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Relationship Between Hemodynamic and Cytokines Disorders Depending of Endogenous Insulin Levels in Hypertensives with Heart Failure

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The study of relationship between blood pressure (BP) disorders and cytokines activation in 114 hypertensives with HF class II-III NYHA (45 male, 69 female), aged 59 ± 12 years, and different endogenous insulin (EI) levels was performed. We revealed the increasing of ABPM parameters depending to plasma EI levels and severe class of HF. Increasing of proinflammatory TNF- α in hypertensives with normal EI levels is more typically for HF class III NYHA. Anti-inflammatory cytokine IL-10 levels are increased in the early HF stages. The patients with 2hr postloading hyperinsulinemia are characterized by a significant increasing of proinflammatory and anti-inflammatory cytokines activity depending to HF progression compared with patients with normal EI levels. The highest plasma TNF- α , IL-6 and IL-10 levels and their ratios were revealed in patient with fasting hyperinsulinemia and HF class III.

Keyword: Arterial Hypertension, Heart Failure, Insulin Resistans, Cytokines.

1. Introduction

Combination of risk factors (hypertension, abdominal obesity, dyslipidemia, insulin resistance, smoking) is the initial stage of cardiovascular events. It is shown in cardio-vascular continuum with terminal period – chronic heart failure (HF) and death^[1,7,10]. In 70% of cases the cause of chronic HF is arterial hypertension (AH) – important risk factor that can be identified and successfully treated^[2]. Metabolic disorders and endothelial dysfunction increase the HF development and progression^[3,5,9].

Presence of risk factors activates cytokines pathway of endothelial dysfunction. Tumor necrosis factor alpha (TNF- α) is a proinflammatory cytokine involved in systemic

inflammation and is a member of a group of cytokines and another one of the proinflammatory cytokines that induced by TNF- α Interleukin-6 (IL-6) stimulates the acute phase reaction^[6]. IL-6 plays an important role in vascular remodeling and was reported to be a useful biomarker in predicting future cardiovascular events^[4]. The anti-inflammatory cytokines are a series of immunoregulatory molecules that control the proinflammatory cytokines response. One of the major anti-inflammatory cytokine is Interleukin-10 (IL-10)^[8].

Identification of risk factors and their timely correction is an important task for the successful treatment of hypertensives with HF and metabolic disorders.

1.1 Purpose: To study relationship between the blood pressure (BP) parameters and cytokines activation depending on the endogenous insulin (EI) levels in hypertensives with HF.

2. Material and Methods

114 hypertensives with HF class II-III NYHA (45 male, 69 female), aged 59 ± 12 years, were examined. Hypertension included grade 1 (systolic/diastolic BP >140 - $159/90$ - 99 mm Hg) and grade 2 (systolic/diastolic BP $\geq 160/100$ mm Hg).

Clinical examination was performed.

The patients were divided into 3 groups according to the plasma EI levels. Group 1 consisted of 67 patients with the normal EI levels. Group 2 included 27 patients with 2hr postloading hyperinsulinemia. Group 3 consisted of 20 patients with fasting (spontaneous) hyperinsulinemia.

Oral glucose-tolerant test with investigation of plasma glucose and EI levels (ELISA method) before and 2 hours after glucose loading were made. Normal plasma EI levels were 4-20 mU/ml before and 2 hours after glucose loading. 2h postloading hyperinsulinemia was investigated by normal fasting plasma EI levels and increase of EI levels ≥ 20 mU/ml after 2 hours after glucose loading. Fasting (spontaneous) hyperinsulinemia was investigated by increase of fasting and postloading EI levels.

Central hemodynamics state by office and ambulatory blood pressure monitoring (ABPM) were measured.

The cytokines of plasma TNF- α , IL-6, IL-10 levels (ELISA methods) were measured.

A control group included 20 people.

3. Results

There were observed 114 hypertensives with HF class II-III NYHA. Increasing of BP $\geq 140/90$ mmHg was revealed in 95 (83.33%) cases and 19 (16.67%) hypertensives have BP 120-140/80-90 mm Hg. It is known that the flow of hypertension is more difficult with metabolic disorders^[2].

Frequency of hypertension grade 1 was presented in 75% patients with normal plasma EI levels and HF class II-III NYHA.

Frequency of hypertension grade 2 increase in patients with hyperinsulinemia compared with patients with normal plasma EI levels. Among patients with normal plasma EI, postloading and fasting hyperinsulinemia hypertension grade 2 was revealed in 8 (27%); 8 (38%) and 9 (45%) cases, respectively.

Parameters of ABPM were depended from plasma EI levels and class of HF (Table 1). In patients with plasma normal EI levels and HF class II-III NYHA index of systolic BP (SBP) daily was increased by 11% vs. control group ($p > 0.05$). Index of diastolic BP (DBP) daily was increased by 16.9% in HF class III NYHA vs. the control group ($p \leq 0.05$).

There was significant BP increasing in patients with hyperinsulinemia and HF class III NYHA. Index of SBP/DBP daily in patients with 2hr postloading hyperinsulinemia and HF class III NYHA increased by 17.64%/20.58% respectively vs. the control group ($p \leq 0.05$). Index of SBP/DBP daily in patients with fasting hyperinsulinemia and HF class III NYHA increased by 19.32%/23.52% respectively vs. the control group ($p \leq 0.05$).

Thus, the flow of hypertension in patients with hyperinsulinemia and heart failure class III is heavier.

Endothelial dysfunction is one of the main component of hypertension pathogenesis^[2]. Insulin resistance intensifies vascular function disorders and promotes systemic inflammation^[1]. Inflammation is accompanied by activation of proinflammatory cytokines such as TNF- α , IL-6 and anti-inflammatory IL-10 [3,4], especially in patients with metabolic disorders^[6].

There were some patterns of cytokine profile parameters changes depending on the presence or absence of hyperinsulinemia and high class of HF (fig.1).

In patients with normal EI levels significant difference of cytokines profile parameters depending on HF class was revealed. In patients with HF class II NYHA levels of proinflammatory cytokine TNF- α were increased almost by 2 times vs. the control group ($p \leq 0.05$). At the same time IL-6 levels had a tendency to increase compared with the control group

($p > 0.05$). We found TNF- α /IL-6 ratio increasing by 1.8 times vs. the control group ($p \leq 0.05$). In patients with normal EI levels and HF class III NYHA plasma TNF- α and IL-6 levels were significantly increased by 2.5 and 2 times vs. the

control group ($p \leq 0.05$). TNF- α /IL-6 ratio was decreased by 23% vs. patients with HF class II NYHA patients ($p \leq 0.05$), but was increased by 40% vs. the control group ($p \leq 0.05$).

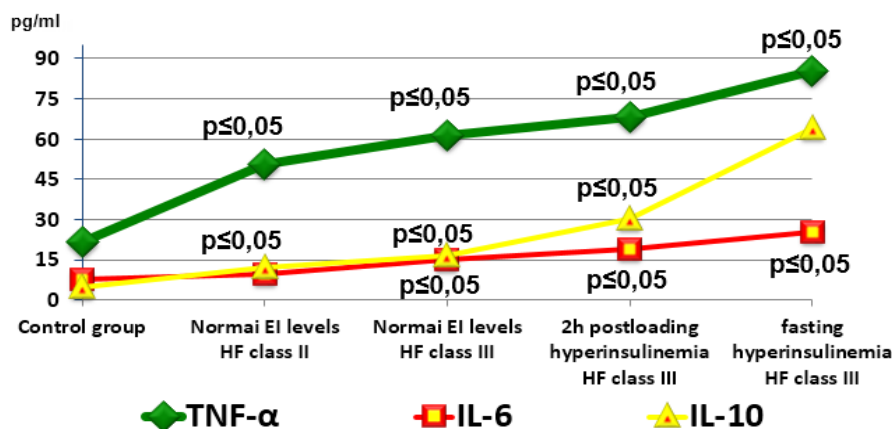


Fig 1: Plasma cytokines levels in hypertensives with HF and different kind of insulinemia. p – vs. the control group

The most significant cytokine profiles changes in the early HF stages were found in anti-inflammatory pathway. In patients with HF class II NYHA the plasma anti-inflammatory cytokine IL-10 levels were higher almost by 3 times vs. the control group ($p \leq 0.05$).

In patients with normal EI levels and HF class III NYHA plasma IL-10 levels were increased almost by 3.5 times vs. the control group and by 36.24% vs. patients with HF class II NYHA ($p \leq 0.05$). There was revealed trend to decrease TNF- α /IL-10 ratio ($p > 0.05$) and significantly decreasing IL-6/IL-10 ratio almost by 2 times compared with the control group ($p \leq 0.05$).

Thus, increasing of TNF- α and IL-10 in hypertensives with normal EI levels are more typical for HF class III NYHA.

Analys of plasma cytokine levels depending on the insulin resistance with hyperinsulinemia and class of HF in hypertensives was performed.

In patients with 2hr postloading hyperinsulinemia and HF class III NYHA the levels of TNF- α and IL-6 were increased more than 3 and 2.5 times respectively vs. the control group ($p \leq 0.05$) and increased by 11.64% and 25.74% respectively vs. hypertensives with normal EI levels and HF class III NYHA ($p \leq 0.05$). There was found decreasing of TNF- α /IL-6 ratio vs. the patients with normal

EI levels ($p \leq 0.05$). It is indicating a more intensive of inflammatory process activation with increasing not only TNF- α , but also IL-6 in patients with hyperinsulinemia^[6,9,10].

In patients with 2hr postloading hyperinsulinemia and HF class III NYHA the plasma IL-10 levels were increased by 6.5 times vs. the control group and almost in 2 times vs. hypertensives with normal EI levels and HF class III NYHA ($p \leq 0.05$). It was accompanied by decreasing of TNF- α /IL-10 ratio by 24% and IL-6/IL-10 ratio by 2.5 times vs. the control group ($p \leq 0.05$).

Consequently, 2hr postloading hyperinsulinemia is characterized by a significant increasing of proinflammatory and anti-inflammatory cytokines activity depending of HF progression vs. patients with normal EI levels.

In patients with spontaneous hyperinsulinemia and HF class III proinflammatory cytokines TNF- α and IL-6 levels were increased by 3-4 times vs. the control group ($p \leq 0.05$) and by 25-30% vs. 2hr postloading hyperinsulinemia ($p \leq 0.05$). Level of TNF- α /IL-6 ratio wasn't significantly different vs. the patients with 2hr postloading hyperinsulinemia ($p > 0.05$). Plasma IL-10 levels were increased by 14 times vs. the control group and more than 2 time vs. 2hr postloading hyperinsulinemia ($p \leq 0.05$). We found decreasing

of IL-6/IL-10 and TNF- α /IL-10 ratios less than 3.5-4 times vs. the control group ($p \leq 0.05$).

We found a direct correlation between of plasma EI and TNF- α levels ($r = 0.4380$, $p = 0.0001$); IL-6 ($r = 0.4810$, $p = 0.0002$); IL-10 ($r = 0.4970$, $p =$

0.0002) in hypertensives with HF class II-III (NYHA).

This indicates a relationship between increasing of systemic inflammation intensity, insulin resistance and severity of HF in hypertensives^[7,9].

Table 1: Mean Blood Pressure and plasma Cytokines profile in hypertensives with Heart Failure and different plasma EI levels.

Index	Control (n=20)	Normal EI levels		Postloading hyperinsulinemia HF class III (n=21)	Fasting hyperinsulinemia HF class III (n=20)
		HF class II (n=24)	HF class III (n=30)		
Office SBP mm Hg	126.45±5.85	141.78±6.45	143.37±6.86	148.58±6.93	152.43±7.76
		$p_1 \leq 0.05$	$p_1 \leq 0.05$	$p_1 \leq 0.05$	$p_1 \leq 0.05$
			$p_2 > 0.05$	$p_{2,3} > 0.05$	$p_{2,3,4} > 0.05$
Office DBP mm Hg	79.53±4.98	89.93±6.82	92.78±6.97	95.63±7.04	97.84±7.15
		$p_1 \leq 0.05$	$p_1 \leq 0.05$	$p_1 \leq 0.05$	$p_1 \leq 0.05$
			$p_2 > 0.05$	$p_{2,3} > 0.05$	$p_{2,3,4} > 0.05$
SBP daily, mm Hg	119.50±5.28	131.41±5.95	133.58±6.03	140.35±5.64	142.37±6.12
		$p_1 \leq 0.05$	$p_1 \leq 0.05$	$p_1 \leq 0.05$	$p_{1,2} \leq 0.05$
			$p_2 > 0.05$	$p_{2,3} > 0.05$	$p_{3,4} > 0.05$
DBP daily, mm Hg	68.10±5.53	79.67±5.12	80.42±5.49	82.63±7.63	84.31±7.85
		$p_1 \leq 0.05$	$p_1 \leq 0.05$	$p_1 \leq 0.05$	$p_1 \leq 0.05$
			$p_2 > 0.05$	$p_{2,3} > 0.05$	$p_{2,3,4} > 0.05$
TNF- α , pg/ml	21.73±3.45	50.53±6.03	61.25±6.31	68.38±4.84	85.2±7.64
		$p_1 \leq 0.05$	$p_1 \leq 0.05$	$p_{1,2,3} \leq 0.05$	$p_{1,2,3,4} \leq 0.05$
			$p_2 > 0.05$		
IL-6, pg/ml	7.5±2.1	9.51±3.38	15.19±2.78	19.1±1.44	25.42±2.45
		$p_1 > 0.05$	$p_1 \leq 0.05$	$p_{1,2,3} \leq 0.05$	$p_{1,2,3,4} \leq 0.05$
			$p_2 > 0.05$		
IL-10, pg/ml	4.6±1.78	12.17±2.32	16.58±2.92	30.21±7.45	63.88±7.75
		$p_1 \leq 0.05$	$p_1 \leq 0.05$	$p_{1,2,3} \leq 0.05$	$p_{1,2,3,4} \leq 0.05$
			$p_2 > 0.05$		
TNF- α /IL-6	2.89±0.47	5.25±0.74	4.04±0.54	3.56±0.41	3.41±0.39
		$p_1 \leq 0.05$	$p_{1,2} \leq 0.05$	$p_{1,3} > 0.05$	$p_{1,3,4} > 0.05$
				$p_2 \leq 0.05$	$p_2 \leq 0.05$
TNF- α /IL-10	4.71±0.68	4.15±0.61	3.69±0.53	3.57±0.44	1.28±0.41
		$p_1 > 0.05$	$p_{1,2} > 0.05$	$p_1 \leq 0.05$	$p_{1,2,3,4} \leq 0.05$
				$p_{2,3} > 0.05$	
IL-6/IL-10	1.63±0.19	0.78±0.15	0.91±0.11	0.63±0.09	0.40±0.07
		$p_1 \leq 0.05$	$p_1 \leq 0.05$	$p_{1,3} \leq 0.05$	$p_{1,2,3,4} \leq 0.05$
			$p_2 > 0.05$	$p_2 > 0.05$	

p_1 – vs. control;
 p_2 – vs. normal EI level and HF class II;
 p_3 – vs. normal EI level and HF class III;
 p_4 – vs. 2h postloading hyperinsulinemia and HF class III.

4. Conclusion

The 2hr postloading and spontaneous hyperinsulinemia presence in hypertensives with HF leads to more severe disease with increasing of ABPM parameters.

Formation of high insulin resistance degree is typical for hypertensives with HF progression, as evidenced direct correlation between the plasma EI levels and cytokines parameters.

In patients with insulin resistance and initial stages of HF systemic inflammatory reaction starts with activation of proinflammatory cytokines and with increasing of TNF- α and antiinflammatory cytokines IL-10 levels.

Hyperinsulinemia and HF progression accompanied by formation of cytokine disbalance with overproduction of proinflammatory cytokines TNF- α and IL-6 and antiinflammatory cytokine IL-10 levels different degrees in hypertensives.

5. Prospects for Further Research

Further scientific research should direct on the study of relationship between cytokines disbalance and lipid metabolism disorders in hypertensives with HF according to the insulin resistance degree and develop optimal treatment schemes to reduce the risk of cardiovascular events in these patients.

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