Galectin-3 In Middle-aged Patients With First Episode Of Non-valvular Atrial Fibrillation: A Speckle Tracking Study

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ABSTRACT

Introduction: We aimed to examine the relationship of early stage of atrial fibrosis and reduced atrial deformation with serum galectin concentration in patients with a first episode of non-valvular atrial fibrillation (AF)

Materials and Method: This study prospectively enrolled 34 patients who were admitted to our emergency service and required either a medical or electrical cardioversion due to a first episode of AF, without any structural or coronary heart disease and with normal left atrial (LA) size and 31 control subjects. Echocardiographic parameters and serum galectin levels were measured.

Results: The avarage age was 48.5±10.4 years. Galectin values were not significantly different between the AF and control groups (r = 0.42 ; p = 0.51) and were found negatively correlated with peak negative SR on apical four chamber (r = -0.31 , p = 0.02) and two chamber (r = -0.25 , p = 0.04) views . Compared with the control group, the AF group had significantly lower values of peak systolic strain on four chamber view (p = 0.037), peak late diastolic strain (p = 0.04), peak positive SR on apical four-chamber view (p = 0.04) and peak late negative SR on apical four chamber (p = 0.03) and two-chamber (p = 0.02) views.

Conclusion: Middle aged patients with first episode of AF, and normal LA sizes had reduced LA reservoir and active atrial functions. Although beginning signs of LA functional remodeling were shown on strain and SR imaging, these were not reflected by serum galectin levels.

Keywords: Atrial fibrillation, strain, strain rate, galectin

İlk Atak Non-valvular Atrial Fibrilasyonlu Orta Yaşlı Hastalarda Galectin-3

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ÖZET

Giriş: Biz bu çalışmada ilk atak non-valvular AF li orta yaşlı hasta grubunda serum galectin konsantrasyonu ile atrial fibrosisin erken evresi arasındaki ilişkiyi araştırdık.

Hastalar ve Metod: Bu çalışmaya acil servisimize ilk atak atrial fibrilasyon ile başvuran, medikal ya da elektriki kardiyoversiyon yapılmış, yapısal ya da koroner kalp hastalığı olmayan normal LA boyuta sahip 34 hasta ve 31 kontrol hastası prospektif olarak dahil edildi. Ekokardiyografik bulgular kayıt altına alındı ve serum galectin düzeyleri ekokardiyografi öncesi alınan kan örneklerinden ölçüldü.

Bulgular: Hastaların ortalama yaşı 48.5±10.4 yıldı. Galectin değerleri arasında AF ve kontrol grubu arasında anlamlı fark saptanmadı (r = 0.42 ; p = 0.51) ve apikal dört boşluk (r = -0.31 , p = 0.02) ve iki boşluk görüntüden (r = -0.25 , p = 0.04) pik negatif SR ile negatif korele bulundu . Kontrol grubu ile karşılaştırıldığında, AF grubunda dört boşluk görüntüden pik sistolik strain (p = 0.037) , pik geç diastolik strain (p = 0.04), pik positif SR (p = 0.04) ve pik geç negatif SR apikal dört (p = 0.03) ve iki boşluk (p = 0.02) görüntüden değerleri anlamlı olarak daha düşük olarak bulunmuştur.

Sonuç: İlk atak AF li orta yaşlı ve normal LA boyutuna sahip hastalarda LA rezervuar ve aktif atrial fonksiyonlar azalmıştır. Strain ve SR görüntüleme ile gösterilmiş LA fonksiyonel remodeling belirtileri başlamış olmasına rağmen bu durum serum galectin düzeyleri ile tam olarak gösterilememiştir.

Anahtar Kelimeler: Atriyal fibrilasyon, strain, strain rate, galectin

Geliş Tarihi: 17.01.2017 - **Kabul Tarihi:** 26.02.2017

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INTRODUCTION:

Atrial fibrillation (AF), is a common rhythm disturbance that is associated with increased morbidity and mortality in the general population.[1] Aside from cardiac conditions, multiple risk factors, including hypertension (HTN), diabetes mellitus (DM), obesity,and old age may predispose an individual to develop AF. Atrial fibrosis is a hallmark of structural remodeling and serves as a substrate for AF.[2] Moreover, atrial remodeling and fibrosis play important roles in persistent AF.[3,4] Recent studies have shown a significant association between left atrial (LA) global longitudinal strain (GLS) and AF progression, with significantly decreased LA GLS in patients with paroxysmal AF.[4,5] In long-term AF, fibrosis is an important factor causing mechanical dysfunction.[2]

Galectin-3 is a β-galactosidase-binding lectin that is mostly expressed in fibrotic tissue. It has been shown to be related to cardiac fibrosis and is accepted as a novel blood biomarker in cardiac diseases.[3] Significantly higher levels of serum galectin-3 have also been found in patients with non-valvular AF.[6] This study was designed to examine the relationship of early stage of atrial strain and fibrosis, as measured by speckle tracking echocardiography, with plasma galectin levels in young patients with a first episode of non-valvular AF

METHODS:

The study prospectively included 34 consecutive patients who were admitted to our emergency service and required either medical or electrical cardioversion due to a first episode of AF. Patients who had any of the following conditions were excluded from the study: structural or valvular heart disease, coronary artery disease, chronic kidney disease, chronic obstructive lung disease, abnormal thyroid or hepatic function, previous history of attempted AF ablation, LA diameter >40 mm, and systolic left ventricular (LV) dysfunction. At least one month after the initial admission, each patient underwent echocardiographic examinations and blood samples were obtained. Exercise stress test was normal in each patient. Weight, height and blood pressure were measured and recorded appropriately. As a control group, 31 age- and gender-matched healthy subjects were enrolled. Local ethics committee approved the study.

Blood samples

Blood samples to determine plasma galectin levels were obtained on the same day of echocardiographic examination. These were collected using pyrogen-free tubes containing EDTA and

santrifuged at 5000 r.p.m. for 10 minutes. Plasma samples were stored at –20ºC and analyzed using human lectin-galactose binding-soluble 3 ELISA kit (Shanghai Yehua Biological Technology Co., Ltd., Shanghai, China,) with an assay range of 1– 380 pg/ml and a sensitivity of 0.51 pg/ml.

Echocardiographic examination

Standard echocardiographic evaluations were performed using a 1 to 5 MHz X5-1 transducer (iE33, Philips Healthcare, Inc., Andover, MA). Patients were examined in the left lateral position. All measurements were averaged over three consecutive heart cycles. All standard two-dimensional (2D) transthoracic echocardographic images (i.e.,parasternal long axis, short axis, and apical four-, three- and two- chamber views) , color Doppler and tissue Doppler images were triggered to the QRS complex and were stored in cine loop format. The LV diastolic and systolic diameters were measured using M-mode or 2D echocardiography. LV ejection fraction (LVEF) was calculated using the Simpson's formula and employing a 2D image of the LV chamber during systole and diastole in the four- and two-chamber apical views.

Mitral inflow velocities were measured by pulsed wave (PW) Doppler, with the sample volume placed at the tip of the mitral valve in the LV. E and A waves were recorded. Mitral annular velocities were measured by PW tissue Doppler imaging (PW-TDI), with the sample volume placed at the level of the lateral and septal mitral annulus. Septal and lateral E' and A' waves were recorded and E/E' for septal and lateral mitral annulus and E/A were calculated.

Pulmonary artery pressure was estimated from tricuspid regurgitation jet. Tricuspid annular plane systolic excursion in the apical four-chamber view and tricuspid annulus peak systolic velocity with TDI were used to evaluate right ventricular function.

Circumferential and longitudinal LV strains were evaluated using 2D speckle-tracking imaging. Global circumferential strain was assessed by applying 2D speckle- tracking imaging to the parasternal short axis views of LV. The longitudinal peak systolic strain was assessed by applying 2D speckle- tracking imaging to the apical four-, three-, and two chamber views.

LA diameter was measured at the end-systole along the parasternal long-axis view. LA volume was calculated from the apical four and two chamber views of the LA using the biplane area length method. LA volume index (LAVI) was calculated on the basis of the patient's body surface area. LA strain (S) and strain rate (SR) values were obtained from apical four and two chamber views by

speckle tracking method (Figure 1). The first positive peak of strain (LAS), plateau (COND.) and return to zero line (ATRIAL) were considered to represent LA reservoir , conduit, and contractile phase, respectively. Accordingly, three SR parameters were evaluated: 1) peak positive strain rate (SRs, which corresponded to atrial reservoir function); 2) peak early negative strain rate (SRe, which corresponded to atrial conduit function), and 3) peak late negative strain rate (SRa, which corresponded to atrial contraction).

Statistical analysis:

Data were analyzed using IBM SPSS Statistics 17.0 software (SPSS, Chicago, IL) and presented as mean ± standard deviation for interval scale variables and as percentage for categorical variables. Categorical variables were compared using the chi square test or Fisher's exact test, as appropriate. One-way MANOVA was applied to interval scale variables. Each variable of atrial strain was considered as a dependent variable for galectin values. In this multivariate analysis , Box's test was used to determine whether the covariance matrices were equivalent . Levene's test, showed homogeneity of the variances. Correlations were determined by Pearson's test or Spearman's correlation test, as appropriate. A *p* value of less than 0.05 was considered statistically significant

RESULTS:

The baseline clinical features and echocardiographic findings of the patients are summarized in Tables 1 and 2, respectively. The AF and control groups were similar in terms of age (p = 0.39), gender (p = 0.66), body mass index (p = 0.45), heart rate (p = 0.33) and systolic (p = 0.25) and diastolic (p = 0.63) blood pressure values. The rate of cigarette smoking was higher in the AF group than the control group (15% *vs.* 9%). Speckle tracking echocardiographic features are presented in Table 3. Galectin levels did not differ significantly in the AF and control groups (p = 0.51) and were found to be inversely correlated with SRa values obtained from both the apical two-chamber (SRa2; r = -0.25, p = 0.04) and four-chamber views (SRa4; r = -0.31, p = 0.02). In addition, heart rate was shown to be significantly correlated with SRs4 (r = 0.3, p = 0.04) , SRe2 (r = -0.36, p = 0.01) , and SRa2 (r = -0.33, p = 0.02).

Compared with the control group, the AF group had significantly lower LAS from the apical four-chamber view (LAS4) (p = 0.037), ATRIAL4 (p = 0.04), SRs4 (p = 0.04), SRa4 (p = 0.03) and SRa2 (p = 0.02) (Table 3). LAS4 was inversely correlated with age (r = -0,35, p = 0.007) but was positively correlated with the E/A ratio (r = 0.40, p = 0.002). The E/A ratio was in significantly correlated with SRe4 (r = -0.37, p = 0.007), SRe2 (r = -0.39, p = 0.006), and SRa2 (r = -0.40, p = 0.005).

Galectin levels were not correlated with LA volume (r = -0.06, p = 0.67), LA volume index r = -0.05, p = 0.70) and the strain and SR values of both two- and four-chamber views .

LA diameter was correlated with SRs2 (r = 0.46, p = 0.001) and SRe2 (r = 0.36, p = 0.01).

In the AF group, galectin was correlated only with SRe2 (r = -0.62, p = 0.001) and SRa2 (r = -0.51, p = 0.01).
Compared with the control group, the AF group had significantly lower LVEF (p = 0,000) and LV GLS (p = 0,002), although the values were in normal range. LV circumferential strain (GCS) (p = 0,79) was not significantly different between the groups.

DISCUSSION:

Our study demonstrated that in with age- and gender-matched healthy individuals, middle aged patients with first episode of AF, had lower LA function, reservoir function, and active atrial function ,regardless of LA size. Although reduced atrial deformation during the reservoir phase of the cardiac cycle is considered to be an early and non-invasive marker of the amount of atrial wall fibrosis, serum galectin-3 concentrations did not seem to validate this assumption in this patient group.
During the cardiac cycle, the LA undergoes three phases: 1) the reservoir phase,in which pulmonary venous return is stored during LV systole; 2) conduit phase, which represents the passive transfer of blood to the LV during early diastole, and 3) contractile phases, which involves active priming of the LV in late diastole [7]. A 2D strain analysis enables identification of these phases. Various studies have demonstrated impaired LA global and regional function in patients with paroxysmal AF despite a normal or mildly enlarged LA.[8-10]. As demonstrated by present study, impairment in the reservoir function was detected even before atrial dilatation occurred , this was due to atrial fibrosis and reduced atrial compliance[11]. LA size has an important role in the onset and recurrence of AF. Therefore, use of atrial strain analysis for early detection of functional remodeling, even before anatomical alterations have taken place, may allow us to predict the risk for AF recurrence. Increased interstitial fibrosis and a high likelihood of local intra-atrial conduction block were considered the cause of susceptibility to AF[11]. Compared with traditional parameters, LA strain was shown to be a better predictor of the degree of fibrosis and to have a close correlation with histologic findings on the atrial wall in patients undergoing surgical correction for severe primary mitral regurgitation[12]. Kuppahally et al, found that larger extension of LA enhancement on delayed contrast enhanced cardiac magnetic resonance imaging was associated with lower performance of the atrial reservoir and the amount of fibrosis.

Furthermore, the corresponding reduction in atrial strain was significantly greater in patients with chronic AF than in those with paroxysmal AF [3]. Reduced atrial deformation during the reservoir phase of the cardiac cycle may be an early and non-invasive marker of the amount of atrial wall fibrosis [11]

Galectin-3, is a β-galactosidase-binding lectin that is highly expressed in fibrotic tissues. It has been shown to be related to cardiac fibrosis and heart failure, age, diabetic nephropathy,and fibrotic conditions of the kidneys, liver and lungs [13]. Galectin-3 induces cardiac fibrosis by promoting cardiac fibroblast proliferation, collagen deposition and ventricular dysfunction [13]. It was also found to be elevated in AF patients with preserved LV function, being more pronounced in persistent AF than in paroxysmal AF [14]. In an age- and gender-adjusted analyses, HO et al. showed that higher plasma galectin-3 concentrations were associated with increased risk of developing AF over the subsequent 10 years, whereas no significant associations were found for the traditional clinical risk factors of AF even after adjustment [15]. In our study, serum galectin-3 concentrations failed to show an upward trend. This probably resulted from the fact that progressive atrial fibrosis is commonly accompanied by older age, HTN, DM and obesity. Our study population was younger than the patient groups reported by other studies (Table 1). The number of women and patients with DM and HTN, which are known to be associated with high serum galectin-3 concentrations, were relatively lower in our study group. The amount of fibrosis increases with the persistence and recurrence of AF. Our patients experienced their first episode of AF and might have relatively less atrial fibrosis. However, atrial fibrosis, involves multifactorial processes that result from complex interactions among neurohormonal and cellular mediators ; therefore, the presence of atrial fibrosis in patients with AF remains a challenging issue [11]. Although serum galectin-3 levels did not differ significantly between the two groups, they were inversely correlated with LA SRa4 and SRa2. This may imply LA functional remodeling caused by atrial fibrosis was still in the beginning stages and has yet to reach an extent that is sufficient to increase galectin- 3 concentration .

The E/A ratio was associated with LAS4 and SR, suggesting a direct relationship between the extent of increase in LA pressure and the degree of cavity dysfunction [10]

CONCLUSION:

Middle-aged patients with a first episode of AF had reduced LA , reservoir , and active atrial functions, despite having normal LA sizes. In this patient group LA functional remodeling might still be in the initial stage , as shown by strain and SR imaging, such that increase in serum galectin-3 levels was not yet involved.

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FIGURE LEGENDS

Atrial strain and strain rate imaging

A-B. In the control group

C_D In the atrial fibrillation group

Table 1: Clinical characteristics of the study population

	New-onset AF	Control	p value
Age (years)	48.5 ± 10.4	46.5 ± 8.7	0.39
Gender (male/female)	19M/15F	19M/12F	0.66
Risk factors: DM, n(%) HTN, n(%) Smoking n(%) HL, n(%)	 2 (5.8%) 10 (39.4%) 5 (14.7%) 4 (11.7%)	 1 (3.2%) 4 (12.9) 3 (9.6%) 7 (22.5%)	 0.61 0.10 0.02 0.25
BMI (kg/m²)	29.0 ± 3.5	26.8 ± 4.41	0.45
HR (bpm)	69.2 ± 10.1	71.9 ± 11.4	0.33
SBP (mmHg)	125.5 ± 19.4	130.3 ± 11.6	0.25
DBP (mmHg)	72.7 ± 10.5	74 ± 10.1	0.63
CRP(mIU/mL)	0.6 ± 1	1.6 ± 2.2	0.19
TSH (mg/dl)	1.9 ± 1.34	1.7 ± 0.98	0.66
Galectin (pg/ml)	208 ± 248	212.5 ± 116	0.94

DM: diabetes mellitus; HTN: hypertension; HL: hyperlipidemia; BMI: body mass index; HR: heart rate; SBP: systolic blood pressure; CRP: C- reactive protein; DBP: diastolic blood pressure; CRP: C-reactive protein; TSH: Thyroid-stimulating hormone.

Table 2: Standard echocardiographic features of the study population

	New-onset AF	Control	P value
LVEDD (cm)	4.8 ± 0.49	4.7 ± 0.47	0.41
LVESD (cm)	3.0 ± 0.43	2.8 ± 0.44	0.17
LVEF (%)	62.6 ± 4.5	65.7 ± 0.97	0.000
LA (cm)	3.4 ± 0.45	3.2 ± 0.47	0.77
LAV (mL)	52.1 ± 14.5	47.9 ± 12.2	0.23
LAVI (mL/m²)	1.8 ± 0.5	1.7 ± 0.58	0.63
E (cm/sec)	70.6 ± 14.6	74.6 ± 19.1	0.33
A (cm/sec)	64.1 ± 14.2	66.2 ± 18	0.59
E/A ratio	1.14 ± 0.29	1.19 ± 0.39	0.57
DECT (msec)	227.6 ± 62.1	198.8 ± 49.7	0.048
LATE/e'	7.36 ± 2.4	6.19 ± 1.6	0.03
SEPTE/e'	8.99 ± 3.2	7.89 ± 2.3	0.13
TAPSE (mm)	25.3 ± 4.6	24.5 ± 3.9	0.42
ST (cm/sec)	14.5 ± 2.5	15.0 ±;2.27	0.40

LVESD: Left ventricular end-systolic diameter; LVEDD: Left ventricular end-diastolic diameter; LVEF: Left ventricular ejection fraction; LA: Left atrium; LAV: Left atrial volume; LAVI: Left atrial volume index; E: Mitral inflow E wave; A: Mitral inflow A wave; DECT: Deceleration time; LATE/e': Lateral annular E/e', SEPTE/e': Septal annular E/e'; TAPSE: Tricuspid annular plane systolic excursion; ST: Tricuspid annular peak systolic velocity.

TABLE-3: Speckle tracking echocardiographic values of study population

	New-onset AF	Control	P value
GCS (%)	22.5 ± 5.2	22.8 ± 4.57	0.79
GLS (%)	18.5 ± 3.6	21 ± 2.25	0.002
LASTR4 (%)	40.0 ± 20.2	50.5 ± 19.4	0.03
COND4(%)	15.4 ± 9	19.6 ± 10.4	0.109
ATRIAL4 (%)	19.8 ± 9.2	25.1 ± 11	0.049
SRs4 (s^{-1})	1.38 ± 1.23	0.85 ± 0.68	0.049
SRe4 (s^{-1})	-1.73 ± 1.14	-2.29 ± 1.3	0.09
SRa4 (s^{-1})	-2.49 ± 1.41	-3.32 ± 1.5	0.03
LASTR2 (%)	36.9 ± 17.1	41.7 ± 16.7	0.26
COND2 (%)	13.0 ± 10.1	15.73 ± 10.1	0.31
ATRIAL2 (%)	17.8 ± 9.5	23.5 ± 12.2	0.05
SRs2 (s^{-1})	0.80 ± 0.2	0.83 ± 0.4	0.73
SRe2 (s^{-1})	-1.66 ± 0.95	-1.90 ± 1.6	0.5
SRa2 (s^{-1})	-2.36 ± 1.35	-3.24 ± 1.44	0.02

GCS: Global circumferential left ventricular strain, GLS: Global longitudinal left ventricular strain; LASTR4-2: Left atrial first positive peak of strain; COND4-2: Plateau and return to the zero line; ATRIAL4-2: The contractile phase; SRs4-2: Peak positive strain rate (SRs corresponds to the atrial reservoir function); SRe4-2: Peak early negative strain rate (SRe corresponds to the atrial conduit function); SRa4-2: Peak late negative strain rate (SRa corresponds to the atrial contraction) values were derived from four- and two- chamber views.