

Paraoxonase (PON1) Possible Biomarker for Risk of Heart Failure

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This study aims to the significance of the possible risk of heart failure biomarker of PON1, paraoxonaza family member, and the degree of correlation between the serum level of its class deficiency resulting study inotropism. The importance stems from the study itself selected theme, the paraoxonase activity, isozyme recognized as having involvement in atherosclerosis, but almost unexplored as involvement in myocardial remodeling processes, specifically in the fibrosis.

Keywords: paraoxonase family, oxidative stress myocardial remodeling myocardial infarction ventricular contractile deficit, biomarker risk

Research worldwide regarding biomarkers in cardiac insufficiency is oriented towards the study of processes or parameters which give information on the relationship of: inflammation, remodeling cardio-vascular, cellular signaling mediated by ion channels, such as those of calcium and / or receptors, cytoskeletal [1, 5].

Paraoxonase family comprises three izomembre human serum (PON1, PON2, PON3) have common structural properties and enzyme activity. Functional isozymes gentle oxidized phospholipids involved in the metabolism of LDL (low-density lipoprotein) cholesterol structure, perhaps by removing hydro-peroxides fatty acids [2].

Representative family hydrolase PON1 is an HDL (high density lipoprotein)-associated calcium-dependent plasma that has been described since 1946 by Abraham Mazur, but whose role was described only in 1991, by the team led by Mackness MI [7, 9, 10, 15].

PON1 effect of inhibiting LDL oxidation, and thereby the pro-inflammatory response is achieved by two types of activity, that it consists of:

- esterase hydrolysis of both the phospholipids and esterified cholesterol hydroperoxides[11];
- homocysteine -tiolactonase (HcyTL-ase) carrying out hydrolysis of homocysteine-thiolactone specific (HcyTL), which is its natural substrate [2, 4, 7].

Achieving these objectives requires the availability of means of identification of risk / prognosis evolving, as are markers, specific parameters revelatory to label a biological or laboratory parameter as indicator of risk in a given disease.

The concept of biomarker (biological marker) was introduced as a medical term in 1989, defined as the *biological parameter measurable and quantifiable which serves as an indicator in assessing the risk of disease, exposure to the environment and its effects, diagnosis of disease processes metabolic substance abuse etc.* [1].

In 2001, the working group for biomarkers from Bethesda standardizes the concept, redefining it as *biomarker is a size / characteristic determined and assessed objectively as an indicator of normal biological processes or the pathological or the pharmacological responses to therapeutic intervention* [1].

Experimental part

Materials and methods

The study includes a total of 208 patients of both sex, hospitalized and diagnosed with heart failure etiology single with chronic ischemic heart disease, whose ages ranged between 35 and 64 years (fig. 1).

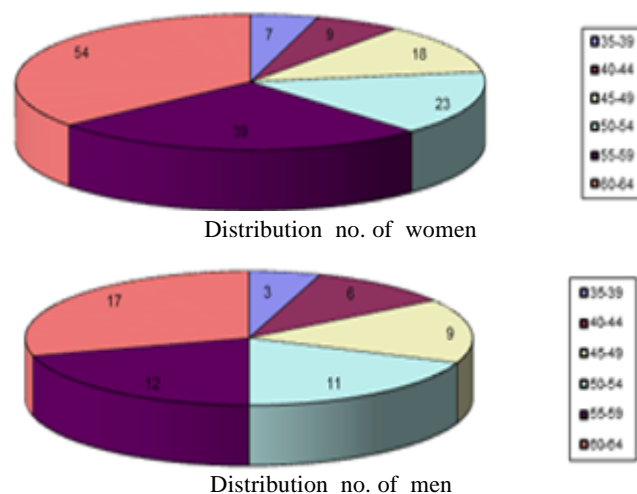


Fig. 1. The composition of the study group in relation to sex and age of patients

The involvement in the study group of patients with selective deficit caused by myocardial contractile cardiac ischaemia was only required to put the whole lot in the same conditions etiopathogenic, to no different initial sources of production of oxidizing radicals. The irrigation shore chronic myocardial contractile heart function offset predominant source of ROS (oxygen free radicals) / RNS (nitrogen free radicals) production is coronary atherosclerosis; by onset heart failure occur additionally at least two sources of ROS / RNS:

- rise in the deficit irrigation of the myocardium by reducing the amount and duration of diastole cardiac output; Last expresses tachycardia mechanism installed as reactive compensation;
- reducing flows organ, the one that allows to admit that cardiac dysfunction with reduced cardiac tissue synthesis of ROS / RNS is widespread.

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Class functional	The distribution by gender lot						The whole lot	
	men			women				
	No. absent	% from		No. absent	% from		No. absent	%
		The whole lot (n = 208)	only men		The whole lot (n = 208)	only women		
II	63	30.3	35.33	17	8.17	29.3	80	38.46
III	71	34.13	47.33	29	13.9	50	100	48.08
IV	16	7.7	10.6	12	5.77	20.69	28	13.4
Total	150	72.21	100	58	27.84	100	208	100

Table 1
THE DISTRIBUTION OF PATIENTS IN THE STUDY OF GENDER AND CLASS DEFICIT HEART PUMP FUNCTION, NYHA CLASSIFICATION CRITERIA ASSESSED

Selecting a group of elderly patients grounds that circulating concentrations of PON1 varies with age; age resulting in a reduction in activity levels [3, 12 - 14].

To interpret the significance of serum PON1 determined for the studied cases, I referred to the normal corresponding average age of our group, which was 54.2 years / lot, by gender and patients 55 years for men and 53.38 for women.

In our study only patients were included normo-, or at most hiperponderals, known as the body mass index influence on serum paraoxonase activity [6].

Also, knowing the records and literature that serum PON1 activity can be altered by smoking or by taking statins, all patients included in the study were smoking for at least two years and had not taken lipid-lowering medication in the last quarter [8,11].

To assess the severity of contractile deficit, NYHA (New York Heart Association) classification criteria we use; distribution in relation to the severity of ventricular myocardial contractile deficit, the gender was shown in table 1.

Although the amount of ejection fraction (EF) is established heart failure in one of the causes of secondary sources of ROS / RNS, and in particular in the event of a reduction in inter-relationship between the serum concentration of PON1 and the flow systolic not the objective of this study is based on dosing activity of serum PON1 esterase substrate using ethyl phenyl.

Determining the circulating blood serum PON1 harvesting was done in the morning, fasting twice within 14 days period is the length of hospitalization. For each set of measurements, the admission or the 14 day average concentration was then calculated, thereby obtaining the two parameters, which we identified:

- average concentration of serum PON-1 admission;
- average concentration of serum PON-1 to discharge.

Tightening first determination to carry out the first two days of hospitalization justified by the possibility that one could develop an established treatment for a disease pursuant to adjust the amounts determined for the enzyme. By imposing this requirement we believe that we excluded possible action developed morphological-functional component therapy, still reverse the myocardium contractile deficit.

Subsequently, the calculated values of the two parameters mentioned have led to a third: the average concentration of serum PON1 per lot, regardless of the time of harvest.

Dynamic tracking values of the three parameters in serum, a fortnight allowed on one side of us directions on how the work of serum PON1 correlate with the clinical course of heart failure therapy, and on the other by determinations on admission to identify a possible correlation between circulating isozyme activity and functional impairment shrink class. Interpretation of the survey was carried out both by comparing between them

the values of three specific parameters / computer, specify, and by reference to the value of normal circulating. I admitted absent risk level indicating concentrations in excess of 75mg / mL, and to assess the risk value below the lower limit of normal, gradual it:

- range between 65-74 mg / mL: minimal risk;
- the circulating levels with values 50- 64 mg / mL: high risk;

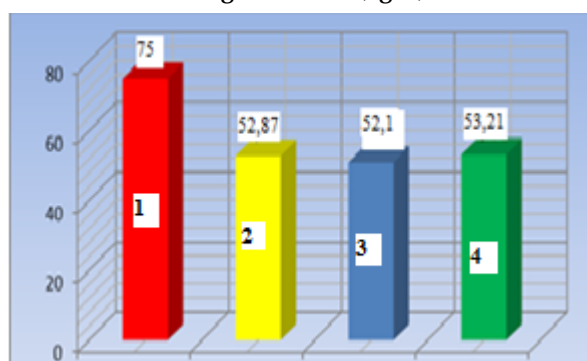
- serum concentrations <50mg / mL: high risk.

Determination of serum PON1

Principle of the method: Paraoxonase hydrolyzed ethyl phenyl and the reaction is activated by calcium ions. Paraoxonase activity is measured according to the change in extinction at 270 nm and expressed in mmol phenylacetate hydrolyzed / min / mL plasma.

Results and discussions

Comparison of mean serum PON1 three concentrations: the entire lot, those at admission or discharge is summarized in the figure below (fig. 2).



Legend:

- 1 ■ = Normal serum levels of PON (mg/ml);
- 2 ■ = The mean serum concentration PON entire lot (mg/ml);
- 3 ■ = The mean serum concentration PON admission (mg/ml);
- 4 ■ = The mean serum concentration PON discharge (mg/ml).

Fig. 2. Comparison of mean serum PON1 concentration values, depending on the determinations

Table 2

HANGES IN MEAN SERUM CONCENTRATION VALUE IN HEART FAILURE CLASS REPORT

Class contractile deficit *	The amount of serum - mg / ml, average		
	per class / group	to internment	to discharge
II	51.9	51.7	52.11
III	53.2	52.1	54.3
IV	53.5	52.2	54.8
The entire group	52.87	52.1	53.21

*the assessment condition is based on criteria class NYHA classification

To study the average serum concentration of PON1 in relation to the class of myocardial contractile deficiency led to the following results (table 2).

Determination of serum paraoxonase batch activity measured by the average dose values determined at admission or discharge, allowed us next stratification of distribution, depending on the areas selected:



Fig. 3. Distribution of serum PON1 batch average, patients regardless of sex

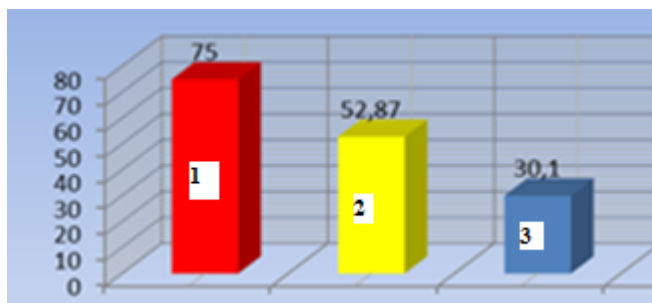
The 93%, reduced serum concentration of 194 cases of PON1 in relation to the class of heart failure were distributed as follows:

Table 3
INCIDENCE OF LOW SERUM PON1 IN RELATION TO HEART FAILURE CLASS

Class contractile deficit	Sick drawn to the lot		Patients with serum reduced		
	No. absent	%	No. absent	% from	
				the whole lot	casuistry class
II	80	38.46	73	35	91.25
III	100	48.08	95	45.6	95
IV	28	13.4	25	12	89
the whole lot	208	100	193	93	-

Interpretation of the results of the study on the variation of PON1 marker serum

Calculation of the average concentration of serum PON1 on its casuistry batch showed reduced below the lower limit of the selected range to define absence of risk / normal with a share of almost 31% of it (fig. 4).

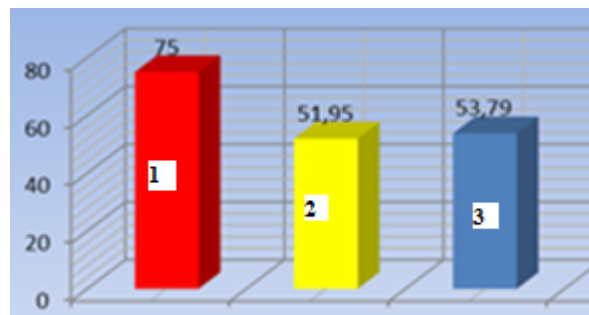


Legend:
1 ■ = The lower limit of the average normal serum concentration (mg/ml);
2 ■ = Mean serum concentration value of PON-1, calculated as the average of the entire batch (mg/ml);
3 ■ = Share value reduction (mg/ml).

Fig. 4. To mean serum concentration compared to the value of PON-1 calculated on case law relative to the lower lot of normal; Highlighting share reduction in serum enzyme activity

Comparison of serum PON1 average concentration value calculated based dosages after discharge in patients with heart failure shows a very low tendency to normalization, with growth of 2.2 percent compared with that based on measurements of their internment (fig. 5).

Label it as expressing a maximal response to therapy and lifestyle recommended, although they were certainly respected by ill since he was hospitalized. We reiterate



Legend:
1 ■ = The normal field circulating PON-1 (mg/ml);
2 ■ = Mean serum concentration value of PON-1 at admission (mg/ml);
3 ■ = Mean serum concentration value of PON-1 at discharge (mg/ml).

Fig. 5. The comparative values mean serum concentration of PON-1 at admission, discharge and reporting respectively to normal circulating

that hospitalized patients, especially if serum dosages of enzyme activity was required because the circulating it among others and is influenced by physical activity.

Insignificant variation of the average concentration of serum PON1după therapy instituted, remaining at discharge to values close to those of admission, and the average over the entire lot interpret as expressing existence in heart failure has multiple production sources species oxidative some of which occur as compensatory mechanisms, such as tachycardia.

The existence of a study group incidences of low serum PON1 average in 93% of cases admitting that allows circulating levels of isozyme is a biomarker of chronic heart failure.

Whenever the determinations and heart failure class average concentration of serum PON1 reduced correlates with this, showing higher value, almost equal in stages III or IV (NYHA classification) (table 2). Table 3 data show that the incidence is substantially equal and constant correlation over 90 percent in grades II and III heart failure, to diminish slightly with a drop in patients whose myocardial contractile deficit fall in fourth grade. We appreciate that the latter correlation expresses in fact, the real situation of the patient with heart failure which is in class AIV was when the patient has no functional reserve mobilized to ensure personal care of yourself, that means that the level of Circulating expression of the enzyme is depleting.

Conclusions

Our results showed:

- A low values of serum PON1 environments for both determinations at admission and discharge, respectively, as well as the average of the entire group of patients with chronic heart failure.

- A significant change in their after 2 weeks of therapy, according to treatment guidelines; - The existence of a high incidence of circulating levels of PON1 average caseload per whole lot.

- Correlation of serum paraoxonase with heart failure class, both in value and as incidence.

We interpret these values articulated the working level, employing the oxidative stress in heart failure existing enzyme in the process of remodeling of the myocardium.

Dosages supported by the results obtained and the hypothetical role of myocardial enzyme research admit that the level of circulating isozyme expression may be a biomarker of heart failure. This is because serum PON1 were persistent reduced admission, and their variation after the start of therapy (discharge) totally insignificant. This

latter mode *behaviour* of PON1 allows us to maintain that strength, the dynamic activity of the enzyme serum is a marker that provides information on how evolution or risk in chronic heart failure [16].

The value study stems from the study's limit, warns that the need correlation between serum enzyme activity and existing flow value in patients with systolic heart failure. Research ejection fraction value if it preserves or not, is required by the pathogenesis of oxidative stress, which in the evolution of heart failure known generating new sources of oxidants or Nitrosyl [17].

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