Research Article

Pharmacotherapy for the prevention of the progression of chronic heart failure in elderly patients with coronary heart disease

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ABSTRACT

Aim: Chronic heart failure (CHF), which occurs as a result of common cardiovascular diseases in the elderly, combined with age-related changes in both structural and functional features of the heart. Myocardial remodeling is an essential substrate that determines the occurrence and progression of CHF in elderly patients. In all forms of left ventricular (LV) myocardial remodeling, there is a decrease in both LV diastolic relaxation and atrial filling. The object of our study was 140 elderly men suffering from CHF who had a myocardial infarction. **Materials and Methods:** The object of our study was 140 elderly men with CHF on the background of long-term chronic coronary artery disease who had suffered AMI, whose average age was 68.4 ± 7.8 years. **Results:** It was determined that the majority of elderly patients with coronary heart disease, post-infarction cardiosclerosis develops hypertrophic remodeling, while a smaller number of patients myocardial remodeling occurs by dilation type. In our study, the maximum reduction of diastolic relaxation was found in patients with eccentric hypertrophy, which is accompanied by the most significant drop in the ejection fraction (EF). **Conclusion:** With concentric hypertrophy of the left ventricle of the heart and concentric remodeling, the decrease in diastolic filling and atrial filling is accompanied by the preservation of the rate of circular shortening of fibers (CSF) and EF.

KEY WORDS: Chronic heart failure, Ischemic heart disease, Post-infarction cardiosclerosis, Remodeling of myocardium of the left ventricle

INTRODUCTION

An age-related increase in the incidence of chronic heart failure (CHF) is due to a number of significant factors: The undoubted increase of coronary heart disease (CHD) in the modern world, arterial hypertension (AH) - especially with their frequent combination; certain successes in the treatment of acute and chronic forms of coronary artery disease and hypertension, which contributed to the chronization of these diseases, an increase in the life expectancy of such patients with the development of circulatory decompensation; sclerosis and myocardial atrophy, increasing atherosclerosis processes. CHF occurs as a result of common cardiovascular diseases in the elderly, combined with age-related changes in both structural and functional characteristics of the heart.[1] CHF significantly represents today a geriatric syndrome in much the same way as dementia.[2] Since aging is a progressive biological process, it is believed that old age begins when an active social contribution is no longer possible. Advances in the treatment of cardiovascular diseases, in particular, AH, ischemic heart disease (IHD) (especially myocardial infarction) and CHF contribute to the increasing number of older population.[3] The prevalence of clinically pronounced CHF in different regions of the Russian Federation is 4.1%.[2] However, it is established that in elderly people (60–74 years) the incidence of CHF increased up to 7%.[4,5] It should be noted that the results of survival on the background of drug therapy, for elderly people with heart failure, have recently improved, but mortality, hospitalization, and re-hospitalization remain still high.[6] The 5-year survival of patients with CHF is still >50%, and the risk of sudden death is 5 times higher than in the population in general.[5]

The mechanisms of CHF progression on the background of IHD due to active structural and

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morphological effects are manifested directly by cardiac remodeling due to both cardiomyocytes and myocardial fibrosis.[7] However, these general provisions need to clarify the features in elderly patients against the background of coronary artery disease, in particular, in those with acute myocardial infarction (AMI). To understand personalized mechanisms of cardiac insufficiency development in this category an additional use of quantitative morphological methods is required since changes in tissue and intracellular components in the myocardium with increasing or decreasing the functional load on the heart are primarily quantitative in nature.[8] At present, to determine the tactics of elderly patients with CHF after a heart attack, as well as to prevent its complications, it is necessary to take into account the pathogenetic mechanisms of this process.[2] There is ample evidence that CHF develops as two different syndromes: Systolic and diastolic heart failure. To date, according to the degree of reduction of the contractile function of the myocardium of the left ventricular (LV), CHF is classified into heart failure with low ejection fraction (LEF) (<40%), CHF with intermediate EF (IEF) (from 40% to 49%) (iCHFEF), and CHF with preserved EF (pEF) (50% and more) (pCHFEF), while in healthy individuals at physiological rest the normal value of EF is considered to be 50–75%, with increase up to 80–85% during physical exercises in healthy people. LCHFEF accounts for 50–70% of cases, iCHFEF and pCHFEF - 30–50% of all patients with CHF.[9] At present, to determine the management of elderly patients with CHF after suffering AMI, as well as to prevent its complications, one shall take into account the pathogenetic mechanisms of the formation of fibrosis, the remodeling of MKM in the 1st year based on the age characteristics of this process.[10,11]

Objective

The objective of the study was to study the optimization of methods of pharmacotherapy and prevention of the progression of CHF in patients with CHD, subject to the individual characteristics of the elderly.

MATERIALS AND METHODS

The research was carried out on the basis of the Scientific-Educational and Innovation Center "Nanostructured Materials and Nanotechnologies," Belgorod State National Research University, the resource center "Development of Molecular and Cellular Technologies," St. Petersburg State University, Department of Pathological Anatomy of City Clinical Hospital №21, Bashkir State Medical University, Pathoanatomical Department of Prof. A. I. Meshchaninov Municipal Clinical Hospital of Emergency Medicine, and Kharkiv Medical Academy of Postgraduate Education.

The object of our study was 140 elderly men with CHF on the background of long-term chronic coronary artery disease who had suffered AMI, whose average age was 68.4 ± 7.8 years. All patients had their functional class (FC) of CHF determined. It was established that FC I was detected in 32 patients (22.8%), FC II was established in 50 (35.7%), FC III was detected in 46 (32.8%), and FC IV was detected in 12 patients (8.7%). The control group consisted of 20 persons without cardiovascular diseases comparable in age (average age - 66.9 ± 6.4 years). All patients received optimal medication; an angiotensin-converting enzyme inhibitor, a beta adreno blocker, a competitive antagonist of aldosterone, and calcium antagonists; if necessary, ivabradine, nitrates/sydnonimines, statins, antiaggregant, diuretics, and cardiac glycosides were additionally prescribed. Echocardiographic study of the heart was performed on Philips En Visor C echocardiograph (USA, 2005) with an electronic sensor 3.5 MHz Vivid-7 (USA, 2004) with a multifrequency sensor.[12] The M-model study was performed under a two-dimensional viewing of the heart in the parasternal position along the long axis of the left ventricle LV, involving measurement of thickness of the interventricular septum and the posterior wall of the left ventricle in systole and diastole (cm), the end-diastolic volume, and end-systolic volume of the LV (cm), and LV EF (%). To assess the diastolic function of the left ventricle, all patients had their transmittal blood flow studied by pulsed Doppler echocardiography using the standard method on Sim-5000 Plus apparatus (Biomedica, Italy). The following parameters were determined: E - the maximum flow velocity of the late reservoir period (cm × s^{-1}), A - the maximum flow rate of the late reservoir period (cm × s^{-1}), and E/A - the ratio between the amplitudes of the E and A waves.

To study the morphological structure of the myocardium, autopsies of 27 samples were taken. The resulting material was divided into three groups: The first group (U1) consisted of patients with LCHFEF (included in the "heart transplantation" protocol and died of terminal heart failure), whose mean EF was 27.87±7.6 (27.9 [18.04–35.13]) (n = 10). The second group (U2) included patients with pCHFEF (died from a hemorrhagic stroke on the background of AH) whose mean EF was 61.54 ± 6.3 (61.55 [50.04–67.24]) (n = 10). Group U3 (control group) is represented by autopsy of the myocardial tissue of healthy individuals without cardiovascular disease, who died in road traffic accidents (n = 7). To assess the autopsy of dead patients, after cardiovascular mass determination (in grams), LV heart muscle samples were taken no later than 12 h from the moment of death. Myocardial biopsy specimens were fixed in a 10% formalin solution on phosphate buffer. Paraffin sections with a thickness of 3–5 μm were prepared on a microtome, Microm HM

350. Hematoxylin-eosin, picrofuchsine, van Gieson staining and further staining of elastic fibers with resorcinol and Weigert fuchsine were used as survey histological stains. The histological examination was carried out using a software microscope complex that included AXIOSKOP 40 light microscope ZEISS, AxioCam MRc digital video camera, and Pentium 4 computer. The obtained images, 20 for each histological specimen, were processed using a complex of hardware software visualization of morphological specimens, analysis, and registration of optical and morphometric indicators of "Video Test" with the program "Video-Test Morphology." The diameter of the muscle fiber, the relative area of muscle tissue, its volume density, the number of nuclei, the average core area, the nuclear-cytoplasmic ratio, and the number of intramyocardial vessels were measured.[13] The statistical processing of data was carried out with the "Statistica 6.0" software package.[14] The values are represented as a mean ± standard mean (M ± m) median; the differences were considered significant at $P < 0.05$.

RESULTS AND DISCUSSION

Our study established that post-infarction remodeling was developing in elderly patients by several types: Early, late, and progressive [Table 1] remodeling. In this case, early remodeling was determined in 33%, late remodeling in 38%, and progressive remodeling in 29% of patients.

It was determined that the majority of elderly patients with coronary artery disease develop myocardial hypertrophy, and a small number of patients have a dilated LV cavity [Table 2].

Remodeling of myocardium after 6 months of supervision over elderly patients on the background of medication with the formation of concentric myocardial hypertrophy was established in 75% of subjects, and eccentric hypertrophy was established in 25%. The presence of concentric left ventricular (LV)remodeling without changing the geometry of the heart was found in 28 (20%) patients, concentric hypertrophy in 77 patients (55%), and eccentric hypertrophy in 35 (25%). Milder course of CHF (FC I, II) was reliably detected in patients with concentric myocardial hypertrophy ($P < 0.01$), while severe CHF (FC III, IV) was significantly more frequent in eccentric myocardial hypertrophy ($P < 0.01$). In this case, the isolated diastolic function also differed. It was established that the isolated diastolic variant of CHF in elderly patients was determined overwhelmingly with concentric hypertrophy, then with concentric remodeling, and to a lesser extent with eccentric hypertrophy. At the same time, the change and damage of the systolic-diastolic function and the course of CHF reaches 76% in case of eccentric hypertrophy ($P < 0.01$), to a lesser extent in concentric hypertrophy 17%, and concentric remodeling 7%.

It is noteworthy that in comparison with the control group in elderly patients with CHF on the background of coronary artery disease with eccentric hypertrophy, a reliable decrease in E by 38% $P < 0.05$, A by 11.7% $P < 0.05$, E/A by 33.4% $P < 0.01$, and EF by 38.8% $P < 0.001$. At the same time, the group of concentric remodeling had a decrease in E by 27.8% $P < 0.01$, A by 23.9% $P < 0.05$, E/A by 8% $P < 0.05$, and EF by 16.6% $P < 0.05$ [Table 3].

Thus, the morphometric study of myocardial tissue in patients with eccentric hypertrophy of the left

Table 1: Post-infarction remodeling in elderly patients during the 1st year after AMI (M±m)

Indicators *n*=140	Early remodeling *n*=46	Late remodeling *n*=53	Progressive remodeling *n*=41
Age, years	71.3±2	68.3±4	69.0±3
EDV, ml	112.3±9.0	141.2±6.9#	149.5±6.0#**
ESV, ml	69.2±13.4	80.0±4.9#	86.1±12.3
EF, %	44.2±17.9	40.8±6.3	38.4±4.1

P<0.05 compared with no remodeling; **P*<0.01 compared with late remodeling; #*P*<0.001 compared with early remodeling. AMI: Acute myocardial infarction, EDV: End-diastolic volume, ESV: End-systolic volume

Table 2: Post-infarction remodeling of the LV myocardium in elderly patients (M±m)

Indicators *n*=140	Nature of remodeling		
	Concentric remodeling *n*=28 (20)	Concentric hypertrophy *n*=77 (55)	Eccentric hypertrophy *n*=35 (25)
Age, years	68.9±5.9	66.4±6.8	64.1±5.1
CHF			
FC I	7 (25)	13 (17.0)	3 (8.6)**
FC II	12 (42.8)	44 (57.0)*	9 (26.0) **
FC III	9 (32.2)	20 (26.0)*	15 (43.0)*
FC IV	-	-	8 (22.4)**
CHF variants systolic diastolic mixed	6 (15)	4 (5.2)	4 (11.4)
	31 (77.5)	61 (79.2)	16 (45.7)**
	3 (7.5)	12 (15.6)*	15 (42.9)**

**P*<0.05; **P<0.01 compared with previous groups. LV: Left ventricular, FC: Functional class, CHF: Chronic heart failure

Table 3: Diastolic and systolic CHF in elderly patients (M±m)

Indicators	Control group *n*=15 (100)	Concentric remodeling *n*=20 (20)	Concentric hypertrophy *n*=77 (55)	Eccentric hypertrophy *n*=35 (25)	Δ; p	
	1	2	3	4	2–3	3–4
E, sm·s^{-1}	77.38±3.77	55.84±2.94**	53.89±2.76**	47.86±6.16**	1.95; >0.05	6.03; <0.05
A, sm·s^{-1}	65.80±3.3	50.08±4.14**	55.62±3.42*	58.12±4.15*	−5.54; <0.05	−2.5; >0.05
E/A, un	1.2±0.34	1.1±0.18	0.9±0.24*	0.8±0.08**	0.2; <0.01	<0.001
EF, %	67.18±4.34	56.04±4.73**	62.92±4.35*	41.13±4.2**	−6.88; <0.05	21.79; <0.01

*P<0.05; **P<0.01 compared with the control group. CHF: Chronic heart failure, EF: Ejection fraction

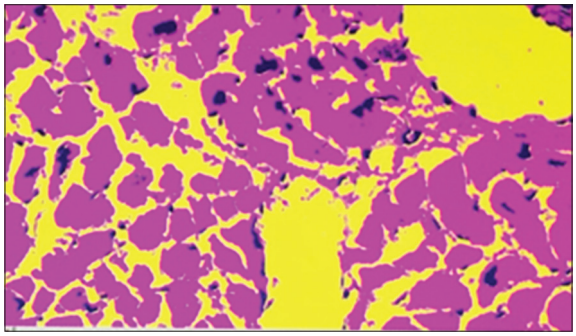

Figure 1: Study of myocardial tissue in a patient with eccentric hypertrophy of the left ventricle

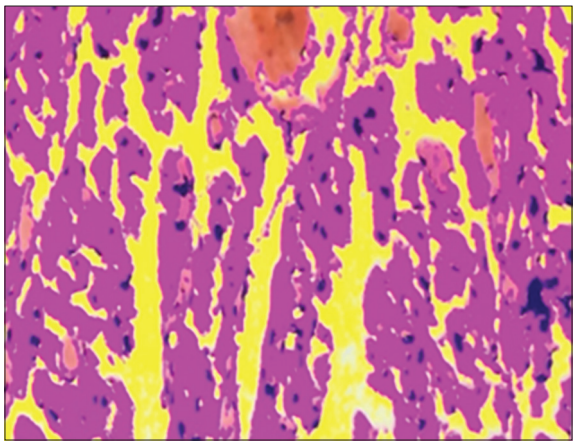

Figure 2: Study of myocardial tissue in a patient with pronounced concentric hypertrophy of the left ventricle

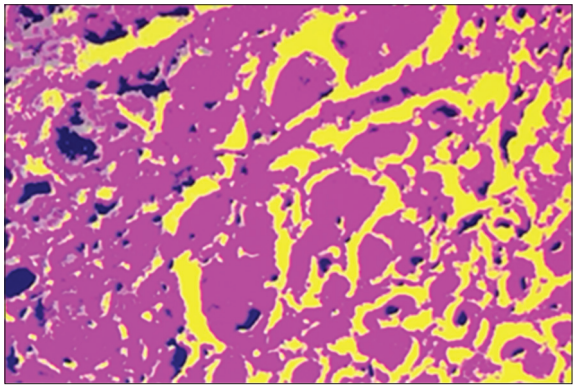

Figure 3: Study of myocardial tissue in a patient without signs of remodeling

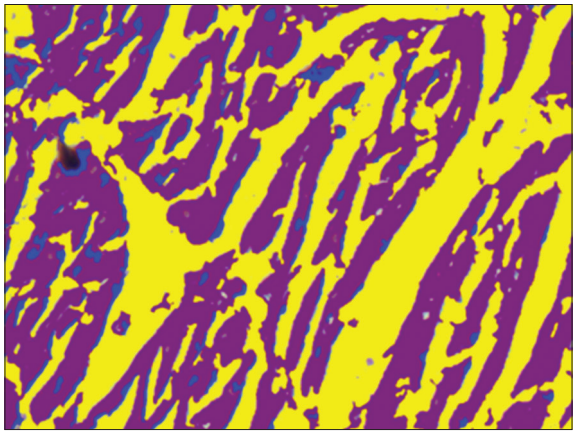

Figure 4: Study of myocardial tissue in a patient of the control group

ventricle revealed a significant reduction in the size of the cardiomyocyte nuclei (94.08 ± 16.41, P = 0.0057) (Figure. 1), in comparison with patients with concentric hypertrophy (Figure 2), with a group without signs of remodeling (Figure. 3), and control group (Figure 4). The assessment of myocardial autopsy in patients with severe concentric hypertrophy found a statistically significant increase in the size of cardiomyocyte nuclei (121.31 ± 30.96, $P \leq 0.05$) as well as a decrease in the cytoplasm volume (165.85 ± 54.95, P = 0.051) in patients with eccentric hypertrophy of the LV and patients without signs of myocardial remodeling. It was established that patients with no signs of pathological remodeling of the LV myocardium have a smaller area of nuclei, a lack of pronounced polymorphism of forms, and a decrease in their number. It was determined that the nuclear-plasma index in the control group was significantly lower (0.246 ± 0.051) than in the group with eccentric hypertrophy (0.487 ± 0.136) and the group with pronounced concentric hypertrophy (0.731 ± 0.176). There were no statistical differences in the area of connective tissue and the phenomena of perivascular and interstitial edema in all three groups.

The progressive increase in LV mass, the decrease in the coronary reserve as a result of blood flow mismatch with the needs of the LV myocardial mass, chronic overload and myocardial hypoxia, due to fibrosis[15] changes the electrophysiological properties of the myocardium, affects the cardiomyocyte contraction-relaxation mechanism[16] and is a substrate of fatal

rhythm disorders in this category of patients. This leads to an increase in the amount of collagen matrix in the myocardium and enhance in apoptosis processes. This leads to a subsequent stage of remodeling of the left ventricle, which leads to a set of changes in its shape and functioning in response to hemodynamic conditions and pathological processes in the myocardium. It has been established that the dilatation of LV cavities is the morphological substrate of these changes, which is the reason and evidence of the appearance of clinically significant CHF, which in our patients were manifested in higher FC of CHF arising and progressing with eccentric hypertrophy.

All forms of LV myocardial remodeling are accompanied by a decrease in both LV diastolic relaxation and atrial filling. In our study, the maximum reduction in diastolic relaxation was found in patients with eccentric hypertrophy, which is accompanied by the most significant drop in the ejection fraction. In concentric hypertrophy of the left ventricle of the heart and concentric remodeling, a decrease in diastolic filling and atrial filling is accompanied by the preservation of EF.

To date, to prevent the progression of CHF in the 1st year of treatment of elderly patients after heart attack, a systematic evaluation of not only known systolic function indices but also the effect of medication on diastolic function is required, which is performed extremely rare and, as a rule, only in patients with so-called diastolic heart failure.

CONCLUSION

It was established that structural changes occur in the formation of post-infarction cardiosclerosis. Morphological studies revealed an increase in size and a decrease in the number of myocytes and an increase in the connective tissue matrix. The density of the myocardium increases accompanied by a diastolic LV disturbance. The existing chronic LV overload causes a structural and morphological restructuring of myocardial tissue, which is characterized by the presence of hypertrophy, dilatation, and subsequently the change in the geometry of the heart. Remodeling of the myocardium is the integral substrate that determines the occurrence and progression of CHF in elderly patients. An important factor in the development of these processes is the age factor. Patients over 60 years with post-infarction cardiosclerosis have a reliable increase in their volumes of the left ventricle; their rate of circular shortening of the myocardial fibers decreases and the fraction of the LV ejection decreases. At the same time, with aging, there is an increase in the ischemic load on the myocardium and a decrease in the reserve capacities of the cardiovascular system. Cardiovascular diseases are extremely common in elderly patients and are the main cause of their death. The increase in the number of elderly people worldwide is accompanied by an increase in the number of patients with cardiovascular diseases. The available guidelines for the management of patients with cardiovascular diseases are mainly based on studies which either included small number or none of elderly patients. In this regard, the evidence base of recommendations for the treatment of common pathological conditions in the elderly is insufficient. To make the best decision when managing elderly patients with CHF, the clinician should know not only the evidence base of the research but also take into account the changes in the cardiovascular system that occurs in the process of aging.

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