The Pharma Innovation Journal 2014; 3(10): 101-102

www.ThePharmaJournal.com

The Pharma Innovation

ISSN: 2277- 7695
TPI 2014; 3(10): 101-102

www.thepharmajournal.com
Received: 15-10-2014
Accepted: 30-11-2014

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The features of immune reactivity in patients with ischemic heart failure

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Abstract
The immune reactivity in 389 patients (300 males and 89 females with average age (69.04±10.99) years) with ischemic heart failure (HF) and in 30 apparently healthy persons (20 males and 10 females with average age (66.14±12.31) years) was examined. The activity of lymphocytes and neutrophils was studied by using of blast transformation reaction test and phagocytic activity tests, respectively. The levels of circulating immune complexes were detected by precipitation method. HF is characterized of decrease of phagocytic activity of neutrophils, increase of serum levels of pathologic low- and middle-molecular mass circulating immune complexes and decline of high-molecular circulating immune complexes. Thus, in patients with ischemic heart failure the immune reactivity disturbances are present which are typical for chronic inflammation.

Keywords: Heart failure, immune reactivity

1. Introduction

It's known, that 18 million deaths annually worldwide are attributed to cardiovascular diseases [1]. According to results of Prospective Urban Rural Epidemiologic (PURE) cohort study, which involved more than 150,000 adults in different economics levels countries, the rates of major cardiovascular events (death from cardiovascular causes, myocardial infarction, stroke, or heart failure) were lower in high-income countries than in middle- and low-income countries (3.99 events per 1000 person-years vs. 5.38 and 6.43 events per 1000 person-years, respectively; P<0.001). Case fatality rates were also lowest in high-income countries (6.5%, 15.9%, and 17.3% in high-, middle-, and low-income countries, respectively; P=0.01) [2].

Heart failure (HF) is the end stage of most diseases of the cardiovascular system and is a major cause of morbidity and mortality. About 26 million adults worldwide are living with HF, leading some to describe it as a global pandemic [3]. Coronary artery disease (CAD) is the main reason of HF.

An inflammatory activation in HF patients has long been recognized. Indeed, immune mechanisms modulate interstitial fibrosis, cardiomyocyte apoptosis, and hypertrophy, all of which are central processes leading to maladaptive remodeling in response to a variety of stimuli (ischemia, glucose intolerance, obesity, pressure overload etc.). Especially for heart failure evolving from large myocardial infarction there is substantial evidence for a causal contribution of immunity early in the course of the disease [4].

The immune system of humans consists of two components: the innate and adaptive immunity. While the adaptive immune system relies on somatically generated and clonally selected antigen receptors, the innate immune system detects the presence of pathogens by their evolutionarily highly conserved, relatively invariant structural motifs. Various components of the innate immune system are activated in cardiac diseases without direct involvement of infectious pathogens. For example, a number of inflammatory cytokines, including TNF (tumor necrosis factor), IL (interleukin)-1β, IL-6 and IL-8, as well as iNOS (inducible nitric oxide synthase), all components of innate immunity, are increased after cardiac injury. Moreover, they are all functionally implicated in ischemia/reperfusion injury, and in the abnormal myocardial remodeling characteristic of advanced congestive heart failure. Additionally, downstream targets of these proteins, the transcription factors nuclear factor kappa B (NF-κB) and activator protein 1 (AP-1), are activated in cardiac injury [5].

The data of experimental and clinical trials for innate immunity values in patients with HF are poor.

The purpose of study was to evaluate of immune reactivity parameters in patients with ischemic heart failure.

2. Material and Methods

We observed of 389 patients (300 males and 89 females with average age (69.04±10.99) years) with HF II-IV functional class (FC) according to New-York Heart Association (NYHA). The syndrome of HF had an ischemic origin in all cases. The diagnosis was verified by laboratory and instrumental methods according to European Society of Cardiology recommendations (2013, 2014). The exclusion criteria were: age over 75 years, acute cardiovascular conditions, kidney or liver failure, known infection diseases, alcohol or drug abuse, non-ischemic HF, decompensated diabetes etc. 30 apparently healthy persons were included into control group (the average age was (66.14±12.31) years; among them 10 persons (33.3%) were females). We studied of functional activity of T-cells by using of blast transformation reaction test (LBT): spontaneous and stimulated by phytohemagglutinin [6]; phagocytic activity of neutrophils was detected by using of phagocytic index and phagocytic count [7]. The level of circulating immune complexes in serum was detected by precipitation methods with Polyethylene glycol of different molecular mass.

The study was performed in accordance with the Helsinki Declaration and Good Clinical Practice Guideline. The study was approved by the local ethics committee and written informed consent was obtained from all patients. Categorical variables are presented as percentages, whereas continuous variables are presented as mean (M) and standart error of mean (m) if normally distributed, or as median and interquartile range (Me [IQR]), if not. Categorical variables were compared by the χ^2 test and continuous variables by the t test or the Mann–Whitney U test. A p value of <0.05 was considered statistically significant. All tests were 2-sided. Analyses were performed with Statistica system software, version 12.0.

3. Results and Discussion

In cohort of observed patients with HF 89 (22.88 %) were females. The middle age was (69.04±10.99) years. II – nd FC of HF (NYHA) was verified in 64 patients (16.45 %); III-rd – in 258 (66.33 %); IV-th – in 67 (17.22 %). The average period of HF was 10,0 [5,0; 15,0] years. 277 (71.21 %) persons had history of myocardial infarction (MI). Among them 27 patients (10.49 %) had history of recurrent MI.

In patients with HF the functional activity of immune cells had some changes (table 1). In particular, the value of spontaneous LBT test were same in HF patients and healthy persons groups (p>0.05). But, the average values of stimulated LBT test was higher for 18.7% in HF group (p<0.05).

Table 1: The functional activity of immune cells in observed persons

Values, M±m	Patients with HF, n=389	Control group, n=30
LBT with PHA, %	71.21±2.31	75.21±1.40
Spontaneous LBT, %	3.48±0.12*	2.83±0.12
Phagocytic index, %	54.75±1.21*	62.60±1.70
Phagocytic count	4.35±0.09*	6.31±0.22

Remarks: 1. HF – heart failure; 2. significance with control group: * - p<0.05.

HF caused of phagocytic activity of neutrophils decline. In these patients we observed decrease of phagocytic index for 11.9% (p<0.05) and phagocytic count for 68.9% (p<0.05).

It should be noted, that in observed patients with ischemic HF the increase of neutrophils number in blood accompanied by decrease of their functional activity. For our opinion, it could be sign of immunodeficiency.

The syndrome of HF caused of circulating immune complexes (CIC) dysbalance (table 2). In particular, the level of physiological high-molecular CIC was lower for 1.74 times compared control group (p<0.01). Simultaneously, the serum concentration of pathological middle-molecular CIC was higher for 1.53 times (p<0.01), and low-molecular CIC – for 3.58 times compared control values (p<0.01).

Table 2: The level of circulating immune complexes in blood of observed persons

Values, M±m	Patients with HF, n=389	Control group, n=30
High-molecular CIC, U	29.65±0.51**	51.70±3.12
Middle-molecular CIC, U	52.97±1.81**	34.54±2.02
Low-molecular CIC, U	39.21±1.13**	10.94±1.13

Remarks: 1. HF – heart failure; 2. significance with control group: ** - p<0.01.

The elevation of high pathological CIC accompanied with phagocytic activity of neutrophils decline that caused to their elimination disturbance. These CIC blocks of CD2 and CD3 receptors on T-cells surface which resulted to complement system activation for alternative pathway. This process supports of chronic inflammation.

4. Conclusion

HF is characterized of decrease of phagocytic activity of neutrophils, increase of serum levels of pathologic low- and middle-molecular mass circulating immune complexes and decline of high-molecular circulating immune complexes. Thus, in patients with ischemic heart failure the immune reactivity disturbances are present which are typical for chronic inflammation.

The perspective of future investigations is study of adaptive immunity changes in patients with HF.

5. References

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