary conventional management, highlighting the role for lifestyle modification in such individuals (10).

Diagnosis is suspected if chest discomfort is typical and precipitated by exertion and relieved by rest. One of the most common and first diagnostic tool that is used for diagnosing IHD is a stress test. Cardiac stress test is done by heart stimulation (treadmill, pedaling stationary bicycle or pharmacological stimulation) an the physician examines

the symptoms, blood pressure response and ECG changes. Coronary angiography is the standard for diagnosing IHD but is not always necessary to confirm diagnosis (11). Intravascular ultrasonography enables us coronary artery structure images. Definitely worth of mentioning is coronary CT. CCTA doesn't show only lumen of coronary arteries (as invasive coronary angiography) but also provides other cardiac structures as large blood vessels and coronary arteries which helps evaluate complex variants of coronary arteries, coronary bypass, myocardial bridging, coronary arterial fistulas, aortic dissection and coronary arteries dissection (12).

Current medical therapies for IHD involve anticoagulants, thrombolytic, beta blockers, calciun channel blockers, nitrates and percutaneous coronary intervention which aim to improve the blood supply of the heart (11). However, these treatments will irreversibly cause myocardial ischemia/reperfusion injury. Over the last 30 years, researches demonstrate that partial inhibition of myocardial fatty acid oxidation, with mutual activation of carbohydrate oxidation, is an effective treatment for ischemia/reperfusion injury (13).

When oxygen supply is decreased, the oxidative processes of free fatty acids and glucose are impaired, what will lead to an increased rate beta oxidation of free fatty acids associated with even greater oxygen consumption—while glucose metabolism decreases, which results in lactate accumulation and, in extreme cases, development of metabolic acidosis (14, 15).

Myocardial ischemia is responsible for angina, unstable angina, and shortness of breath secondary to ischemic left ventricular dysfunction as well as cardiac arrhythmias.

Myocardial oxygen demand

Organs that are very oxidative such as the heart have a high demand for oxygen and therefore have a relatively high oxygen consumption. Myocardial oxygen consumption (MVO_2) is required to regenerate ATP that is utilized by membrane transport mechanisms (Na^+/K^+-ATPase pump) and by myocyte contraction and relaxation (myosin ATPase) .

Cardiac State	MVO_2 (ml O_2/min per 100g)
Arrested heart	2
Resting heart rate	8
Heavy exercise	70

Table 1:Myocardial oxygen demand

Determinants of myocardial oxygen consumption ($M\dot{V}O_2$) are myocardial mass, myocardial work (heart rate, blood pressure), precontraction tension (left ventricle size) and inotropic status (16).

Oxygen delivery to the myocardium depends upon oxygen carriage by the blood and coronary blood flow. Oxygen carriage by the blood can be disrupted by a fall in hemoglobin, and a sudden worsening of symptoms of angina in a patient who has been stable for many months or years may often be explained by the development of anemia.

Indeed, in patients with severe coronary disease a pronounced and rapidly acquired anaemia may induce ischaemia to such a degree that subendocardial infarction may ensue.

Pathophysiology

As the myocardium becomes ischemic, coronary sinus blood pH falls, potassium in the cell is lost, lactate becomes more abundant, abnormal changes in ECG appear, and ventricular function (both systolic and diastolic) happens. LV diastolic pressure usually increases during angina, sometimes inducing pulmonary congestion and dyspnea. The exact mechanism by which ischemia causes discomfort is unclear but may involve nerve stimulation by hypoxic metabolites.

Atherosclerosis in the conduit, has its effect by disrupting the coronary physiology, and the introduction of a new resistance to coronary flow. This acquired resistance is in series with the physiological resistors and thus has its impact on coronary flow reserve reducing this on occasions to levels not allowing sufficient oxygen delivery to the myocardium.

Atherosclerotic epicardial plaques have a complex relation to coronary resistance. Some of these (20–30%) are dynamic, although within a reasonably small range of reactivity where exercise or constricting agents may induce a 20% reduction in the stenosis diameter. Others, however, appear to be fixed. In addition, the longer the coronary lesion the greater the resistance and, of course, two lesions in parallel add further to stenosis significance.

The assessment of the relation between the degree of epicardial coronary narrowing and the measured coronary flow reserve is complex. Within instrumented animals the classic work of Gould and Lipscomb in the 1970s suggests that a stenosis in a conduit vessel of less than 50% is unlikely to be of hemodynamic significance (17). For stenoses with luminal narrowing greater than 50% there is a complex and curvilinear relation to the reduction in maximum coronary flow. Lesion length also affects the coronary flow reserve, with longer lesions producing greater haemodynamic changes (18).

Evaluation of coronary stenosis and influence on coronary flow

Evaluation of patients by angiography have shown a very loose relation between the level of coronary narrowing and coronary flow reserve (19, 20). However, the use of positron emission tomography (PET) scanning to measure coronary flow reserve has increased ability to measure this difficult parameter accurately under basal conditions in humans (21). These studies have confirmed a complex relation, curvilinear, between coronary stenosis diameter and coronary flow reserve, but it should be noted that the individual points for patients studied show remarkable scatter around any statistically defined relation. Nonetheless the PET data would not wildly disagree with the animal data indicating that stenoses less than 50% in diameter are unlikely to be of functional haemodynamic significance.

The advent of intracoronary wires able to carry Doppler and pressure transducers has allowed cardiologists to "interrogate" epicardial coronary stenoses that appear to be of borderline significance. Broadly, however, these devices all rely on the induction of maximal hyperemia with a microvascular vasodilating drug (usually adenosine) administered either intravenously or intracoronary. Devices either record the change in coronary blood velocity (Doppler wires) or measure the pressure gradient induced across the lesion (pressure wires, RADI). Doppler wires, because of technical considerations and the influence of side branches and the variability of signal if moved, have been largely an experimental tool. The pressure wire appears more stable and is easier to use. The important work of Pijls in this area has suggested that a ratio of mean distal coronary blood pressure to mean proximal coronary blood pressure following maximum

hyperaemia of less than 0.75–0.8 indicates a stenosis that is of functional significance (19).

Trimetazidine

Percutaneous or surgical revascularization are these days the best options to enhance myocardial blood flow. However in some patients none of these two options are accetable and the medicament therapy which is usually consisting of beta blockers, calcium channel blockers and/or nitrates is not enough. Some drug had to be introduced at the level of metabolic pathways in ischemic myocardial cells, especially in those patients for whom optimal control of symptoms cannot be achieved with other antianginal drugs.

Trimetazidine is a drug used for angina pectoris and it seems to provide anti-ischemic effect by preserving energy balance and prevent changes in ion homeostasis during ischemia due to modulatory effects on intracellular calcium. It also has action that stimulates glucose oxidation and acts as a partial fatty acid oxidation inhibitor through a reduction of the mitochondrial activity of 3-ketoacyl coenzyme A thiolase (enzyme that catalyzes the terminal step of fatty acid β-oxidation). In this manner trimetazidine can shift cardiac energy metabolism from fatty acid oxidation to glucose oxidation (22). Mitochondrial matrix is the place where fatty acid oxidation and pyruvate oxidation both occur and have common substrates and products. Suppression of myocardial fatty acid oxidation lowers the mitochondrial ratios of NADH/NAD+ and acetyl-CoA/free CoA,

which relieves inhibition on pyruvate dehydrogenase (PDH) and increases glucose and lactate oxidation (23). However, the detailed mechanism has not been clarified yet.

Cardiac metabolism

The human heart must contract all the time, thus, the requirement for energy to fuel optimal function is very important. The heart is capable of using all energy substrates, including carbohydrates, lipids, amino acids, and ketone bodies, which are necessary for ATP production in the mitochondria (24, 25). In cardiac myocytes, mitochondria are possessing one third of cardiac cells, which makes them the cell type with the highest mitochondria content (26). As it is known that fatty acids are the predominant substrate used in the adult myocardium. However, the cardiac metabolic

network is highly flexible in using other substrates when they become abundantly
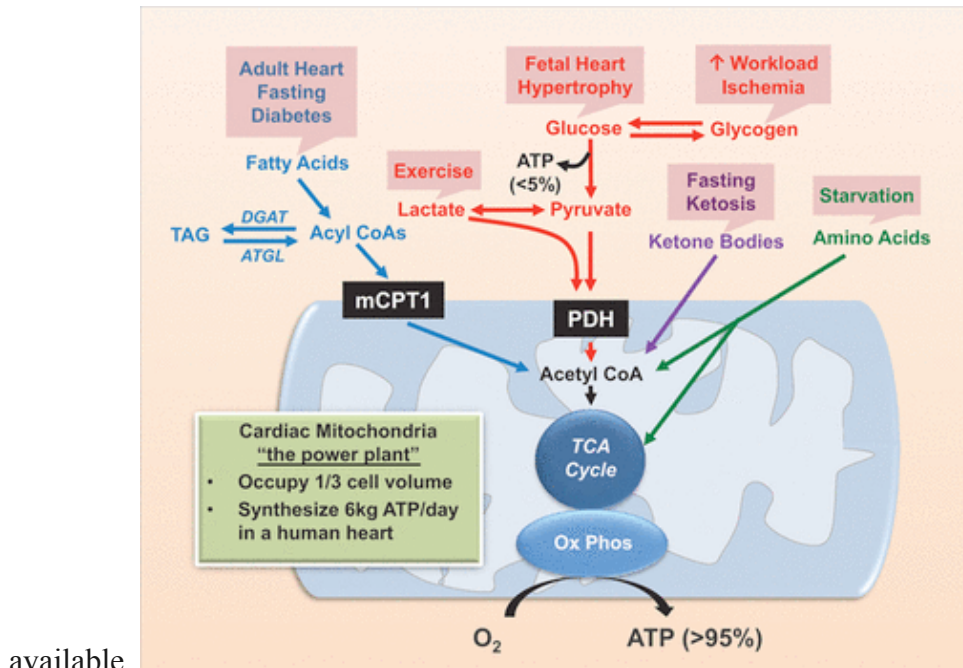
available.

Fig. 1: Overview of the metabolic network. The energy-yielding substrates (fatty acids, glucose, ketones, and amino acids), via specific catabolic pathways, converge on acetyl-CoA production with subsequent entry into the tricarboxylic acid (TCA) cycle.

For example, cardiac extraction and oxidation of lactate becomes predominant during exercise as skeletal muscle lactate production increases (27 , 28). However, cardiac metabolism changes as oxygen supply to myocardium becomes limited, which leads to decreased energy production through beta-oxidation of fatty acids and glucose oxidation, as well. As a major source of energy becomes anaerobic glycolysis. Validity of cardiac metabolism is reflected by its highest oxygen consumption rate on the per unit weight basis. For a human heart, the amount of ATP turned over during a 1-day period is 15 to 20 times of its own weight. In a normal heart, mitochondria are largely fueled by

fatty acyl-coenzyme A (CoA) and pyruvate, which are the primary metabolites of fatty acids and carbohydrates, respectively. The entry of long-chain acyl-CoA into the mitochondria is a regulated process, with the rate-limiting step at the muscle form of the carnitine-palmitoyl transferase-1 (CPT1) reaction. The oxidation of pyruvate is regulated at the pyruvate dehydrogenase (PDH) reaction. Other substrates, including lactate, ketone bodies, and amino acids, can enter mitochondria directly for oxidation. Metabolism of ketone bodies yields acetyl-CoA, whereas amino acid catabolism yields keto-acids, which are further metabolized to enter the tricarboxcylic acid cycle. The contribution of ketone bodies and amino acids to overall cardiac oxidative metabolism is considered to be minor because of the low availability of these substrates under normal physiological conditions.
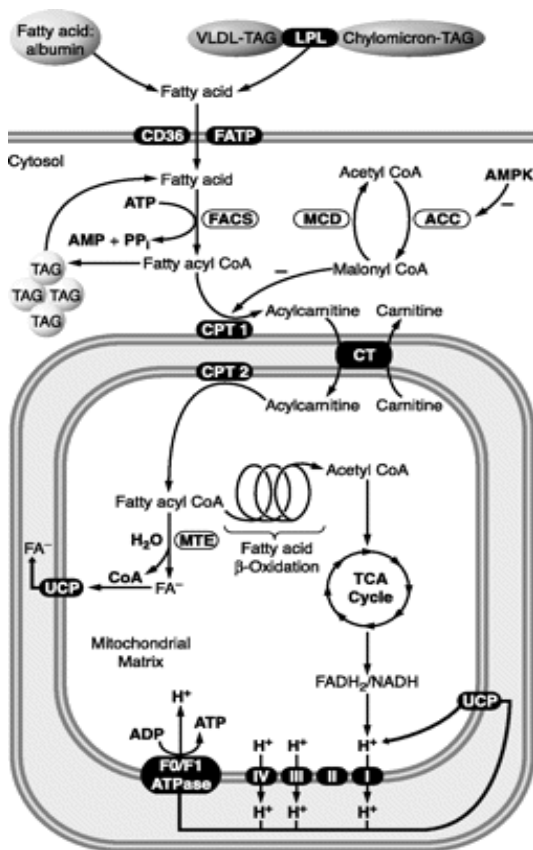

Fig. 2: Overview of fatty acid beta oxidation in the heart

Apart from substrate availability, complex regulatory mechanisms contribute to metabolic flexibility at multiple levels, including transcriptional regulation and post-translational modification of key proteins involved in each metabolic pathway as well as allosteric regulation by substrates and their metabolites. Transcriptional regulation of the proteins involved in fatty acid oxidation (FAO) by the peroxisome proliferator–activated receptor (PPAR)/estrogen-related receptor/PPARγ coactivator-1 α (PGC1α) circuit is a major mechanism in the transition of the glycolysis-dependent fetal heart to oxidative metabolism in the adult heart (29, 30).

Hypothesis

By administration of trimetazidine 35 mg twice a day we expect to have:

- decrased number of VES

- ST segment closer to the isoelectric point

- improvement in MET results

Material and methods

To examine association between effect of trimetazidine in IHD we referred them for a stress test and analyzed their results in a fashion to create categories. Categories are made by age, younger and older then 65, gender, diabetic and non-diabetic patients, and patients distributed in 3 EF groups: those who had EF <40%, 40-50%, and > 50% . Data was obtained from KBC Rebro. The data that was relevant to us was incorporated into an excel spreadsheet which was then analyzed. Microsoft excel was used to organize and evaluate parts of the data, such as grouping into male and female and further into age groups with appropriate EF values, metabolic equivalents from stress test before and after therapy and number of VES also captured by 24 hour Holter monitoring. We had 82 patients (53 men and 29 women, mean age 61.6 years, SD 9.11) with ischemic heart disease and left ventricular dysfunction who were followed at KBC Rebro outpatient department. Trimetazidine was given to a patients 35mg, twice a day.

Trimetazidine has been in clinical use for more than two decades. It is a very useful and potential drug for treatment of several conditions like systolic dysfunction in cardiac failure patients. In vivo and in vitro studies have shown that in ischemia, trimetazidine has a specific effect: reduces intracellular acidosis, inhibits accumulation, maintains intracellular ATP levels, decreases kreatinine kinase release an preserves myocardial function (14). Several studies reveal that patients who were taking trimetazidine experienced less angina episodes and had longer interval period onset in

stress test compared to patients treated with other anti-anginal drugs or they were consuming placebo (31).
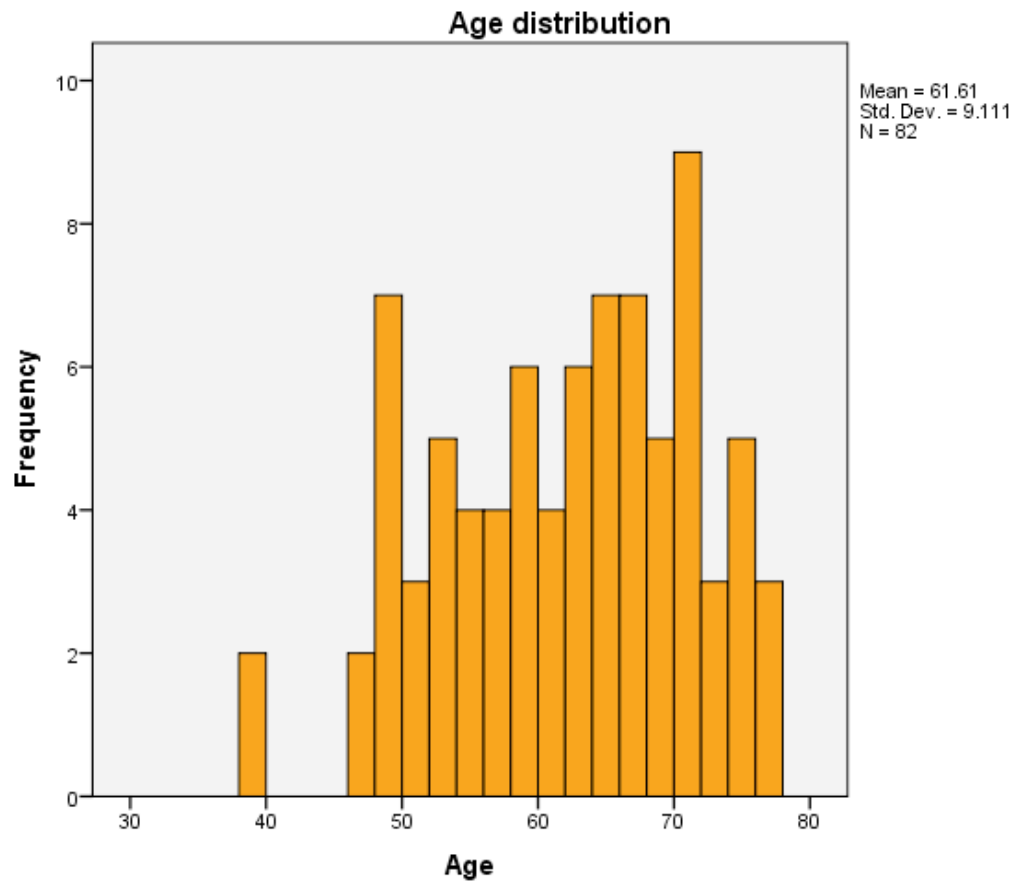

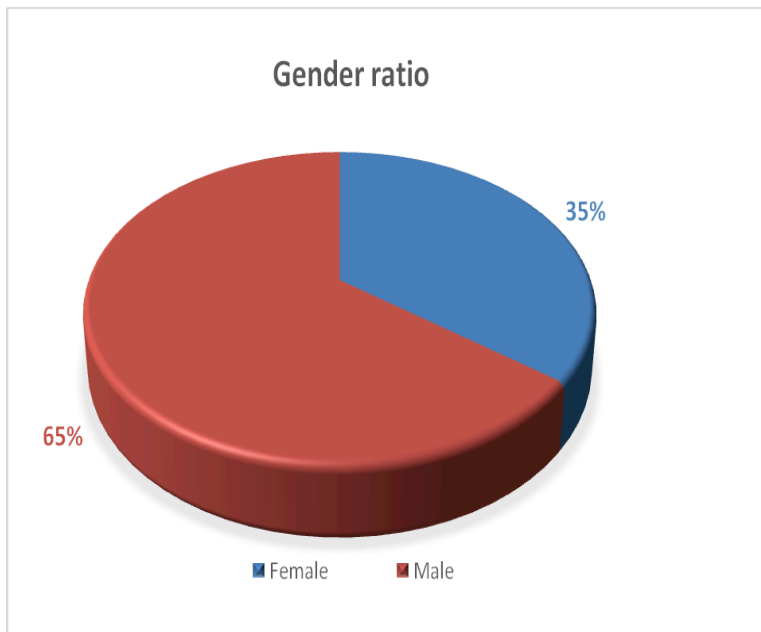*Fig.3:Age distribution*

Chart 1: Gender ratio

Gender ratio

35%

65%

■ Female   ■ Male

Chart 2: Age groups

Age groups

43%
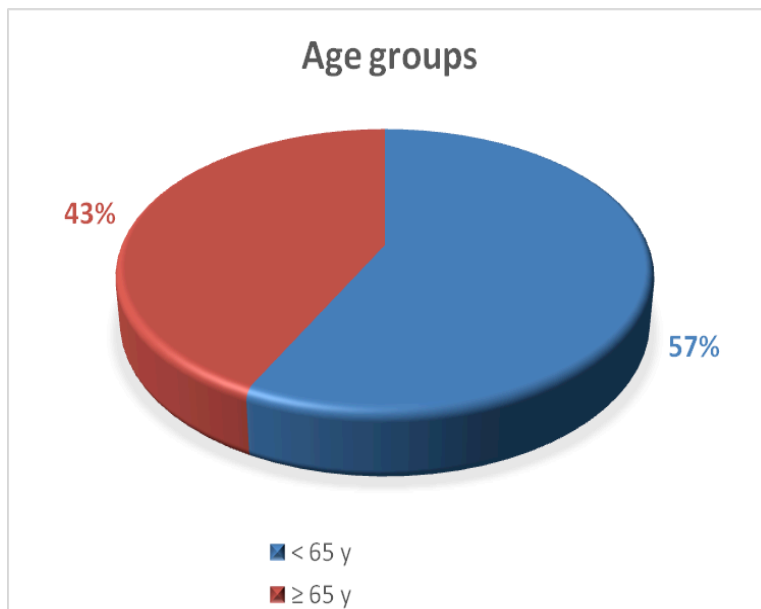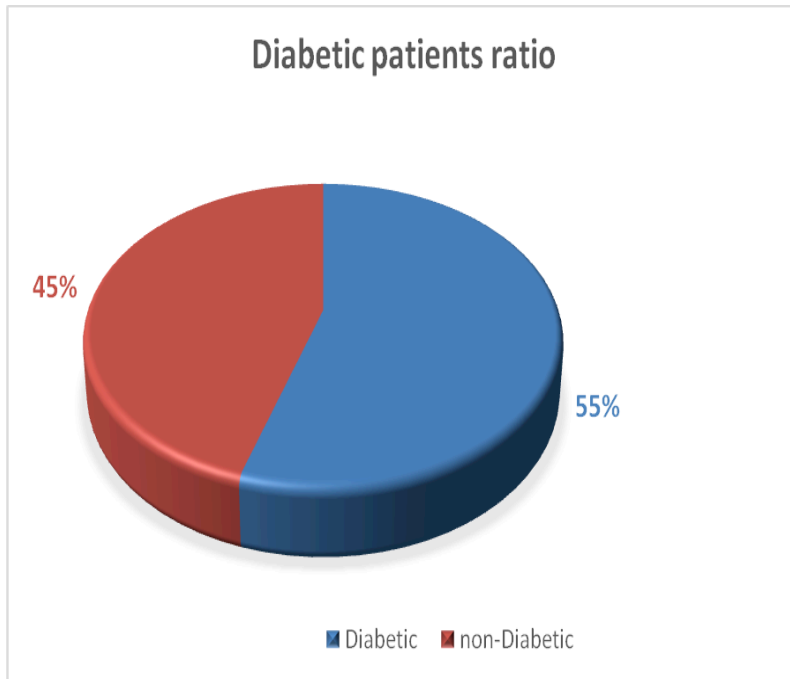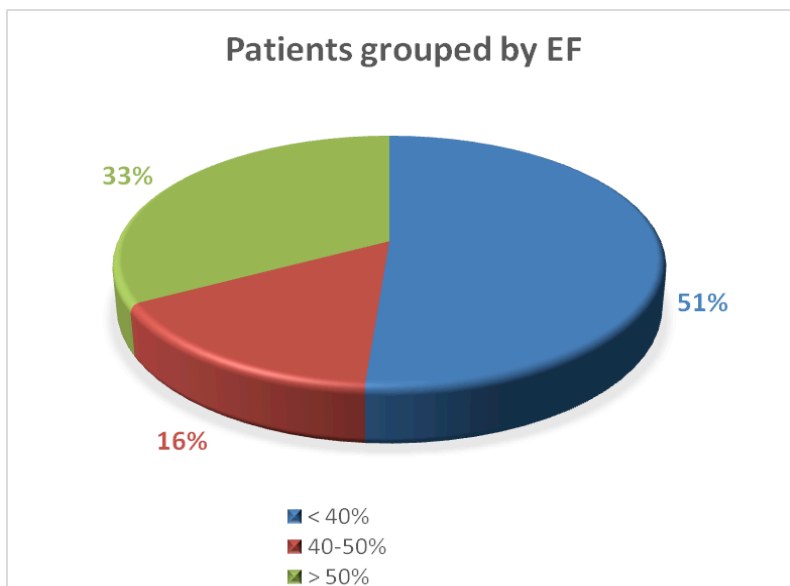
57%

■ < 65 y
■ ≥ 65 y

Chart 3: Diabetics

Chart 4: EF values

Results

All of them received trimetazidine dihydrocloridum 35 mg twice daily. After 6-12 months of follow-up, they repeated exercise testing, and had 24 hour Holter monitoring. The results were compared according to diabetes, sex, age and ejection fraction. Statistics: Wilcoxson rank test.

Analyzing MET values for total sample, results showed significat improvement on stress test after therapy with trimetazidine.

Comparison of MET values for total sample, before and after trimetazidine:

Ranks

		N	Mean Rank	Sum of Ranks
Erga after (MET) - Erga before (MET)	Negative Ranks	0[a]	.00	.00
	Positive Ranks	82[b]	41.50	3403.00
	Ties	0[c]		
	Total	82		

a. Erga after(MET) < Erga before (MET)

b. Erga after (MET) > Erga before (MET)

19

c. Erga after (MET) = Erga before (MET)

Test Statistics[a]

	Erga after (MET) - Erga before (MET)
Z	-7.878[b]
Asymp. Sig. (2-tailed)	.000

a. Wilcoxon Signed Ranks Test

b. Based on negative ranks.

Deviations of ST values for total sample, before and after trimetazidine:

Ranks

		N	Mean Rank	Sum of Ranks
Erga ST after - Erga ST before	Negative Ranks	24[a]	13.71	329.00
	Positive Ranks	2[b]	11.00	22.00
	Ties	56[c]		
	Total	82		

a. Erga ST after < Erga ST before

b. Erga ST after > Erga ST before

c. Erga ST after = Erga ST before

Test Statistics^a

	Erga nakon (MET) - Erga prije (MET)
Z	-7.878^b
Asymp. Sig. (2-tailed)	.000

VES number comparison before and after trimetazidine:

Ranks

		N	Mean Rank	Sum of Ranks
VES Holter after - VES Holter before	Negative Ranks	66^a	46.89	3094.50
	Positive Ranks	16^b	19.28	308.50
	Ties	0^c		
	Total	82		

a. VES Holter after < VES Holter before

b. VES Holter after > VES Holter before

c. VES Holter after = VES Holter before

Test Statistics[a]

	VES Holter after - VES Holter before
Z	-6.440[b]
Asymp. Sig. (2-tailed)	.000

a. Wilcoxon Signed Ranks Test

b. Based on positive ranks.

Disscusion

Patients who are diagnosed with IHD and cannot undergo procedure such as catheterization, or are not well controlled in terms of angina pain by using standard medication for angina (beta blockers, calcium channel blockers, nitrates) are very good candidates for taking trimetazidine. Trimetazidine has been in clinical use for more than 20 years and since then has been a lot of researches on that topic that are proving the effectiveness of trimetazidine in IHD. One also says that trimetazidine can reduce myocardial infarction size through AMPK and ERK signaling pathways (32). Trimetazidine exerts its protective effect via both AMPK signaling pathway as well via regulating ERK pathway. The role of AMPK is regulation of lipids oxidation in myocardial cells by inactivating acetyl-CoA carboxylase (ACC) and reducing malonyl-CoA levels, which as a consequence, increase CPT-I activity and mitochondrial lipid oxidation (33, 34).

Clinical studies comparing trimetazidine with placebo or reference anti-ischemic drugs as well as in combination with other anti-ischemic agents have been performed (35). Studies comparing trimetazidine and placebo: The acute effects of a single oral dose of 60 mg trimetazidine were evaluated in a double-blind, placebo-controlled, crossover study by Sellier et al.(36). Two hours after oral intake, the mean total work performed by patients treated with trimetazidine was 30% greater than that performed by patients treated with placebo. Time to 1-mm ST segment depression was significantly longer in the trimetazidine-treated patients than in the placebo group. Two double-blind, placebo-controlled studies (37, 38) with a similar design have evaluated the effects of trimetazidine in patients suffering from chronic stable angina. In both studies, an exercise

test was performed at the beginning and at the end of a 2-week preselection period to verify the stability of ischemic parameters. Subsequently, the patients were randomized to receive either trimetazidine 20 mg 3 times daily or placebo 3 times daily for 1 month and at the end of the study period a final exercise test was conducted. Passeron11 documented an increase in total workload of 62% in patients treated with trimetazidine and 25% in patients receiving placebo. There was a significant reduction in the number of angina attacks per week in trimetazidine and placebo group.

The greatest progress in the use of metabolic therapy came in the last 15 years with the advent of compounds that partially inhibit myocardial fatty acid oxidation, specifically trimetazidine (1-[2,3,4-trimethoxibenzyl]- piperazine) and ranolazine, for the treatment of chronic stable angina pectoris (39).

Improvement of ischemic regional myocardial dysfunction at rest and during stress-induced ischemia in patients with chronic coronary artery disease, was also proven by one study that demonstrated administration of trimetazidine without affecting the hemodynamic determinants of myocardial oxygen consumption in patients with coronary artery disease (40).

From the other hand there was a study which was using objective (stress test parameters) and subjective (questionnaire) values to evaluate the effect of trimetazidine, comparing results of both. In this research mean workload before starting therapy with trimetazidine was 6.5 METs and after was 6.8 METs. The difference of 0.3 MET is statistically significant (p<0.03).

From the KBC Rebro experience, starting the therapy with trimetazidine 35mg twice a day to the patients with ischemic heart disease provided a great results:

improvements in functional capacity, better results in exercise testing (significant increase in METs, as it is shown in our results all of 82 patients had better METs after administration of trimetazidine) , less ventricular premature beats regardless of age, sex or diabetes (in 66 patients out of 82). The effect of trimetazidine on glucose oxidation optimizes cellular energy processes, thereby maintaining proper energy metabolism during ischemia. By preserving energy metabolism in cells exposed to hypoxia or ischemia, trimetazidine prevents a decrease in intracellular ATP levels, thereby ensuring the proper functioning of ionic pumps and transmembrane sodium-potassium flow whilst maintaining cellular homeostasis, which is indirectly confirmed with our results.

Conclusion

In conclusion I can say that our results shows that we proved our hypothesis. Trimetazidine indeed provided anti-ischemic effect by preserving energy balance and prevent changes in ion homeostasis. It also has action that stimulates glucose oxidation and acts as a partial fatty acid oxidation inhibitor. Our results showed that trimetazidine has significant effect in our variables:

- Less anginal problems after administration of trimetazidine

- ST segment was closer to the isoelectric line

- Decrease in ventricular extrasystole activity

Trimetazidine is a very valuable drug in a treatment of IHD, especially when standard treatments as PCI and CABG aren't sufficient, therefore it's action plays a significant role in treatment of IHD.

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Biography

Tena Jukić was born on the 26th of March 1991 in Zagreb. After she finished high school in Zagreb (7. gymnasium) she enrolled at the University of Zagreb in 2009. During academic years 2014/2015 and 2015/2016 she was honored to work as a student demonstrator, for the subject Hystory taking and physical examination on the cardiology department in KBC Rebro, mentored by Asst. Prof. Joško Bulum.

Since 2012. She is an active member of a medical student choir "Lege Artis".

She fluently and actively uses English (writing, understanding and speaking) and German language.

In spring 2016 she did a one month internship at the cardiology department in Jamaica Hospital, New York, mentored by dr. Zoran Lasić.