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Ferritin as a potential biomarker of efficacy of treatment of atrial fibrillation - preliminary report

Ferrytyna jako potencjalny marker skuteczności leczenia migotania przedsionków - doniesienie wstępne

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: Complex mechanisms of responsible for originating and maintaining of atrial fibrillation (AF) are involved in pathophysiology of this arrhythmia. Inflammation substantially contribute to arrhythmic remodelling of atrial tissue.The aim of the present study is to assess an applicability of ferritin and high sensitive C-reactive protein (hs-CRP) as biomarkers of atrial fibrillation and their usefulness in evaluation of efficacy of cryoablation.

Materials and methods: The study population consisted of 40 patients who underwent first AF cryoablation procedure. The whole follow-up time was for 6 months. The efficacy of cryoablation was defined as lack of episodes of AF longer than 30 s reported either in patient's medical documentation or present in standard or Holter ECG records. Concentrations of hs-CRP (latex method) and ferritin (immunochemical method) were determined in standard way in hospital laboratory.

Results: The recurrence of atrial fibrillation during follow-up was detected in 7 of 40 patients (efficacy 82.5%). Basal concentrations of hs-CRP and ferritin were significantly higher in patients who underwent ablation during AF. Ablation resulted in an increase of either hs-CRP or ferritin concentrations. After seven days, both hs-CRP and ferritin concentrations returned to basal level. The trend toward the higher concentration of hs-CRP was observed in AF recurrence subgroup in 30^{th} and the 90^{th} day after the procedure. Ferritin concentrations were significantly higher in recurrence subgroup after 30 and 90 days.

Conclusion: Our results suggest that the evaluation of ferritin serum level can be a potential tool for assessment of AF treatment efficacy.

Key words: **Atrial Fibrillation • Biomarker • Ferritin • Inflammation**

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Abbreviations: **AF -** Atrial Fibrillation, **hs-CRP -** high sensitive C Reactive Protein, **IL-1α:** Interleukin 1 α, **IL-10 -** Interleukin 10, **ILGF-** Insulin Like Growth Factor, **MCP1 -** Macrophage Chemotactic Protein 1, **TNF-α -** Tumor Necrosis Factor α, **VEGF -** Vascular Endothelial Growth Factor.

Introduction

Atrial fibrillation (AF) is the most common supraventricular arrhythmia. It's prevalence in general population is estimated on 1-2 % [1]. Complex mechanisms responsible for originating and maintaining of AF are involved in pathophysiology of this arrhythmia [2]. Identification by Haissaguerre and colleagues ectopic foci responsible for initiating of AF in transition zone of ostia of pulmonary veins enabled its invasive treatment [3]. Balloon cryoablation of pulmonary veins, recently introduced novel invasive treatment of atrial fibrillation method is characterized by efficacy reaching 70-80% [4,5]. Inflammatory mechanisms substantially contribute to arrhythmic remodelling of atrial tissue responsible for maintenance of the arrhythmia [6]. The inflammatory infiltration has been found in myocardial biopsies of atrial tissue in patients with atrial fibrillation [7,8]. Elevated level of circulating C-reactive protein (CRP) was identified as a prognostic factor of ineffectiveness of cardioversion of atrial fibrillation [9]. Sustained high CRP level after cardioversion was associated with early recurrence of AF [9]. Increased plasma CRP level was also shown to be independent predictive factor of lack of effectiveness of RF ablation of atrial fibrillation [10]. Furthermore, the RF ablation itself resulted in increase of CRP concentration. Sustained elevated CRP level after ablation was associated with more frequent recurrence of this arrhythmia [11]. Apart from CRP, elevated concentrations of circulating either interleukin-18 and metalloproteinaze -9 [12] or IL-10, TNF-α, MCP1, VEGF [13] were correlated also to atrial fibrillation.

Ferritin is a well-known biomarker of iron turnover [14]. However it was also shown to be a sensitive inflammation biomarker in rheumatic and neoplastic diseases [15,16]. The aim of present study is assessment of applicability of ferritin and CRP as a biomarkers in atrial fibrillation and its usefulness in evaluation of efficacy of cryoablation.

Materials and methods

Study population

The present investigation was a prospective observational single-center study. The study population consisted of 40 patients who underwent first AF cryoablation procedure and fulfilled the following eligibility criteria:

- age 18-70 years;
- symptomatic paroxysmal atrial fibrillation; 3 no or minimal structural heart abnormalities. Exclusion criteria consisted of : 1. history of cardiac-surgical procedure;
- pregnancy or breastfeeding;
- any surgical procedure or severe injury in last three months;
- stroke in last three months;
- severe hypertension;
- unstable angina 8. heart failure NYHA III and IV;
- hyperthyreosis;
- infective disease (including typical respiratory infections) in last three months;
- history of autoimmune or neoplastic disease;
- GFR< 30 ml/min.

The investigation conforms to the principles outlined in the Declaration of Helsinki. The protocol of the trial was approved by the Ethics Committee of Silesian Medical University (Decision KNW/00220KB/1/137/12). Written informed consent has been obtained from all study participants.

Follow-up and analysed parameters

The whole follow-up time accounted for 6 months. Durind this time patients were evaluated before procedure, 24 hours after the procedure, 7 , 30 and 90 days after the procedure. Standard patient's assessment included anamnesis, clinical evaluation and ECG. Echocardiographic examination was performed at baseline and at final visit. The 24 hours Holter examination was performed always at the final visit. Additionally, the 72 hours Holter examination was scheduled in case of symptoms suggesting presence of AF. Efficacy of cryoablation was defined as lack of episodes of AF longer than 30 s reported either in patient's medical documentation or present in standard or Holter ECG records. Venous blood for determination of circulating hs-CRP and Ferritin was collected before cryoablation, 24 hours after the procedure and 7, 30 and 90 days after the ablation.

Laboratory analysis

Concentrations of hs-CRP (latex method) and ferritin (immunochemical method) were determined in standard way in hospital laboratory using Roche Diagnostics reagents according to the manufacturer instructions

Statistical analysis

All analyses were performed using the Statistica version 10 software (Statsoft, Dell corp.). The results were expressed as mean ± SD for variables with Gaussian distribution and medianand range for others. Because either hs-CRP or ferritin has non-Gaussian distribution significance of differences between concentrations of analysed biomarkers in various time points (0, 1 and 7 days) were established on basis of Friedman ANOVA for dependent variables. Other comparisons were performed using the Mann-WhitneyU test for independent variables. P<0.05 was considered as significant

Results

Demographic and clinical characteristic is sghown in Table 1. During follow-up the recurrence of atrial fibrillation was detected in 7 of 40 patients (efficacy 82.5%). In 12 of 40 (30%) cryoablation was performedduring atrial fibrillation and conversion to sinus rhythm was obtained by cardioversion directly after procedure. Median basal concentration of hs-CRP and ferritin were significantly higher in patients who underwent ablation during AF than in these ablated during sinus rhythm and amounted respectively 4.8(3.6-8.7) mg/l *vs* 2.1 (1.6-5.1) mg/l for hsCRP and 293 (197-920) ng/ml vs 210 (135-280) ng/ml for ferritin (median and range; P<0.05). One day after the ablation the significant increase of either hs-CRP concentration from 3.2 (1.6-8.7) mg /l to 6.1(2.4-8.9) mg/l or ferritin concentration from 225 (135-920) ng/ml to 330 (160-1056) ng/ml was observed (median and range; P<0.05). After seven days hs-CRPand ferritin concentrationsdid not differ significantly from basal levels. Analysis of hs-CRP concentration in subgroups of patients with and without of AF recurrence showed trend toward higher concentration in recurrence subgroup 30 and 90 days after procedure. (Fig. 1A). In contrast to this finding ferritin concentrations were significantly lower in patients without arrhythmia than in patients with recurrence of atrial fibrillation in these time points (Fig. 1B).

Discussion

The results of our study suggest that atrial fibrillation is associated with elevated ferritin level. This observation has not been earlier reported. Either ferritin or hs-CRP are biomarkers of systemic inflammation. Concentrations of both biomarkers were lower in patients without AF recurrence but only for ferritin this difference reached the statistical significance. This observation is concordantto results of Mattioli at al.[17]. These authors reported the prolonged atrial stunning after cardioversion in subgroup of patients with high both ferritin and hs-CRP concentrations but not in patients with elevated only concentration of hs-CRP. Other authors reported significant increase of CRP in population of patients with recurrent atrial fibrillation comparede to patients without AF [10,11]. However, the number of patients in those studies was higher. Furthermore rigorous inclusion and exclusion criteria could

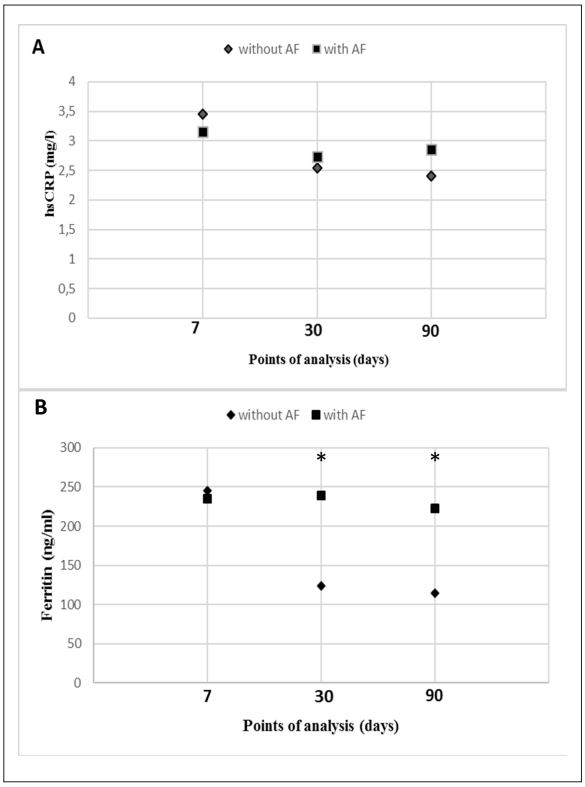

Fig. 1. A Concentration of hs-CRP in analysed time points, median, B - Concentration of ferritin in analyzed time points, median; * P<0.05

Table 1. Demographic and clinical characteristic of study population

Age (median)	54 years (44-70)
Gender (% women)	55%
Diabetes	38%
Arterial hypertension	78%
Ischaemic heart disease	38%
BMI (mean)	28±5
Ejection fraction EF% (mean)	54±7
LA diameter mm (mean)	47±7

EF- ejection fraction, LA-left atrium

also contribute to lower increase of CRP concentration in patients with recurrent atrial fibrillation. The observation that the hs-CRP baseline level is higher in patients ablated during AF is not surprising. Several authors showed that hs-CRP concentration decreases rapidly after successful cardioversion and is maintained at low level in patients without recurrence [9, 18]. Additionally, meta-analysis of Wo et al demonstrated elevation of hs-CRP in permanent and persistent AF but not in paroxysmal [19]

Ferritin is a well-known marker of iron deficiency. However, its elevation was also observed in clinical inflam-

matory conditions and trauma. It was suggested to be a useful marker in evaluation of the acutely ill patient.[20] Ferritin synthesis is stimulated by array of pro-

-inflammatory cytokines like: TNFα, IL-1α i ILGF [21]. Increase of release of these cytokines were observed in atrial fibrillation [13]. Increased ferritin might directly linked to elevated cytokines production. Another potential explanation of increased ferritin concentration associated to AF assumes the existence of micro disturbancesof iron turnover. This phenomenon has never been described but is plausible. Atrial fibrillation is associated with macrophages activation (22). Most of the iron delivered to plasma is provided by macrophages involved in recycling of senescent erythrocytes (23). Iron uptake into macrophages, via transferrin or scavenger receptor mediated erythrophagocytosis, increase intracellular iron level and accelerate ferritin synthesis and release (24). Sequestration of iron in macrophages is responsible for inflammation induced disturbances of erythropoiesis (25). Indeed, the association between red cell distribution with (RDW), the sensitive marker of increased red cells turnover and atrial fibrillation has been recently reported in general population [26,27] and in patients after ineffective cryoablation [28]. The increase of RDW levels are correlated with inflammatory markers and are accepted as a sign of ineffective erythropoiesis that occurs in critically ill patients [29]. Furthermore, Mattioli et al. reported that return of left atrium mechanical activity is attenuated in patients with high CRP, high ferritin and low iron level but not in patients with alone high CRP concentration itself [17].

Conclusions

Our results suggest that the evaluation of ferritin serum level can be a potential tool for assessment of AF treatment efficacy.

Study limitation

Small size of study group and absence of confirmation of freedom from AF with a method based on long term monitoring,capable to detect episodes of silent atrial fibrillation, are limitations of this study.

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