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Systemic Inflammation Caused by Comorbidietes and Echocardiografically Established Diastolic Dysfunction in Heart Failure with Preserved Ejecion Fraction in the Elderly

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Abstract

Introduction: The treatment of chronic heart failure reached significant progress within the last decades. However, the progress is mainly limited only to patients with reduced ejection fraction, and recently to those with medially reduced ejection fraction, while the heart failure with preserved ejection fraction (HFpEF) remains enigma even beside significant morbidity and mortality. One of suggested hypotheses is, that comorbidities cause systemic inflammation, coronary microvascular dysfunction and oxidative stress, which lead to myocardial fibrosis, stiffness of myocytes and, at the end to diastole dysfunction (DD) and HFpEF. **Material and methods:** Clinically prospective average study, which included 124 patients, aged above 65 years, out of which 85 patients were in the investigated group, which completed the criteria for existence of HFpEF and present comorbidities, and 39 patients—control group. **Results:** The values of the investigated inflammation mediators highly sensitive (hs - CRP) and interleukin - 6 (IL-6) from peripheral blood, significantly differed among the old individuals with HFpEF and comorbidities, compared to the control group. However, the applied statistical methods mostly showed a direct correlation of inflammation mediators with the parameters of DD and heart remodelling, which has been characteristic for HFpEF. **Conclusion:** Our investigation went in favor to the hypothesis that the chronic, with low degree - inflammation, present in the most frequent comorbidities in the old age, brought to increased atheromatosis, DD and heart remodelling, being characteristic for HFpEF in old people.

Keywords

Heart Failure With Preserved Ejection Fraction, Diastole Dysfunction, Systemic Inflammation, Comorbidities

1. Introduction

Aging is complex dynamic biological process being characterised with constantly remodelling of the organism [1].

One of the newest aging theories has been focused to immunologic response and takes into account the activation of the subclinical chronic inflammation of low degree, which appears with aging, the so-called "chronic inflamma-

tion" [2, 3]. The normal process of aging has been connected with deep changes of the immunologic system of the organism. Firstly, there are significant changes of T and B lymphocytes, involution of thymus glands, functional decrease of macrophages, poor expression of the receptors from the activated splenic and peritoneal macrophages and changes of different chemokines and cytokines. Aging causes failure of the humoral as well as the cellular immune factors [3]. Activated peripheral, mononuclear cells isolated in adult population that show not only increased production of pro-inflammatory cytokines, such as IL-1, IL-6 and TNF-α, ex vivo, compared to young people, but also one increased expression of COX - 2 receptors, which together with prostaglandins are considered as main regulators of the aging - caused inflammatory changes [4, 5]. Also, in that way, also the changes in B-cells are verified, which are also recognized as aging caused changes of the immune system, it is established in percentage that their number significantly decreased from aging [4]. In that way, one concept has been made that the chronic antigen stress during lifetime causes accumulation of chronic cell scars, which are potential trigger in occurrence of inflammatory response by association with pathogenesis of all diseases related to aging [3, 4].

Immune system and metabolic syndrome:

Metabolic fatty tissue is associated with insulin sensitivity through production of adipo - cytokines, including leptine, TNF - α, angiotensinogen, IL-6 and non-esterified fatty acids which activate the way to renin - angiotensin – aldosterone and development of insulin resistance [5].

Insulin resistance is more recognized as a "chronic one, with low degree of inflammatory condition". Similarity between the insulin resistance with other type of inflammatory condition, the atherosclerosis, is proved many times in the last several decades [6, 7]. Atherosclerosis and insulin resistance share similar pathophysiologic mechanisms, mostly caused by secretion of two main pro - inflammatory cytokines, TNF - alpha and IL - 6, the response of the organism in the acute phase through secretion of cytokines is closely included in the pathogenesis of type 2-diabetes mellitus and the accompanying complications such as dyslipidemia and atherosclerosis [8, 9].

Diastolic dysfunction and HFpEF:

The high prevalence of comorbidities such as: obesity, diabetes, COPD and hypertension induce systemic pro - inflammatory condition [11, 12]. Systemic pro-inflammatory condition causes coronary microvascular endothelial inflammation, which decreases the NO bioavailability, the contents of cyclic guanosine monophosphate and the activity of protein kinase in the adjacent cardio-myocytes [13]. The low protein kinase activity favours development of hypertrophy and hypertrophic cardio-myocyte, while the interstitial fibrosis cause for high diastolic ventricular stiffness and development of HFpEF [14, 15]. In a major published study in Clinical Research in Cardiology, 2011, by Frank Edelman et al., it was found that comorbidities had a stronger effect on the prognosis of HFpEF than HFrEF, that the overall effect of comorbidities of the NYHA class in multivariate analyzes was approximately 1.5 times higher in HFpEF, and also much stronger than the effect of a 10% decrease in EF in HFpEF or a decrease of 5 mm in the left ventricular end - diastolic diameter in HFpEF [16]. The number of comorbidities is confirmed by other studies, such as one published in In J.of Cardiology (Streng KW, Nauta JF at al.), 2018, which in 1780 respondents determined the frequency of comorbidities (with HFpEF, HFrEF and with a transitional form, mid-range (40-49%), it has been found that comorbidities are most common in patients with HFpEF [17]. In a study of 111 patients with DD and more pronounced dyspnea, published in the Cardiovacular Ultrasound 2014, Ratanasid et al. have proven that the LAVI - max parameter is most important for determining chronic diastolic load. Using echocardiography, Zopinni at al, proved that tissue Doppler imaging E/e' ratio is a reliable predictor of left ventricular filling pressure. They performed a systematic review and meta-analysis to investigate the averaged E/e' ratio value in patients with type 2 diabetes compared to non-diabetic controls [18].

Inflammatory cytokines in heart failure: mediators and markers:

In the last decade an exciting progress has been noticed in the field of biomarkers that are used for managing the patients with HF. It appears that determination of specific, sensitive biomarkers which reflect the complex HF pathophysiology and their usage for discovering of asymptomatic cardiac changes can become a key tool for screening, helping to identify the patients who need additional diagnostic examinations [19].

Useful and generally accepted marker for HF is BNP, although that marker has high sensitivity to exclude the HF, it is not completely specific, because their values are increasing also in other conditions [20]. Many studies showed that combination of BNP together with the inflammatory markers could increase detection of the asymptomatic left ventricular systolic dysfunction and the early HF phases. Higher levels of the inflammatory mediators, including the IL-1, IL-6, IL-18, hs-CRP, TNF-α are increased with HF, regardless the etiology of the disease [21, 22]. CRP and aging**:** Increased proofs show that CRP is not only an inflammatory biomarker, but it is also an important risk - factor, associated with diseases connected with aging, including cardiovascular diseases, hypertension, diabetes, and the renal disease. It is well known that CRP and its receptor, CD32/CD64, in order to induce the inflammatory

process [23, 24, 25].

2. Material and Methods

Study design: clinically prospective cross sectional study, a total of 124 patients were included.

Investigation group: 85 patients**. Control group:** 39 patients. **Inclusion criteria:** above 65 years, on ECG – sinus rhythm. Symptoms and signs for HF (ESC/ASC, 2016) criteria, and presence of comorbidities. **Selection of comorbidities:** arterial hypertension, diabetes, obesity and chronic renal disease. Only patients for whom HFpEF was established (criteria ASE/ESC 2016) proved clinically and with echocardiography (M-mode, 2D) were examined, volume measures, Doppler measures (pulse, continuous, tissue Doppler, pulmonary venous Doppler). According to functional classification, patients who were after NYHA (2-4 stadium) were examined. **Exclusive criteria:** age under 65 years, on ECG signs for absolute arrhythmia, evidence for implanted permanent pace-maker, evidence for advanced valve heart disease (from moderate to severe grade), evidence for congenital heart disease. Anemia and proved coronary arterial disease, asthma, chronic obstructive pulmonary disease, chronic inflammatory and immunologic diseases, malignant disease. Also were excluded patients with value of peripheral venous blood hs CRP > 10mg/ml and Le > 10 x 10^9/l, suspect and acute infection as well as patients being on chronic therapy with corticosteroids or other immunomodulatory therapy. Patients with advanced cognitive illness, due to difficult cooperation during the investigation were also excluded.

2.1 Methodology

1. Anamnesis and physical examination; 2**.** Questionnaire for HF and a questionnaire for comorbidities; 3. Electrocardiography; 4. BMI 5.Transthoracal echocardiography—all measures were made according to Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging 2015 и Recommendation for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: an Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging 2016. The four recommended criteria for diagnosis of diastole dysfunction were: annular lateral e' < 10cm/s, i.e, E/e`>14, LA volume index >34ml/m^2 and maximal TR velocity > 2.8m/s. DD was considered if more than two of these recommendations were fulfilled. Gradation of DD was made in already established criteria: 1 grade—delayed relaxation. 2 grade—pseudo - normalisation, and 3 grade—restrictive type.

Carotid Doppler ultrasonography – gradation for carotid score was made in the following way: - score 0: no plaques and thickening of the IMT <1 mm, score 1 thickened IMT (≥ 1 mm) - score 2 – no stenotic plaque on ACI, score 3 stenotic score on ACI (≥ 50% stenosis).

Laboratory analyses, inflammatory mediators IL - 6, hs - CRP—were analyzed after the method of Turbidimetry, Integra 400 Roche) (mg/L) from samples of venous peripheral carotid black, IL - 6 – was analyzed (after the method ECLIA) (pg/ml) from the samples of venous peripheral blood.

2.2 Statistical analysis

Results were elaborated with statistical computer program SPSS 23 for Windows. Numerical signs were presented with descriptive statistics (arithmetical mean, standard deviation, mediana, inter-quartile rank). For comparison of the analyzed groups independent parametric and non-parametric tests were used (Chi-square test, Fisher exact test, Student t test, Mann-Whitney Z test, Analysis of Variance with Post Tukey test, Kruskal-Wallis ANOVA test). To analyze the relation between two variables were used Pearson coefficient of linear correlation, Spearman coefficient of rank correlation.

3. Results

3.1

Patients with HFpEF and comorbid diseases were significantly older than the patients in the control group, the difference of 5,9 years has been showed as significant. Women older than 65 years had more comorbidities compared to men (see Figure 1).

3.2

Distribution of the patients with IG in relation to the number of comorbidities showed that more than of them had three or more comorbidities (55.3%). Arterial hypertension was present in all patients as comorbidity, and diabetes

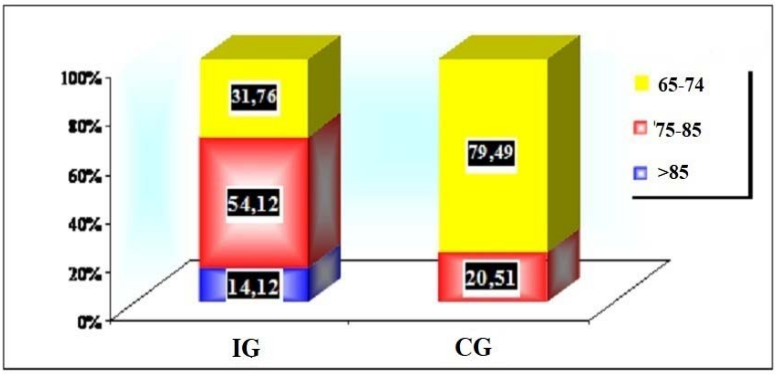
was present in all groups with two or three and more comorbidities. Obesity, being a comorbid condition, is one of the most frequently described in literature, in our IG was present only in 26% of the patients, i.e. in the age group from 65 to 75 years (see Figure 2).

3.3

There was significant difference in increase of the hs - CRP value with rise of the number of comorbidities (p=0.00000) (see Figure 3).

3.4

The average value of IL-6 in the group with one comorbidity were significantly lower than the group with three or more comorbidities (8.46 ± 4.3 vs 15.2 ± 5.1; p=0.00019) (see Figure 4**).**



Figrue 1. Age distribution in the investigated and control group.

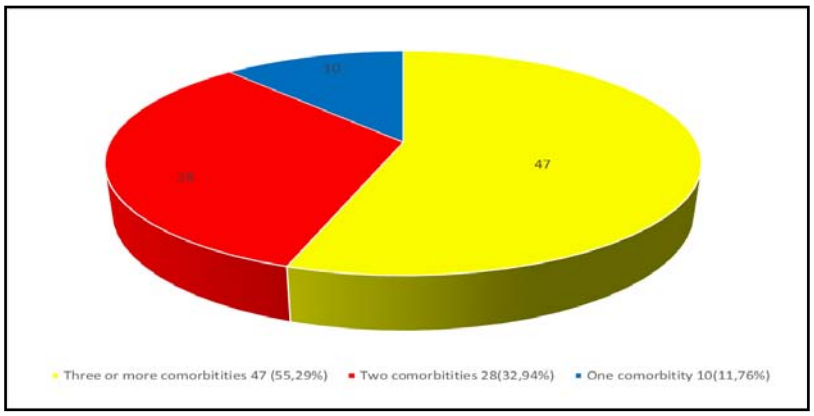


Figure 2. Number of comorbidities in the IG.

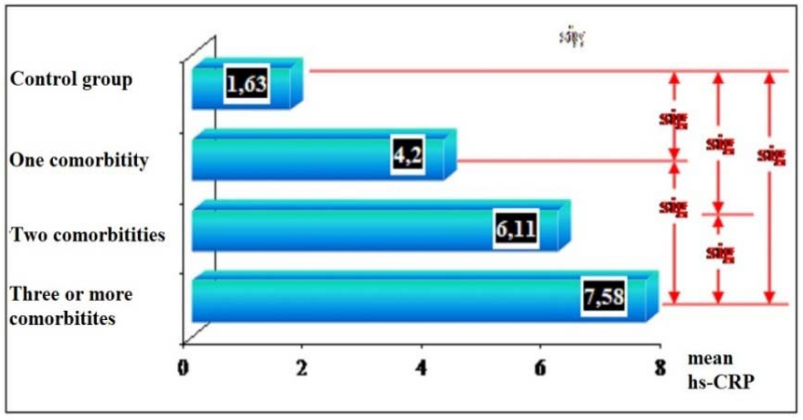


Figure 3. Values of hs-CRP depending on the number of comorbidities.

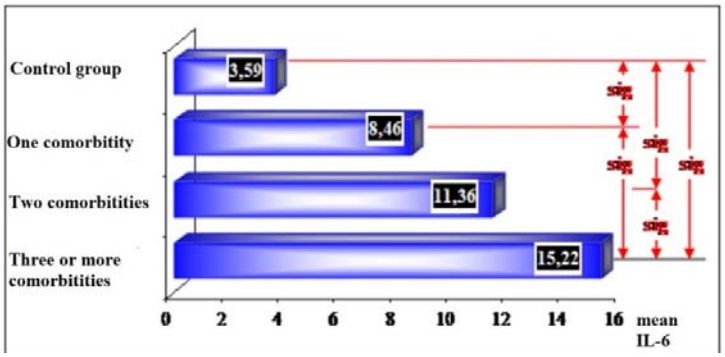


Figure 4. Values of IL-6 depending on the number of comorbidities.

3.5

The HF degree and the number of comorbidities correlate positively i.e. directly between each other (R = 0.0176). NYHA class was increasing with the increase of the number of comorbidities (see Figrue 5).

3.7

In the group of patients with comorbidities, LV mass parameter significantly correlated with IL-6 ($p<0.001$), and non-significantly with hs-CRP ($p=0.098$) (see Table 2).

3.6

Carotid score as an indicator for the degree of atheromatosis of the blood vessels, was in a direct, statistical significant, positive right-proportional relation with the number and the comorbidities time-duration. hs-CRP and IL-6 were in direct correlation with the degree of carotid crore per se (see Table 1).

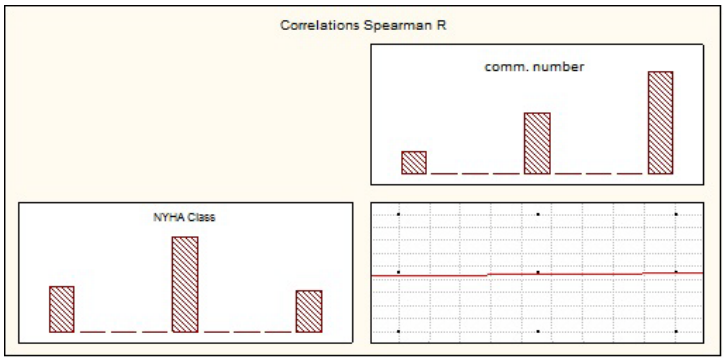


Figure 5. Correlation between number of comorbidities and the level of HF (NYHA).

Table 1. Correlation of IL-6 value on the degree of carotid score in IG

Correlation	Spearman R	p
IL-6 /carotid score (right)	0.093	p=0.4
IL-6 / carotid score (left)	0.072	p=0.51

Table 2. Correlation between IL-6 and hs-CRP and LV mass

Correlation	Pearson r	p
hs-CRP & LAVI max	0.085	p=0.044
IL-6 & LAVI max	-0.0009	p=0.099

3.8

In agreement with Pearson coefficient value of correlation for the analyzed correlation between LAVI max and hs-CRP (r = 0.085, p=0.49), and between LAVI max and IL-6 (r = - 0.0009, p=0.99), these correlations in IG were significant (see Table 3).

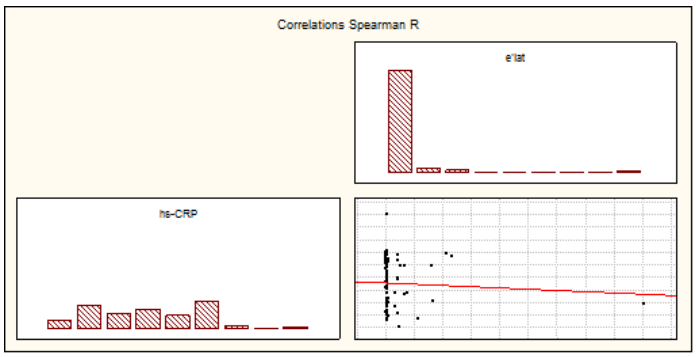
Table 3. Correlation between IL-6 and hs-CRP and LAVI-max

Correlation	Pearson r	p
hs-CRP & LAVI max	0.085	p=0.044
IL-6 & LAVI max	-0.0009	p=0.099

3.9

e' lat parameter in IG was negative, i.e. indirectly related with hs-CRP (R= - 0.196) (see Table 4).

Table 4. Correlation between e' lat and hs-CRP



3.10

hs - CRP significantly correlated with the degrees of DD (p=0.000025), and with the degree of HF (p=0.0012). The degree of DD had significant influence on IL-6 value in patients from the IG (p=0.0019). Spearman coefficient of correlation value for relation of the IL-6 with the HF degree was R=0.214 and p=0.052, that also showed to positive or direct correlation in the limit of significance (see Table 5).

Table 5. Correlation between IL-6 and degree of DD and HF

Correlation	Spearman R	p
IL-6 / degree of DD	0.356	p=0.00089
IL-6 / degree of HF	0.214	p=0.052

4. Discussion

Treatment of chronic HF reached significant progress within the last decade. However, the progress mainly was limited to patients with HFpEF, and after the newer classification, also to those with medium reduced (HF-mr EF 40-49%), while HFpEF remained enigma, even beside the significant morbidity and mortality [27, 28, 29]. This investigation denotes possible inflammatory mechanism in occurrence of the left ventricular DD [30, 31]. Systemic—with low degree inflammation could contribute to heart remodelling, with left atrial dysfunction and left-ventricular hypertrophy, as well as DD in concordance with the age, in presence of accompanying comorbidities, which bring to appearance of HFpEF [32, 33, 34]. Many such extensive investigations are necessary with inclusion of greater number of inflammatory markers which will prove this connection [34, 35].

The advance of medicine, most probably, will contribute the way in which HF will be treated in the coming years. As it is noted in the survey entitled as "Transition from usual care to personified and precise remedy based on biomarkers in HF: call for action" by Antoni Bayés-Genís et al. from Hospital Universitari Germans Trias and Pujol in Badalona, - Spain, the authors consider that circulatory biomarkers, measured by highly sensitive, specific and reproductive tests, will have more important role in risk of HF estimation at patient's level and his therapeutic targeting [36, 37, 38]. However, many questions remain unanswered, starting from complexed clinical usage and adequateness of the referent average values, up to cell and molecular mechanisms for production of biomarkers and their liberation from extra-cardiac organs, up to critically important therapeutic implications [39, 40]. While data, in the moment, has been focused to usage of biomarkers in order to identify HF, the risk is restricted and, most probably, generally, the therapy has been used with anti-inflammatory drugs for other diseases, the authors believed that the future must bring more individualized and focused strategies for treatment, usage of complex analyses of phenotype/genotype as well as usage of precise therapy focused to mediators and their pathways to HF. A broad investigation agenda will be necessary which will comprised spectrum of studies, up to substitutes of clinical investigations which will examine the new therapies and their effect among the groups, defined according to biomarkers values in order to achieve proved accompanying biomarkers for precise diagnosis of HF [41]. As a great number of studies are published which document the increased risk of unwanted cardiovascular events related to the level of inflammatory mediators in serum, increased interest is developing to use them as a part the clinical practice [40].

In a number of studies in the last decade, it was shown than the normal aging in people has been accompanied with disturbed control on production of multi-functional cytokines IL-6. It is established that this cytokine has been quantitatively raised in more serum samples obtained from "normal" older people. Also, in "Interleukin - 6 in Aging and Chronic Disease" published in J Gerontology. A Biol (2009), has been denoted that the IL-6 serum concentration has been raised with age. In this study, the IL-6 values ranges from 1.4 pg/ml (men) and 1.1 pg/ml (women) in the age group from 65-74 years to 3.5 pg/ml (men) and 2.1 pg/ml (women) in persons at the age of 85 yr and older, and in the older, but the rise of IL-6 has not been explained by differential prevalence of polymorphisms of the IL-6 gene, but that the excessive production or decreased clearance of free oxygen radicals, which stimulates the IL-6 production, which has been characterized for many diseases related to atherosclerosis and aging, are related to its higher concentration in blood of the old people with comorbidities [49, 16]. William Ershler (1993) in his paper: IL-6 cytokine for gerontologists" denoted IL-6 as one of the main signal pathways which modulate the complex relation between aging and chronic morbidity. During the last 12 years, the knowledge for the role of IL-6 in human physiology and pathology has been significantly increased, although some of the questions which have been initially raised by Eshler are still debating [39, 40]. Although hs-CRP has been clinically useful as a biomarker for risk-foreseeing, more investigations suggest that CRP per se, probably will not be a goal for intervention. Shifting of the inflammatory cascade from CRP of interleukin IL-6 to IL-l enables new therapeutic possibilities for athero-protection. Agents for blockade of inflammatory pathways are more and more used, but in older population, it should be pay attention for increased risk and vulnerability toward infections dangerous for life or sepsis which could be caused by agents which are focused towards the key mediators of the inflammatory cascade, such as TNF-álfa or IL-6 [8, 9]. New studies are necessary which will point to modulation or liberation of inflammation more than the blockade of markers for inflammation, i.e. discovering of agents which will work to the basic reasons for inflammation being more safe and efficacious than those which block the very inflammatory pathways [40].

5. Conclusion

Our investigation went in favor to the hypothesis that the chronic, with low degree - inflammation, present in the most frequent comorbidities in the old age, brought to increased atheromatosis, DD and heart remodelling, being characteristic for HFpEF in old people.

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