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RESEARCH ARTICLE

CARDIOMYOCYTE MEMBRANE PATHOGENETIC MECHANISMS AND BIOCHEMICAL-INDUCED ENDOTHELIAL - CORONARE IN CHRONIC ISCHEMIC HEART DISEASE

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ABSTRACT

Regardless of the form which is manifested clinically by degenerative diseases such as cardiovascular diseases, it triggers the pathogenic mechanism as a first modification of the fluidity, that the membrane permeability, in particular of the cellular and mitochondrial. The process begins at membrane level and endothelium coronary to cardiomyocyte sarcolemma through the release of arachidonic acid and catalytic conversion. Secondary functionality disruption occurs receptors and membrane pumps, especially those cationic consequences for the balance transmembrane ion compounds and availability of macro downward energy capital of cardiomyocytes. This work synergistically with ionic concentration camps sarcoplasmatice disorders, particularly Ca2 + will interfere-contract excitation coupling process and that of acto-myosin contractile achieve complex, leading to myocardial contractile deficit installation.

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INTRODUCTION

Cardiovascular diseases are one of the major causes of morbidity and mortality in the world, predominantly in industrialized countries (Damasceno *et al*., 2009; Florescu *et al*., 2007). Social impact that they develop it, particularly chronic ischemic heart disease and its forms on both quality of life and on health systems justifies constant interest for research in cardiovascular pathology of these diseases (Dincă and Manole, 2013). Illustrative in this respect is heart failure as one of the clinical manifestations of chronic ischemic heart disease, with prevalence increasing syndrome (2.3 - 2.5%), which "commits" the most costly expenditure by schemes health in European countries for cardiovascular diseases (Leal *et al*., 2006). Pathogenic mechanism morpho-functional heart disease chronic involve dynamic coexistence of two processes: the installation of coronary atherosclerosis, as an expression of endothelial dysfunction as early stage that the secondary drives reduce microcirculation level body responsible for presence of hypoxia/ischemia the myocardium. The persistence of this pathogenic mechanism consisting of flow reduction regional level leads to myocardial fiber secondary myocardial dysfunction induced by at least the following mechanisms:

- Stress local oxidative;
- Local inflammation, with the particular character of being diffused;
- Remodeling of the myocardium;
- Cardiomyocytes apoptosis;
- Alter qualitative organelles cardiomyocytes;
- To prevent the expression of the contractile myofibrils to perform their duties as a result of the existence of a production deficit or deficit control energy use, but also pertur-link bar ca2 + sarcoplasmatic concentration.
- Remodelare myocardium;
- Participation immune.

Agonist doing all these mechanisms lead to deterioration of contractility and / or myocardial diastolic relaxation, that is, heart failure (IC).[Fig.1].

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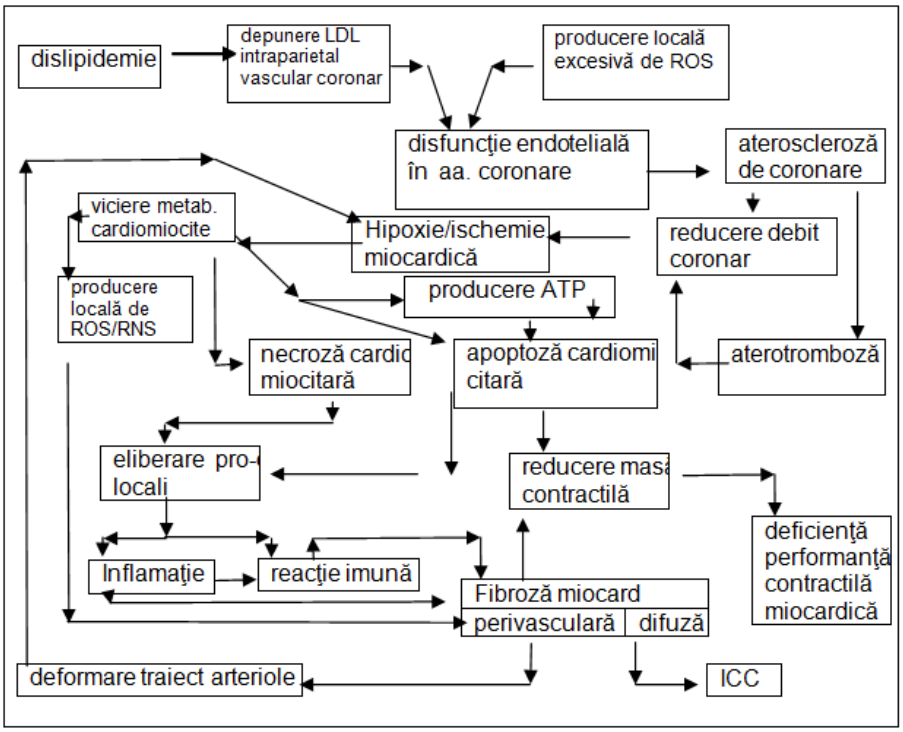

Fig.1. The pathophysiological mechanisms of the ICC, installed by ischemic heart disease (Manole Gh, 2003)

As shown in the previous figure, dynamic, morphological and pathophysiological coronary atherosclerosis implies the existence of two distinct processes: one difficult to reverse, which causes a progressive narrowing of the arterial lumen, and other dynamic and potentially reversible one, which is superimposed the first leading to rapid occlusion, total or partial, by thrombosis or spasm. Histopathological studies of the myocardium supplied by the damaged vessels are in the first process described, the decrease of coronary blood flow, they found a wide range of modifications, of normal appearance to highlight the varying degrees of focal necrosis, surrounded by areas of inflammation. Compared to ischemic myocardial contractile deficiency the stage, histopathology revealed the coexistence of three processes: quantitative reduction of cardiomyocyte replacement by segmental interstitial fibrosis and hypertrophy miocardocitelor waste (Forţofoiu *et al*., 2010). Developing these changes syncytia infarction heart failure of ischemic came amid aggression is an expression of oxidative stress at the cellular level and coronary infarction, caused primarily by activation of NAD (P) H and the secondary of myeloperoxidase. In the human body to produce endogenous source deployment catabolism oxidizing agents is that the conditions of a hypoxia / ischemia leading to myocardial concentration increases their oxidative stress. Of the two forms that coexist reactive oxygen species (free radicals and non-radicals), first because of the structure characterized by the presence of a doublet electronic incomplete are unstable molecules chemically eager to extract electrons from other molecules, especially functional or structural proteins are oxidized default. (Hein *et al*., 1995)

Particular biochemical behavior, transforms ROS, namely nitrogen (RNS) in the carrier's carriers extracellular signals that modulate intracellular can expression of genes involved in cardiovascular diseases, thus influencing rates synthesis of most cytokines mediator in development (Bobescu, 2007; Dincă *et al*., 2013; Dincă and Manole Gh, 2013). The process begins by the destructive action of ROS / RNS on polyunsaturated fatty acids, oxidative-minded constituents of biomembranes, present in a proportion of 60-65 in structural mass. Pro-oxidative action of oxygen free radicals is dual: direct the oxidative catabolism of lipids and secondary by intermediate products generated after peroxidative cascade of reactions that implicitly quantitative amplifier has a role.(16).(Fig.nr. 2)].

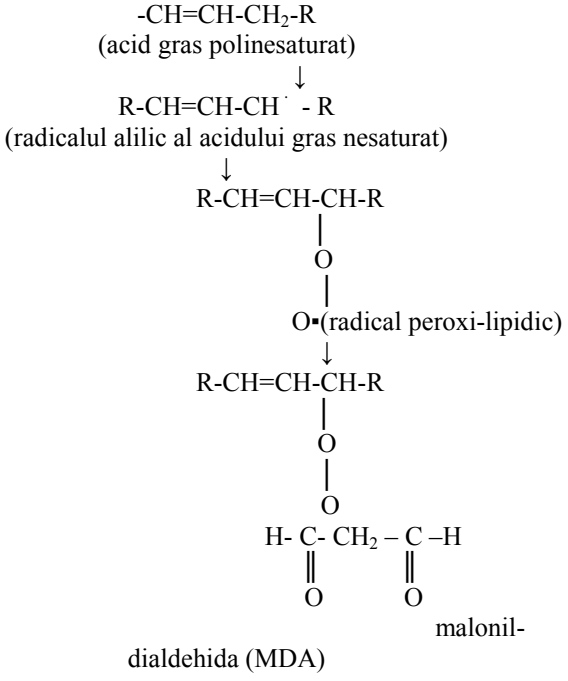

Fig.2. Waterfall lipid peroxidation (Radu *et al*., 2010)

Oxidative Sensitivity of membrane phospholipids results in bad modify both the fluidity and membrane permeability, and in particular cellular or mitochondrial affecting:

a. passive transport of intra- and extra cellular compartments / cardiomyocyte;

b. reducerea activity-dependent ATPase pump;
c. decrease calcium ion transport membrane by ATP-ase involvement of Ca2 + and calmodulin;
d. reducing oxygenation intra-cardiomyocyte;
e. loss of sensitivity and affinity of various membrane receptors;
f. the reduction of their number and cross-linking the possibility of, in particular, NMDA receptors and the cholinergic - muscarinic.

A.The process starts on the membrane destructive endothelium coronary to cardiomyocyte sarcolemma and through the release of arachidonic acid activation cyclooxygenases and lipoxigenase involved in the formation of peroxides (129). Fig. no.3

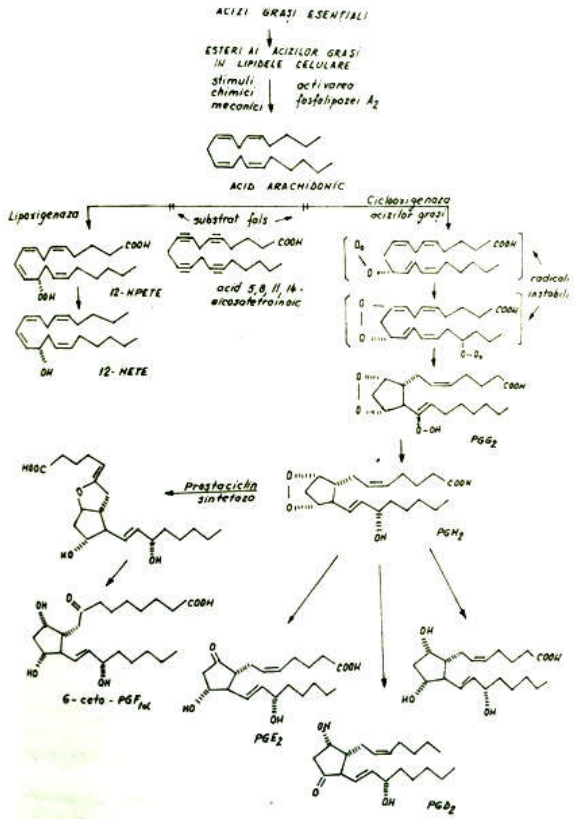

Fig. 3. Biosynthesis of eicosanoids derived from arachidonic acid (Manole Gh, 2003)

B. Subsequently, the decomposition of the peroxide takes place in the peroxy or alkoxy radicals that initiate and propagate lipid peroxidation, membrane proteins as well as the degradation of the vicinity (Bobescu, 2007). a. Figure No. 3 highlights how the activation of cyclooxygenases generate unstable cyclic endoperoxides, such as prostaglandin G2 (G2 PG), which generates hydroperoxidase under the catalysis of H2 (Pg.H2). The process is only one step in the development cardiomicitelor destruction, as it continues through the formation of lipid peroxidation products of prostanoids and / or thromboxanes. (Fig. No. 4)

b. From lipoxigenase action on arachidonic acid activated from the sarcolemma form two groups of leukotrienes:

1. Sulfidopeptide (LTC4, LTD4, LTE4) to be stimulated by tumor necrosis factor (TNF). (Fig.5).
2. Sulfopeptide, leukotriene B4 type that develops direct effect of increasing vascular resistance and reduced myocardial fiber inotropism (Fig.5).

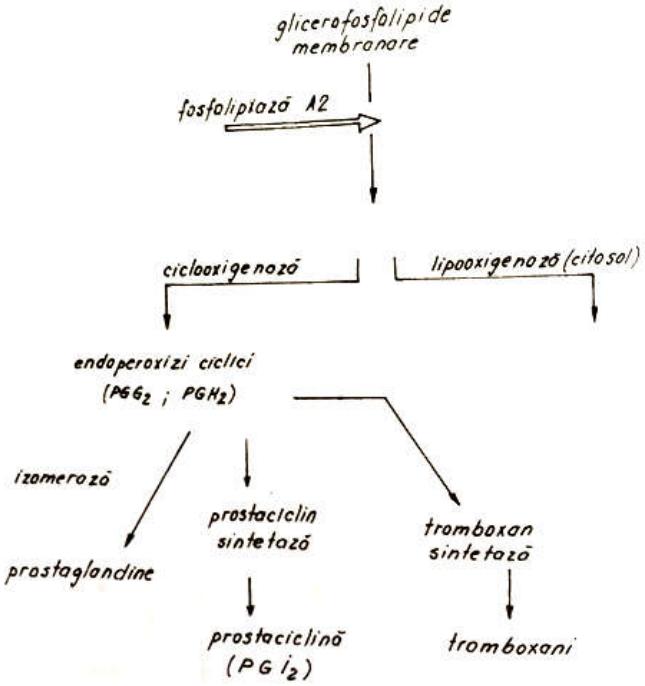

Fig.4. Cyclooxygenases involvement in various membrane synthesis (Manole Gh, 2003)

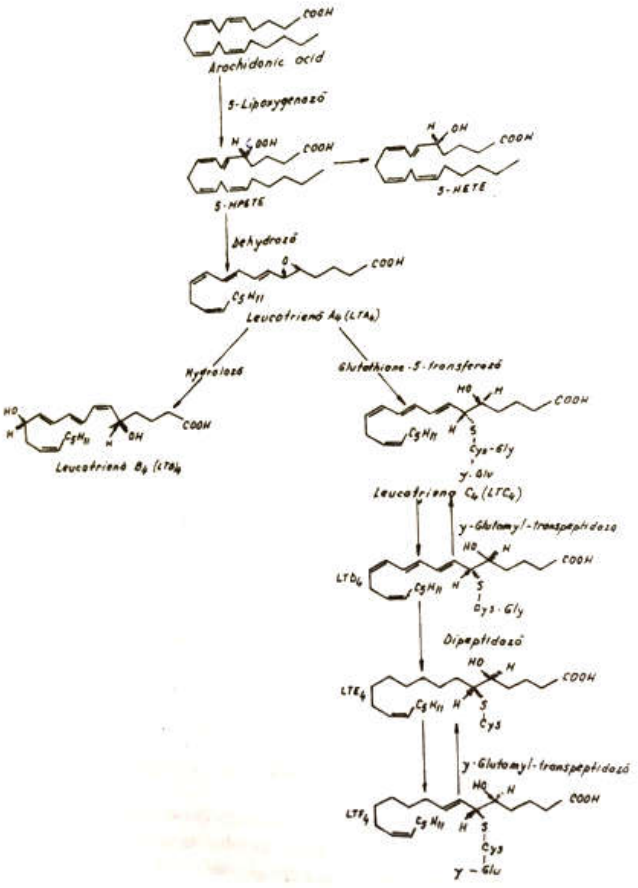

Fig. 5. Leukotriene synthesis structure (Manole Gh, 2003)

C. The resulting compounds subsequently develop dual effect: disrupting affinity receptors in the sarcolemma cardiomyocytes

ligands signal carriers, such as hormones and cytokines, as well as the functionality of the enzymes involved in the metabolism of the tissue at this level, such as glucose-6-phosphatase and glycerol -3-phosphate acyl transferase. Thus, they are respon-bili oxidation of SH groups methionine-rich transmembrane channels, with direct consequence on the production of compounds macroergic. [(1) Fig.6.].

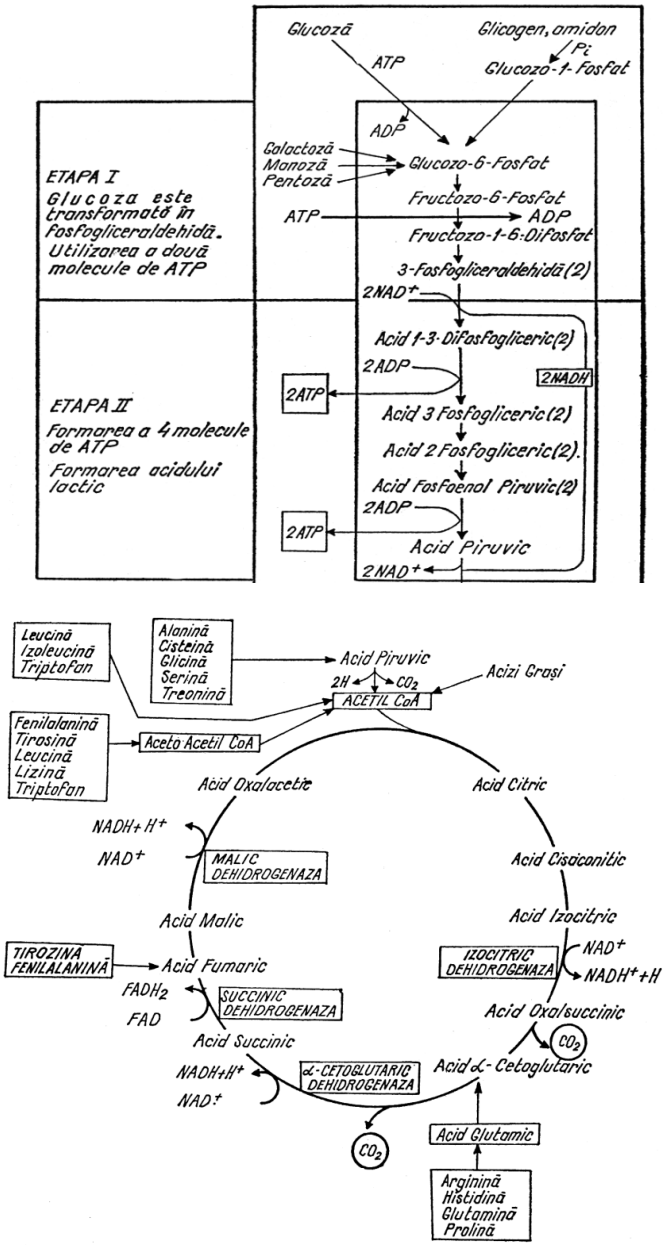

Fig.6. Interference pathways of carbohydrate catabolism (Manole Gh, 2003)

D. Capital decrease energy myocardial fiber contributes additional functionality to disruption of membrane receptors and pumps, especially those cationic consequences for the transmembrane ion balance. Under oxidative stress are affected, in particular, cationic endoplasmic reticulum pumps that are involved in the relaxation of cardiac Na + - K + -ATPase and Ca_2+ -ATPase (Bobescu, 2007). Installs it diastolic dysfunction, as an expression of double interference mechanism by which the myocardial relaxation: the mechanical detachment consisting of myofibrils myosin and actin from those of the ionic-electric charge repolarization.

E. The mechanism whereby actin and myosin mechanically interact is dependent on the concentration intra - cardiomyocyte Ca_2 +. This is accomplished both by the influx / efflux of Ca_2 + membrane, and by increasing the process releaser / reuptake ion in cardiomyocyte tanks. The membrane-cation is carried out by activating the Na + - K + -ATPase, and the Ca_2 + -ATPase.

a. Pump Na + - K + -ATPase discovered in 1957 by Jons Skou is dependent on the energy source located on the internal face of the sarcolemma. Molecular pump mechanism postulated by Hodgkin and Huxley Eccles operates only during the rest period of the cell membrane, providing uneven distribution of the ions sodium, potassium, respectively. Exchange membrane disruption physiological expulsion of three sodium ions against the concentration gradient and electric, with the influx of two potassium ions takes place throughout the process of depolarization of the sarcolemma (phase III). Pump is coupled to ion exchange Na + / Ca_2 + and explaining the underlying mechanisms involved in myocardial contractile install diastolic dysfunction. Physiologically, ion exchange Na + / Ca_2 + is a system of counter-transport functions in both directions, according to membrane potential and ionic gradients existing at a time, following the maintaining of a low concentration of Ca_2 + the intra-fiber infarction.

b. In the process of inducing and maintaining a low concentration of calcium ions in cardiomyocytes monoionic pump intervenes, Ca2 + -ATPase. The pump is activated by calcium ions increase the myocardial fiber sarcoplasm and functional process is regulated through phosphorylation-dependent cAMP. Ca2 + from intracellular transport which is reduced to the extracellular concentration (where the concentration is high) consumes energy, but poor in fiber oxidative stress myocardial subject. (Manole Gh, 2003). In myocardial fiber, electrochemical gradient of Ca_2+, sarcoplasmatic concentration = 10-7 / extracellular concentration = 10-3 maintain and involving mitochondria and endoplasmic reticulum cisterns to absorb cation. In cardiomiocitul undergoing an excess concentration of oxidants, both organelles were disrupted functionality (Manole Gh, 2003). At the level of cardiomyocytes and endothelium coronary subjected to hypoxia, the ROS / RNS-cell destruction is self-sustaining not only affected the energy metabolism, but also the ability antioxidative defense.

a. Process responsible for disrupting the synthesis of ATP by increasing the tissue concentration of ROS / RNS is to restructure the mitochondrial DNA with the formation of abnormal respiratory chain complex. Their formation directs abnormal and chaotic "game" of electrons, that leads to a double effect: stop the multiplication synthesis of compounds macroergic and concentration particularly radical oxygen species by positive feedback mechanism. The dynamic augmentation of oxidative stress leads to impaired functional device and the mitochondrial membrane from the space intermembranar by hiperpermeabilizare. Pathogenic process becomes responsible for mass reduction in myocardial contractile cardiomyocyte apoptosis and activation of fibroblasts synthesize collagen in excess (Moraru *et al*., 2013). In clinical plan, their installation transforms into ischemic myocardium deficient in terms inotropismului, appearing in this way by systolic dysfunction heart failure (Dincă *et al*., 2013; Dincă and Manole Gh, 2013).

b. Disruption of protein-synthesis at the level of the occurrence of the expression of DNA mutations or alterations of the correct expression of the gene by changing the type of nitrogenous bases, deoxyribose oxidation, chain breakage and development of cross-linkage between nucleotides, and proteins (Sandu, 2010).

Membrane-affected by oxidative stress and protein constituents of connexin gap junction and family members. However, Cx37, Cx43 and Cx45 are integral membrane proteins that contain four transmembrane domains, and both ends N and C-termini in the cytoplasm. At the sarcoplasmic cardiomyocytes are currently last two members of the family, the latter prevailing. Of the two types of membrane are presented in the Cx43 isoform, it is the active phosphorylated. In chronic ischemic cardiomyopathy and left ventricular hypertrophy occurring as a compensatory mechanism induced by oxidative stress histological studies revealed the existence of alteration of the number, organization and distribution of connexin 43 gap junctions loss (Hoshida *et al*., 1996; Kaminischi *et al*., 1989; Jovanovic *et al*., 1998). Destructive process oxidative stress protein is localized exclusively membrane but also sarcoplasmatic.As an histological arguments in this regard are the findings of acto-myosin myofilaments like that are damaged, staple and arranged disorderly, and troponin I is a functional molecule is truncated insensitive to Ca_2 +. (Taus *et al*., 2010). Summarizing myocardial degenerative diseases that lead ultimately to the inotropism deficit are in fact biochemical complication of coronary atherosclerosis lesions from the cardiomyocyte membrane and extending sarcoplamatic, including affecting the proper functioning of the nuclear chromatin.

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