Dyssynchrony of the Heart as a Pathogenetic Mechanism of the Chronic Cardiac Insufficiency Progression on the Backgroound of Ischemic Heart Disease or Physiological Aging of the Heart

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Abstract

Chronic heart failure is an epidemic of the XXI century that is confirmed by its prevalence, progressive course and place in the structure of morbidity causes and mortality from CVD. In recent decades, significant progress has been made in the development of therapeutic algorithms of treatment of CHF using the different groups of the drugs and their combinations, but the specifics of the treatment of elderly patients remains poorly understood. The steady aging of the population of developed countries increases the share of cardiovascular diseases in the overall structure of morbidity that leads to an increase of the number of elderly patients in the practice of doctors of many specialties. It should be noted that elderly patients are more frequently suffered from CVD such as IHD, CHF, arrhythmias, diabetic cardiomyopathy and hypertension. Myocardial dyssynchrony is one of the main causes of chronic heart failure (CHF) in the elderly. At the same time, normal aging is associated with deterioration of global left ventricular dyssynchrony. This publication covers the mechanisms of fibrous remodeling of the aging heart, formation of the fibrosis and dyssynchrony. There are presented the information about the details of the types of dyssynchrony, diagnosis, course and influence on the progression of CHF. The publication also presents the changes of myocardial synchrony after the improvement of myocardial blood supply as a result of revascularization. Most likely this is due to decrease of the mass of the hibernated myocardium and improving of its energy supply and conductivity, because the other positive changes caused by revascularization are usually developed later.

Introduction

The steady aging of the population of developed countries increases the share of cardiovascular diseases (CVD) in the overall structure of morbidity that leads to an increase of the number of elderly patients in the practice of doctors of many specialties. As a result, the understanding of geriatric aspects of cardiology is an important element of knowledge not only for the modern cardiologist, but also for geriatrician, family doctor and general practitioner [1].

Until recently, it was believed that only symptomatic treatment of CVD in elderly patients was necessary and that the drug intervention had weak effect on the prognosis for the life at this age. However, recent large clinical studies strongly suggest that the patient's age is not a contraindication for the active medical and surgical treatment of many CVD – coronary heart disease (CHD), stenotic atherosclerosis of the main arteries, arrhythmias and impaired cardiac conduction. In addition, the absolute risk of cardiovascular complications in elderly patients is high and CVD treatment of this category of the patients is considered as more effective than in young and middle–aged patients.

Chronic heart failure is an epidemic of the XXI century that is confirmed by its prevalence, progressive course and place in the structure of morbidity causes and mortality from CVD [2]. The steady increase in the number of patients with CHF in economically developed countries is primarily associated with the whole aging of the population, an expansion of cardiac risk factors and improvement of the survival of patients with cardiovascular disease [3]. According to experts, the prevalence of CHF in the European population ranges from 0.4% to 2%. Annually CHF develops in 1% of persons older than 60 years and in 10% of those that is older than 75 years. As a result, the elderly population (with age that is greater than or equal to 65 years) will double from 2010 to 2040 and the number of the elderly persons will increase from 40 million in 2010 to 81 million in 2040 [4]. Since there is a worldwide intensive growth of the elderly population and progression of the clinical manifestations of CVD according to the ageing, it is supposed that the prolongation of the life expectancy will significantly

increase the expenses on the health care. It should be noted that ageing nowadays has been identified as the dominant risk factor for CVD. At the same time, in the elderly, the aging heart is characterized by both structural and functional changes [5]. Among asymptomatic individuals without clinical symptoms of CVD, there are with aging significantly more often diagnosed increase of the left ventricular (LV) mass, decrease of myocardial perfusion, lag of regional myocardial contraction and systolic myocardial dysfunction [6].

Material and Methods

In recent decades, significant progress has been made in the development of therapeutic algorithms of treatment of CHF using the different groups of the drugs and their combinations, but the specifics of the treatment of elderly patients remains poorly understood. The main reason for this was the purposeful exclusion of the persons who are over 75 years old from the most part of prospective clinical trials (CT) of treatment CHF – primarily women who are more than a half of the all elderly persons with CHF and persons with concomitant diseases who are also elderly ones, as a rule. Therefore, before obtaining of CT data that is specially designed for the elderly with CHF, it should be guided by the proven principles of treatment of CHF for middle-aged people, taking into account the age characteristics of the elderly and their individual contraindications. The prognosis for elderly and senile patients remains serious regardless of the stage of the disease. In this regards, it is natural to continue the searching of mechanisms of CHF development and progression with using of personalized approaches for different age groups. All possible measures aimed at the struggle against the aging of the heart, improve the health of the elderly, their quality of life, reduce morbidity and mortality from CVD.

It should be noted that elderly patients are more frequently suffered from CVD such as IHD, CHF, arrhythmias, diabetic cardiomyopathy and hypertension [7]. Risk factors and main diseases lead to a gradual decrease of the heart function, and development of fibrosis is a key component of this impairment.

The mechanisms of fibrous remodeling of the aging heart are well studied in both clinical and experimental studies. Fibrous remodeling of the heart is promoted by the predominance of synthesis of I-III collagen types over their degradation that leads to the accumulation of excess fibers. Age induced collagen restructuring is characterized by interstitial and perivascular accumulation of type I collagen and defective activation of reparative fibroblasts in response to action of growth factors that leads to scarring and unfavorable relaxation remodeling [8]. Fibrous remodeling of the aging heart is characterized by structural and functional alterations, including left ventricular (LV) hypertrophy, diastolic and systolic dysfunction of the heart. It is shown that normal aging is associated with the deterioration of global LV dyssynchrony due to the elongation of isovolumic timings and the Tei index that leads to a reduction of the time of filling and ejection. In this case, the systolic and electrical function of LV does not depend on age, but diastolic and synchronous functions are significantly age related [9]. The collagen accumulation in the aging heart leads to a progressive increase in the stiffness of the ventricles and impairment of diastolic function. Aging also interferes into the balance of matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases [10] that increases the residual myocyte size and myocardial thickness [11] followed by reactive fibrosis and increased cardiac stiffness. Diastolic dysfunction plays a dominant role in the pathogenesis of heart failure and impairment of exercise tolerance in the elderly [12]. Framingham study of structural and functional alterations of the heart depending on the patients age [13] and Baltimore Longitudinal Study of Aging [14] demonstrated that according to the aging of the healthy population it is increased the prevalence of LV hypertrophy accompanied by impairment of diastolic heart function. Respectively subsequent fibrotic remodeling and pathological activation of matrix-degrading pathways promote the heart inotropic dysfunction, progressive dilatation of heart ventricles, impairment of the cardiac systolic function and conduction disturbance [15].

Intraventricular dyssynchrony (DS) is one of the important prognostic factors in patients with heart diseases. In the modern understanding, DS is the dissociation of the contractions of the heart chambers and myocardial segments that is happened due to impairment of the impulse conduction that in turn leads to lowering of the cardiac pumping function and increasing of energy consumption by the myocardium. Kinetic impairment and formation of the asynergic zones in LV myocardium provoke the pathological remodeling with progressive LV dilatation that in turn leads to increased tension of the ventricular walls and worsening of cardiac contractile function.

Results and Discussion

Desynchronization is the result of myocardial fibrosis, especially in patients with ischemic heart disease, regardless of the degree of clinical manifestations. It was found that the impairment of the mechanical synchronicity of the left ventricle (LV) during the aging can be explained by fibrosis and increased lipid containing in elderly hearts [16]. Regional interstitial fibrosis is certainly associated with LV dysfunction regardless of global LV function. It is shown that interstitial myocardial fibrosis and ID coexist at an early stage of many CVD [17]. It is founded that aging alters the LV diastolic function due to increase of regional diastolic asynchrony. Indicators of diastolic asynchrony increase with aging, while indexes of systolic synchrony do not depend on the age [18]. Angiography with radionuclides demonstrated that aging is associated with a lag and decrease of early diastolic filling that is associated with regional LV dyssynchrony. Fonseca et al. also showed that there is

increase of regional asynchrony in elderly [19] and aging is associated with a progression of dyssynchrony degree.

It is important because the elderly population is increased and we need to identify new methods of management of aging induced cardiac dysfunction.

LV synchronicity has an important impact on the efficiency of LV functioning. Delayed electrical activation and a weakened coordination between excitation and contraction lead to a dispersion of regional mechanical activation known as intraventricular dyssynchrony that has a negative effect on cardiac performance [20]. LV mechanical discoordination leads to impairment of its contractility, abnormal relaxation, stretching of the contractile segments and positive left ventricular remodeling with progressive LV dilatation that causes increase of ventricle wall tension and worsening of LV contractile function. Incomplete systole, caused by mechanical dyssynchrony, can lead to increase of the LV filling pressure and, ultimately, to alteration of the LV diastolic function [21]. Progressive dilatation and reduced contractility of the left ventricle via increasing degree of tension of chordal apparatus and reducing of closing speed of the mitral valve, promote the development or increase of mitral regurgitation (MR). Uncoordinated activation of papillary muscles can further weaken the overall LV contractility by increasing of the MR severity. Uncoordinated contraction of the LV basal segments during the systole leads to enlargement of the annulus of the mitral valve and changing of the mitral valve leaflets orientation that promote increase of the mitral regurgitation [22]. Cardiac DS is divided into electrical and mechanical ones. Electric DC is associated with retardation of the ventricle conductivity that leads to extended duration of QRS [23]. Mechanical DS is a mechanical discoordination that is most often associated with simultaneous contraction and stretching of different segments of the LV, as well as time delays of peak contraction from one segment to another [24]. Disorders of intraventricular conduction are recorded in 15-47% of patients with CHF, it is manifested by the extension of the QRS complex of the ECG, that is more often due to left bundle branch block (LBBB) (25-36% of the cases) and less frequent due to the right bundle branch block (RBBB) (in 46% of the cases). Severity of the electrical dyssynchrony in CHF cases closely correlated with lowering of the LV ejection fraction and the level of mitral regurgitation. In addition, the width of the ventricular complex of the ECG is an important prognostic criterion; its increasing is accompanied by the growth of the mortality rate and incidence of sudden cardiac death in CHF cases. Systolic asynchrony is often revealed in patients with CHF, the share of the patients with extension of QRS complexes reaches to 50%. The length of QRS complexes is used as a marker of mechanical DS in patients with severe systolic dysfunction [25], and it is a criterion for resynchronizing heart therapy in cases of CHF with systolic dysfunction. It is proved that QRS extension is associated with growth of mortality rate [26]. At the same time, several studies have demonstrated a poor correlation between the duration of the QRS complex and the indices of mechanical asynchrony. Recent studies have shown that DS is revealed in 30-40% of patients with normal length of QRS complex and it poor correlates with electromechanical DS that is detected on the basis of tissue Doppler data. It was found that mechanical DS is a predictor of deterioration of CHF, regardless of the duration of QRS and LV ejection fraction (EF) [27]. Yu CM et al. shown that about 30% of patients with CHF and length of QRS more then 120 ms did not demonstrate significant reverse of LV remodeling in response to resynchronization therapy (RST), while patients with narrow QRS with proven mechanical DS had a positive response to RST [28]. Thus, mechanical DS is more important than electrical DS, because it is associated with a higher risk of unfavorable outcomes and can be a predictor of serious cardiac events in patients with CHF [29]. Regardless of the QRS length, the patients with CHF could form systolic and diastolic LV asynchrony that causes to ineffective contraction and relaxation. It was shown that dilation and decrease of LV systolic function are predictors of systolic asynchrony, while diastolic dysfunction and QRS extension are predictors of diastolic heart asynchrony [30]. Both systolic and diastolic dissynchrony was observed in 40% of patients with narrow QRS complexes and about 70% of patients with wide QRS complexes [31].

Echocardiography (EchoCG) has been several years applied in basic and translational researches for studying of the heart disease models, including age-related cardiac dysfunction. Echocardiographic evaluation of DS is widely applied because it is non-invasive, widely available and has no risks or side effects. The technique ranges from conventional Doppler EchoCG to more advanced Doppler tissue imaging (DTI), three-dimensional echocardiography, and two-dimensional speckle tracking imaging (STI), and more recently for 3D Speckle Tracking Echocardiography (3D-STE) [32]. New EchoCG methods, such as tissue synchronization imaging (TSI) and 2D speckle tracking, allow to analyze the peak systolic velocity and deformational delays of various LV walls and, therefore, to evaluate mechanical DS [33]. Evaluation of deformation parameters (the magnitude and speed of deformation) allows to differentiate passive (movement of cicatricial tissue) and active movements (contraction) of LV walls that make this type of the study more reliable. However, the real potential for evaluating of myocardial dyssynchrony in the context of aging and cardiac dysfunction requires further study.

There are 3 types of mechanical DS: atrioventricular DS (in which the time of atrial contraction does not immediately precede to the contraction of the ventricles); interventricular DS (in which the contractions of the right and left ventricles are not simultaneous); intraventricular DS (in which different walls of the LV are not contracted simultaneously).

EchoCG criterion for interventricular DS is interventricular mechanical delay (IVMD) more than 40 ms (it is time between the onset of systolic flows in the aorta (APEI) and pulmonary trunk (PPEI)). The sensitivity of the method is 66%, its specificity is 55%. The criteria of interventricular DS is the maximum inter-segment delay (Ts) more than 100 ms [34] and the index of mechanical dissynchrony (Ts-SD) more or equal than 31 ms. Ts-SD is the best predictor of reverse remodeling. In patients with QRS length more than 150 ms, this indicator has 96% sensitivity of and 78% specificity, for the patients with a borderline QRS duration (120-150 ms), the sensitivity is 83% and specificity is 86% [35].

De Sutter et al. founded that cases of symptomatic CHF have 18% patients with systolic intraventricular dyssynchrony for the cases with preserved EF and 36% of dyssynchrony for the cases with low (<40%) EF. However, if QRS extension is more or equal to 120 ms, the prevalence of systolic intraventricular dyssynchrony in cases of CHF with preserved EF increases nearly to 50% that is comparable with the appropriate indexes of the patients with low EF and a QRS length more or equal to 120 ms [36, 37].

LV myocardial ischemia is one of the main causes of DS. CHF that is caused by ischemia has prevalence of DS from 20.8% to 79.6% [38] and this DS is associated with a significantly increased risk of cardiac events in patients that is treated. Intraventricular asynchronous has a prognostic value in patients before and after coronary artery bypass grafting (CABG). Gibson et al. reported about resolving of LV dyssynchrony after CABG in 12 (86%) from 14 patients with preserved EF. The presence of severe myocardial DS before and after revascularization is associated with high hospital and long-term mortality in patients with ischemic CHF. In cases without DS, survival is associated with a greater improvement of CHF symptoms and LV EF, compared to patients with DS [38]. DS of the heart is an essential pathogenetic factor of development and progression of CHF with reduced EF on the background of IHD in elderly. Coronary revascularization, in particular CABG, is one of the most adequate methods of restoring the synchronicity of contractility and functional capabilities of the myocardium. Indications for revascularization in patients with ischemic CHF are unstable angina and severe coronary artery stenosis according to coronary angiography. The risk of death in this group of patients is increased and ranges from 5 to 30%. Treatment of ischemic CHF that is not accompanied by high functional class of angina pectoris is a problem, because the randomized controlled trials of such category of the patients have not been performed. It is established that plan of examination of patients with CHF and confirmed CHD have to include the assessment of myocardium viability. Some prospective and retrospective studies, meta-analyses revealed improvement in LV function and survival after revascularization of cases of ischemized but still viable myocardium. If the viable myocardium is absent, revascularization is ineffective and surgical treatment should be avoided because of its risks. Patients with severe LV dilation have low probability to improve the EF in spite of presence of the viable myocardium [39]. After myocardial revascularization, there was a decrease in the some parameters that are the criteria of DS, in particular, the frequency expansion of QRS more or equal 120 ms by 31%, interventricular mechanical delay by 14.5%, intraventricular delay by 20.1% and presystolic mitral regurgitation by 16.5%. These changes suggest the improvement of myocardial synchrony after the improvement of myocardial blood supply as a result of revascularization. Most likely this is due to decrease of the mass of the hibernated myocardium and improving of its energy supply and conductivity, because the other positive changes caused by revascularization are usually developed later. This suggests that the aging of the heart is characterized by structural and functional changes of the myocardium, including firstly diastolic and later systolic dysfunction, concentric LV hypertrophy, fibrous remodeling with myocardial dissynchronization and subsequent formation of eccentric myocardial hypertrophy, diminishing of inotropic reserve and decrease of tolerance to physical activity [40].

Conclusions

Despite the significant progress achieved in the treatment of CHF in recent years, the problem of manifestation, progression and prognosis of this category of patients remains relevant. Recently, DS is considered as one of the possible pathogenetic aspects of the CHF progression. In our opinion, this mechanism underlies the deterioration of patients' condition and the progression of CHF with chronic coronary artery disease in elderly. Further study of the role of DS in the pathogenesis of CHF that is induced by IHD will allow to obtain deeper understanding of this problem which, in turn, create conditions for the finding of the new drugs with the necessary pleiotropic pharmacological effects.

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