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THE VALUES OF CARDIAC TROPONIN IN ACUTE CORONARY SYNDROME

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Abstract

Acute Coronary Syndrome (ACS) is the factor with the highest rate of morbidity and mortality. ACS compromises Myocardial Infarction (MI), and Unstable Angina or sharp, sudden chest pain which typically appears when the person is resting.Approximately 1.4 million people suffer from ACS in Europe, each year. Symptoms of ACS include: chest pain or discomfort (the pain may radiate to the shoulder, arms, neck, lower jaw, or back; the chest pain may be described as substernal, un-clear, pressuring, burning, and sometimes sharp pain. The pain which lasts approximately 30 minutes is in accordance of diagnosing Acute Myocardial Infarction (IAM)). Except the known etiologic factors for Cardio-Vascular Diseases (CVD) such as: (genetical predisposition, age, gender, hypertension, smoking, diabetes, adiposity, sedentary life style, physical inactivity, psychological stress, oxidative stress, dyslipidaemia, hyperfibrinogenaemia), as a new risk factor is included Troponin also, during the last years, which in patients with ACS appears in very higher-than-normal concentrations, and servers as a new biomarker in patients suffering from CVD. Atherosclerosis is the most often causative factor which contributes to ACS, in more than 90 % of the cases of IAM.
Purpose of this research: to determine the level of cardiac troponins (cTn) during the acute phase of the myocardium injury, which is utilized as a new biomarker for myocardium injury – ACS. The high levels of troponin have a very important role for detection and early diagnosis of CVDs.
Materials and methods: patients' venous blood was used as a working material and as a control group. The environments' conditions in which blood was drawn were: room temperature of 19 – 24 °C, at 8 o'clock in the morning, and the patients were in a lying position. The cardiac troponin I (cTn-I) was determined in 60 patients (35 male patients, and 25 female patients), with a mean age of 51.0 ±12 years. The troponins' values were determined within 20-30 minutes after appearance of symptoms and hospitalization. We divided the patients based on the primary disease: ACS (AMI) = 25 patients, post-AMI state = 15 patients, stable angina = 10 patients, unstable angina = 10 patients. Out of the total patients' number (60 patients, mixed gender), 40 patients were smokers, and 28 patients were diabetic (18 were insulin-supplement depended, whereas 10 patients were under oral therapy). In this study we had the control group consisting of 50 (30 male and 20 female) healthy individuals who also were voluntary blood donors, with a mean age of 50.6 ±10.8 years old, Table 1.
Statistical analysis: the software package SPSS (Statistical Package for the Social Sciences, ver. 17) was used. The normal distribution of the obtained results was tested by utilising the method of Skewness and Kurtosis. The obtained results from the parameters tested in this research will be described with the basic statistical methods (average value, standard deviation, etc.).
Conclusion: in all of the examined ACS (AMI, stable and unstable angina) patients, high concentration of cardiac troponin (cTn-I) was found and the obtained results correspond to the published and evidenced results in a large number of studies for the role of the new cardiac biomarker (cTn-I) and its effect in the appearance of CVDs.

Keywords: Acute Coronary Syndrome (ACS), Cardiac Troponin (cTn-I).

INTRODUCTION

ACS is a life-threatening disease CVD, which develops when the myocardium's oxygenated blood supply does not meet its blood supply demands. ACS compromises MI, and Unstable Angina or sharp, sudden chest pain which typically appears when the person is resting. Approximately 1.4 million people suffer from ACS in Europe, each year. Symptoms of ACS include: chest pain or discomfort (the pain may spread to the shoulder, arms, neck, lower jaw,

or back; the chest pain may be described as substernal, un-clear, pressuring, burning, and sometimes sharp pain. The pain which lasts approximately 30 minutes is in accordance of diagnosing AMI). Radiation towards the left arm and neck appear during myocardial ischaemia. The pain subsides after the cessation of the physical activity which has initiated the pain, or by administering nitro-glycerine. Chest pain may be associated with nausea, vomiting, tiredness, and palpitations. The atypical chest pain may appear in diabetic patients, and in older people, and may be described as epigastric pain, which is associated with dyspnoea, cold sweats, nausea, and/or a feeling of emptiness of the head. Coronary Arterial Diseases (CAD) are the most common etiological factor of disability, morbidity and mortality, with the highest prevalence in the modern society. Except the known etiologic factors for CVD such as:genetical predisposition, age, gender, hypertension, smoking, diabetes, adiposity, sedentary life style, physical in-activity, psychological stress, oxidative stress, dyslipidaemia, hyperfibrinogenaemia, as a new risk factor is included cTn also, during the last years, which in patients with ACS appears in very higher-than-normal concentrations, and servers as a new biomarker in patients suffering from CVD. Atherosclerosis is the most often causative factor which contributes to ACS. In more than 90 % of the cases, the AMI results from an acute thrombus which forms on the atherosclerotic plaque located in the coronary arteries. Atherosclerotic plaque rupture is the first step in the coronary thrombosis. Its rupture is followed by the initiation of the coagulation cascade, and appearance of endothelial vasoconstrictive factors. All of the abovementioned factors, contribute to, and lead to the occlusion of the coronary artery. Cardiac enzymes, should be taken into consideration whenever AMI is suspected, and repeated analysis during the following 24 hours should be provided. Except the troponin, during ACS, other biochemical factors must be examined, also, such as: Muscular Creatine-Kinase (CK-MB) which is found mainly in the heart muscle. CK-MB increases after 3-12 hours, after the patient has complained for chest pain, and the peak values reach after 24 hours, after which they return to normal values (48-72 h later). Cardiac troponin – I (cTn-I) is one of the safest biomarkers for diagnosis and prognosis of AMI. Troponin increases 3-12 hours after the patient has complained for chest pain, reaches its peak in 24-48 hours, and returns to normal values within 5-14 days. In ACS the concentrations of CRP should be determined, because CRP is very high in the cases of ACS. ECG has a key role in diagnosis of examination of patients suffering from CVDs, ECG has the key role in diagnosis of CVDs, due to the fact that ECG may show changes typical for AMI, dysrhythmias, focus of injury, blood flow disorders, and cardiac hypertrophy. ECG should be performed routinely regardless if the patients shows signs of pain or discomfort, or not, with the purpose to see and observe the changes. This should continue for the first 2 – 3 days. ECG shows ST-segment elevation associated with a vertical increase, or a negative T wave, and associated with a clinical presentation of AMI. ST segment depression with changes in T wave, may be a clue for Q wave lacking infarction. (Maisel *et al.*, 2011, Thygesen *et al.*, 2012). Lately, a key factor in diagnosis of AMI has been echocardiography, because by utilising this method, the part of non-contractile or dysrhythmic myocardium may be visualised, and the location of the infarction zone on the myocardium can be determined (left, or right ventricle). Echocardiography, also determines the complications arising from MI such as myocardial rupture, or presence of liquid in the pericardium. Myocardial perfusion imagery serves to determine whether the ischaemia results from a residual blocking, and at the same time as a guide for parenteral therapy or angiograph insertion, i.e. coronarography.

Purpose of this research: to determine the level of troponin during the acute phase of the myocardium damage, which is utilized as a new biomarker for myocardium damage – ACS. The high levels of troponin have a very important role for detection and early diagnosis of CVDs.

MATERIALS AND METHODS

Patents' venous blood was used as a working material and as a control group. The environments' conditions in which blood was drawn were: room temperature of 19 – 24 °C, at 8 o'clock in the morning, and the patients were in a lying position. The cTn-I was determined in 60 patients (35 male patients, and 25 female patients), with a mean age of 51.0 ±12 years. The troponins' values were determined within 20-30 minutes after appearance of symptoms and hospitalization. We divided the patients based on the primary disease: ACS (AMI) = 25 patients, post-AMI state = 15 patients, stable angina = 10 patients, unstable angina = 10 patients. Out of the total patients' number (60 patients, mixed gender), 40 patients were smokers, and 28 patients were diabetic (18 were insulin-supplement depended, whereas 10 patients were under oral therapy). In this study we had the control group consisting of 50 (30 male and 20 female) healthy individuals who also were voluntary blood donors, with a mean age of 50.6 ±10,8 years old, Table 1.

Table 1. Presentation of patients, grouped by gender and age

Num. of patients = 60	**Average age ±SD**	**Control group = 50**	**Average age ±SD**
Females = 25	51.0 ±12.0 Years old	20	50.6 ±10.8 Years old
Males = 25	51.0 ±12.0 Years old	30	50.6 ±10.8 Years old

Table 2. Patients presentation, grouped by primary CVD

Number of patients	**Primary CVD**	
ACS (AMI)	25	41.7 %
AMI	15	25 %
Stable Angina	10	16.7 %
Unstable Angina	10	16.7 %
Smoker	40	66.7 %
Non-smoker	20	33.3 %
Diabetic Patients on Insulin	18	30 %
Diabetic Patients on oral therapy	10	16.7 %

Statistical analysis: the software package SPSS (Statistical Package for the Social Sciences, ver. 17) was used. The normal distribution of the obtained results was tested by utilising the method of Skewness and Kurtosis. The obtained results from the parameters tested in this research will be described with the basic statistical methods (average value, standard deviation, etc.). By utilizing the method of correlation, the degree of mutual influence of the examined parameters will be verified. The differences between the trimesters of pregnancy (first, second, and third trimesters) will be analysed by utilizing the method of Variance analysis – ANOVA.

RESULTS

Table 3. Obtained cTn-I values from the patients, grouped by primary disease

Primary disease	**Troponin-I Cardiac (cTn-I)**	**p**
ACS	4.60 ±0.05 μg/ml	0.0001
AMI	4.50 ±0.04 μg/ml	0.0001
Stable Angina	4.45±0.80 μg/ml	0.0001
Unstable Angina	4.75 ±0.80 μg/ml	0.0001

Smoker	4.80 ±0.90μg/ml	0.0001
Non-smoker	4.58 ±0.60 μg/ml	0.0001
Diabetic Patients on Insulin	4.62±0.07 μg/ml	0.0001
Diabetic Patients on oral therapy	4.70±0.09 μg/ml	0.0001
Control Group = 50	0.004 - 0.090 μg/ml	0.0001

We analysed the obtained cTn-I Concentrations grouped by primary disease. The table shows that the obtained results from the patients suffering from CVD are with a higher concentration of cTn-I in relation to the control group (cTn-I = 0.004 – 0.090 μg/ml), and appear with a statistically significant difference of <0.0001. The obtained results correspond to other published results, from researches on the role and effect of the high concentrations of cTn-I in patients with ACS. The examination of cardiac Tn-I concentration was determined based upon the enzymatic immunoassay methods, and by using Immulite® 2000.

DISCUSSION

CVDs remain one of the main and most prevalent causes of mortality in patients compared to mortality rates from other diseases. Various studies have verified CVD to be a multifactorial aetiologic disease. It has been proven that patients suffering from CVD have many associating pathologies: early atherosclerosis which leads to the development of the CVD and cardiac ischaemia, angina, ACS in a higher percentage in the vulnerable population compared to the healthy population. This pathologies manifest with a high concentration of cardiac biomarkers especially cTn. cTn is the primary biomarker for diagnosis of MI in an ACS. The levels of cTn may also increase in many other conditions such as heart failure, and the values of cTn in such cases have a very important prognostic value. High levels of cTn may be found in acute and chronic chest pain, and its presence is supposed to be due to the many pathophysiological processes underlying the pain. cTn is the main biomarker for diagnosis of an AMI (Yancy *et al.*, 2013). cTn does not have solely diagnostic value, but it also has prognostic value which may be clinically utilized to monitor the patient's state and therapy effect. The role of cTn as a new biomarker in the detection of CVD is unclear. The guidelines recommend evaluation of the cTn values in ACS patients, with the purpose of detecting an AMI, stable-, or unstable angina (Yancy *et al.,* 2013, Perna *et al.*, 2005). Pathophysiological mechanism of ACS may ensue due to atherosclerotic plaque rupture, erosion, functional changes of epicardial arteries, or as a vasoconstrictive response to coronary microcirculation. Inflammatory cells activation is an important phenomenon happening after the rupture, or erosion of atherosclerotic plaques. Activation of monocytes, neutrophils, and lymphocytes, during atherogenesis, is supposed to be the basis of the process of plaque erosion. The role of activation of eosinophils and basophils in the development of atheromatous plaque erosion is not fully established. Nicole et al. by using flow cytometry verified a higher activation rate of eosinophils and basophils in infected and ACS patients in relation to uninfected patients but suffering from stable angina. Many studies have verified high levels of Eosinophil Cationic Protein (ECP) in patients with ACS and a more severe clinical presentation. Troponins are part of a protein family found mainly in the skeletal and cardiac muscle fibres and have a role in muscle contraction. cTn testing measure the levels of cTn levels in blood, and thus help in detection of cardiac muscle injury. Three types of cTn proteins exist: cTn-C, cTn-T, and cTn-I. cTn-C initiates contraction by forcing calcium and moves the cTn-I in such a manner that both proteins pulling short muscle fibres may cooperate. cTn-T anchors the troponin complex within the structure of the muscle fibres. There is some or no change in cTn-C within the skeletal and cardiac muscles, but the other forms – cTn-I and cTn-T are different (Cummins *et al.,* 1978, Kooij *et al.,* 2011). 30 years ago,cTn-I was known as a "sure" marker of the injury and damage of cardiac muscle, thus cTn-

I during the last few decades was considered as the “Golden marker” as the most specific marker of myocardial injury for the diagnosis for MI and complemented with CPK, CK-MB, LDH, and myoglobin. Coronary reperfusion is closely associated with an even higher number of changes of cardiac biomarkers. The earliest detections of cTn are considered to be due to the release of a cytoplasmic component and the prolonged presence of cTn in serum. The American College of Cardiology has proposed that the increased values of cTn-I serve as a marker for AMI. It is evidenced that higher-than-normal values of cTn exist even during a pericarditis. Increased values of troponins persist not only during MI but also in patients suffering from a cerebrovascular stroke, subarachnoid stroke, intracerebral haemorrhage, endocrine diseases, polyomiositis, dermatomyositis, and haematological malignancies. Many studies conducted in Intensive Care Units in intubated and septicaemic patients, have had increased cTn-T and cTn-I values, which prove a close association between the dysfunction of the left ventricle and the presence of multiorgan injury, but the correlation between the time-duration of the disease, survival rate, and the injury of the vital organs with increased cTn-T and cTn-I, has not been described and is not very clear. After more than 1 year, the concentration of cTn-I may undergo a change of approximately 50 %. Having in mind the frequency of abnormal cTn-I in patients with CVD, it has been proposed by many scientists, that the level of cTn-I should serve as a specific marker of heart ischaemia. The changes, biochemical modifications and the effects of cTn-I in uremic patients are still unknown. In ACS patients, the presence of high concentration of oxidised cholesterol (LDLox), IDL, and VLDL increase and make fasterthe secretion of inflammatorycytokines: IL-1, Il-6, Il-1α, IL-1β, which even further increase the negative effect of cTn-I and the manifestations of ACS. The atheromatous plaques which may be observed in the intima of the middle carotid artery in many cases positively correspond to the increased values of cTn-I. the abovementioned lesions are verified with the help of non-invasive methods: high resolution B-Mode Ultrasonography utilized for detection and following of the atherosclerotic changes in CIM. The myocardial injury biomarkers: CPK, CK-MB, and myoglobin in patients with ACS appear in higher-than-normal values. Troponin is a protein found in the skeletal muscle fibres and is composed of actin and tropomyosin. The concentrations of the cardiac isoforms in serum may be correctly and quickly detected by using monoclonal antibodies. The concentrations of cTn-I in patients with ACS, are extremely sensitive and serve as a prognostic factor of changes and dysregulations which will affect the mode of therapy and the lowing of the mortality rate in this group of patients, thus the early examination of the cTn-I may help in diagnosis of ACS (Mallamci *et al.,* 2002). Some studies on the role of basophils and eosinophils in the pathophysiology of the ACS, were published in 2016. Also new and interesting information has appeared describing the pathophysiological mechanism of thrombosis and the role of neutrophils in the remodelling of the clinical presentation of ACS. The mechanism and pathophysiology of ACS may appear as a result of the fragmentation and erosion of the atheromatous plaque and functional changes of the epicardial arteries, or as the result of a vasoconstrictor response to the coronary microcirculation. Activation of inflammatory cells is avery important step in the formation of the fissures or erosions of the atheromatous plaques, as a consequence of the mechanisms which make the atheromatous plaque unstable. Whereas the activation of monocytes, neutrophils, and lymphocytes in the development of the fissuration of the atheromatous plaques is supposed to be basis of the plaque erosion process. The role of activation of eosinophils and basophils in the development of the atheromatous plaque erosions is not completely described. A group of experts in their studies, have found a degree of higher activation of eosinophils and basophils by using flow cytometry in infected patients and with ACS in relation to the non-infected patients but who suffer from stable angina. A large number of studies have verified high levels of ECP in patients with ACS, and a very severe clinical presentation (Taniwaki *et al.*, 2016, Horckmans *et al.,* 2017, Shah *et al.*, 2015, Conskunpinar

et al., 2016, Al-Obaidi *et al.,* 2000). Patients with high levels of cTn-I are a potential candidate for development of myocardial ischemia, ACS, AMI, cardiac failure, left ventricular hypertrophy, etc.The high concentrations of cTn-I and cTn-T positively correlate to the very high degree of morbidity and mortality in patients suffering from MI. From previous studies, it is known that higher concentrations of cTn and the fraction of ejection are closely correlated to the myocardial necrosis in patients with ACS (Klingenhebeten *et al.,* 2003, Yuri *et al.,* 2010). The high concentrations of troponin are: high positive correlation with to the spread of ischaemia and infarction.

CONCLUSION

The high values of cTn-I obtained from the examined patients (AMI, post-infarct state of the myocardium, stable angina, unstable angina, necrosis of myocardium and cardiac ischaemia) have shown a statistical positive significant ($p<0.0001$) in relation to the values obtained from the control group composed of healthy individuals. Lastly, we may conclude that in all of the examined ACS (AMI, Stable and unstable Angina) patients, high concentration of TnI was found and the obtained results correspond to the published and evidenced results in a large number of studies for the role of the new cTn-I and its effect in the appearance of CVDs. Thus, we suggest to primary care physicians, and also to third degree care that during check-up of the patients with a history of CVD or with symptoms of discomfort, the patient is referred to examine the biomarker cTn-I and other biomarkers such as CK-MB, CPK, LDH which help to make it easier the treatment of CVD and their prevention. However further studies are needed to be conducted to evidence the effect of troponin influence upon the cardiac injury ruling: ACS, CVD, and the diagnostic role of cTn in the diagnosis of SAK.

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