"Ovidius" University Constanta

Doctoral School of Medicine

DOCTORATE THESIS

MARKERS THE ACUTE MYOCARDIAL INFARCTION WITH ST SEGMENT

- *SUMMARY -*

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CONTENTS

FOREWORD

Cardiovascular disease is a major public health problem worldwide. While cardiovascular disease mortality recorded in the last 20 years a tendency to decrease in Western and Central European countries, in Romania there is still an upward trend.

Ischemic heart disease holds the first place among cardiovascular disease, the number of patients with this disease Romania is increasing. One of the major changes in recent years regarding the epidemiology of this disease is decreasing age at the first signs and symptoms, registering an increasing number of young patients aged <50 years.

Acute myocardial infarction is principal cause of death in patients with ischemic heart disease. The risk of death is greatest in the early hours of the onset of the disease, many of the complications happening before reaching the hospital.

One of the major challenges of recent years has been the discovery and improvement of markers that can help clinicians to diagnose acute myocardial infarction since the debut, to ease its differential diagnosis with other facets of ischemic heart disease.

This paper wants to be a clarification from the point of view of the serum markers that can be detected in the first 12 hours from the onset of acute myocardial infarction with ST segment elevation, and the correlations that exist between them.

I assure my full gratitude and thank to Professor Doctor Elvira Craiu, which was more than a mentor to me and guided my steps since the beginning of my career, with a role in my training as a cardiologist and in the teaching plan.

Finally, thanks to my family, without whose support the elaboration of this thesis would not have been possible.

GENERAL PART

1. ATHEROSCLEROSIS - INTRODUCTION

Atherosclerosis continues to be one of the main research topics. The complexity of its pathogenesis and its clinical sequelae importance provides a justification for this. Atherosclerosis is a metabolic disease, chronic disorder whose cause is lipid metabolism and result pathologist thickening of the arterial wall leading to stenosis of the lumen and, consequently, impaired irrigation.

The disease is very common in the adult population and affects mainly men menopausal women presenting to a relative immunity. Atherosclerosis the long-term evolution (15-20 years), and therefore the clinical manifestations appear after 30-40 years (1).

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If we refer to the risk factors of the disease, they can be divided into modifiable and modifiable, the latter representing therapeutic targets. Unchangeable risk factors are: age (> 55 years for women,> 45 years for men), sex, heredity (cardiovascular disease in first degree relatives - parents, brothers, sisters - ages younger than 55 years for men and under 65 women). Modifiable risk factors are: dyslipidemia, high blood pressure, smoking, diabetes / insulin resistance, obesity, sedentary life, atherogenic diet (2). To those, considered" classics", are added new risk factors, whose participation in the pathogenesis of atherosclerosis is still widely debated in numerous studies: serum markers of inflammation / thrombosis (high sensitive C-reactive protein, TNF-α, IL6, IL1, ESR, fibrinogen) (3), homocysteine (3), lipoprotein (a) (3), lipoproteins of small dense LDL, infections (Chlamydia pneumoniae, Helicobacter pylori), autoimmune diseases, periodontal disease

1.1.ATHEROSCLEROSIS AND THE IMMUNE RESPONSE

Just three decades ago, atherosclerosis was seen as a arterial collection of cholesterol, complicated by the accumulation of smooth muscle cells. According to this concept, endothelial denudation injury leads to platelet aggregation and release of platelet-derived growth factors that trigger the proliferation of smooth muscle cells in the arterial intima. These cells then develop an extracellular matrix that holds lipoproteins, forming the nidus of the atherosclerotic plaque. This

cell model of atherosclerosis updated on atherosclerosis Virchow's concepts formulated in the middle of the 19th century.

The occurrence of cell biology era replaced simplistic concept of plaque seen as a passive deposition of lipid residues on the arterial wall. Beyond the role of vascular smooth muscle cells long recognized in atherosclerotic lesions, subsequent investigations identified immune cells and mediators involved in atherosclerosis, bringing to the fore the role of inflammation in its pathogenesis (4).

The appearance of technologies that allow the detection of different genes has led to testing the roles of specific molecules in the development of experimental atherosclerosis in mice. These data demonstrated a critical role for hypercholesterolemia and also supported the participation of immune mechanisms in the pathogenesis of atherosclerosis (5). This revolution in our thinking about the pathophysiology of atherosclerosis has begun to provide clinical insight and practical tools that can help in patient management.

With the evolution of the human species, inflammatory response increased in complexity and provided complex mechanisms by host defenses against infections and various types of injuries.

" Primitive" arm of immunity, known as innate immunity, has its origins in early eukaryotes existing immunity pathways (6). Innate immunity is inherited from parents and can not be influenced by the end of life, is antigen independent and shows no immunological memory (figure 6).

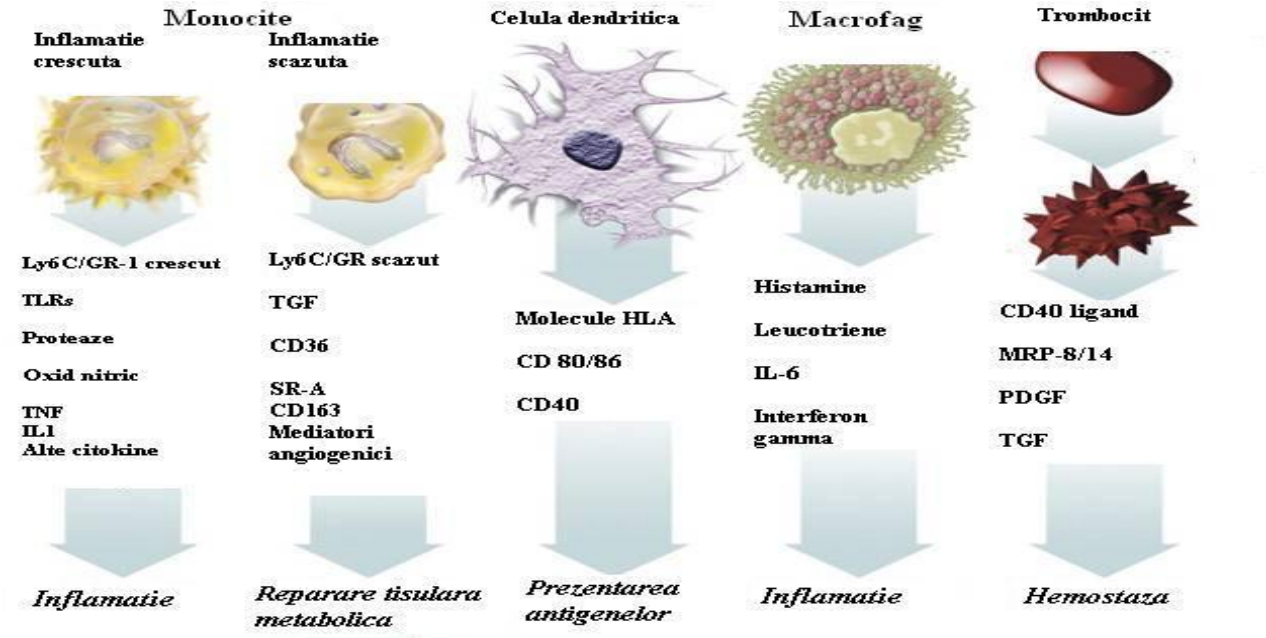

Figure 1 : Elements of innate immunity (modified after Libby, 2009)

Adaptive immune response appeared later in the evolution of species (Figure 2). This arm of the host defense system, in contrast to the innate immune response, ask "education" preceding the immune system.

The inflammatory response in atherosclerosis involves elements of both arms of immunity: the innate and the adaptive.

The role of innate immunity in atherosclerosis. Considerable evidence supports the early involvement of monocytes / macrophages, the major cellular components of the innate immune response during atherogenesis. Human arterial samples, as well as several experimental models of atherosclerosis, have identified the recruitment of monocytes as an early event in atherogenesis. Recent evidence has also highlighted the potential participation of mast cells in atherosclerosis. Identified as a minority population of leukocytes in arterial adventitia and atherosclerotic intima, mast cells exhibit numerous functions involved in atherogenesis (7,8). There are multiple links between lipoprotein and innate immunity. Modified lipoproteins interact with receptors" scavenger", and thus can send proinflammatory signals. Oxidized phospholipids derived from modified lipoproteins can also lead to inflammation.

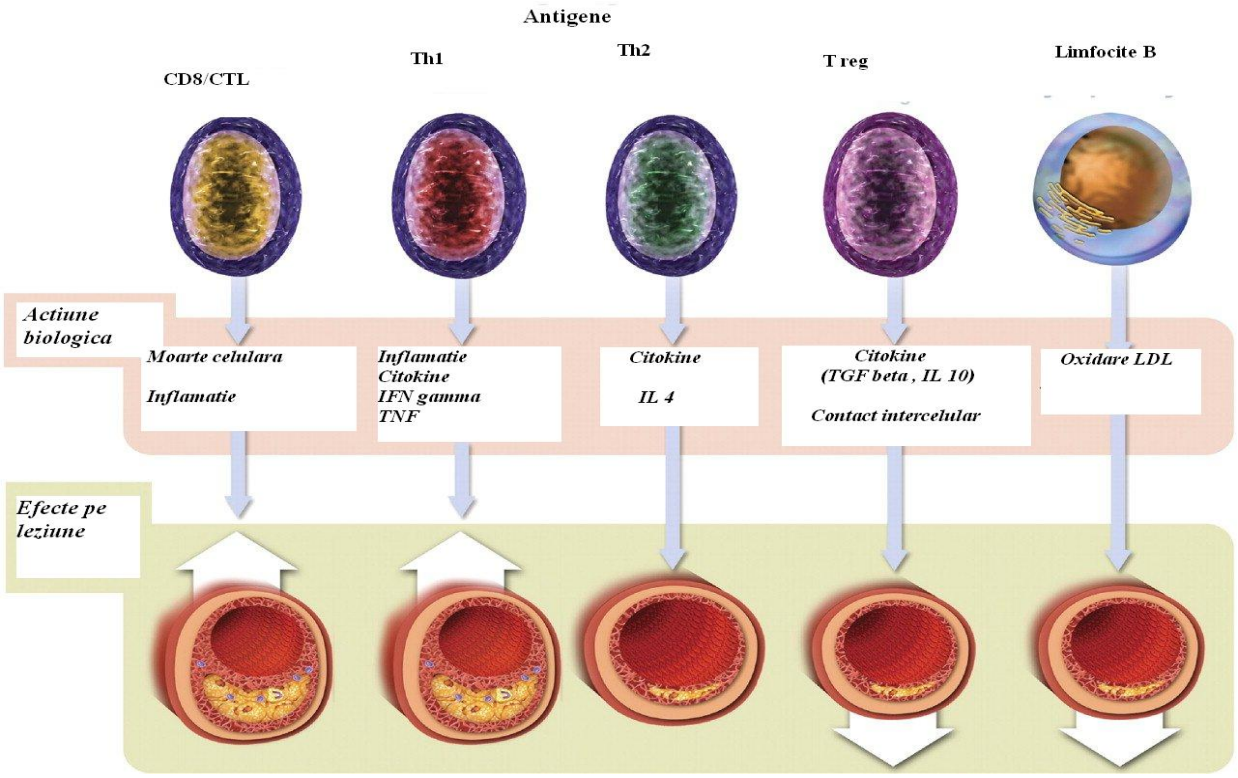

Figure 2 : The functional role of the 5 classes of lymphocytes described in atherosclerosis (modified after Libby, 2008)

Another recently studied relationship, regarding role of the innate immune response in atherogenesis, is the one between thrombosis and inflammation. Previously considered independent pathways in host defense, current evidence shows a significant cross activity (9).

For example, the prostaglandins produced on the cyclooxygenase pathway controls the inflammation, and the thrombogenic process.

The role of adaptive immunity in atherosclerosis. Evidence accumulated over time support a regulator key role of adaptive immunity in atherosclerosis and its complications. Interacting with a particular subset of mononuclear phagocytes specialized in antigen presentation - dendritic cells (figure 1), T lymphocytes will initiate a cellular immune response. Dendritic cells populate the atherosclerotic plaques and regional lymph nodes, where they present antigens to T cells. Antigens presumed to stimulate T cells in the context of atherosclerosis includes certain heat shock proteins, components of the plasma lipoproteins, and possibly some microbial structures.

1.2.CELLULAR AND BIOCHEMICAL MECHANISMS OF ATHEROSCLEROSIS

The first hypothesis regarding atherogenesis belong to Rudolf Virchow (1852) who considered that a minimum damage of the arterial wall produces an inflammatory reaction that will cause accumulation of plasma constituents in arterial intima. In 1856 von Rokitansky issue a new theory, supplemented later by Duguid (1946), which argues that "injuries are covered by small blood clots, which are organized by increasing the muscle cells inside them, incorporating them into the lesion" (Figure 3).

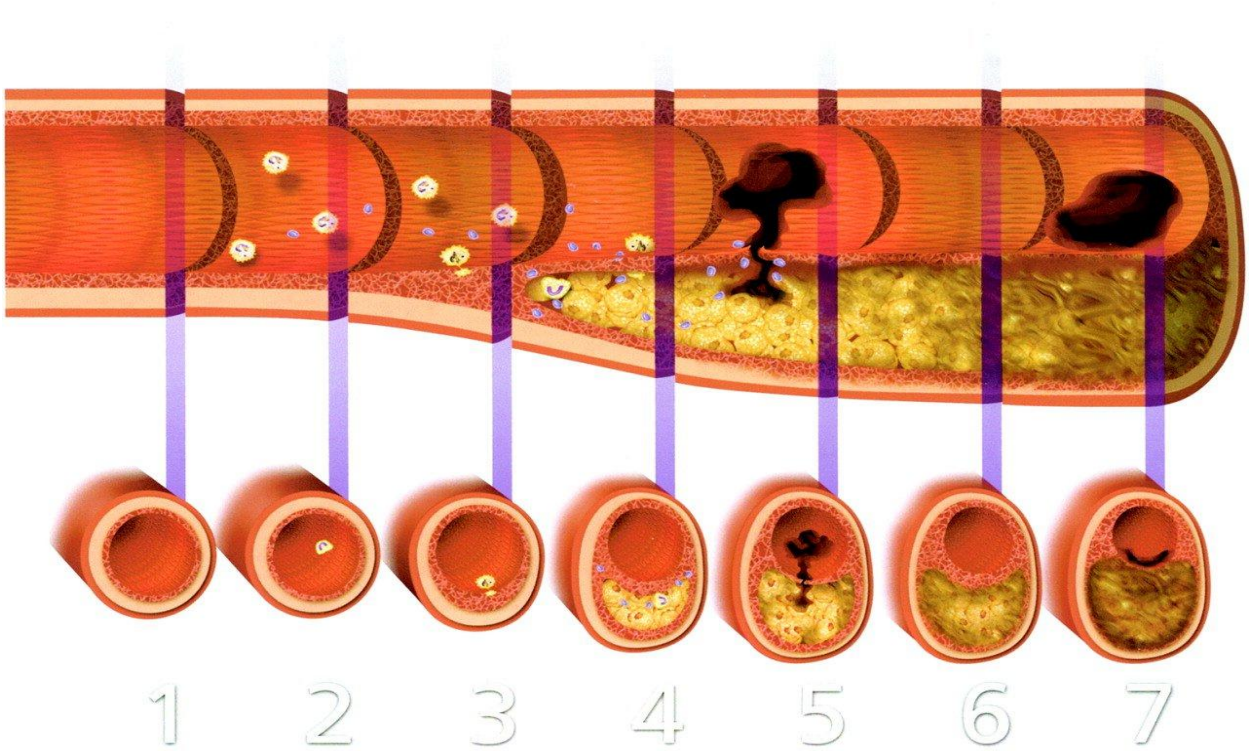

Figure 3 : Progression of atheromatous lesions (modified after Libby, 2001)

Three hypotheses are currently under active investigation. These hypotheses are not mutually exclusive, but rather emphasizes the different concepts of events necessary and

sufficient for the development of atherosclerotic lesions. These assumptions are: "response to injury" hypothesis, "response to retention" hypothesis, "oxidative modification" hypothesis.

A." Response to injury hypothesis". Response to injury" hypothesis" states that "the initial event in the pathogenesis of atherosclerosis is the endothelial damage" (10). This theory belongs Ross and Glomset and was first published in 1973. A whole variety of agents (hyperlipidemia, mechanical agents, toxic, viral, immunological) can produce an inflammatory response in which white blood cells, mainly monocytes, migrate into the injured area (11). The result is the sequestration and lipoprotein oxidation and transformation of monocytes into macrophages, who will ingest lipids which are oxidized, in particular LDL. Electrostatic interactions between lipoprotein particles, glycosaminoglycans and intercellular matrix proteins are considered as the primary factor responsible for the accumulation and retention of LDL in the arterial wall. Smooth muscle cells, macrophages and endothelial cells in the intima vessel generates oxygen free radicals, which cause changes in lipoprotein oxidation. Monocytes differentiated into macrophages generate a wide range of products: reactive oxygen and nitrogen species, proteases, lipases. Incorporation of oxidized LDL in macrophages (recognized by receptors "scavenger") will lead to the formation of foamy cells. Gradual accumulation of foamy cells will cause fatty streaks, the first visible morphological optic change. The accumulation of lipids and the formation of foamy cells perpetuate an inflammatory response that leads to the recruitment of macrophages and lymphocytes continue (12). Continuing inflammation results in cell necrosis concomitant release of cytokines, growth factors and proteolytic enzymes.

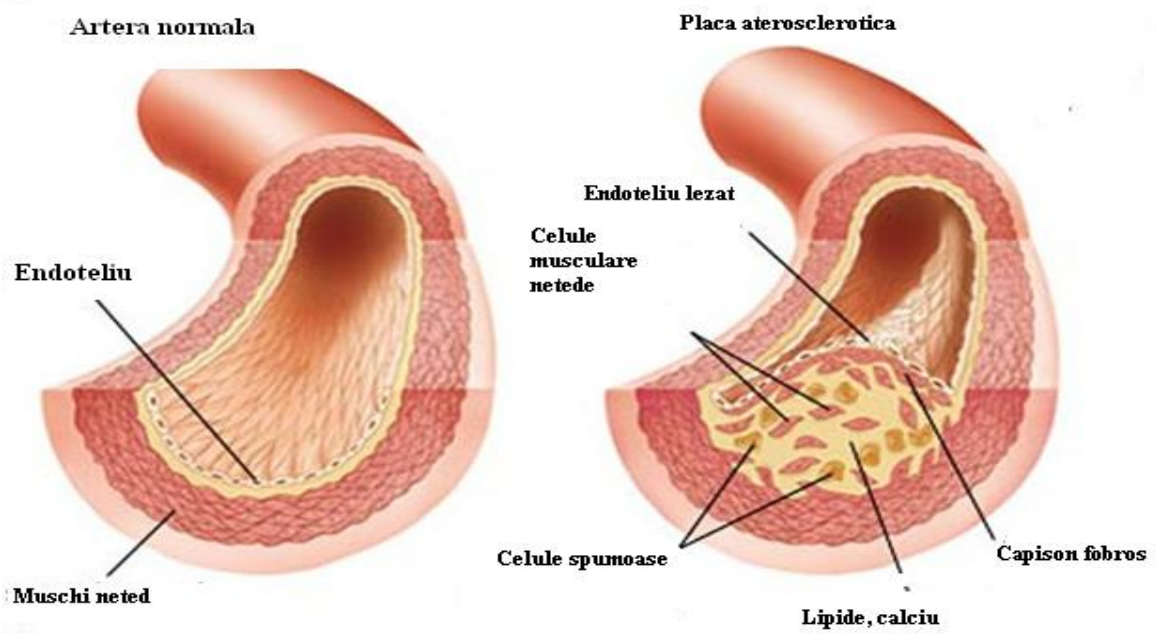

Figure 4 : Plaque (modified after Rohde and Lee, 2003)

Foamy cell necrosis results in the release of lipids in the extracellular space. Factors involved are represented by oxidized LDL cytotoxicity and secondary hypoxia to the massive infiltration with macrophages (13). The migration and proliferation of smooth muscle cells to intima is induced by growth factors and chemotactic factors that may be synthesized by any cell type involved in atherogenesis. The main factors are chemotactic and mitogenic PDGF (platelet derived growth factor), IL1, IL6, thrombin, TNF-α, IFN γ. Proliferated muscle cells acquire macrophage-like properties, encompassing LDL and secretory properties producing collagen fibers and proteoglycans carrying a fibrous capsule which includes extracellular lipid material and cellular debris. Foamy cell necrosis and migration of smooth muscle cells of atherosclerotic lesions cause irreversible.

Atherosclerosis is associated with the breaking of advanced atherosclerotic plaques, especially those with higher lipid deposit and characterized by smooth muscle cell ratio / low foam cells. Plaque rupture may be superficial, occurs only when endothelial denudation or deeper, when rupture include all collagen layer extending to atheromatous deposit (Figure 5).

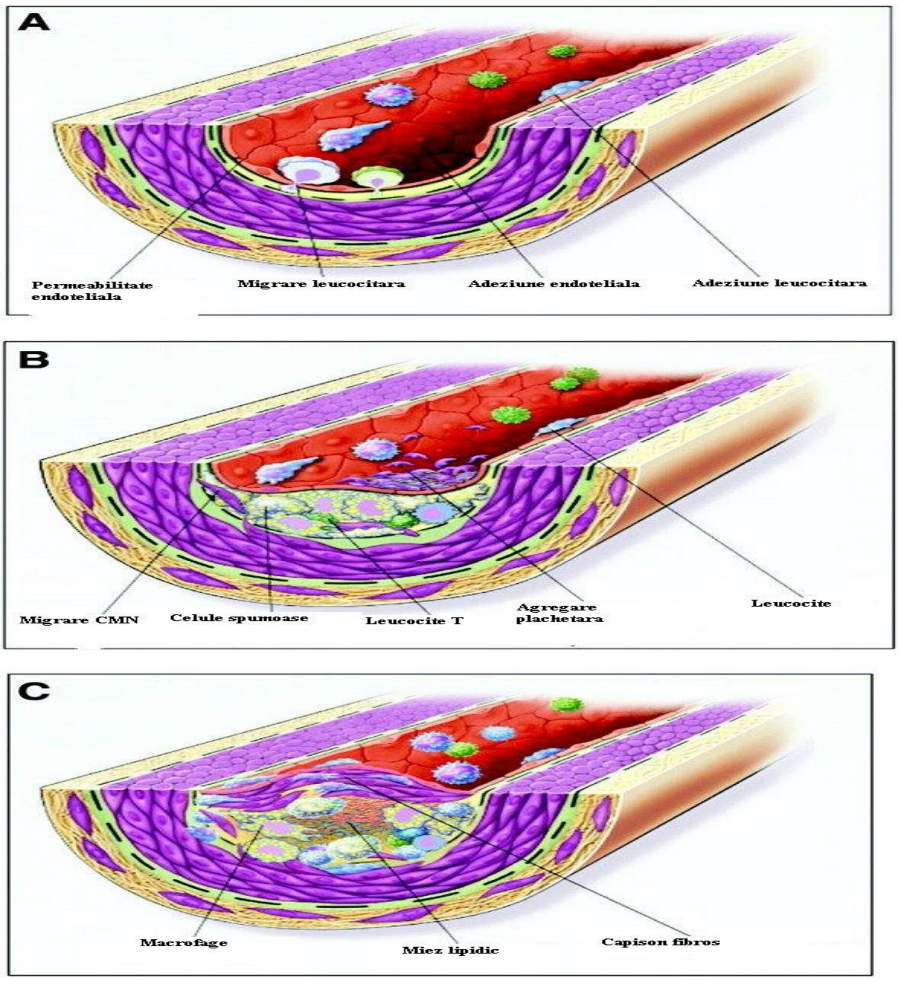

Figure 5 : Hypothesis "response to injury" (modified after Ross, 1999)

In the case of deep ruptures triggers the activation of platelets and the coagulation system, initially forming microthrombi intramural, allowing them to propagate downward or upward. In advanced atherosclerosis is emphasized also an abundant lymphocyte infiltration in the adventitia. Lymphocyte influx begins in a previous phase, but obviously only in the last stages of development of atherosclerotic lesions. Bleeding is the result of rupture of vessels in the granulation tissue of plaque. When this accident suddenly increase in atheroma volume, it can become obstructive, causing a heart attack.

B. "Response to retention" hypothesis. This hypothesis argues that "retaining lipoproteins is the initiating event of atherosclerosis" (14). Studies in rabbits have shown that 2 hours after injection of LDL arterial sequestration could be observed, well as the presence of microaggregates (15). It is estimated that ~ 85% of the lipoproteins pass through the subendothelial transcytosis, and the process is limited to particles <70 nm in diameter. This size restriction is important because it suggests that lipoprotein lipase activity is required for the passage of triacylglycerol-rich lipoproteins in the subendothelial space. Lipoprotein retention within the arterial wall seems closely linked to extracellular matrix components. Apolipoprotein B-100, the only LDL-associated protein , is maintained in close association with the arterial wall by the arterial proteoglycans (16). These data support an important role of proteoglycans in the early stages of atherosclerosis.

C. " *Oxidative modification" hypothesis.* Oxidative modification hypothesis was affirmed by Joseph L. Witztum in 1994 and is focused on the concept that native LDL is atherogenic. The central component of the atherogenic process is the oxidative modified LDL, which acts as an immunogenic stimulus for the recruitment of monocytes to the vascular wall and phagocytic uptake of oxidized LDL by macrophages.

2. *MYOCARDIAL INFARCTION WITH ST SEGMENT ELEVATION*

2.1. GENERAL CONSIDERATIONS

2.1.1.Incidence

Myocardial infarction is defined as myocardial cell death due to prolonged acute ischemia exceeding 20 minutes. It is a frequent cause of death in countries with high economic level. In terms of incidence, myocardial occurs after 40 years, especially after 50 years, the frequency has increased after 60-70 years, but 45% of cases occur in 65 years. It has propensity for males, typically 2:1. Women of childbearing potential presents some protection, represented by ovarian hormonal factors. (17)

Risk factors present in etiopathology atherosclerosis are found in people who have suffered a myocardial infarction. The presence of a risk factor produces a double heart, the combination of two factors increases the risk 4 times, 3 of them 7 times. For persons under 40 years incidence of myocardial infarction is about 5% for their being found frequently lipid metabolism disorders, overlaid hypertension, smoking or diabetes.

Frequently, the injury is due to obstruction of major branches of the coronary system, leading to deprivation of blood to a specific area of the heart muscle. Coronary arteries originate from the ascending aorta, at the level of two of the three aortic sinuses, represented by the core of the left coronary artery that branches off the anterior interventricular artery and the circumflex artery (left anterior descending artery, LAD) artery and right coronary. Dominance of left or right heart failure is defined by the origin of the right coronary or, respectively, left posterior interventricular artery. Frequently (70-80%) occurs right dominance situation.

The most common cause of occlusion of arterial lumen, is the complete or nearly complete thrombosis . In 15-20% of cases are due to spasm of prolonged myocardial levels of plaque. Very rare coronary arteries are obliterated by injuries, rheumatism, syphilis, embolism, immune arthritis.

2.1.2. Pathologic anatomy.

The occlusion often interested in the left anterior descending artery branch of the left coronary artery (40-50%), right coronary artery (30-40%) and less than the circumflex artery (15-20%), occlusion, in most cases 5 -6 cm from the origin. Regardless of the obstructed artery lesions with predilection interested necrotic left ventricular wall and interventricular septum. Right ventricular or atrial infarction the rare (5% of cases). Explanation for this could be that the thinner right ventricle wall receives extra oxygen by the system path of Thebesius or imbibition of endocardium.

Histopathologic can be described two types of lesion overt morphological imaging and different. Transmural myocardial necrosis interested ventricular wall entirely or almost entirely, and usually occurs in the territory irrigated by a specific artery. Subendocardial myocardial necrosis interested third or half the wall thickness without coincides with the territory of an artery, these changes may represent also the early phase of transmural infarction in the early lysis of thrombus occlusion resulted in remediation. Place the coronary artery obstruction plays an important role in influencing the size of the infarction.

2.1.3. Consequences and complications.

The onset of acute myocardial infarction can be represented in 10-15% of cases of sudden cardiac death or cardiogenic shock. Even in the early days of development of myocardial fiber may develop pericarditis or fibrinohemoragică. May also occur, myocardial wall rupture (ascending to cardiac tamponade), ventricular septal rupture or valve apparatus, thrombosis of the left ventricle, ventricular aneurysm formation. Large infarcts or repeated, leading to the presence of extensive fibrous tissue, can lead to chronic heart failure.

2.2. CLINICAL MANIFESTATIONS

Acute myocardial infarction may have unique events individually. Symptoms may vary in their absence (silent heart attack"") to sudden cardiac death. Up to 20% of cases are silent infarcts"", which appeared mainly in the elderly and diabetics.

" Classic" symptoms of acute myocardial infarction include:

-anterior chest pain (retrosternal or precordial) can be described in the following forms: tightness, pressure, heaviness, tightness, burning, discomfort, sharp pain (sometimes), pain confusion that may radiate into the posterior thorax, left shoulder, arm , mandible, unilateral or bilateral, lasting over 30 minutes. Sometimes, epigastric pain may be localized (often inferior myocardial infarction);

-profuse sweating;

-dyspnea;

-syncope;

-anxiety, palpitations;

-digestive symptoms: nausea, vomiting, diarrhea, hiccups (vagal symptoms, especially in inferior myocardial infarction)

In terms of gender, women present with atypical symptoms relatively common, most often being about breathlessness, weakness, indigestion, fatigue. There is a circadian variation in acute myocardial infarction: frequency of occurrence in the early morning (6-12 AM), due to increased sympathetic tone and tendency to thrombosis. Approximately 50% of patients with

acute myocardial infarction has prodromal symptoms, which usually consist in angina or anginal equivalents, appeared a month, a few days or hours before the acute episode

Physical examination is an important role, especially in the exclusion of other potentially life-threatening acute illness: aortic dissection, acute pericarditis, pulmonary embolism, pneumothorax, pneumonia, perforated ulcer, acute pancreatitis, etc.

Physical examination can detect: sinus tachycardia, sinus bradycardia: appears in inferior myocardial infarction by increasing vagal stimulation; hypertensive reaction: adrenergic stimulation or in response to pain, hypotensive response: the response to the medication (nitroglycerin, morphine) and / or due to the Bezold-Jarisch reflex, abnormal precordial pulsations: right ventricular overload, dyskinetic left ventricular hypertrophy, left ventricular; auscultation: noise detection in III, IV sound, systolic murmur of mitral regurgitation, pericardial friction, etc

2.3. PARACLINICAL DIAGNOSIS

2.3.1.Electrocardiogram

Standard 12-lead ECG is the main" tool" used to detect myocardial ischemia.

Depending on the type and extent of electrocardiographic abnormalities can immediately determine the risk profile and the division of acute coronary syndromes in acute coronary syndromes with or without ST-segment elevation, ECG recording ideally be done during the painful episode or as close , the time it (figure 6)

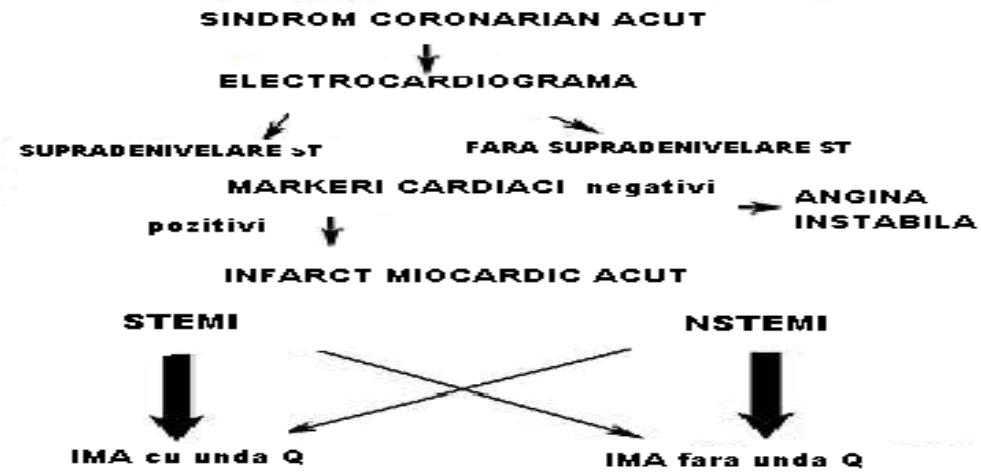

Figure 6 : Classification of acute coronary syndromes

Ischemic necrosis most commonly affects ventricular myocardium and therefore changes in the electrocardiogram interested QRST complex. AMI incidence ratio of right ventricle and left ventricle is 40 to 1. Atrial infarcts are rare and produce change, often insignificant, the P wave and PQ segment. Ischemic necrosis of myocardial infarction is segmental (limited portion

of the myocardium interested), transmural and major (area / mass myocardial segment is relatively large) (figure 7)

Dynamic ECG recordings are of real importance in the diagnosis of acute myocardial infarction. The classic signs of ischemia-lesion necrosis are direct changes in acute myocardial infarction ischemia (T wave broad, symmetrical, sharp = subendocardial lesion, negative T wave, broad, symmetrical = subepicardic injury), injury (ST segment elevation = lesion subepicardic , ST-segment depression = subendocardial lesion), necrosis - pathologic Q wave: duration> 0.04 "and width of more than 25% of the R wave accompanying no change in inspiration. wave Q does not occur in the first hours of development and may be lacking. acute and chronic pulmonary heart, SS, HBAs, WPW syndrome, myocarditis can mimic wave Q.

To determine the size of the ST segment elevation using the J point, with some differences in terms of gender. J point elevation in men decreases with age, which is not observed in women (18) (tabel 1).

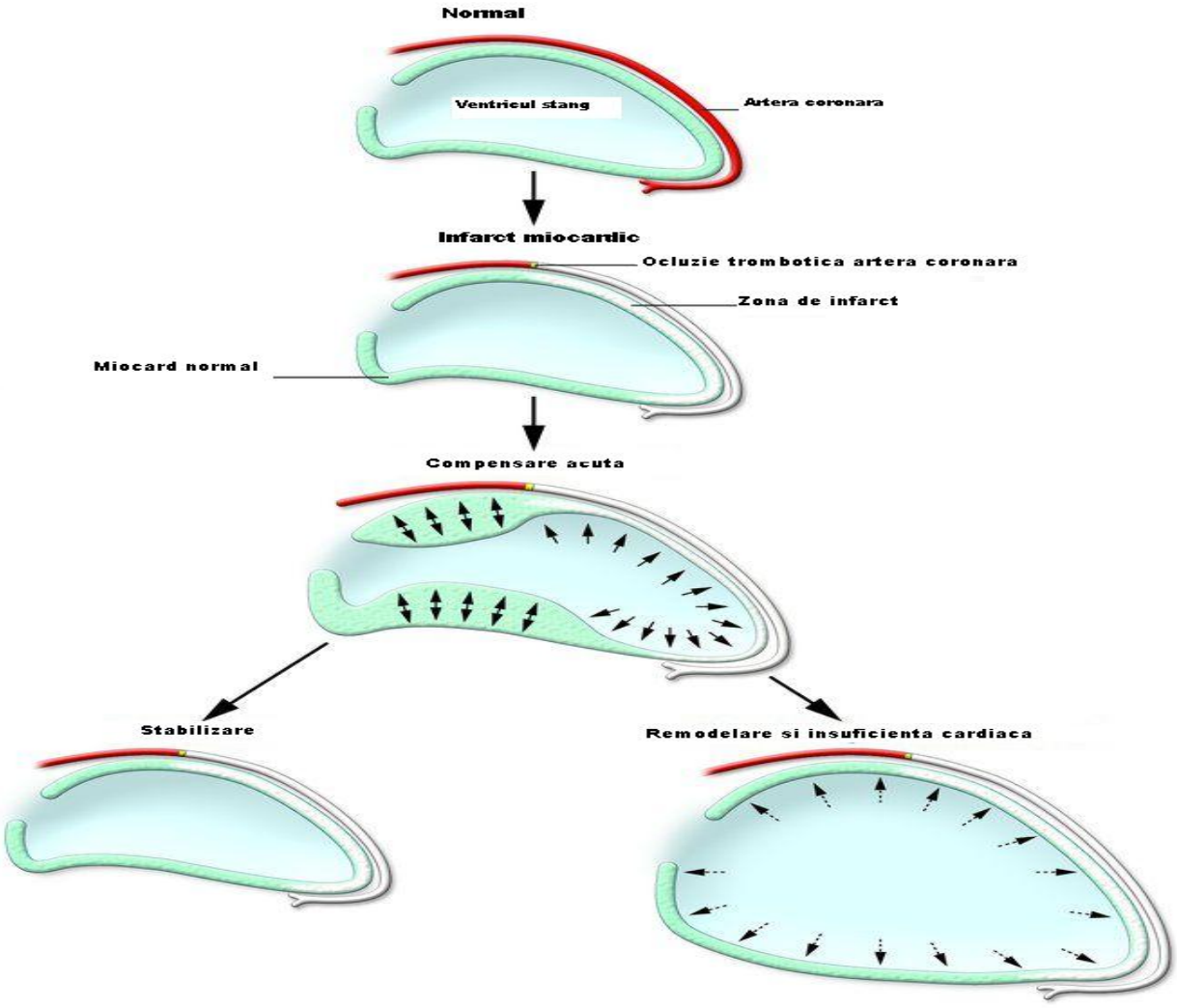

Figure 7 : Evolution infarction (modified after Russell, 2007)

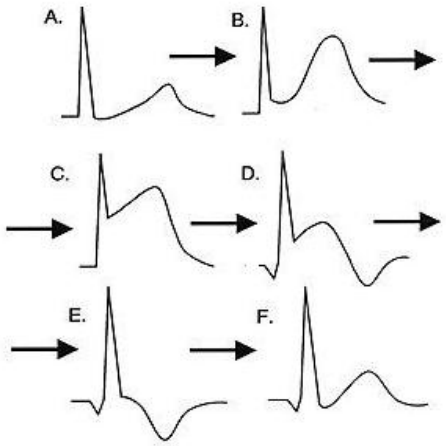

Figure 8 : Evolution of acute myocardial infarction with ST segment elevation

Table I

ECG manifestations of acute myocardial ischemia (in the absence of LVH and LBBB) (43).

ST-segment elevation
New ST elevation at the J point in two contiguous> 2 mV in men or> 0.15 mV in women in leads V2-V3 and / or> 0.1 mV in other derivatives
ST-segment and T-wave changes
Supradenivvelare new horizontal or descending ST> 0.05 mV in two contiguous leads, and / or T wave inversion> 0.1 mV in two contiguous leads with prominent R wave or R / S ratio> 1

The terrain of myocardial infarction is determined by changes in the ECG leads well expressed (Figure 9)

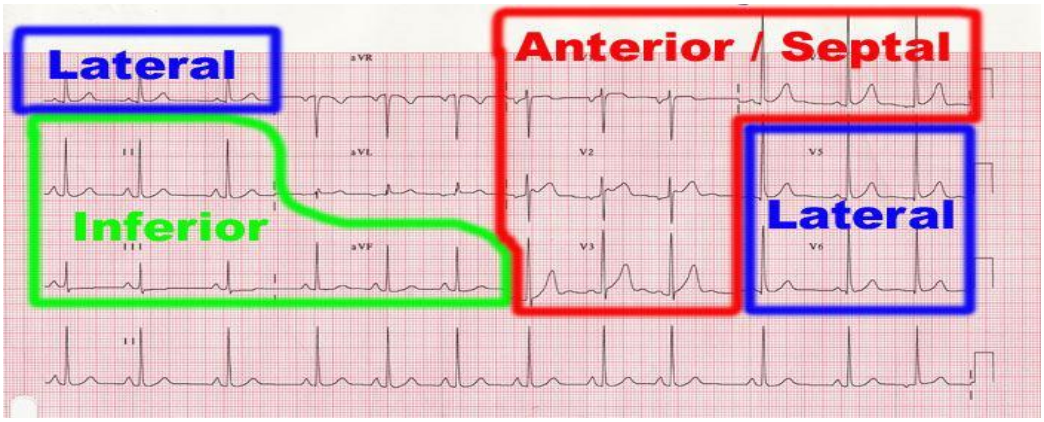

Figure 9 : Topography AMI

2.3.2.Serum Biomarkers

In cardiovascular disease biomarkers can meet the following classes:

- A.Markers of ischemia / myocardial necrosis: myoglobin, troponin T and I, creatine kinase isoenzyme MB, lactate dehydrogenase (LDH), hepatic cytolysis enzymes (AST / SGOT)
- B.Markers of inflammatory syndrome: C-reactive protein, high sensitive C-reactive protein, TNF-alpha, fibrinogen, ESR, number of leukocytes
- C.Markers of plaque instability: homocysteine, adiponectin, myeloperoxidase, matrix metalloproteinases, soluble CD40 ligand
- D.Markers of lipid profile: total cholesterol, LDL cholesterol, HDL cholesterol, VLDL cholesterol, triglycerides, apolipoproteins
- E.Markers of heart failure: natriuretic peptide type B (Brain Natriuretic Peptide), N-terminal pro BNP

A.Markers of ischemia / myocardial necrosis

A.1. Cardiac troponins

Troponin is a complex of three regulatory proteins (troponin C, troponin I and troponin C) that are integral to muscle contraction in skeletal and cardiac muscle, but not smooth muscle.

Troponin is found in both cardiac muscle and in the skeletal, but the specific types differ in the two muscle types. The major difference is that skeletal muscle troponin C has four calcium binding sites opposed to the heart muscle that is three. Individual subunits have different functions: Troponin C binds to calcium ions to produce conformational changes of troponin I, Troponin T binds to tropomyosin, locking it in troponin-tropomyosin complex, Troponin I binds to actin stabilized troponin-tropomyosin complex (19)

Determination by quantitative techniques of troponin T and I currently approved by the FDA for clinical use. It is not necessary to simultaneously test both proteins. Troponins I and T are released into the circulation in situations where membrane integrity is lost, or when myocyte necrosis occurs from any cause . Repeated measurements of troponin T or I have become an important tool for stratification of patients with acute coronary syndromes. Troponin T is released early in acute myocardial infarction, namely at a time with significant within 3-4 hours after the onset of clinical symptoms and the persistence of elevated for 6-8 days, possibly up to 14 days. The persistence of high values over a long period of time is possible due to the slow release of the troponin complex in the contractile apparatus of myocytes and is used in the diagnosis of acute myocardial infarction older than 48 hours, but up to 14 days. It is important to note that the persistence of TnT growth is not influenced by thrombolytic therapy (20).

Different manufacturers offer different immunological tests with different cut-off values, and different sensitivity for detecting troponin. In contrast to the different levels of troponin I

assays, which are not standardized, troponin T is measured by the use of a single assay. Therefore, the results are directly comparable between different laboratories worldwide.

Most commonly, increased troponin is due to myocardial ischemia in acute myocardial infarction or acute coronary syndromes. However other mechanisms that lead to increased serum troponin may be relevant. One of these mechanisms is the "leak" through the cell membrane miocitare troponin. It has been shown that TNF alpha increases the permeability of the endothelial monolayers macromolecules (21). Experimental evidence for this hypothesis was provided by Piper et al. (22), which showed "reversible formation of bubbles in the membrane rat cardiomyocytes during limited periods of hypoxia, followed by myocardial enzyme release in the supernatant of the cells. The rat cardiomyocytes, just 15 minutes of ischemia light and have been shown to be sufficient to cause the release of troponin I at a range too short to induce cell death. "

Another mechanism of troponin increase in clotting may be related to the capillary bed during sepsis, hypoxia leading to reversible myocardial apoptosis associated with "leakage" cardiac Troponin in serum. Unfortunately, experimental evidence to support this hypothesis are not far.

Other conditions associated with increases in cardiac troponins: cardiac disease and interventions - cardiac amyloidosis, cardiac contusion, cardiac surgery, shock cardioversion, closure of atrial defects, coronary vasospasm, dilated cardiomyopathy, chronic heart failure , hypertrophic cardiomyopathy ,myocarditis, pericarditis, percutaneous coronary intervention, post heart transplant, radiofrequency ablation, supraventricular tachycardia, non-cardiac disease - patients with critical illness, high-dose chemotherapy, primary pulmonary hypertension, pulmonary embolism, renal failure, subarachnoid hemorrhage, scorpion sting, sepsis and septic shock , stroke, strenuous exercise (marathon)

A.2. Creatinekinase MB

Creatine is a dimeric enzyme. This enzyme catalyses the conversion of creatine and adenosine triphosphate (ATP) in phosphocreatine and adenozindifosfat (ADP). This reaction is reversible. Cytoplasmic creatine kinase consists of two subunits with a combined molecular mass of 86,000 daltons. The molecular weight of the individual sub-units is half of that of the intact molecule. Each subunit is either Type I or Type B. Combinations of the two subunits M and B will produce three different CK isoenzymes: CK-MM (skeletal muscle), CK-MB (the heart muscle), and CK-BB (brain and intestine). Isoforms have the same molecular weight and catalyze the same reaction, differing in terms of molecular structure and source.

Creatine kinase MB is one of three distinct forms of creatine. CK-MB is found primarily in cardiac muscle and, therefore, elevated levels of damage occurring when cardiac muscle cells. CK-MB, along with total CK, are tested in patients with symptoms of chest are useful in the diagnosis of acute myocardial infarction.

Elevated serum creatine kinase levels may be the expression of other territories muscle damage than heart muscle and therefore calculate the relative index of total CK and CK-MB can be helpful in determining the etiology of heart.

$$Relative\ index\ (RI) = \frac{CK-MB\ (micrograms/L)}{CK\ total\ (U/L)}\ X\ 100$$

In the case where the relative index is less than 2.5-3, it is likely the source of the heart muscle serum. A high CK with a relatively very low index suggests muscle sources.

In patients with acute myocardial infarction increases in CK-MB may be detected within 3-4 hours of symptom onset, with maximum concentration at 18-24 hours and returning to normal in 72 hours. Elevated CK isoenzymes may occur in different conditions:- CK-MB: acute myocardial infarction, myocarditis, pericarditis, cardiac surgery, ventricular arrhythmias, cardiomyopathy, electrical conversion;- CK-MM trauma, intramuscular injections, rhabdomyolysis, muscular dystrophy, crushing syndrome, dermatomyositis, hypothyroidism, strenuous exercise, hypokalemia, convulsions, shock, malignant hyperthermia; -- CK-BB: stroke, brain tumors, subarachnoid haemorrhage, neurosurgery, seizures, cancers (ovarian, digestive, prostate, breast, testicular, lung), intestinal infarction or pulmonary postpartum, renal failure.

A.3. Lactate dehydrogenase (LDH)

Human cells produce two major types of lactate dehydrogenase: form I and form H (there is a third form which is found only in semen). These forms are very similar in size and shape, but have different catalytic properties. Form M, the major form of large skeletal muscles, mainly involved in converting pyruvate to lactate and occurs especially when the muscles perform anaerobic exercise. Form H is involved in the opposite reaction, the conversion of lactate into pyruvate. It is the major form in the heart, which has a constant supply of oxygen and can easily be used as a source of aerobic energy lactate. The two forms are similar in structure and can form complexes. Thus different lactate dehydrogenases cells can adapt to suit the needs of the moment.

In acute myocardial infarction increased serum LDH shows a peak at 3-4 days after onset, remained high up to 10 days (86).

A.4. Aspartate aminotransferase (TGO/ASAT/AST)

Aspartate is an enzyme that is part of transaminases class, she catalyzing the reversible transfer of an α-amino group between aspartate and glutamate. In contrast to the alanine aminotransferase is found mainly in the liver, AST is found in a number of tissues: the myocardium, liver, skeletal muscle, kidney, pancreas, brain tissue, spleen.

There are two isoenzymes of aspartate:-TGO1/ASTc, Cytosolic isoenzyme derives mainly from red cells and heart; -TGO2/ASTm, Mitochondrial isoform present in the liver.

Since 1954, aspartate was considered a biochemical marker used in the diagnosis of acute myocardial infarction. Serum AST increase in the first 6-9 hours of the onset of symptoms and may remain up until 6 days after infarction . Over the years AST was replaced in the diagnosis of acute myocardial infarction by cardiac troponins.

B. Markers of inflammatory syndrome

B. 1. C-reactive protein - high sensitive C-reactive protein

C-reactive protein was first described in 1930 by Tillett and Frances, as "a serum component present in patients with acute, reacting with a specific extract of Streptococcus pneumoniae that they called Fraction C '(23) . In subsequent years CRP has been extensively studied. C-reactive protein is the prototype of acute phase protein in humans and an important mediator of host defense. PCR of normal circulating levels are low, but increases up to 10 000 times the first few hours of the onset of inflammation, from any cause.

Myocardial infarction is accompanied by major acute response of C-reactive protein. PCR serum peak occurs at about 50 hours after the onset of myocardial infarction and pain are closely correlated in magnitude, although the time to maximum serum levels of cardiac isozymes. In patients recovering from heart without major events, the PCR rapidly falls to normal, normal, exponential. Complications such as reinfarction, aneurysm formation, intercurrent infections are associated with elevated CRP levels constant or secondary growth after initial fall. Angina pectoris without heart and invasive investigations such as coronary angiography, is not stimulating the production of CRP, while other causes of chest pain, such as pulmonary embolism, pleurisy or pericarditis are usually associated with high levels of CRP. Routine PCR testing after heart attack or chest pain patients may thus help in the diagnosis, recognition and management of complications.

The study of Ridker PM et al (2000) (24) of the measurement, showed that the addition of C-reactive protein in screening based on the level of serum lipids may provide a better method

for the identification of women at risk of developing cardiovascular events, which is defined as death due cardiovasculare disease, non-fatal myocardial infarction or stroke, or the need for coronary revascularization procedures. The study by Kitpatric ES et al (2000) suggest that high serum CRP level is an independent risk factor in patients with type I diabetes (25)

B.2. Tumor necrosis factor alpha (TNF-α)

The gene for TNF was cloned in 1985, is located on chromosome 6 and contains four exons, the latter being responsible for coding exon of more than 80% of secreted protein. Serum levels of TNF-α may be a marker of systemic inflammatory response associated with sepsis, trauma, heart failure. In healthy individuals, the concentration of TNF-α is the heart at low TNF-α is localized mainly in the resident mast cells and endothelium . TNF-α receptor (TNF-R1 and TNF-R2), are expressed in most of cardiac cells including cardiomyocytes (26). From the first minutes of myocardial ischemia, TNF-α released from macrophages and preformed mast cells resident (121). If the ischemia persists, TNF-α is released and in the cardiomyocytes . In studies in mice that suffered a heart attack, it was observed that TNF-R1 receptor density is increased for 10 days, while TNF-R2 density remains unchanged (27).

B.3. Fibrinogen

Fibrinogen is synthesized in the liver by hepatocytes in the form of a soluble plasma glycoprotein with a molecular weight of 340 kDa.

Numerous studies have identified fibrinogen as an independent cardiovascular risk factor. It was also associated with traditional risk factors, studies suggesting that increased levels of fibrinogen may be a way for these risk factors exert their effect. Incriminated several mechanisms by which fibrinogen may increase cardiovascular risk: - Binds to activated platelets via glycoprotein IIb / IIIa, thereby inhibiting platelet;- High levels promote the formation of fibrin from fibrinogen;- Fibrinogen is an important contributor to plasma viscosity;- Is an acute phase reactant, is increased inflammatory reaction.

C. Markers of plaque instability

C.1. Homocysteine

Homocysteine is a non-protein amino acid, synthesized during the metabolism of methionine by removing its terminal C-methyl group. Plasma homocysteine is largely protein bound, but there are free oxidized forms. Hyperhomocysteinemia entail an increased risk of cardiovascular disease (is an independent risk factor for women - even in premenopausal and men), increased risk of venous thrombosis or complications of pregnancy and neural tube defects . The way in which hyperhomocysteinemia promotes atherosclerosis development has been the subject of several theories . Some of them supporting the role of the molecule sulfhydryl group

of homocysteine in the process because of the ease with which this group may be oxidized. Others focus on the mechanisms by which homocysteine promotes platelet aggregation, endothelial damage development, altered smooth muscle cell proliferation and increased production of reactive oxygen species, leading to increased oxidative stress

C.2Adiponectin

Adiponectin is an anti-inflammatory adipocytokines circulating presenting. It is a protein hormone consists of 244 amino acids arranged in four distinct regions involved in the regulation of glucose levels, as well as the breakdown of fatty acids . Adiponectin is secreted exclusively by adipose tissue, but there are a small amount produced by the placenta during pregnancy. Compared to most other hormones, plasma adiponectin level is very high. Its plasma level is inversely correlated with body fat percentage in adults, this correlation is less clear in infants and young children. Adiponectin secretion has a circadian rhythm, with a nocturnal decrease in plasma levels and peak early morning .

There have been numerous studies - in vitro, in animal models, clinical - which highlighted the relationship between serum levels of adiponectin and cardiovascular diseases.

D. Lipid Markers

D.1. Total cholesterol, LDL-cholesterol, HDL-cholesterol

All body cells contain cholesterol, it can be found in large quantities on the membrane, which serves to maintain the integrity and facilitate intercellular signaling .About 20-25% of the total daily cholesterol is produced in the liver and other sources are represented by the intestine, adrenal gland, the reproductive organs.

However, water soluble cholesterol is not enough to dissolve in the blood data, so it is carried through the bloodstream by lipoproteins such as LDL and HDL (171). The lipoproteins are, in fact, "carriers" for cholesterol, fat and other fat-soluble nutrients such as vitamins A, D, E, K and coenzyme Q10. Lipoproteins consist of the following parts:- A kernel fats (triglycerides), cholesterol esters (cholesterol linked to fatty acids), vitamins, fat-soluble; - Membrane phospholipids and a small amount of cholesterol; - A protein (apoprotein) that "weave" through the membrane phospholipids.

LDL particles vary in size and density. Studies have shown that small dense LDL particles (pattern B) is a higher risk factor for coronary heart disease than the larger and less dense (model A), this is due to the fact that smaller particles are more easily able to penetrate the

endothelium. LDL particles are a risk factor for cardiovascular disease when invade the endothelium and oxidized, because the oxidized forms are easier to remember by proteoglycans. LDL oxidation is promoted by the presence of necrotic cells and endothelium free radicals. Lipoprotein a (Lp (a)) is a subset of LDL. Apo (a) binds to LDL particles, containing also ApoB-100. Lp (a) levels may be found in the atherosclerotic plaque, as an independent risk factor for atherosclerosis. Recent research has shown that virtually all particles are oxidized LDL associated with Lp (a), moreover, it directly transfers the oxidized phospholipid membrane lipoprotein A. The liver produces particles of HDL containing ApoA-I . HDL particles can extract free cholesterol in the cell membrane, which it attaches fatty acids, producing cholesterol esters. They are disposed molecules and other protein containing LDL-apo B, the parts of fat (triglycerides) and fat-soluble vitamins (such as vitamin E). The HDL particle tends to be high in fat and vitamin E, whereas the other lipoproteins such as LDL is rich in cholesterol. In healthy individuals, 30% of blood cholesterol is carried by HDL. HDL particles are able to extract cholesterol from arterial plaques and transporting it to the liver for excretion or re-use . From the point of view of equality, men appear to have low levels of HDL than women , small particles being less loaded with cholesterol. Data from the "Framingham Heart Study" showed that for a given level of LDL, the risk of developing heart disease increases 10 times with HDL variation from high to low. Conversely, for a given level of HDL, the risk increases 3-fold variation from small to large LDL.

D.2.Apolipoprotein B

Apolipoproteins are proteins that bind the lipid to form lipoproteins. These lipids carry the lymphatic and circulatory systems, acting as structural components of lipoprotein particles, enzyme cofactors, ligands for cell surface receptors . Apolipoprotein synthesis occurs in the intestine (mainly controlled fat content of the diet) and liver (controlled by hormones - insulin, glucagon, thyroxine, estrogen, androgen-, alcohol and various drugs). Apolipoprotein A is the main component of HDL (90%), and apolipoprotein B is the main component of LDL. Apolipoprotein B feed into the chylomicrons (apo B - 48), LDL (apo B - 100) and VLDL (apo B - 100). Observational and interventional studies have shown that apolipoprotein B is more closely associated with cardiovascular risk than plasma lipids, the risk of coronary heart disease-induced plasma levels of apolipoprotein B is 4-5 times higher than the level of total cholesterol.

PERSONAL RESEARCH

1. *MATERIALS AND METHODS*

1.1. SELECTION OF THE STUDY GROUP

Measurements covered by this study were performed on a sample consisting of 30 patients consecutively enrolled from June 2012 - November 2012, aged 30 and 99 years, admitted to the Cardiology Clinic of Constanta County Emergency Hospital with a diagnosis acute myocardial infarction with ST-segment elevation. All patients were informed of their enrollment in this study.

The diagnosis was based on: history of prolonged ischemic chest pain, electrocardiographic changes in dynamics, changes in markers of myocardial necrosis.

For the patients in this study were carried out: Anamnesis, Clinical exam, Laboratory tests

1. Medical history included: age, gender, reasons for hospitalization (date and time at which debuted pain, pain characteristics), personal history of disease, current medical history, living and working (home environment - rural or urban, the education - elementary school, high school, higher education, smoking status), family history, previous treatment during hospitalization followed.

2. Patient's clinical examination included:

 Assessment of general condition and state of consciousness

 Measuring height and weight to calculate body mass index (BMI). Based on this index to determine nutritional status and degree of obesity:

~underweight: BMI <20

~normal weight: BMI = 20-25

~overweight: BMI = 25-30

~grade I obesity: BMI = 30-35

~grade II obesity: BMI = 35-40

~grade III obesity: BMI > 40

 Clinical examination body system

3. Laboratory tests:

 Electrocardiogram was performed at rest, using a 12-lead electrocardiograph - unipolar limb derivatives, derivatives chest. For objectification posterior and right ventricular infarctions were performed extreme right and left derivatives.

 Echocardiography: fasting, transthoracic

 Biochemistry

1.2. STRUCTURE OF THE LOT

1.2.1. Distribution by gender, age

Of the 30 patients of the lot, 11 patients were female and 19 male. Gender distribution is shown in Figure 10. In terms of age, and most patients, were in the range 50-70 years. The age distribution is shown in Figure 11.

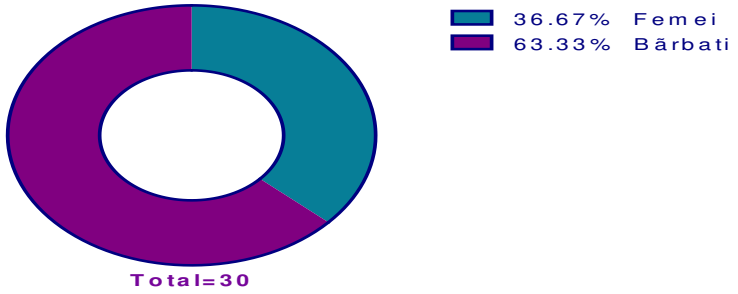

FigurE 10: Distribution by gender

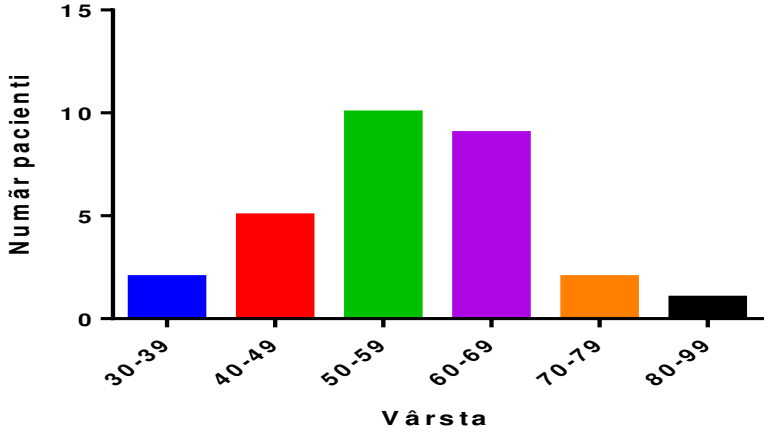

Figure 11 : Distribution of patients by age

1.2.2. Distribution of patients according to the conditions of life and work

Most patients were from urban areas (60% vs. 40%), and smoking was found as a risk factor in over half of the patients included in the study (figure 12 and 13).

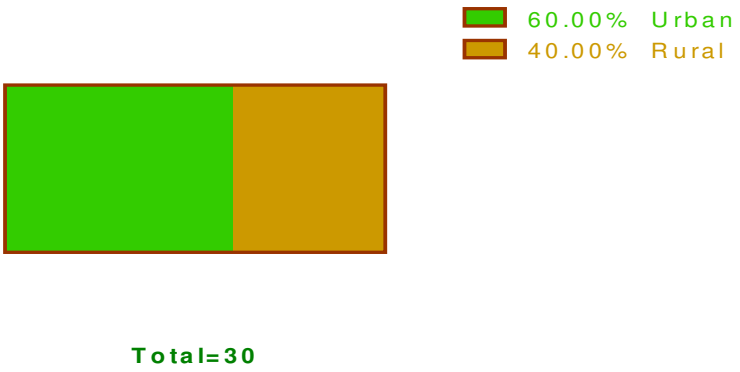

Figure 12 : Distribution of patients according to area of origin

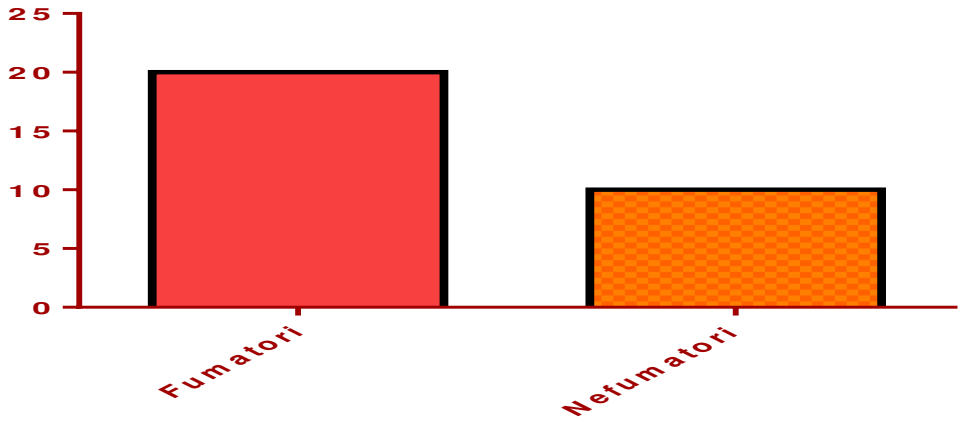

Figure 13 : Distribution of patients according to smoking status

1.2.3. The distribution of patients with acute myocardial infarction with ST segment elevation according to history of atherothrombotic cardiovascular existence of pre-existing dyslipidemia and diabetes.

Of the 30 patients included in the study, 20 patients, ie 66% of those enrolled were diagnosed with dyslipidemia. Normal lipid profile was defined as follows: HDL-cholesterol > 40 mg / dL, LDL-cholesterol <100 mg / dL total cholesterol <200 mg / dl and triglycerides <150 mg / dl. 10 patients (33.3%) had pre-existing type 2 diabetes, treated, being in outpatients with oral agents and / or insulin

Table II

Age of patients with atherothrombotic cardiovascular history, dyslipidemia and type 2 diabetes

		AGE
APP	med. art.	62.6
	dev. Std	9.8
DLP	med. art.	56.58
	dev. Std	11.48
DZ tip 2	med. art.	62.1
	dev. Std	8.8

1.3. EXCLUSION CRITERIA

Exclusion criteria from the study patients were:

 Inflammatory intercurrent active cancer, recent surgery or trauma (<3 months), sepsis, extensive burns, systemic lupus erythematosus, rheumatoid arthritis - conditions that can alter the acute phase reactants

 Patients who gave their consent for participation in this study

1.4. BIOLOGICAL MATERIAL COLLECTION

All determinations were performed in blood collected by venipuncture at the time of admission in the Department of Cardiology, the existing analyzers Synevo Laboratory, Constanta.

RESULTS

2.1. RESULTS OF MYOCARDIAL NECROSIS MARKERS

A number of biochemical markers have been studied with a view to early diagnosis of patients with acute myocardial infarction. Studies in recent years have sought to identify new cellular markers that allow rapid diagnosis of myocardial ischemia, thus allowing earlier treatment. Troponin was and is the preferred biomarker for the diagnosis of acute myocardial infarction. The recent development of tests to measure highly sensitive troponin T (high-sensitive) allowed the detection of very low levels of troponin T. Troponin T hs use test to improve diagnostic accuracy in patients with suspected acute myocardial infarction, while the results negative also has a negative predictive value. Studies last year showed a gain in terms of timeliness of diagnosis of acute myocardial infarction especially in patients presenting in a short time from onset of symptoms. However serious testing and clinical context and existing comorbidities, are important in interpreting the results of this test.

Until recently, the serum CK MB was traditionally considered the standard test for diagnosing acute myocardial infarction. Studies showed an initial increase in serum CK MB in the first 4-9 hours of the onset of chest pain, a serum peak within 24 hours and return to baseline in 48-72 hours, the advantage of this marker is that it can help to detect early reinfarction by serial measurements

In our study, patients diagnosed with acute myocardial infarction with ST segment elevation on admission showed a statistically significant increase in all markers of myocardial necrosis (tabel nr.3,4,5) compared with controls, p <0.05, results confirming data in the literature.

		Troponin T hs	**CK MB**	**LDH**	**TGO**
CONTROL	med. Art.	8.294	17	183.2	22.9
	dev. Std.	2.99222	4.47214	26.7781	7.86624
PACIENT	med. Art.	1211.15467	86.6	244.2667	95.43333
	dev. Std.	1941.61086	74.3916	61.76704	74.92234
P		0.029882	0.002843	0.002294	0.002193

Tabel 3: The value of serum markers of myocardial necrosis

The same statistically significant (p <0.05) remains valid for group studied gender breakdown (tabel 4 si tabel 5).

		Troponin T hs	CK-MB	LDH	TGO
Female Control	Med. Art	8.94	16.6	177.6	27.4
	Dev. Std.	3.01214	4.39318	26.44428	7.30068
Female Pacient	Med. Art.	725.45455	86.63636	255.63636	79.18182
	Dev. Std.	740.42857	59.96878	80.16018	35.62532
P		0.026039	0.011352	0.027643	0.003461

Tabel 4: The value of serum markers of myocardial necrosis in women

		Troponin T hs	CK-MB	LDH	TGO
Male Control	Med. Art	9.648	17.4	188.8	18.4
	Dev. Std.	3.04775	5.02991	28.90848	5.94138
Male Pacient	Med. Art.	1492.34947	97.10526	237.68421	104.84211
	Dev. Std.	2354.02839	93.03219	49.51885	89.90999
P		0.089906	0.036436	0.024023	0.023057

Tabel 5: The value of serum markers of myocardial necrosis in males

From the point of view of the correlation between time from onset of symptoms and the amount of myocardial necrosis markers, the results are presented in Table. 6

	Female Pacient	Male Pacient	Total Pacient
Troponin T hs	-0.1282	0.5141	0.4231
CK MB	0.1916	0.6595	0.5513
LDH	-0.4236	0.4836	0.12
TGO	-0.0519	0.7351	0.6857

Tabel nr. 6: Correlations between time from onset of symptoms and the amount of myocardial necrosis markers

According to Table 7 there is a positive correlation between hs Troponin T and CK MB, LDH and SGOT for Male patient group and Total patients. For Women Patient group has been demonstrated a positive correlation only between troponin T hs and LDH (Table no. 7)

Parameter	Female Pacient	Male Pacient	Total Pacient
CK MB	-0.0926	0.4021	0.3284
LDH	0.8104	0.3706	0.3343
TGO	-0.1293	0.6963	0.6532

Tabel 7 : Correlations between hs troponin T and CK MB, LDH and SGOT

2.2. RESULTS ON MARKERS OF THE INFLAMATORY SYNDROME AND RELATIONSHIP WITH MARKERS OF MYOCARDIAL NECROSIS

Because in the process of atherosclerosis and rupture of plaque, inflammation plays an important role, this study sought to reveal the importance of several markers of inflammatory syndrome in the first hours of myocardial infarction with ST segmenr. Inflammatory infiltrates present in the unstable coronary plaque inflammation suggest that contribute to the pathogenesis of acute myocardial infarction.

2.2.1. High sensitive C-reactive protein

C-reactive protein is one of the most studied markers of inflammatory syndrome vis-a-vis of its involvement in acute coronary syndromes. PCR appears to be involved in different stages of atherosclerosis, from early stages until the appearance of clinical events (myocardial infarction). In recent years the emphasis was on the determination of high sensitive C-reactive protein in cardiovascular risk. This is due to the fact that older PCR assays which are suitable for the control of severe inflammatory conditions, lack the ability to accurately measure the level required for the detection of cardiac risk.

In Tables 8, 9, 10 are set high sensitive C-reactive protein values obtained at study of patients diagnosed with myocardial infarction with ST segment now.

HIGH SENSITIVE C-REACTIVE PROTEIN		
	Control	Total Pacient
med. Art.	0.921	3.37833
dev. Std.	0.30701	2.28336
p		0.000901

Tabel 8 : The value of serum high sensitive C-reactive protein

HIGH SENSITIVE C-REACTIVE PROTEIN		
	Female Control	Female Pacient
med. Art.	0.852	3.11182
dev. Std.	0.26864	1.18199
p		0.000489

Tabel 9: The value of serum high sensitive C-reactive protein in women

HIGH SENSITIVE C-REACTIVE PROTEIN		
	Male Control	Male Pacient
med. Art.	1.002	3.54211
dev. Std.	0.33767	2.74712
p		0.027289

Tabel 10 : The value of serum high sensitive C-reactive protein in males

According to the table above, there is a statistically significant increase of highly sensitive C-reactive protein, regardless of gender.

The study found, in terms of high-sensitive C-reactive protein: - a moderate positive correlation with Troponin T high sensitive in Male Patient group and Total Pacient group; - A weak positive correlation with CK-MB in the group Female Patient, Male patient, Total Pacient, with LDH in Male Pacient group and Total Patient and with TGO in Female Patient group, Male Patient and Total Pacient ; - A weak negative correlation with high sensitive Troponin T and LDH in Female Patient group (Table 11)

Parameter	Female Pacient	Male Pacient	Total Pacient
Troponin T hs	-0.3601	0.6804	0.6101
CK-MB	0.111	0.4864	0.416
LDH	-0.0682	0.2224	0.104
TGO	0.3741	0.4997	0.494

Tabel 11: Correlations between high-sensitive C-Reactive Protein and Troponin T high sensitive CK-MB, LDH and SGOT

2.2.2. Tumor necrosis factor alpha (TNF α)

Evaluation of tumor necrosis factor alpha (TNF-α) in the acute phase of myocardial infarction has been the subject of several studies in recent years. Inflammatory response and cytokine release are particularly active in the acute phase of myocardial infarction and contributes to cardiac remodeling. Triggers that trigger the release of cytokines are represented by ischemic stimuli, mechanical deformation, reactive oxygen species and autoamplificare own horses. Cytokines, such as TNF-α and IL-6, are released quickly in the center of the infarct, but having high expression in the necrotic lesion border. Exploding wall myocardial mechanics is a powerful regulator of cytokine production, Kapadia et al. showing that it can trigger myocardial production of TNF-α de novo within 30 minutes of the onset of myocardial infarction.

From the survey data found that patients diagnosed with acute myocardial infarction with ST segment elevation, there is a statistically significant increase ($p < 0.05$) of TNF-α compared with controls, regardless of is sex (table no. 12, 13, 14).

TNF α		
	Control	Total Pacient
med. Art.	6.59	8.90667
dev. Std.	0.93029	1.06639
p		< 0.00001

Tabel 12: Valoarea plasmatică a TNF α

TNF α		
	Female Control	Female Pacient
med. Art.	7	9.03636
dev. Std.	1.03682	0.95002
p		0.00085

Tabel 13: Valoarea plasmatică a TNF α la sexul feminin

TNF α		
	Male Control	Male Pacient
med. Art.	6.18	8.83158
dev. Std.	0.67231	1.14652
p		0.00305

Tabel14: The serum TNF-α in males

Comparative analysis of TNF-α in myocardial necrosis markers showed a weak positive correlation between TNF-α and troponin T high-sensitive CK-MB, LDH and SGOT, regardless of gender (r between 0.0853 and 0.487) (Table no. 15)

Parameter	Female Pacient	Male Pacient	Total Pacient
Troponin T hs	0.0853	0.4022	0.3172
CK-MB	0.371	0.4488	0.4268
LDH	0.3916	0.1746	0.2629
TGO	0.487	0.4555	0.4201

Table no. 15: Correlations between TNF-α and Troponin T high sensitive CK-MB, LDH and TGO

2.2.3.Fibrinogen

Numerous studies in recent years have identified fibrinogen as an independent cardiovascular risk factor, as described several mechanisms by which it may increase cardiovascular risk. The link between inflammation and pathophysiology of atherosclerosis and myocardial infarction has become increasingly evident. The lesions of the vascular wall leading to the joining of monocytes and T-lymphocytes to the endothelial surface and, on the other hand, the release of various cytokines by both endothelial cells as well as of leukocytes. Cytokines, especially interleukin 6 stimulates the hepatic synthesis of acute phase reactive proteins (such as fibrinogen).

In patients with acute myocardial infarction with ST segment elevation at the time of admission there was a statistically significant increase in fibrinogen levels in all patients and female patient group, while its level in the group Male patient, even if they have a moderate to control group did not reach statistical significance .

FIBRINOGEN		
	Control	Total Pacient
med. Art.	343.9	412.4
dev. Std.	40.50363	64.49785
p		0.00162

Table 16: The fibrinogen

FIBRINOGEN		
	Female Control	Female Pacient
med. Art.	328.4	424.36364
dev. Std.	43.47758	53.37091
p		0.001745

Table no. 17: The amount of fibrinogen in women

FIBRINOGEN		
	Male Control	Male Pacient
med. Art.	359.4	405.47368
dev. Std.	34.64535	70.58043
p		0.087898

Table no.18: The fibrinogen level in males

In relation to markers of myocardial necrosis at the time of admission, in terms of plasma fibrinogen value is found: - a strong positive correlation with LDH in Male Patient group and Total Pacient ; - A moderate positive correlation with LDH in Female Patient group; - A weak positive correlation with high sensitive troponin T in all study groups, with CK-MB in Male Patient and Total Patient group and with TGO in all study groups; - A weak negative correlation with CK-MB in Female patient group (Table 19)

Parameter	Female Pacient	Male Pacient	Total Pacient
Troponin T hs	0.2568	0.3372	0.2779
CK-MB	-0.0384	0.2514	0.1821
LDH	0.5949	0.9272	0.7456
TGO	0.0047	0.372	0.2798

Table 19: Correlations between fibrinogen and Troponin T high sensitive CK-MB, LDH, TGO

2.3. RESULTS ON MARKERS OF PLAQUE INSTABILITY AND RELATIVE MARKERS OF MYOCARDIAL NECROSIS

2.3.1. Homocysteine

Studies in recent years have shown that elevated levels of homocysteine are an independent risk factor for developing coronary artery disease. Many of the effects of homocysteine are thought to be due to its atherogenic and prothrombotic.

In patients with acute myocardial infarction with ST-segment elevation data of our study showed a statistically significant increase in serum levels of homocysteine compared with the control group where women and Total Patient Patient. Men In patient group there was an increase in serum levels of homocysteine, but without reaching statistical significance.

HOMOCYSTEINE		
	Control	Total Pacient
med. Art.	10.83	14.14
dev. Std.	1.35241	3.83357
p		0.005748

Table 20: Value of plasma homocysteine

HOMOCYSTEINE		
	Female Control	Female Pacient
med. Art.	10.38	12.98182
dev. Std.	1.47716	1.96765
p		0.01008

Table 21: The plasma homocysteine in women

HOMOCYSTEINE		
	Male Control	Male Pacient
med. Art.	11.28	14.81053
dev. Std.	1.19457	4.49801
p		0.05038

Table 22: The plasma homocysteine in males

In terms of correlations with markers of cardiac necrosis, the study proved : a moderate positive correlation with Troponin T hs, regardless of gender; - A weak positive correlation with CK MB, regardless of sex, with LDH in Women Pacient group and Total Patient and with TGO in Male Pacient group and Total Pacient; - A weak negative correlation with LDH in Male Patient group and with TGO in Women Patient group

parameter	Female Pacient	Male Pacient	Total Pacient
Troponin T hs	0.5065	0.5694	0.5822
CK-MB	0.4061	0.2298	0.245
LDH	0.4337	-0.0389	0.0436
TGO	-0.1145	0.3014	0.293

Table 23: Correlations between homocysteine and high sensitive Troponin T, CK-MB, LDH and TGO

2.3.2. Adiponectin

Studies in recent years ("in vitro" animal models, clinical) had involvement of adiponectin in foreground different physiological or pathological processes. These studies have shown that adiponectin decrease inflammatory phenomena associated with atherosclerosis, reducing the expression of cell adhesion molecules (VCAM-1, ICAM 1) and cytokines. To induce activation of adiponectin vascular nitric oxide synthase. This enzyme is involved in the

synthesis of nitrogen monoxide (endothelium-derived relaxing factor - EDRF) responsible for vascular smooth muscle relaxation and inhibition of platelet aggregation.

Patients with acute myocardial infarction with ST segment analyzed in our study had serum adiponectin levels lower than those analyzed in the control group, this difference showing statistical significance relationship that was maintained regardless of sex. Men had lower serum adiponectin than women

ADIPONECTIN		
	Control	Total Pacient
med. Art.	9.1	6.42667
dev. Std.	1.3325	1.41005
p		< 0.00001

Table 24: The plasma adiponectin

ADIPONECTIN		
	Female Control	Female Pacient
med. Art.	10.08	7.24545
dev. Std.	1.01833	1.30028
p		0.000377

Table 25: The serum adiponectin in women

ADIPONECTIN		
	Male Control	Male Pacient
med. Art.	8.12	5.95263
dev. Std.	0.74632	1.27164
p		0.000771

Table 26: The serum adiponectin in males

In terms of correlations with markers of cardiac necrosis, the study proved : a strong negative correlation with high sensitive troponin T in Men Patient group; - A moderate negative correlation with high sensitive Troponin T in Female Pacient group and Total Patient and with TGO in Male Patient group and Total Pacient; - A weak negative correlation with CK MB in Male Pacient and Total Patient, with LDH and TGO in Female patient; - A weak positive correlation with CK MB in Female Patient Group

parameter	Female Pacient	Male Pacient	Total Pacient
Troponin T hs	-0.5712	-0.86	-0.7399
CK-MB	0.1648	-0.4728	-0.2535

LDH	-0.4465	-0.3553	-0.2797
TGO	-0.1757	-0.6096	-0.5115

Table no. 27: Correlations between adiponectin and high sensitive Troponin T, CK-MB, LDH and TGO

1.4. RESULTS ON MARKERS AND RELATIONSHIP LIPID MARKERS OF MYOCARDIAL NECROSIS

2.4.1. Total Cholesterol

Numerous studies of the last decades have shown that, in patients with acute myocardial infarction, serum lipids should be evaluated in the first 24 hours of symptom onset, because after this time, the values obtained do not reflect the true status of the patient , detecting serum concentrations are lower. This was attributed to an acute phase reaction that develops in the early hours of the onset of acute myocardial infarction, with the emergence of various local and systemic responses. This decrease lipid markers is not permanent, but noted a return to the level before the onset of myocardial infarction in 2 to 3 months after the acute event.

Our survey data showed an increase in serum levels of total cholesterol in patients with acute myocardial infarction compared with controls, the increase reaching statistical significance in the case group and Total Patient Female Patient.

TOTAL CHOLESTEROL		
	Control	Total Pacient
med. Art.	200.8	234.2
dev. Std.	17.69997	38.03574
p		0.005623

Table 28: The plasma total cholesterol

TOTAL CHOLESTEROL		
	Female Control	Female Pacient
med. Art.	192.2	229.81818
dev. Std.	18.61988	39.17861
p		0.031634

Table 29: The plasma total cholesterol in women

TOTAL CHOLESTEROL		
	Male Control	Male Pacient
med. Art.	209.4	236.73684
dev. Std.	13.16435	38.2039
p		0.067284

Table no. 30: The plasma total cholesterol in males

In terms of correlations with markers of cardiac necrosis, the study showed: - a moderate positive correlation with TGO in Male Patient group; - A weak positive correlation with high sensitive Troponin T in Male Pacient and Total Patient group, with CK-MB in Male Pacient group and Total Patient, with LDH in Male Patient group and with TGO in Total Patient group; - A weak negative correlation with Troponin T high sensitive in Female patient group, with CK MB in Female Patient, with LDH in Total Patient and Female Patient and with TGO in Female Patient group

parameter	Female Pacient	Male Pacient	Total Pacient
Troponin T hs	-0.1304	0.4423	0.3339
CK-MB	-0.1335	0.2664	0.1474
LDH	-0.4189	0.196	-0.1078
TGO	-0.129	0.5029	0.3694

Table 31: Correlations between total cholesterol and high sensitive Troponin T, CK-MB, LDH and TGO

2.4.2.LDL Cholesterol

It is confirmed by studies last year that LDL-cholesterol is a major risk factor for cardiovascular disease.

Comparing the mean values of LDL-cholesterol at admission (control group), there was an increase in serum LDL-cholesterol in patients with acute myocardial infarction, regardless of gender, without reaching statistical significance when Men group patients ($p = 0.099252$). Whether it is the study or control group, men had higher serum compared to women.

LDL CHOLESTEROL		
	Control	Total Pacient
med. Art.	104.6	129.9
dev. Std.	10.17841	32.07249
p		0.009844

Table 32: The plasma LDL Cholesterol

LDL CHOLESTEROL		
	Female Control	Female Pacient
med. Art.	98.8	126.81818
dev. Std.	4.54973	27.81301
p		0.022627

Table 33: The plasma LDL cholesterol in women

LDL CHOLESTEROL		
	Male Control	Male Pacient
med. Art.	110.4	131.68421
dev. Std.	11.32696	34.90472
p		0.099252

Table 34: The plasma LDL cholesterol in males

Correlations between LDL-cholesterol and myocardial necrosis markers showed the following: a moderate positive correlation with Troponin T high sensitive and TGO in Male Patient group; - A weak positive correlation with Troponin T high sensitive in Total Patient group, with CK-MB in Male Pacient and Total Patient, with LDH in Male Patient group and with TGO in Total Patient; - A moderate negative correlation with CK-MB in Female Patient group - a weak negative correlation with Troponin T high sensitive in Female Patient group, with LDH in Female Patient group and Total Pacient , with TGO in Female Patient

parameter	Female Pacient	Male Pacient	Total Pacient
Troponin T hs	-0.3494	0.61	0.4741
CK-MB	-0.503	0.415	0.1797
LDH	-0.4618	0.1808	-0.0919
TGO	-0.3661	0.5155	0.4294

Table 35: Correlations between LDL cholesterol and high sensitive Troponin T, CK-MB, LDH and TGO

2.4.3.HDL Cholesterol

Numerous epidemiological studies in recent years have shown an inverse relationship between HDL-cholesterol and cardiovascular diseases. The serum level of HDL-cholesterol decreased is one of the markers of the metabolic X syndrome.

Our survey data showed a statistically significant decrease in serum HDL-cholesterol in patients with acute myocardial infarction with ST-segment elevation in all patients and Female patient group, while its level in the group Male Patient has slightly decreased compared to group witness, without reaching statistical significance.

HDL CHOLESTEROL		
	Control	Total Pacient
med. Art.	51	44
dev. Std.	8.32666	0.43932
p		0.001971

Table 36: The plasma HDL Cholesterol

HDL CHOLESTEROL		
	Female Control	Female Pacient
med. Art.	56	45.72727
dev. Std.	5.47723	5.04164
p		0.001227

Table 37: The plasma HDL cholesterol in women

HDL CHOLESTEROL		
	Male Control	Male Pacient
med. Art.	46	43
dev. Std.	7.96869	5.53775
P		0.167403

Table 38: The plasma HDL cholesterol in males

The survey data allowed the correlation of HDL-cholesterol in serum markers of myocardial necrosis. Was obtained: - a moderate negative correlation with TGO and Troponin T high sensitive in Male Pacient group; - A weak negative correlation with Troponin T high sensitive in Total Patient group, with CK-MB in Male Pacient and Total Patient, with LDH in Male Patient group and with TGO in Total Patient; - A weak positive correlation with markers of myocardial necrosis in Female Patient group.

parameter	Female Pacient	Male Pacient	Total Pacient
Troponin T hs	0.2488	-0.5203	-0.4159
CK-MB	0.4674	-0.3815	-0.1296

LDH	0.1658	-0.2012	0.0018
TGO	0.4214	-0.5293	-0.4051

Table 39: Correlations between HDL cholesterol and high sensitive Troponin T, CK-MB, LDH and TGO

2.4.4. Triglycerides

Numerous studies in the last decades have shown an association between increased serum levels of triglycerides and cardiovascular disease. The importance of measuring triglycerides is demonstrated and their introduction in defining metabolic syndrome X. However, the extent to which triglycerides directly promote cardiovascular disease or is merely a biomarker of risk, yet arousing intense debate. Meta-analysis of recent years tend to fall into the category value triglycerides independent predictors for cardiovascular diseases.

Patients with acute myocardial infarction with ST segment elevation on admission showed serum triglyceride levels higher than those measured in the control group, reaching statistical significance but only in Total Patient Group.

TRIGLYCERIDE		
	Control	Total Pacient
med. Art.	135.8	181.13333
dev. Std.	16.75178	58.56722
p		0.010794

Table 40: The plasma triglycerides

TRIGLYCERIDE		
	Female Control	Female Pacient
med. Art.	129	161.81818
dev. Std.	18.50676	50.56643
p		0.093551

Table 41: The plasma triglycerides in women

TRIGLYCERIDE		
	Male Control	Male Pacient
med. Art.	142.6	178.89474
dev. Std.	13.16435	71.78277
p		0.139915

Table 42: The plasma triglycerides in males

In terms of correlations with markers of myocardial necrosis, the data obtained showed: - a moderate positive correlation with CK-MB and TGO in Male Patient group; - A weak positive correlation with Troponin T high sensitive in both sexes, with CK-MB in Female Pacient group and Total Patient, with

LDH in Male Patient group and with TGO in Total Patient Group; - A weak negative correlation with LDH in Total Patient and Female Patient and with TGO in Female Patient group (Table 42)

parameter	Female Pacient	Male Pacient	Total Pacient
Troponin T hs	0.0511	0.378	0.2969
CK-MB	0.016	0.5157	0.315
LDH	-0.1715	0.2288	-0.0008
TGO	-0.0102	0.5406	0.4409

Table 43: Correlations between triglycerides and high-sensitive troponin T, CK-MB, LDH and TGO

2.4.5. Apolipoprotein B

The data analyzed in the study demonstrated a statistically significant increase in serum levels of apolipoprotein B in patients with acute myocardial infarction with ST-segment elevation. This increase has been in both subgroups - Female Patient, Patient-Men, but without reaching statistical significance in the case group patient Men.

APOLIPOPROTEIN B		
	Control	Total Pacient
med. Art.	1.189	1.67233
dev. Std.	0.23024	0.5734
p		0.006957

Table 44: The levels of apolipoprotein B

APOLIPOPROTEIN B		
	Female Control	Female Pacient
med. Art.	1.16	1.66182
dev. Std.	0.24083	0.48064
p		0.023263

Table 45: The levels of apolipoprotein B in women

APOLIPOPROTEIN B		
	Male Control	Male Pacient
med. Art.	1.218	1.67842
dev. Std.	0.24325	0.63346
p		0.06498

Table 46: The levels of apolipoprotein B in male

Correlations with markers of cardiac necrosis showed: - a strong positive correlation with Troponin T high sensitive in Male Patient group; - A moderate positive correlation with Troponin T high sensitive in Total Patient group, with CK-MB in Total Patient and Male Pacient

and with TGO in Male Patient group and Total Patient; - A weak positive correlation with CK-MB in Female Pacient, with LDH in Male Patient group and Total Pacient and with TGO in Female Patient group

parameter	Female Pacient	Male Pacient	Total Pacient
Troponin T hs	-0.0022	0.7606	0.6349
CK-MB	0.2057	0.6199	0.5181
LDH	-0.0966	0.3011	0.1273
TGO	0.06	0.6592	0.601

Tabel 47: Corelații între apolipoproteina B și Troponina T înalt sensibilă, CK-MB, LDH și TGO

2.5. CORRELATIONS BETWEEN MARKERS STUDIES

According to Table 48 there is a strong negative correlation between adiponectin and total cholesterol in women control group (r = - 0.55) and in total control group (r = - 0.6) and one moderately negative for the group of men patients (r = - 0.28). Between adiponectin and HDL cholesterol there was a strong positive correlation for the control group women (r = 0.56) and a moderately positive for the male patient group (r = 0.42), total control (r = 0.42) and all patients (r = 0.39). Strong negative correlation existed between adiponectin and LDL cholesterol in men control group (r = - 0.77), total control (r = - 0.64) and a moderately negative for men patient group (r = - 0.49) and all patients (r = - 0.36). Between adiponectin and triglycerides found a strong negative correlation in women control group (r = - 53), female patient group (r = - 0.58) and a moderately negative for total control group (r = - 0.41) and all patients (r = - 0.38). Strong negative correlation with high sensitive C-reactive protein existed in men control group (r = - 0.66), male patients (r = - 0.89), all patients (r = - 0.64). Strong negative correlation with high sensitive troponin T was recorded for female patient group (r = - 0.57), male patients (r = - 0.86) and all patients (r = - 0.74).

	Female Control	Male Control	Female Pacient	Male Pacient	Total Control	Total Pacient
Total Cholesterol mg/dl	-0.55	-0.02	0.02	-0.28	-0.6	-0.19
HDL mg/dl	0.56	-0.75	0.14	0.42	0.42	0.39
LDL mg/dl	0.22	-0.77	-0.12	-0.49	-0.64	-0.36
Triglyceride mg/dl	-0.53	0.57	-0.58	-0.3	-0.41	-0.38
PCR hs mg/l	- 0.05	-0.66	0.04	-0.89	-0.24	-0.64
Troponin T hs pg/dl	-0.23	-0.11	-0.57	-0.86	-0.08	-0.74

Table 48: Correlation between adiponectin and lipid profile, high-sensitive C-reactive protein and troponin T high-sensitive among the groups studied

According to Table 49 there is a moderate negative correlation between homocysteine and fibrinogen in women control group (r = - 0.5115), a moderately positive for control men group (r = 0.7225), female patients (r = 0.4062) and a weak negative for men patient group (r = 0.0522), total control (r = 0.0831) and total patient (r = 0.068). Between homocysteine and HDL cholesterol there was a moderate positive correlation for the control group women (r = 0.7891), male controls (r = 0.5848), a weak positive for women patient group (r = 0.3845), total control (r = 0.261) and a weak negative for men patient group (r = -0.1238) and all patients (r = -0.0856). Moderate positive correlation existed between homocysteine and LDL cholesterol in men control group (r = 0.7549), total control (r = 0.511), a moderate negative for female patient group (r = -0.8021), and a weak positive in women control group (r = 0.0043), male patients (r = 0.2249) and total patient (r = 0.0716).

	Female Control	Male Control	Female Pacient	Male Pacient	Total Control	Total Pacient
Fibrinogen mg/dl	-0.5115	0.7225	0.4062	0.0522	0.0831	0.068
HDL mg/dl	0.7891	0.5848	0.3845	-0.1238	0.261	-0.0856
LDL mg/dl	0.0043	0.7549	-0.8021	0.2249	0.511	0.0716

Table 49: Correlations between homocysteine and fibrinogen, HDL-cholesterol, LDL-cholesterol between the groups studied

CONCLUSIONS

1. Markers of myocardial necrosis (Troponin T high sensitive CK-MB, LDH, SGOT) are significantly increased ($p < 0.05$) in patients with acute myocardial infarction with ST segment elevation, regardless of sex or age.
2. Use highly sensitive assay for troponin T improves diagnostic accuracy in patients with suspected AMI, while a negative result is also a negative predictive value.
3. Research and testing cardiac Makers (old or new), continues to evolve based on the emergence of improved technologies and according to results of clinical trials among patients with acute myocardial infarction with ST segment elevation.
4. Combined use of these markers may provide valuable information for clinicians in the diagnosis of acute myocardial infarction with ST-segment elevation in the context of joint line data evaluation and treatment specialist guides.
5. Measurement highly sensitive troponin T is more specific than CK-MB for the diagnosis of acute myocardial infarction and more sensitive for detecting minor myocardial damage, and we suggest that this test will eventually replace the need for measurement of CK-MB.
6. Regarding lipid fractions determined in the first 12 hours of admission, nostrum study confirm the data from the literature: in patients with acute myocardial infarction with ST segment elevation recorded a statistically significant increase in total cholesterol, LDL-cholesterol and triglycerides compared to the control group, while HDL-cholesterol if there was a statistically significant decrease.
7. Our study showed a negative correlation between adiponectin and total cholesterol, LDL cholesterol, triglycerides, and a positive one between adiponectin and HDL cholesterol, indicating adiponectin as a protective factor in the risk profile of the patient.
8. Negative correlation exists between adiponectin and high-sensitive troponin T may be a demonstration of increased accumulation of adiponectin in vascular subendothelial in trying to fix and limit infarct.
9. Acute phase reactants shows a significant increase in all patients with acute myocardial infarction with ST-segment elevation compared to the control group.
10. Myocardial infarction is accompanied by major acute response of C-reactive protein. Studies have shown recently that C-reactive protein and complement-related cardiovascular diseases: C-reactive protein induces the expression of adhesion molecules in human endothelial cells. These findings support the assumption that CRP plays a direct role in promoting the inflammatory component of atherosclerosis.

11. Our study demonstrated the negative correlation between adiponectin and high-sensitive C-reactive protein, TNF-alpha, respectively, in the early hours of acute myocardial infarction with ST segment elevation, which supports the idea of anti-inflammatory effect of adiponectin.

12. Strong link between serum levels of fibrinogen and LDL cholesterol suggests that the increased risk of cardiovascular disease associated with elevated levels of LDL may be mediated in part by fibrinogen.

13. During the first hours of the onset of myocardial infarction with ST segment there was an increase in serum levels of homocysteine, which can be considered an independent risk factor for ischemic heart disease, similar to dyslipidemia.

14. Elevated serum levels of TNF-α since the onset of acute myocardial infarction with ST segment elevation, make us believe that this therapeutic intervention may be an objective marker for future studies.

15. Previous studies have shown that a decrease in CRP levels can be achieved with statins, and this seems to be associated with a better prognosis of patients with acute myocardial infarction. A possible role for C-reactive protein in patients with STEMI guide treatment may make the subject of future work.

16. Values at admission plasma fibrinogen and strong positive correlation with LDH, reflecting increased inflammatory activity in acute myocardial infarction with ST segment elevation, and similar data from the literature, fall into the category of fibrinogen independent risk factors ischemic heart disease.

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