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Research Article

Novel Potential Biomarkers in Cardiovascular Diseases

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Abstract

One of the critical medical topics researched is identifying the most diverse diseases of new molecular biomarkers that would establish a positive diagnosis, and respond to an indeed shown treatment (risk biomarkers). Prolonging the lifespan of individuals and increasing the frequency of heart failure from 1-2% in the adult population, regardless of age, to 10 - 12% in people over 70 explains the worldwide interest in identifying biomarkers and in this condition, regardless of etiology, which offers the possibility of complex assessment of the situation, including the prognosis.

In the studies published so far, we aimed to demonstrate the involvement of enzymes as biomarkers of diastolic dysfunction generating heart failure (i.e. we studied the possibility of osteopontin as a biomarker of heart damage and injury, because it is involved in the generation of myocardial inflammation, a process present in the deficient contractile myocardium). For medical practice, in the variant in which the research efforts of some of these will impose them as biomarkers, they become a means/method of diagnosis of the studied heart disease, which allows significant reduction of decision times and prompt/early initiation of therapy. The effects are beneficial for both the patient, the family and society, as they are real forms of secondary prevention and reduction of hospitalization costs.

Keywords: *Cardiovascular Diseases; Atherosclerosis; Risk Biomarkers*

Introduction

After the studies about biomarkers in 1989 as a means of diagnosis and prognostic evaluation in cardiovascular diseases, although a considerable number of serum compounds (cytokines, chemokines, or even hormones) have been studied for use as markers, only circulating natriuretic peptides have were admitted as specifically expressing the existing myocardial contractile deficit.

In current medical practice, biomarkers have proven useful in terms of current challenges and the impact they have in establishing diagnosis, risk assessment and therapeutic response. This is because the dynamic follow-up of biomarkers allows the attending physician to draw up the disease management plan, but also the individual therapeutic plan (personalized medicine).

In cardiology, the intake of biomarkers is low, because their recognized number is small and their positivity does not allow an early diagnosis of the disease. Such a desideratum is the main argument for which, worldwide, efforts are focused to identify biomarkers, espe-

cially in chronic ischemic heart disease and diastolic myocardial contractile dysfunction. Research efforts to identify biomarkers specific to such conditions from the stage when they evolve latently/silently are fully justified, as they allow to adequately treat their evolution, preventing and delaying the occurrence of complications that generate sequelae and require high financial costs (secondary prevention).

The usefulness/need to identify new biomarkers in cardiovascular diseases is demonstrated by the intake of established dosage, which determined as laboratory parameters, contribute in daily medical practice to significantly reduce decision time and allow the initiation of prompt therapy.

One of the areas of global medical research is the one that aims to identify new biomarkers in diseases such as chronic ischemic heart disease or congestive heart failure. These biomarkers, structurally, are peptides/proteins and microRNAs, which can be measured in plasma and can demonstrate that they represent structural changes in cardiomyocytes, functionally expressing the underlying pathophysiological processes.

Pathogenic, it is considered that biomarkers in these diseases are the result of exposure of myocardial fibers to oxidative stress, responsible for inducing apoptosis and/or necrosis, which lead to massive reduction in myocardial mass, pathogenic substrate generating congestive heart failure.

Another study objective that we proposed was to investigate the possibility of constituting complex biomarkers, compounds that result from the association of at least two possible individual biomarkers or by their association with some paraclinical parameters.

For a medical practice, the identification of possible circulating biomarkers associated with data provided by other paraclinical investigations (echocardiography) could constitute complexes/associations of markers is a real help to establish a definite positive diagnosis and possibly risk in the evolution of the disease.

Materials and Methods

Our studies were performed on patients diagnosed with heart failure due to chronic ischemic heart disease as a unique etiology. In particular, we conducted research on cases of diastolic heart failure with preserved ejection fraction because it represents about half of the total morbidity of this type, and the symptoms presented are nonspecific, make positive diagnosis difficult and delay the establishment of appropriate therapy. These arguments fully justify the interest of research to identify molecules that allow an early diagnosis of myocardial inotropic deficiency caused by myocardial ischemia. Although the pathogenesis of this form of heart failure is relatively little known, the hypothesis of the existence of a diastolic dysfunction materialized by the depreciation of isovolumetric ventricular relaxation and the reduction of left ventricular compliance is unanimously accepted. In our studies, we selected cases of heart failure caused by myocardial ischemia caused by atherosclerosis (ATH) because this is the most common etiological condition in cardiovascular diseases (75% of them). Thus, ATH is the cause of strokes (ischemic and/or hemorrhagic) in a percentage of 43%, but also of the installation of chronic ischemic heart disease, 47% recognizing as aetiopathogenesis the presence of coronary localization. The results of our studies undertaken in the last three years, following the research of possible biomarkers on the two mentioned heart diseases, were published in the form of seven articles, of which three in the Journal of Enzyme Inhibition and Medicinal Chemistry (published by Taylor and Francis Group), a journal listed by Clarivate Analytics in ISI Thomson Master Journal List (IF = 4.673), other five other articles in the Romanian Journal of Revista de Chimie (Bucharest), and presentations at national and international Conferences or Congresses [1-9].

Results and Discussion

In the dynamics of its development, ischemic heart disease "take on" different forms of manifestation, from the silent form to the one that generates severe or painful arrhythmias such as angina or acute myocardial infarction. Also, the onset of chronic heart failure is an-

other etiopathogenic way of developing coronary localization of atherosclerosis. ATH with coronary localization at the myocardial level disrupts the optimal irrigation of cardiomyocytes, induces by oxidative stress and a deficit of energy synthesis the progressive deterioration of the myocardial inotropic. The condition known as myocardial contractile dysfunction, more common in diastolic form, manifests as congestive heart failure, with or without preservation of the ejection fraction. Diastolic myocardial contractile dysfunction usually precedes the onset of the state that also alters the systolic function and is among the disabling morbid conditions and those that lead to death. For this reason, worldwide, one of the objectives of research in cardiovascular diseases is to identify biomarkers that allow early positive diagnosis or be established as risk markers, to monitor the evolution of the disease.

The topicality of such topics studied in the research team and the published results on possible biomarkers in chronic ischemic heart disease and/or heart failure due to diastolic dysfunction results from the data of the international medical literature of recent decades which record that risk prediction models are a constant concern of large-scale research, are still in the search period. Although numerically, quasi-continuously, new serum, genomic or proteomic markers are proposed for the prediction of risk in cardiovascular diseases that have as etiology atherosclerosis in general, for those with coronary localization manifested as chronic ischemic heart disease or heart failure with such an aetiopathogenesis, so far only two specific biomarkers have been identified, namely atrial natriuretic hormones, primarily type B and troponin. The need to identify such biomarkers to allow on the one hand the early evaluation of the two diseases we selected for the study, and on the other hand the optimization of treatment to delay their complications is imposed by the goal of minimizing some consequences such as significant deterioration of the quality of life, high medical and social costs etc.

Diastolic heart dysfunction was recognized in medical practice as a new clinical form of heart failure in 1991, is defined as a clinical syndrome generated pathogenic by abnormalities of filling and ventricular relaxation, especially the left, expressing, at least in the initial periods of the disease, in the form of heart failure with diastolic dysfunction with preserved ejection fraction. Echocardiographically, its defining characteristic is maintaining the systolic flow (≥ 45% of the value accepted as expected), contrary to the diastolic function that is already disturbed. In conditions of hypoxia/myocardial ischemia, the distensibility disorders of the left ventricular myocardium are the expression of the existence in the heart of healthy areas and ischemic areas, even fibrous, which alter its intrinsic and extrinsic distensibility, generating a delay and inhomogeneity of relaxation, phenomena which increase the effort. The primary pathological mechanism by which such histological changes are induced, generating alterations in myocardial contractile function, is oxidative stress caused by myocardial dysfunction due to coronary atherosclerosis. Coronary atherosclerosis, etiologically responsible for chronic myocardial irrigation, induces excessive reactive oxygen and nitrogen species (ROS/RNS) production, developing evolutionary diastolic heart dysfunction.

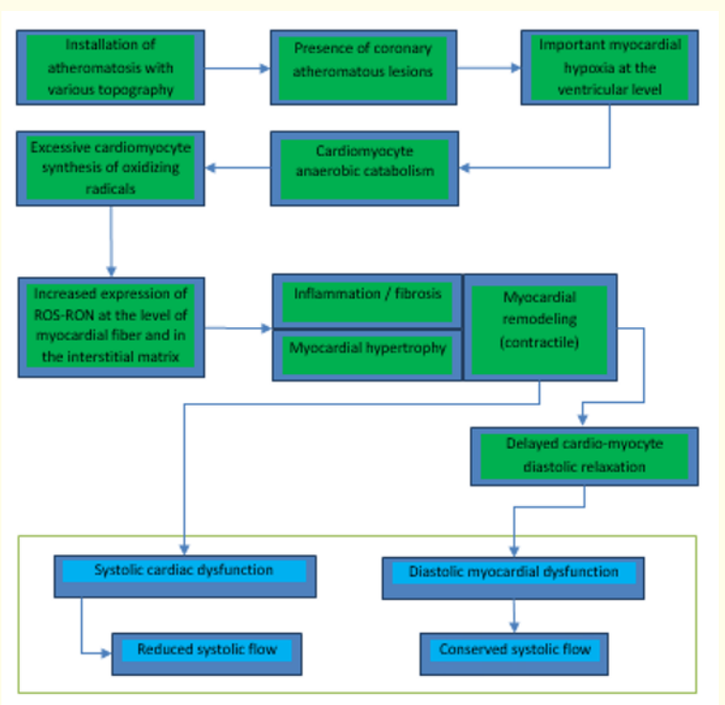

Figure 1: *Sequentiality of pathogenic mechanisms in heart failure caused by myocardial ischemia [10, modified].*

To exemplify the timeliness and necessity of research on the two heart diseases for which we studied possible biomarkers, in the figure below, based on published findings on the mechanisms of myocardial inotropic deficit, we found it useful to present how to install it.

Annotation: the upper part of the figure, colored in green, summarizes the main processes that occur from coronary atheromatosis to the installation of cardiac dysfunction, via irrigation deficit - oxidative stress. If this part highlights the installation of ischemic heart disease, the lower part, colored in blue, illustrates the installation of the contractile functional deficit of the myocardial fiber, i.e. congestive heart failure with or without affecting the ejection fraction of the left ventricle.

When disturbing redox homeostasis, two mechanisms intervene in chronic heart failure:

- A local one, namely the production of oxidizing agents by involving the structural cells of the organ and/or those migrated and infiltrated at this level (tissue) which is poorly irrigated;
- Another systemic, by the synthesis in other tissues and organs, due to the reduction of the organ flow, effect of the decrease of the systolic flow. For ischemic cardiomyopathy induced by arteriolosclerosis developed in the coronary territory, in the first category, that of local sources producing oxidizing agents, are included myocardial fibers, myocytes and endothelial cells of regional vessels, and in that of migrated cells, the elements involved in inflammation, neutrophils, but especially monocytes that become macrophages by activation. This monocyte activation process comprises three stages:
    - Mobilization of resident/responsive monocytes, to be marginalized from the central axis of the laminar blood flow, to pass through diapedesis in the interstitium;
    - Initiating the stimulatory process on the monocytes that become partially activated/initiated;
    - Full activation of monocytes allows them to metamorphose into macrophages.

Activated monocytes, by chemoattractant factors, ensure the dynamics of the evolution of myocardial oxidative stress, the development of inflammation, which generates other chemokines and cytokines. The destructive structural-functional processes developed in the ischemic myocardium are effects of at least 24 such factors, such as tumor necrosis factor (TNF), interleukin-1 (IL 1) or stimulation factors (e.g. granulocyte and monocyte colony (GM-CSF), granulocyte colony-stimulating factor (G-CSF), monocyte colony-stimulating factor (M-CSF), etc.

Conclusion

Data from the medical literature from the last decades record that risk prediction models are research objectives in cardiovascular diseases, including heart failure. To date, the research effort has failed to impose in medical practice as a biomarker with specificity for myocardial inotropic deficiency other than serum dosing of atrial natriuretic factors.

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