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EVALUTION OF THE EFFECT OF OBESITY-ASSOCIATED INFLAMMATION ON THE RESPONSE TO COMPLEX THERAPY IN HYPERTENSIVE ELDERLY PATIENTS WITH CORONARY ARTERY DISEASE

N. V. Tofan, S. A. Tykhonova, V. B. Iablonska, O. V. Khyzhnyak

Odessa National Medical University, Odessa, Ukraine
Internal Medicine Department №2
ORCID: 0000-0003-2588-5725

Abstract

Object: to identify factors that limit the effectiveness of pharmacotherapy of hypertension (HT) with comorbid coronary artery disease (CAD) in elderly obese patients by determining laboratory and spectroscopy features related to inflammation.

Material and methods: 60 patients (68.2 ± 5.9 y.o.) were observed and treated in Internal Medicine Department of University Clinic of Odessa National Medical University. Patients were divided into 2 groups. The 1st group included patients (n = 30) with body mass index (BMI) ≤25 kg/m2, HT and co-morbid CAD; the 2nd group (n = 30) - patients with BMI≥30 kg/m2, HT and with co-morbid CAD. For each patient's group antihypertensive combination of Lisinopril and Bisoprolol was prescribed. The Laser correlation spectroscopy (LCS) was a special method for investigation.

Results: before pharmacotherapy (PT) in both groups according to LCS 11-150 nm particles are prevailing. But in obese patients 75th percentile of 31-70 nm particles exceeds that one in non-obese group (56.7% vs 30.5%). During PT systolic blood pressure (SBP)

value normalized in the patients of 1st group (without obesity), while in the obese patients (2nd group) SBP remained above target level. Creatinine level increased in patients of 1st group (without obesity) by 16.5 μmol / L ($p < 0.05$) with a decrease in GFR by 17.1 ml/min/1.73 m^2 ($P < 0.05$). LCS data during PT show increase of 11-30 nm and decrease of 75-150 nm particles in non-obese patients, while in obese patients 71-150 nm particles are prevailing and 150 nm particles have appeared ($p<0.05$).

Conclusions: 1. In elderly hypertensive patients with concomitant CAD, obesity is a factor limiting the effectiveness of complex antihypertensive therapy. **2**. An increase of proportion of allergic-directed and appearance of autoimmune-directed homeostatic shifts in serum according to LCS are associated with a decrease of antihypertensive therapy efficacy in elderly hypertensive patients with CAD and obesity. **3**. In hypertensive non-obese patients with CAD under the influence of complex antihypertensive therapy deteriorating of renal function is observed while in obesity renal function is not changed. **4.** Homeostatic changes revealed in the second group by LCS values probably reflect manifestation of low grade inflammatory process caused by excessive activity of adipose tissue.

Keywords: pharmacotherapy; efficacy; hypertension; obesity; inflammation

Background

Obesity takes a leading position among the most significant risk factors of cardiovascular complications and it is the most common associated comorbidity in patients with coronary artery disease (CAD) combined with arterial hypertension (HT) [1, 2]. Besides obesity is an independent risk factor of CAD development and progression [3]. It is known that combination of CAD with HT is considered particularly prognostically unfavorable, especially in the elderly. Risk stratification of cardiovascular complications in HT with such a concomitant disease as angina pectoris provides a very high risk of complications even at normal high blood pressure [4]. As well one study notes that CAD is one of the independent prognostic markers of sudden cardiac mortality, along with age, diabetes mellitus (DM) and left ventricular hypertrophy [5]. In our previous study, a positive correlation between an increase in body mass index (BMI) and the progression of heart failure was found ($r=0,78$; $P<0.05$). It was also found that obesity provokes more frequent joining of atrial fibrillation compared to the group without increased BMI [1]. According to the Framingham study, there is a reliable correlation between BMI and left ventricular size and thickness of it's wall. This correlation remained significant even when gender, age, and blood pressure (BP) were taken into account [6]. It has been proved that even a slight increase in BP in obese patients leads to

growth of myocardial mass of left ventricle [7].

Also obesity leads to homeostatic changes – development of systemic inflammation generally and adipose tissue particularly which is a background for development of cardio-vascular diseases, DM, fatty liver disease and uric acid metabolism violation. Inflammation of adipose tissue starts with chemokines synthesis, which are produced by adipocytes, mostly monocyte chemoattractant protein-1 (MCP-1) [8]. Chemokins are responsible for adhesion and migration of monocytes, which become macrophages after crossing of vessel barrier [9]. So, infiltration of adipose tissue by macrophages is developing which preventing transformation of preadipocytes into mature adipocytes leading to adipocytes hypertrophy [10]. Moreover, chemokins are also synthesized by macrophages which causes vicious circle of inflammation formation: chemokins attract monocytes, which will transform into macrophages after extravasation and block preadipocytes, thereby leading to adipocytes hypertrophy, which also secrete chemokins by mean of which inflammation will maintain [9, 11]. Thus macrophages will synthesize tumor necrotizing factor α (TNF-α), which inhibits adiponectin secretion and stimulates IL-6 production [12]. Besides, TNF-α inducts arachidonic acid metabolism which will lead to inflammation progression, stimulates MCP-1, which increases adipose tissue infiltration and decreases NO production which causing vasodilation and inducts endothelium dysfunction [13]. It was found C-reactive protein (CRP) concentration elevation in obesity [14]. Furthermore, microcirculation will be slowed down in obesity which leads to hypoxia and ischemia what will induct cytokins synthesis and prevent adipocytes formation [15-17]. Thus, hypoxia of adipose tissue will support inflammation progression and development of such consequences of inflammation as atherosclerosis and DM [18].

Thus, obesity is a considerable factor which contributes to decompensation of patient's state and decreases pharmacotherapy efficacy.

The purpose of the one-site prospective study was to identify factors that limit the effectiveness of pharmacotherapy of HT with comorbid CAD in elderly obese patients by determining laboratory and spectroscopy features related to inflammation.

Material and methods

During 2011–2012 years 60 patients (25 males / 35 females) aged from 64 to 75 y.o. (average, 68.2 ± 5.9 y.o.) were observed and treated in Internal Medicine Department of University Clinic of Odessa National Medical University [19]. Inclusion criteria: age above 60 y.o., HT, CAD: angina pectoris II-III CCS, mandatory presence of acetylsalicylic acid and statins in patient's therapy. The patients were not to included, if they had myocardial

infarction or stroke during previously 3 months, valvular heart diseases, active oncology diseases, acute or exacerbated bacterial and viral infections, serum creatinine □115 □mol/l, hepatic transaminases 3 times higher than the upper limits of the norm, respiratory failure II-III degree, BMI 25-30 kg/m^2.

Patients population

Patients were divided into 2 groups. The 1st group included patients (n = 30) with body mass index (BMI) □25 kg/m^2, HT and co-morbid CAD; the 2nd group (n = 30) - patients with BMI□30 kg/m^2, HT and with co-morbid CAD. For each patient's group antihypertensive combination of Lisinopril and Bisoprolol was prescribed.

Laboratory investigation

The Laser correlation spectroscopy (LCS) was a special method for investigation. LCS is a multiparameter biophysical method of laboratory analysis based on the measurement of the spectral characteristics of induced monochromatic radiation when passing through a biological fluid [20, 21], which provides an opportunity to register particles with hydrodynamic diameter 1 – 10 000 nanometers (nm). There are 5 zones according to light-scattering particles size in serum. Previous studies by Bazhora Yu. I. and Noskin L. O. demonstrated that the 1st zone (0-10 nm) included low-molecular monomeric albumins and glycolipid free complexes; the 2nd zone (11-30 nm) - globulin proteins and low-molecular lipoprotein complexes; the 3 zone (31-70 nm) - high-molecular lipoprotein complexes, ribonucleoproteins and deoxyribonucleoproteins, the low-molecular immune complexes; the 4th zone (71-150 nm) - mainly constitutive immune complexes of the average size; the 5th zone - huge particles (≥150 nm) presented in patients with allergization and an autoimmune sensibilization [20, 21].

It was proposed the program "Semiotic classificator" that distinguishes 3 directions of homeostatic shifts and each of the following has subdivisions [20, 21]. I subdivision - hydrolytic-directed shifts: Ia – intoxicational-like shifts with increasing of the 2nd and 3rd zones particles; Ib – catabolic-like shifts with increasing of the 2nd zone particles; Ic – dystrophic-like shifts with increasing of the 1st zone particles. II subdivision - synthetic-directed (anabolic) shifts: IIa – allergy-like shifts with increasing of the 4th zone particles; IIb – autoimmune-like shifts with increasing of the 5th zone particles. III - mixed shifts: IIIa – allergy-intoxicational-like shifts with increasing of the 2nd and 4th zones particles); IIIb – autoimmune-intoxicational-like shifts with increasing of the 2nd and 5th zones particles); IIIc – allergy-dystrophic-like shifts with increasing of the 1st and 4th zones particles).

Blood serum was used as investigated biomaterial. The first blood sampling was took before the start of PT prescription, and the second one at 10th day of PT according to the method developed by Yu.I. Bazhora and L.O. Noskin [20].

The following parameters were analyzed in observed patients: BMI (kg/m2) and glomerular filtration rate (GFR) by MDRD formula.

Statistical methods

The obtained data were processed using non-parametric statistics (Statistica-10.0).

Results

In the patients' the 2nd group 40% men had the 1st grade of obesity and 36,7% - the 2nd degree. Among women the 1st degree of obesity dominates - 53.9% vs 44.6%. The patients with abdominal obesity is very high among both men and women with a predominance among women (84.6% vs 76.7%).

Table 1 shows the initial clinical and laboratory data of patients depending on BMI at the time of inclusion.

Table 1 - **Clinical and laboratory data in the patients at the time of inclusion, depending on BMI**

Clinical and laboratory parameters	1st group (n=30) BMI ≤25 kg/m^2	2nd group (n=30) BMI ≥30 kg/m^2
Age, years	67,2±7,7	63,8±10,4
Waist circumference, cm	75,4±5,2	100,8±10,1
HR, b.p.m.	72,0 (68,0; 82,5)	77,0 (67,5; 80,0)
SBP, mm Hg	165,0 (150,0;165,0)	172,5 (155,0; 180,0)
DBP, mm Hg	90,0 (80,0; 90,0)	87,5 (80,0; 96,2)
Cholesterol, mmol/l	4,8 (4,5; 5,7)	4,9 (4,7; **7,6*)**
Glucosae, mmol/l	5,3 (4,7; 5,7)	**6,4*** (5,4; **8,3*)**
Microalbuminuria, g/l	0,01 (0,00; 0,03)	0,03 (0,00; 0,10)
Creatinine, μmol/l	83,5 (69,2; 96,7)	69,5 (61,7; 98,7)
GFR, ml/min/1.73 м^2	75,3 (58,6; 85,7)	**98,6*** (68,7; 113,1)

Note: * - p<0,05 before PT in the studied groups

In patients of both groups heart rate (HR), systolic and diastolic blood pressure (SBP

and DBP) levels were comparable.

75^{th} percentile of the cholesterol level in patients of 2^{nd} group was higher in comparison with its value in 1^{st} group (7.6^{75} vs 5.7^{75} mmol / l, p <0.05).

Glycemia level in the group without obesity didn't exceed normal values, while in the 2^{nd} fasting hyperglycemia was observed. 75^{th} percentile of glycemia level in patients with BMI ≥30 kg/m^2 was elevated and exceeded that one in patients with BMI ≤25 kg/m^2 ($8,3^{75}$ vs $5,7^{75}$ mmol / l, p <0,05).

Serum creatinine level doesn't differ statistically. The GFR value is higher in the obese group (98.6 vs 75.3 ml/min/1.73 m^2, p <0.05). Despite comparable median of creatinine levels in both groups of patients, GFR values were higher in obese patients (98.6 vs 75.3 ml/min/1.73 m^2, p <0.05).

Table 2 - **Initial subfractional redistribution of blood serum in patients groups depending on BMI**

Type of blood serum subfractional redistribution	1^{st} group (n=30)	2^{nd} group (n=30)
	BMI ≤25 кг/м2	BMI ≥30 кг/м2
I DDZ, %	4,0 (2,0; 9,7)	5,0 (0; 12,0)
II DDZ, %	16,0 (11,0; 33,7)	16,5 (13,7; 39,5)
III DDZ, %	24,5 (17,2; 30,5)	23,5 (19,7; **56,7*)**
IV DDZ, %	16,0 (0,7; 41,7)	16,5 (5,2; 37,7)
V DDZ, %	10,5 (0,5; 36,5)	0,6 (0; **7,7***)

Note: * - p<0,05 before PT; DDZ – discrete-dynamic zone.

Subfractional redistribution in blood serum according to LCS in both groups shows prevalence of low-, medium- and large-molecular particles with a size of 11-150 nm, which correspond to intoxicational and allergy-intoxicational homeostatic shifts (Tabl. 2) Their substrates are low- and high-molecular lipoprotein complexes and medium-sized immune complexes [20, 21]. Meanwhile, in the non-obese patients (1^{st} group) particles of V zone are revealed which are not defined in the obese patients (10,5% vs 0,6%). Besides, the 75^{th} percentile of these particles is also higher in the non-obese group (36,5% vs 7,7%). These are very high-molecular particles (>150 nm) which associated with autoimmune reactions [20, 21]. Also, in obese patients 75^{th} percentile of III zone particles exceeds that one in non-obese

group (56.7% vs 30.5%). This zone is composed of high-molecular lipoprotein complexes and low-molecular immune complexes [20, 21]. These particles are observed when intoxicational-directed homeostatic shifts are present. This means that in obese patients these changes in blood serum prevailing in comparison with non-obese patients, which corresponds to the inflammatory pathogenesis of obesity.

Table 3 - **Dynamics of clinical and laboratory data in the studied patients during PT depending on BMI**

Clinical and laboratory parameters	1st group (n=30)	2nd group (n=30)
	BMI ≤25 kg/m^2	BMI ≥30 kg/m^2
Age, years	67,2±7,7	63,8±10,4
Waist circumference, cm	75,4±5,2	100,8±10,1
HR, b.p.m.	69,0 (57,5; 80,0)	66,0 (60,7; 73,0)
SBP, mm Hg	130,0 (120,0; 132,5)	**160,0*** (151,2; 167,5)
DBP, mm Hg	80,0 (80,0; 90,0)	80,0 (76,2; 87,5)
Cholesterol, mmol/l	4,7 (4,3; 4,8)	4,6 (4,4; **6,2*)**
Glucosae, mmol/l	5,2 (4,8; 5,8)	5,8 (4,9; **7,5*)**
Microalbuminuria, g/l	0,01 (0,00; 0,09)	0,02 (0,00; 0,07)
Creatinine, μmol/l	100,0 (93,5; 110,0)	93,5 (82,2; 106,5)
GFR, ml/min/1.73 м^2	58,2 (51,2; 66,2)	**76,6*** (62,6; 99,1)

Note: * - p<0,05 during PT in the studied groups.

During PT (Tabl. 3) SBP value normalized in the patients of 1st group, while in the obese patients (2nd group) SBP remained above target level.

Glycemia level in obese patients during PT according to 75th percentile level is higher in comparison with non-obese group and corresponds to hyperglycemia criteria (7.5^{75} vs 5.8^{75} mmol / l, p <0.05).

There was an increase in the mean values of plasma creatinine concentration in patients of 1st group (without obesity) by 16.5 μmol / L (p <0.05) with a decrease in GFR by 17.1 ml/min/1.73 m^2 (p <0.05), which corresponds to the progression of renal dysfunction.

Subfractional redistribution according to LCS showed (table 4) significant dynamics in patients with normal BMI (1st group), where particles with a size of 11-30 nm increased by

13.0% (p <0.05).

Table 4 - **Dynamics of blood serum subfractional redistribution according to LCS in studied patients during PT depending on BMI**

Type of blood serum subfractional redistribution	1st group (n=30)	2nd group (n=30)
	BMI ≤25 кг/м2	BMI ≥30 кг/м2
I DDZ, %	6,0 (2,0; 12,0)	4,0 (2,2; 7,0)
II DDZ, %	29,0 (14,0; 40,5)	21,0 (14,2; 22,0)
III DDZ, %	26,0 (11,5; 36,5)	25,5 (14,0; 32,2)
IV DDZ, %	28,0 (4,0; 51,5)	**40,0*** (18,5; 51,5)
V DDZ, %	8,0 (0; 18,5)	12,0 (3,5; 19,2)

Note: * - p<0,05 during PT.

It means that during PT contribution of catabolic-directed shifts has increased (Tabl. 4). In the 1st group growth of 71-150 nm particles by 12.0% (p <0.05) was observed. This means that the therapy also contributed to the growth of allergy-directed shifts [20, 21]. These changes clinically were associated with the decrease of renal functional ability during drug therapy. Opposite, in the patients with obesity (2nd group) in subfractional redistribution 71-150 nm particles were prevailing and their contribution was higher than in the 1st group (p <0,05). As well, in the patients with obesity particles of the V zone has appeared which are correspondent to anabolic homeostatic shifts, specifically – autoimmune-like subfractional changes [20, 21].

Discussion

Before PT prevalence of II DDZ particles which refer to low-molecular lipoproteins in the non-obese patients (1st group) is in accordance with pathogenetic theory of atherosclerosis progression in AH and CAD [22]. Moreover, detected by mean of LCS intoxicational-directed shifts in the blood serum may be homeostatic manifestations of inflammation in HT and CAD.

In patients of the 1st group the dynamics of subfractional redistribution according to the LCS demonstrates that during PT the initial allergy-intoxicational shifts increase significantly, which is accompanied by a decrease of functional renal capacity. In our previous works also were obtained data on a negative correlation between functional renal

state and increase of 31-70 nm particles in the subfractional structure of blood serum which is correspond to intoxicational-directed shifts [20, 21].

In patients with obesity (2nd group) hyperglycemia and hypercholesterolemia are components of metabolic syndrome. In serum subfractional redistribution characterizes prevalence of intoxicational-directed shifts which may be homeostatic manifestation of inflammatory process caused by proinflammatory activity of adipose tissue. The most manifested peak in serum redistribution is presented with III zone particles, which are low molecular immune complexes. This assumedly may refer to presence of such inflammatory cytokins as TNF-α and IL-6, which are also of low molecular weight.

During PT such changes as prevalence of allergy-like shifts and appearance of autoimmune-like shifts according to LCS in patients with obesity (2nd group) may reflect reaction as a response on antigen stimulation by prescribed drugs combination. However, both of these shifts are considered synthetic (anabolic) homeostatic shifts and usually they appear in recovery process [20, 21].

In the group of elderly patients with obesity was revealed an interesting feature, namely absence of renal dysfunction period as a response on antihypertensive therapy initiation. One of the possible explanations could be the so-called "obesity paradox". In recent years, the results of a number of studies have been published, which show that patients with overweight or obesity may have more favorable prognosis than those with normal weight in various diseases [23], including acute coronary syndromes [24], percutaneous coronary interventions [25, 26] and myocardial infarction with ST segment elevation [27]. Paradoxical interrelations were also identified in one of the studies, where the group with abdominal obesity and without epicardial obesity was more successful than the group without abdominal obesity, but with epicardial obesity due to a smaller number of rhythm violations cases, atherosclerosis 2- and 3-coronary arteries, leptin resistance, albuminuria [28].

Obtained results require further researches to reveal interrelation of intoxicational homeostatic shifts in LCS with the level of cytokines, as well as to detail the mechanisms of obesity and its types impact in elderly with HT and CAD on renal dysfunction in different variants of antihypertensive therapy.

Conclusions

1. In elderly hypertensive patients with concomitant coronary artery disease, obesity is a factor limiting the effectiveness of complex antihypertensive therapy.

2. An increase of proportion of allergic-directed and appearance of autoimmune-directed homeostatic shifts in serum according to LCS data are associated with a decrease of

antihypertensive therapy efficacy in elderly hypertensive patients with coronary artery disease and obesity.

3. In hypertensive non-obese patients with coronary artery disease under the influence of complex antihypertensive therapy deteriorating of renal function is observed while in obesity renal function is not changed.

4. Homeostatic changes revealed in the second group by LCS values probably reflect manifestation of low grade inflammatory process caused by excessive activity of adipose tissue.

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