

Identification of Possible Biomarkers in Cardiovascular Diseases

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Abstract: Currently, one of the major medical topics researched is the identification in the most diverse diseases, of new molecular biomarkers that would allow the establishment of a positive diagnosis, but also of the response to a certain established 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 condition, including the prognosis.

Keywords: Cardiovascular diseases, Atherosclerosis, Risk biomarkers.

INTRODUCTION

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

For medical practice, the identification of possible circulating biomarkers that in association 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.

MATERIAL AND METHODS

Our studies were performed on patients diagnosed as having 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 the our studies undertaken in the last 3 years, following the research of possible biomarkers on the two mentioned heart diseases were published in the form of 7 articles, of which 3 in the Journal of Enzyme Inhibition and Medicinal Chemistry (published by Taylor & Francis Group), a journal listed by Clarivate Analytics in ISI Thomson Master Journal List (IF = 4.673), other 4 other articles in the Romanian Journal of Revista de Chimie (Bucharest), and presentations at national and international Conferences or Congresses [1-9].

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RESULTS AND DISCUSSIONS

In the dynamics of its development, ischemic heart disease "takes 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 another aetiopathogenic way of developing coronary localization of atherosclerosis.

At the myocardial level, ATH with coronary localization, because it disrupts the optimal irrigation of cardiomyocytes, induces by oxidative stress, but also by deficit of energy synthesis the progressive deterioration of the heart inotropism. 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 form that also alters systolic function and is among the not only disabling morbid conditions, but also 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 to 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, especially 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, being 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 the preservation of the systolic flow ($\geq 45\%$ of the value accepted as normal), contrary to the diastolic function which 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 main pathological mechanism by which such histological changes are generated generating alterations in myocardial contractile function is oxidative stress, generated by myocardial dysfunction, due to the existence of 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.

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 synthesis in other tissues and organs, as a result of the reduction of the organ flow, effect of the decrease of the systolic flow.

For ischemic cardiomyopathy induced by arteriosclerosis 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, in order 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 which allows them to metamorphose into macrophages.

Activated monocytes, by producing chemoattractant factors, ensure in the dynamics of the evolution of myocardial oxidative stress, the development of inflammation, which in turn 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.

CONCLUSIONS

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

REFERENCES

- [1] Diaconu A, Coculescu BI, Manole G, Vultur H, Coculescu EC, Stocheci CM, Tudorache IS, Dincă AL, Dincă GV. Lipoprotein-associated phospholipase A2 (Lp-PLA2) - possible diagnostic and risk biomarker in chronic ischemic heart disease, *J Enzyme Inhib Med Chem* 2021; 36(1): 68-73. <https://doi.org/10.1080/14756366.2020.1839447>
- [2] Coculescu BI, Manole G, Dincă GV, Coculescu EC, Berteanu C, Stocheci CM. Osteopontin - a biomarker of disease, but also of stage stratification of the functional myocardial contractile deficit by chronic ischaemic heart disease, *J Enzyme Inhib Med Chem* 2019; 34(1): 783-788. <https://doi.org/10.1080/14756366.2019.1587418>
- [3] Coculescu BI, Dincă GV, Bălăeț C, Manole G, Bălăeț M, Stocheci CM, Myeloperoxidase, a possible biomarker for the early diagnosis of cardiac diastolic dysfunction with preserved ejection fraction, *J Enzyme Inhib Med Chem* 2018; 33(1): 1292-1298. <https://doi.org/10.1080/14756366.2018.1499626>
- [4] Coculescu BI, Dincă GV, Manole G, Purcărea VL, Oproiu AM, Stocheci CM. Serum concentration of hsCRP - possible marker for therapy evaluation in left ventricular dysfunction with preserved ejection fraction, *Rev de Chimie (Bucharest)* 2018; 69(10): 2885-2890. <https://doi.org/10.37358/RC.18.10.6646>
- [5] Coculescu BI, Manole G, Dinca AL, Harsovescu T, Tudorache IS. The possible serum complex-biomarkers for the early diagnosis of diastolic dysfunction with preserved systolic function, *Rev. de Chimie (Bucharest)* 2019; 70(6): 2229-2231. <https://doi.org/10.37358/RC.19.6.7311>
- [6] Coculescu BI, Harsovescu T, Tudorache IS, Manole G. PON-1, possible biomarker for diagnosis but also for risk in diastolic dysfunction with preserved ejection fraction, *Rev. de Chimie (Bucharest)* 2019; 70(4): 1210-1214. <https://doi.org/10.37358/RC.19.4.7093>
- [7] Tudorache SI, Coculescu BI, Manole G, Harsovescu T, Tone MB, Dinca AL. Myeloperoxidase (MPO), possible biomarker in heart failure, *Rev. de Chimie (Bucharest)*, 2019; 70(6): 2173-2176. <https://doi.org/10.37358/RC.19.6.7299>
- [8] Coculescu BI, Dincă GV, Manole G. A novel biomarker in diastolic dysfunction with preserved ejection fraction, *Mædica - a Journal of Clinical Medicine*, 2019; 14(Suppl): 39.
- [9] Coculescu BI, Dincă GV, Manole G. Clinico-biological significance of serum myeloperoxidase in diastolic dysfunction with preserved ejection fraction, 24th Congress of Balkan Military Medical Committee (BMMC), 30 April - 3 May 2019, Tirana, Albania.

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