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POTENTIAL MARKERS IN CARDIAC HYPERTROPHY?

Potential markers in cardiac hypertrophy?

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Abstract

Cardiomyopathies are diagnosed based on medical history of patient (symptoms and family history), physical examination, results of echocardiogram and in some situations additionally ECG or chest-X-ray results. Currently used non-invasive diagnostic methods, could be complemented by biochemical tests. In this review some emerging potential biomarkers such as: osteopontin, ST-2 receptor, osteoprotegerin, neopterin, urocortins, growth differentiation factor 15 and urotensin II are described. In current article human and non human investigations have been reviewed, since rat is most commonly used model in experimental cardiology and gives important foundations to clinical knowledge.

Key-words

Cardiomyopathy, biomarkers of cardiac remodeling, heart failure, osteopontin, ST-2 receptor, osteoprotegerin, neopterin, urocortins, growth differentiation factor 15, urotensin II.

Background

In the recent few years, due to epidemiological and clinical studies, new risk factors in pathogenesis of atherosclerosis and cardiovascular disease have been found. Special attention has been paid to inflammation and immunological responses. Number of markers of inflammatory processes involved in cardiovascular diseases keep growing.

Cardiac remodeling is an adaptive response to the myocardial infarction heart damage and attempt to work in the "new" hemodynamic conditions. Postinfarction cardiac remodeling was defined as a complex of pathological lesions, which take the place at the cellular, tissue and organ level, lead to an increase of left ventricular volume, shape and the mass of the heart muscle (1, 2).

There are many initiation factors involved in the process of cardiac remodeling, such as mechanical load, inflammation, neuroendocrine system stimulation (especially renin-angiotensin-aldosterone) (2,3). Interactions between these factors, through the receptor pathways, lead genes expression in cardiomyocyte.

Also age, gender and race play an important role in the pathogenesis of cardiac hypertrophy. In Framingham Study the relationship between cardiac hypertrophy and age, gender, hypertension has been showed. Electrocardiographic features characteristic for hypertrophy were found in approximately 1% of younger persons (<30 years) and around 12% in older subjects (> 70 years). Left ventricular hypertrophy was diagnosed in 1,3% of younger males (29-44 years of age) with systolic pressure 120 mmHg and in 5,9% in the older ones (55-62 years of age). However, a group of males in the same age ranges but with systolic blood pressure >200 mmHg demonstrated cardiac hypertrophy, accordingly in 33,3 % and 47,1% (2).

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Cardiac muscle hypertrophy accordingly to the Law of Laplace, means the increase of ventrical volume that results in the higher tension of the heart's wall. "Compensation" of this mechanism are cardiomyopathies (4). There are few types of cardiomyopathies such as hypertrophic cardiomyopathy, dilated cardiomyopathy (congestive), restrictive cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy (5).

Hypertrophic cardiomyopathy (HCM) is defined as left ventricular (LV) hypertrophy that is not associated with LV dilation and that occurs in the absence of another systemic or cardiac disease capable of producing wall thickening (e.g., systemic hypertension, aortic valve stenosis). Clinical diagnosis is customarily made with 2-dimensional echocardiography (or alternatively with cardiac magnetic resonance imaging) by detection of otherwise unexplained LV wall thickening, usually in the presence of a small LV cavity, after suspicion is raised by the clinical profile or as a part of family screening (5).

Dilated cardiomyopathy (congestive) is the most common type of cardiomyopathy, characterized by dilated lesions, enlargement of the whole heart with hypertrophy of the heart muscle. Heart efficiency is significantly decreased with a small ejection fraction. Etiology of this disorder is multifactorial. Genetic causes are responsible for 30% of cases. There are many causes which lead to dilated cardiomyopathy, such as viruses (COX, HIV, HSV), bacteria (Mycobacterium tuberculosis), neuromuscular diseases, endocrine disorders (hypothyroidism, hyperthyroidism, hypoparathyroidism) (6).

Restrictive cardiomyopathy (RCM) is an uncommon heart disorder. Classical idiopathic form of RCM mainly occurs in Europe and North America. In central Africa, the most common form of RCM is endomyocardial fibrosis caused by hypereosinophilic syndrome. RCM is characterized by diastolic dysfunction due to impaired relaxation of left ventricular wall.

Arrythmogenic right ventricular cardiomyopathy (ARVC) is an uncommon form of heart muscle disease (aproximately 1:5000). ARVC involves predominantly the right ventricle with progressive loss of myocytes and fatty or fibrofatty tissue replacement, resulting in segmental or global abnormalities. In addition, evidence of LV involvement with fibrofatty replacement, chamber enlargement, and myocarditis is reported in up to 75% of patients.
ARVC/D has a broad clinical spectrum, usually presenting clinically with ventricular tachyarrhythmias (eg, monomorphic ventricular tachycardia). A recognized cause of sudden cardiac death in the young. Diagnosis often requires a high index of suspicion, frequently triggered by presentation with arrhythmias, syncope, or cardiac arrest, as well as global or segmental chamber dilatation or wall motion abnormalities (7).

DIAGNOSIS OF CARDIOMYOPATHY

Cardiomyopathies are diagnosed based on medical history of patient (symptoms and family history), physical examination, results of echocardiogram and in some situations additionally ECG or chest-X-ray results. According to ACCF/AHA guidelines, there are two initial methods for cardiomyopathies diagnosis (8).

Transthoracic echocardiography is recommended in initial evaluation of all patients with suspected cardiomyopathy. Comprehensive TTE and Doppler studies should be performed in the initial evaluation of all patients with suspected HCM, as well as during follow-up, particularly when there is a change in cardiovascular symptoms or an event. Echocardiographic studies are essential for establishing the diagnosis and the nature and extent of hypertrophy, defining prognosis, and guiding management **(2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy)** (8).

Cardiac magnetic resonance (CMR) imaging is indicated in patients with suspected HCM when echocardiography is inconclusive for diagnosis. There have been significant advances in CMR in recent years, and most centers now have access to this advanced imaging technique. Compared with other noninvasive cardiac imaging modalities, CMR provides superior spatial resolution with sharp contrast between blood and myocardium, as well as complete tomographic imaging of the entire LV myocardium and therefore the opportunity to more accurately characterize the presence, distribution, and extent of LV hypertrophy in HCM. Because of the technical complexity of CMR imaging, data from the published literature are only generalizable if imaging is performed with high technical quality by experienced operators and interpreted by well-trained and experienced readers **(2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy)** (8).
Currently used non-invasive diagnostic methods, could be complemented by biochemical tests. Therefore, it would be good to perform further analysis of new potential markers suggested by some researchers.

EMERGING POTENTIAL BIOCHEMICAL MARKERS

Many molecular and cellular changes are involved in heart muscle disorders, such as: activation of different signaling pathways, switch of fetal gene program of myocardium, apoptosis.

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All the mentioned events contribute in some way in a consequent change/alteration in the contraction, ion homeostasis and expression of growth factors, chemokines and hormones (9). Also the increase of the extracellular matrix components expression, adhesion molecules, proteins, integrin receptors are important in the evolution of heart failure process (10, 11, 12).

One of such potential biomarkers is osteopontin (OP) that has been found for the first time in bone tissue (13). It is synthesized by a variety of tissues, as: fibroblasts, osteoblasts, some bone marrow cells, immune cells (macrophages, neutrophils, dendritic cells, T and B cells) (14). Osteopontin has a chemotactic activity important in the cell recruitment to the inflammatory site: acts as an adhesion protein and mediates the cell activation and cytokines production, beside the apoptosis regulation (15). OP is released in the form of immobilized extracellular matrix molecule or as a soluble form. For its characteristic has been suggested that OP is involved in the communication between the extracellular matrix and cardiomyocytes (16).

OP mediates cardiac fibrosis probably by the cell adhesion and proliferation and is upregulated in left ventricular hypertrophy where it is stimulated by angiotensin II (17). Thus OP may play a role in the myocardial remodeling after biochemical stress. Early studies have shown that OP can be upregulated also in patients with CVD (17).

In patients with significantly altered systolic function and NYHA class I and II symptoms, only moderate increases of OP have been shown whereas in patients with NYHA class III and IV marked increases of OP have been found. It suggests, that OP may be a possible biomarker for the advanced heart failure. Moreover, osteopontin showed to be an independent predictor of 4-year death, and gave more information of the risk evaluation in patients with heart failure (18).

The ST-2 receptor is a novel biomarker of cardiac stress with adverse cardiac remodeling and tissue fibrosis that occurs in response to myocardial infarction, heart failure or acute coronary syndrome (19). ST-2L receptor (a transmembrane form) is a kind of toll-like receptor superfamily and its pathophysiological role is not clearly understood yet (20). Interleukin-33 (IL-33) has been identified as a functional ligand of ST-2 and involved in the functions of several tissues and the complex IL-33/ST-2 has cardioprotective functions by inducing Th1-to-Th2 switch and by IL-5 synthesis stimulation, which increases the level of oxLDL antibodies (21, 22, 23).

The cardioprotective effect starts when the IL-33 binds the ST2 receptor and the complex plays a similar role to B-type natriuretic peptide (BNP) by protecting the heart from harmful cardiomyocyte hypertrophy (24). Increased concentrations of sST2 (soluble form) in patients 1 day after acute myocardial infarction has been found (25). However, it has been shown that high base concentrations of sST2 predict heart failure and mortality in patients with acute myocardial infarction at 30 days (26). The combination of ST2 and BNP significantly increase the stratification's risk (27). In conclusion, it has been proven, that patients with known CVD and increased sST2 level, have higher mortality rates at 1 year after episode. Rehman et al, examined a group of 346 patients with acute heart failure and assessed ST2 concentration. ST2 values were correlated with severity of heart failure (p<0,001), left ventricular ejection fraction (r =-0.134; p = 0.014), B-type natriuretic peptide (r = 0.293; p < 0.001), amino terminal B-type natriuretic peptide (r = 0.413; p < 0.001), and C-reactive protein (r = 0.429; p < 0.001). In a multivariable Cox model containing established clinical and biochemical predictors (including natriuretic peptides), ST2 remained a predictor of mortality (hazard ratio: 2.04, 95% CI: 1.30 to 3.24, p = 0.003), and was equally predictive in patients with HF and preserved or impaired systolic function (28).

Osteoprotegerin (OPG) is a member of the tumor necrosis factor (TNF) receptor superfamily which plays many important roles: in bone remodeling, in pathogenetic mechanisms of bone malignancies and mineral metabolism disorders. There are evidences, that OPG can promote cell survival by the inhibition of TNF related apoptosis inducing ligand (TRAIL) (29).

OPG acts as a soluble decoy receptor activator of nuclear factor kappaB ligand (RANKL or OPG ligand) and shows homologies with other TNF receptor members. RANKL has an central role in the osteoclast functions and bone remodeling, also in immune cell cross-talks, dendritic cells survival, lymph node organogenesis and vascular biology (30).

Arterial calcification is characteristic of arterial atherosclerosis and is associated with the AMI's occurrence. OPG links the skeletal system with the vascular system (31).

OPG is associated with a higher left ventricular mass and reduced left ventricular systolic function, suggesting that the OPG activation play an important role in initial phase of left ventricular hypertrophy and dysfunction. Furthermore, OPG has been linked with atrial fibrillation in general population but the association with the outcomes in patients with stable chronic heart failure are still unknown.

Higher OPG levels were found in older females with severe heart failure (29, 32). Moreover, OPG and body mass index are inversely related. Higher levels of circulating OPG are associated with higher serum creatinine concentration and lower glomerular filtration rate (impaired renal function). Increased OPG concentrations are connected with a higher systolic blood pressure, higher heart rate, and higher risk of diabetes mellitus and chronic obstructive pulmonary disease. It has been found that increased concentrations of OPG may be associated with higher concentration of BNP and hsCRP. In subjects with chronic heart failure OPG is an independent predictor of mortality from all causes (32).

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Neopterin is a low molecular weight, stable compound, produced mostly by macrophages from GTP. GTP-cyclohydrolase plays a council role in the first stage of neopterin synthesis. GTPCH induces GTP conversion to 7,8-dihydroneopterin triphosphate and in the next step to neopterin (33).

In cardiovascular diseases such as unstable angina, myocardial infarction or heart failure, number of lymphocytes is significantly higher, especially monocytes, macrophages and their increased activity. Published results show positive correlation between higher activity of monocytes and neopterin concentration (34).

In atherosclerosis, the release of neopterin is linked with atherosclerotic plaque rupture. It affects activation and migration of macrophages into the artery wall. Also, positive correlation between neopterin concentration and severity of illness has been observed. Results of experiments performed by Van Haelst et al, showed that higher neopterin concentration is a better indicator of MI without Q-wave elevation than initial ECG. In the group of patients with MI, neopterin values were significantly higher, depending on duration of cardiac incident and pharmacotherapy (35). We have to note the fact, that there were no correlations between neopterin, C-reactive protein or creatine phosphokinases (36). Hennig et al investigated role of inflammatory biomarkers and neopterin for prediction of right ventricular failure in group of 40 patients after left ventricular assist device. Patients were divided into two groups -I (without postoperative right ventricular failure) and- II (with defined right ventricular failure after implantation). Level of neopterin and NT-proBNP were significantly lower in group I 10.5 vs. 20.7 ng/ml, P = 0.018, and 6322 vs. 17174 pg/ml, P = 0.032, respectively (37).

Urocortins (UCN). The family include three structurally-related peptides, named urocortin 1 (UCN-1), urocortin 2 (UCN-2), and urocortin 3 (UCN-3) (38). The mechanism of action of these peptides is mediated through the binding to G-coupled protein receptors – CRF-R1 and CRF-R2. However, only CRF-R2 is specific for the heart ventricles and circulation system. Earlier data suggested that the urocortins are involved in modulating cardiovascular function and mediating cardiovascular responses to stress (39). Nishikimi et al observed significantly higher concentration of urocortin 1 in a rat model with left ventricular hypertrophy (LVH). Higher level of UCN-1 was found by Ikeda et al in human dilated cardiomyopathy. This suggests participation of the CRF-related peptides in congestive heart failure. Moreover, it has been shown that experimental application of UCN-1, UCN-2 and UCN 3 in congestive heart failure may have advantages on cardiac function (40). Advantegous effects of the urocortins on cardiac function are mediated by the intracellular Ca2+ ions administration.

Growth differentiation factor (GDF) 15 is a member of the transforming growth factor β (TGF-β) superfamily, which has an important role in inflammation, apoptosis, cell proliferation and differentiation during some injury or disease's process (41). The mRNA of GDF 15 is mostly presented in the liver cells in high quantities, and the expression is upregulated during injuries in some organs as lungs, heart, kidney and liver. The myocardial expression of that factor is hyper-regulated by the stress but, in physiological conditions it is weakly expressed (42, 43). It is important to predict the mortality and heart failure in patients after acute myocardial infarction combining those results with the informations obtained from New York Class Association (NYHA), left ventricular ejection fraction (LVEF) and N-terminal-pro-B-type natriuretic peptide (NT pro-BNP) levels (44). TGF-β is a locally generated growth factor which stimulates the fibroblast proliferation and extracellular matrix (ECM) production, especially collagen and fibronectin, reducing degradation of those elements. TGF-β has been shown to be significantly increased not only during cardiac hypertrophy but also after MI, leading to structural remodeling and heart failure (42, 43, 44, 45, 46). However, the inducted expression of TGF-β, as well as the exogenous supplementation, may protect cardiomyocytes against ischemia-reperfusion injuries, by the inhibition of TNF-α and prevention of reactive oxygen species (ROS) accumulation (47). The GDF 15 expression is induced very quickly by IL-1, TNF- α and β in macrophages, limiting in that way the inflammation and macrophages activation (48, 49, 50). In the cell culture, recombinant GDF-15 has shown to have a protective role for cardiomyocytes from ischemic injuries (51, 52, 53). These studies may bring to the development of a novel therapies which can be used in treatment of the heart failure.

Human urotensin-II is a circle peptide, synthesized from preprohormone after the enzymatic proteolysis. At first, this peptide was isolated from a spinal cord of osteichthyes and it was called a neurohormone. Its presence has been demonstrated in human's central nervous system. Concentration of urotensin-II is significantly higher in patients with hypertension, congestive heart failure, diabetes mellitus. Urotensin shows numerous effects in circulation system, dependent on the type of vascular placenta and their condition. Urotensin is synthesized by endothelial cells, heart muscle, kidneys, pituitary gland. Its presence has been found also in atherosclerotic lesions (54). Urotensin acts indirectly through the specific receptor (GPR14), bound with the effector system. This action is fully mediated by the G protein. Concentration of GPR 14 receptors within vascular wall is higher in patients with congestive heart failure, caused by myocardial infarction. It leads to the hypertrophy and fibrosis of the heart muscle. Under these conditions, U-II induces mRNA transcription for procollagen type I and III. Urotensin shows positive inotropic mechanism of action, accordingly to the vascular wall tension and blood pressure (55).

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CONCLUSIONS

Previously used diagnostic methods for assessing cardiac remodeling/cardiac hypertrophy, do not provide the answers to all clinical questions. New, specific and sensitive biomarkers emerged, which can be implement to routine diagnostic of cardiomyopathy, however they still need further investigations.

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