CORRELATION BETWEEN THE PLASMATIC LEVEL OF THE SOLUBLE TUMOR NECROSIS FACTOR-α RECEPTOR (sTNFα-RI) AND THE PRESENCE OF ATRIAL FIBRILLATION IN PATIENTS WITH DILATED CARDIOMYOPATHY AND HEART FAILURE

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Keywords: *atrial fibrillation, heart failure, dilatative cardiomyopathy, TNF-a, sTNFα-RI*

Abstract: *Atrial fibrillation is the most common arrhythmia, as well as the major cardiovascular mortality and morbidity cause,the identification of new mechanisms involved in the pathogenesis of this disease being important. Tumor necrosis factor (TNF) and plasma levels of soluble tumor necrosis factor receptor I (sTNFα-RI) are elevated in patients with heart failure due to chronic inflammation, being a negative prognostic factor. Atrial fibrillation (AF), whose relationship with sTNFα-RI has been less studied, is also a negative prognostic factor. Our study is based on 54 NYHA III-IV congestive heart failure (CHF) and dilated cardiomyophaty (DCM) patients, 40 ischemic and 14 non-ischemic, 35 males and 19 females, mean age 65±10 years, ejection fraction 46.63±9.88% and NYHA class III-IV. Chronic heart failure was defined according to the European Society of Cardiology criteria. In all patients, sTNFα-RI serum value was determined using ELISA method, with normal level deemed <3 pg/ml.: sTNFα-RI levels were high in patients with CHF-222.79±97.08 pg/ml. Although this cytokine level was elevated in 64.81% of the patients with atrial fibrillation, no statistically significant differences were identified compared to patients with normal sinus rhythm (211.95±92 vs. 220.82±105.67 pg/ml). Moreover, no differences related in the presence/absence of DCM were noticed (211.95±92.22 vs. 220.82±105.67 pg/ml). However, the ischemic etiology was accompanied by higher levels of sTNFα-RI, regardless patients with AF (234.70±98.26 vs. 217.93±94.06 pg/ml) or normal sinus rhythm (237.12±112.75 vs. 207.04±89.7 pg/ml). In conclusion, sTNFα-RI level was elevated in patients with CHF, DCM and atrial fibrillation; however no significant differences were noticed compared to patients with normal sinus rhythm or between ischemic and non-ischemic patients.*

Cuvinte cheie: *fibrilaţie atrială, insuficienţă cardiacă, cardiomiopatie dilatativă, TNF-α, sTNFα-RI*

Rezumat: *Fibrilaţia atrială reprezintă în prezent cea mai frecventă aritmie şi totodată o cauză majoră de morbiditate şi mortalitate cardiovasculară. De aceea se pune un accent deosebit pe identificarea unor noi mecanisme care intervin în patogeneza acestei boli. Factorul de necroză tumorală TNF-a şi nivelele plasmatice ale receptorului I solubil al TNF-a (sTNFα-RI) sunt crescute la pacienţii cu insuficienţă cardiacă, datorită inflamaţiei cronice, reprezentând un factor de prognostic negativ. Scopul studiului: evaluarea posibilului rol al segmentului I solubil al TNF-a în patogeneza fibrilaţiei atriale la pacienţii cu cardiomiopatie dilatativă şi insuficienţă cardiacă congestivă. Material şi metodă: S-au luat în studiu 54 pacienţi cu insuficienţă cardiacă congestivă (ICC) NYHA III-IV şi cardiomiopatie dilatativă (CMD), 35 bărbaţi şi 19 femei, cu vârsta medie de 65±10 ani şi fracţie de ejecţie 46.63+/-9.88% internaţi în Clinica Cardiologie - Recuperare, Cluj-Napoca. Diagnosticul de ICC şi CMD s-a pus conform criteriilor Societăţii Europene de Cardiologie. Tuturor pacienţilor li s-a determinat nivelul plasmatic al receptorului I solubil al TNF-a (sTNFα-RI) utilizând metoda ELISA (VN 3<pg/ml). Pentru analiza statistică s-a utilizat testul t Student. Rezultate: Valorile sTNFα-RI au fost mult crescute la pacienţii cu ICC-222,79 ± 97,08 pg/ml. Deşi valoarea acestei citokine a fost crescută şi la cei 64,81% de bolnavi cu fibrilaţie atrială, nu au existat diferenţe semnificative statistic faţă de cei aflaţi în ritm sinusal (211,95±92 vs 220,82 ± 105,67pg/ml). De asemenea, nu s-au decelat diferenţe nici în funcţie de prezenţa sau absenţa CMD (211,95 ± 92,22 vs 220,82 ± 105,67pg/ml). În schimb etiologia ischemică a fost însoţită de valori mai crescute ale sTNFα-RI, indiferent dacă bolnavii au prezentat FiA (234,70 ± 98,26 vs 217,93 ± 94,06 pg/ml) sau ritm sinusal (237,12 ± 112,75 vs 207,04 ± 89,7 pg/ml). Concluzie: nivelul sTNFα-RI a fost crescut la pacienţii cu ICC, CMD şi fibrilaţie atrială, fără a exista însă diferenţe semnificative faţă de bolnavii aflaţi în ritm sinusal sau între cei ischemici şi nonischemici.*

INTRODUCTION

The causes of atrial fibrillation (AF) are extremely varied, including hypertension, valvulopathies (especially mitral), ischemic cardiomyopathy, diabetes mellitus and hyperthyroidism. It currently represents the most common arrhythmia and a major cause of cardiovascular morbidity and mortality (1, 2). For example, the estimated costs of this disease in the USA are more than a billion dollars/year. If in 2000 a number of 2.3 million patients were diagnosed with atrial fibrillation in the USA, it is estimated that in 2050 the number

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will rise to 16 million (3). Accordingly, in economically developed countries, it is a real health issue as its prevalence increases with age, 20% of the patients of more than 80 years old are suffering from this disease (4).

Obviously, the role of various mechanisms involved in the AF pathogenesis was discussed: the genetic factor, the presence of atria multiple re-entry circuits, the role of structural and electrical atrial remodeling. Recently, special emphasis was placed on the involvement of inflammatory factors in the pathogenesis of this disease.

THE AIM OF THE STUDY

In this context, the present study aims at evaluating the role of an important cytokine involved in AF – the sTNFα-RI it patients with dilated cardiomyopathy (DCM) and congestive heart failure (CHF).

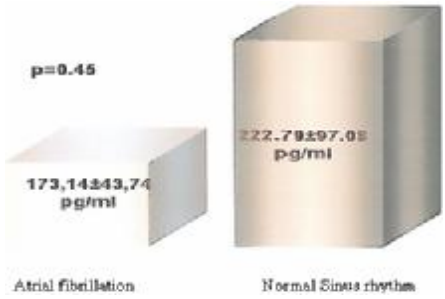
MATERIAL AND METHOD

The study included 54 patients with CHF hospitalized in the Rehabilitation Hospital, Cluj-Napoca. CHF and DCM diagnoses were based on the European Society of Cardiology criteria. sTNFα-RI plasmatic level was measured in all patients, using ELISA (VN 3<pg/ml) method. For statistical analysis, the t Student test was used.

RESULTS

Of the 54 patients (p) with CHF included in the study 64.81% were men (35p) in the functional class NYHA III-IV. Among patients, 74.074% (40p) presented ischemic aetiology and 25.92% (14p) non-ischemic etiology. The average ejection fraction was 46.6±39.88%. sTNFα-RI mean level was very high (222.79±97.08 pg/ml), however levels varied greatly (from 26 pg/ml lowest level to 455.3 pg/ml highest level). 64.81% (35p) presented chronic atrial fibrillation, with no differences regarding the general characteristic of patients with or without AF. sTNFα-RI average level in patients with AF was lower by -173.12±43.74 pg/ml as compared to patients with normal sinus rhythm (SR) 222.79±97.08 pg/ml, but without statistically significant differences, p=0.45 – Figure 1.

Figure no. 1. V sTNFα-RI levels in patients with and without AF



Moreover, there was no evidence of statistically significant differences when considering the CHF ischemic or non-ischemic etiology, regardless the fact of whether the patients had AF or normal sinus rhythm – Table 1. It is however worth mentioning that ischemic patients presented higher levels as compared to non-ischemic patients, regardless of whether they presented SR or AF on ECG.

60% (21p) of the patients with AF were diagnosed with DCM. Their characteristics are summarized in Table II. The table shows that sTNFα-RI levels were lower in patients with DCM, without statistically significant differences as compared to those without DCM: 211.95±92.22 vs. 220.82±15.67 pg/ml, p=0.39. Moreover, in the DCM group, men were predominant.

Table no. 1. sTNFα-RI levels in relation to CHF aetiology (pg/ml)

	Ischemic CHF	Non-Ischemic CHF	p
FiA	234.70 ± 98.26	217.93 ± 94.06	**0.32**
SR	237.12 ± 112.75	207.04 ± 89.7	**0.08**
p	**0.47**	**0.49**	

Table no. 2. Characteristics of patients with atrial fibrillation

Patients' characteristics	AF with DCM	AF without DCM
% patients	61% (21)	40% (14)
Mean age (years)	69,4±10,20	70,78±9,18
Women (%)	23,81 (5)	57,14 (8)
Men (%)	76,19 (16)	42,85 (6)
EF (%)	37,65±3,065	55,69±6,55
sTNFα-RI (pg/ml)	211,95±92	220,82±105,67

DISCUSSIONS

From a chemical point of view, TNF α is a homotrimer whose effects are exerted through certain soluble receptors whose number positively correlates with the plasmatic levels of this cytokine. There are two types of such receptors (type I or CD 120a, with molecular mass of 55Kd and type II or CD 120b, with molecular mass 75Kd) that belong to transmembranar receptors type I family and are found at the level of several cell types, among which cardiomyocytes and endothelial cells (6). In normal myocardium there is no TNF α. It appears only in the case of injuries at this level, stimulating two types of soluble receptors: sTNFα-RI and sTNFα-RII. Most of the detrimental effects of TNF-α are exerted through TNFα-RI, the stimulation of TNFα-RII having cytoprotective (6, 7). Like TNF-α, the sTNFα-RI has high levels in CHF, especially in patients with severe congestive cardiovascular syndrome (8). Unlike TNF-α, sTNFα-RI is also elevated in patients with CHF and no casexia and it does not oscillate throughout the day (9). It must not be forgotten that CHF is currently considered as part of chronic inflammatory diseases. The immune activation (playing an important role) may be: direct, through antigenic stimulation (viral, transplant) or secondary to heart injury caused by 'new' peptidic antigens emerging after myocardial infarction or in various cardiomyopathies (5, 6, 7). Cytokines play an essential role in the propagation and determining the magnitude of the immune response, especially TNF-α, IL-I and IL-6 (6). Furthermore, serum level increase of inflammatory factors is correlated with the severity and clinical aggravation degree of the disease (8, 10). Among these, TNF-α plays is central in generating inflammation. However, there are differences of TNF-α level in various studies, arising largely from the fact that TNF-α level vary throughout the day and the use of different tests to determine such cytokines.

As early as 17 years ago, it was clinically and experimentally proven that plasmatic levels of TNF-α are very high in CHF, with direct correlation to patients' survival (6, 7). According to our results, sTNFα-RI plasmatic levels are very high in patients with heart failure included in the study, data which correlate with those in the specialty literature. On the other hand, it seems that inflammation plays an important role in atrial fibrillation pathogenesis, especially if we notice that its incidence highly increases after various cardiovascular surgery procedures (11, 12) after coronary artery bypass surgery (13). Moreover, even the presence of the inflammation was associated with the risk of thrombosis occurrence, as well as with the

occurrence of other complications (14, 15). Upon the analysis of atrial biopsies of some patients with isolated AF, Frustaci detected inflammatory signs, especially myocarditis, in 66% of the cases (16). There are many studies on patients with AF that found high levels of circulating reactive C protein (RCP), hsRCP and interleukins (12). RCP, a well-known inflammation marker, is released under the action of IL-6, IL-1 and TNF-α at liver level. There are also some less extensive studies that demonstrated increase of TNF-α and FGF-β (12). Sata studied a number of 15 patients with atrial fibrillation in whom plasmatic levels of RCP, IL-6 and TNF-α were measured in three distinct times: upon enrolment, after 24 hours and two weeks after cardioversion (17). These three inflammation factors were also detected in patients with NSR. There were significantly higher levels in the AF group and they did not regulate in two weeks after cardioversion (17).

In our study, however, sTNFα-RI levels were lower, but not statistically significant, in patients with AF and CHF compared to those in NSR. Moreover, there were no differences between patients with AF and DCM as compared to those with AF without DCM. However, when considering ischemic etiology vs. non-ischemic etiology, we noticed that sTNFα-RI levels were much higher in the first case. In the specialty literature, we did not encounter data regarding sTNFα-RI role in patients diagnosed with DCM, CHF and AF. We also underline that most of the studies carried out on the topic (the relation of inflammation in general and of sTNFα-RI in particular) were performed on an extremely small number of patients (18, 19, 20, 21).

Nevertheless, the final question is whether AF occurrence may be the consequence of inflammatory mechanisms or whether the existence of atrial fibrillation triggers the release of inflammatory factors (22, 23, 24, 25, 26).

CONCLUSION

In conclusion, sTNFα-RI level was high in patients with CHF, DCM and atrial fibrillation, but no significant differences were found compared to the patients with normal sinus rhythm or between ischemic and non-ischemic patients.

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