Research Article

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Correlation between serum homocysteine, Galectin-3 concentration and atrial structural remodeling in atrial fibrillation patients

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Abstract: Objective To investigate the correlation between serum homocysteine (Hcy), Galectin-3 concentration and atrial structural remodeling in atrial fibrillation (AF) patients.

Methods Twenty-five patients with persistent atrial fibrillation (PeAF), 24 patients with paroxysmal atrial fibrillation (PaAF) and 23 healthy controls were included in the present work. All subjects received an echocardiography examination. Serum concentration of Hcy and Galectin-3 were also examined by Enzyme Linked Immunosorbent Assay (ELISA).

Results Echocardiography examination demonstrated that there were significant differences for LAD ($p=0.002$), LVEF ($p=0.005$) and LVAI ($p=0.0001$) between the control, PaAF and PeAF groups. However, LVSD and LVDD were not significantly different between the three groups ($p_{\text{all}} > 0.05$). There was a significant positive correlation between LAVI and serum Hcy level in both PaAF ($r_{\text{pearson}}=0.49$, $p=0.016$) and PeAF ($r_{\text{pearson}}=0.51$, $p=0.009$) groups. The correlation between LAVI and serum Galectin-3 concentration was also statistically significant for PaAF ($r_{\text{pearson}}=0.54$, $p=0.006$) and PeAF ($r_{\text{pearson}}=0.60$, $p=0.001$) groups. Using serum Hcy as reference, diagnostic sensitivity and specificity were calculated as 72.00 (95%CI: 50.61-87.93) and 62.50 (95%CI: 40.59-81.20), respectively, with an AUC of 0.68 for PaAF and PeAF. For serum Galectin-3, the

sensitivity and specificity values were 64.00 (95%CI:42.52-82.03) and 66.67 (95%CI:44.68-84.37), respectively, with an AUC of 0.68.

Conclusion: Serum Hcy and Galectin-3 were elevated in AF patients and thus may be potential markers of atrial structural remodeling. However, the diagnostic efficacy of PeAF from PaAF was limited by low AUC values.

Keywords: Hcy; Galectin-3; atrial structural remodeling; atrial fibrillation; serological marker.

Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias seen in clinical practice. An epidemiological study reports the total incidence of AF in China to be 1.1% [1]. As the proportion of older persons in a population continues to increase, so does the incidence of atrial fibrillation. AF can lead to hemodynamic changes, left atrial thrombosis, and increased risk of stroke and heart failure. More generally, it is associated with a high rate of death or disability. In recent years, basic research on atrial fibrillation has made encouraging progress, and novel treatment methods (such as radiofrequency catheter ablation) have also improved the prognoses of AF patients. However, the recurrence rate after traditional drug therapy and radiofrequency catheter ablation remains high, especially in patients with persistent atrial fibrillation. Despite the great harm caused by AF, treatment options remain limited; therefore, it is of great significance to identify the mechanism of occurrence, development and maintenance of AF.

At present, the pathogenesis of AF is not clear [2, 3]. Atrial remodeling [4], inflammatory response and oxidative stress [5-7] are considered to be important pathophysiological mechanisms of AF. Atrial structural remodeling is characterized by atrial fibrosis, dissolution of atrial myofibrils, apoptosis of atrial myocytes, increased

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or over-accumulated collagen in the extracellular matrix (ECM), obvious increase in collagen content and changes to components. Ultimately, this leads to uneven atrial conduction, further promoting atrial electrical remodeling and providing a pathological basis for the occurrence and development of atrial fibrillation [8, 9].

Hcy is an amino acid containing a sulfhydryl group; it mainly participates in the oxidative stress reaction in vivo and is a marker of oxidative stress in vivo [10, 11]. It produces a large number of oxygen free radicals and peroxides in the process of oxidation-reduction in vivo. Active oxygen then directly affects calmodulin to cause intracellular calcium overload, change atrial ion channels and promote atrial electrical remodeling [12, 13]. Galectin-3 is a member of the galectin family and can be expressed in many organs, such as the small intestine, spleen, colon and kidney, as well as in inflammatory cells such as mast cells [14], neutrophils and macrophages [15]. Galectin-3 is involved in a variety of pathophysiological processes, including inflammatory response and fibrosis [16], both considered to be key mechanisms and important markers of atrial and ventricular remodeling and heart failure [17-19]. However, the relationship between serum Hcy, galectin-3 levels and atrial structural remodeling in patients with atrial fibrillation remains unclear. In this study, we investigated the expression of Hcy and galectin-3 in serum of patients with atrial fibrillation and assessed the relationship with atrial structural remodeling.

Material and methods

Patients

Twenty-five patients with persistent atrial fibrillation (PeAF), 24 patients with paroxysmal atrial fibrillation (PaAF) and 23 healthy controls were included in the present work. The subjects in the AF group had at least one 24-hour ambulatory ECG or had a clear history of atrial fibrillation confirmed by ECG. AF diagnosis was performed in accordance with the European guidelines for the management of atrial fibrillation [20-22]: 1) the absolute RR interval of ECG is different; 2) no obvious P wave can be seen on ECG; 3) the interval between the two atrial electrical activities is usually variable, and the time limit is generally less than 200ms.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance with the tenets of the Helsinki Declaration, and has been approved

by the Ethical Committee of 1st People's Hospital of Fuyang District Hanzhou City, Zhejiang Province 311400 PR China.

Informed consent: Informed consent has been obtained from all individuals included in this study

Echocardiography examination

All subjects were examined with echocardiography performed by experienced doctors in the ultrasound department of our hospital. Left atrial diameter (LAD), ascending aortic diameter (AO), right ventricular diameter, left ventricular posterior wall thickness (LVPWT), interventricular septal thickness (IVST), left ventricular end diastolic diameter (LVDD), left ventricular end systolic diameter (LVSD), pulmonary artery diameter and right and left atrial diameter were all recorded. The left ventricular ejection fraction (LVEF) was measured by the Simpson method.

Measurement and calculation of left atrial volume

Before measuring, subjects rested for 15 minutes. After minutes of calm breathing, probes were placed about 1-2cm from the inner side of the apical beat to show the apical four chamber section toward the right shoulder. The image was frozen, and the left atrium volume was outlined and recorded as A1. The distance from the top of the left atrium to the midpoint of the line between the mitral annulus was measured and recorded as L1. The probe was rotated 90° anticlockwise to display the apical two chamber section. The image was frozen, and the left atrium area was outlined and recorded as A2. The distance from the top of the left atrium to the midpoint of the line between the mitral annulus was measured and recorded as L2. The smaller value between L1 and L2 was selected and recorded as L. All the above measurements were continuously recorded for three cardiac cycles, and the average value was taken, **Figure 1**. The left atrial volume was calculated according to the formula: $8 (A1) (A2) / 3 \pi (L)$ and LAVI was calculated by: $LAVI = LAV / BSA (ml/m^2)$.

Serum Hcy, Galectin-3 examination

After patients had fasted for eight hours, 5 ml of peripheral venous blood was collected from common vacuum vessels in the morning. After two hours of standing at room

Figure 1: Measurement and calculation of left atrial volume(A: the distance from the top of the left atrium to the midpoint of the line between the mitral annulus; B: the distance from the top of the left atrium to the midpoint of the line between the mitral annulus; C: outline the left atrium volume corresponding to L1; D outline the area of the left atrium corresponding to L2:).

temperature, the blood was centrifuged at 4000 r/min for 15 minutes. The upper serum was transferred to an EP tube and stored at -80°C until use. Serum Hcy and Galectin-3 level was detected using an ELISA assay according to the manufacturer's instructions.

Statistical analysis

Statistical analysis was performed using STATA11.0 statistical software (<http://www.stata.com>). Measurement data were expressed with $\bar{x} \pm s$, and the comparison between groups was made based on the AVOVA test of the sample mean. Enumeration data were expressed with a relative number, and the comparison between groups was made based on the χ^2 test. The correlation was evaluated by Pearson correlation test. Regarding the diagnosis test, sensitivity, specificity, and the area under the ROC curve were calculated according to Bayes' theorem. $P < 0.05$ indicates statistical significance.

Results

General characteristics of the included subjects

General characteristics of the three subject groups are shown in **Table 1**. There were significant statistical differences between the three groups with respect to age ($p < 0.05$) and hypertension ($p < 0.05$). However, gender, body weight, height, diabetes, serum Scr, TC and TG were not statistical different between these groups ($p_{\text{all}} > 0.05$).

Echocardiography

Echocardiography examination revealed significant differences in LAD ($p = 0.002$), LVEF ($p = 0.005$) and LVAI ($p = 0.0001$) between the control, PaAF and PeAF groups. However, LVSD and LVDD were not significantly different across the groups ($p_{\text{all}} > 0.05$), **Table 2**.

Serum Hcy, Galectin-3 concentration

The serum Hcy concentrations of control, PaAF and PeAF groups were 8.43 ± 2.79 ($\mu\text{mol/L}$), 10.91 ± 4.28 ($\mu\text{mol/L}$), and 14.08 ± 5.00 ($\mu\text{mol/L}$), respectively. For serum Galectin-3, concentration values were 1.44 ± 0.18 (ng/ml), 1.59 ± 0.26 (ng/ml) and 1.81 ± 0.33 (ng/ml) for the control, PaAF and PeAF groups, respectively, **Table 3**. There is a statistically significant difference in serum Hcy and Galectin-3 concentration between control, PaAF and PeAF groups, **Figure 2**.

Correlation between serum Hcy Galectin-3 concentration and LAVI

The correlations between serum Hcy, Galectin-3 concentration and LAVI are shown in **Table 4**. There were a significant positive correlation between LAVI and serum Hcy level in PaAF ($r_{\text{pearson}} = 0.49$, $p = 0.016$) and PeAF ($r_{\text{pearson}} = 0.51$, $p = 0.009$) groups. The correlation between LAVI and serum Galectin-3 concentration was also statistically significant for PaAF ($r_{\text{pearson}} = 0.54$, $p = 0.006$) and PeAF ($r_{\text{pearson}} = 0.60$, $p = 0.001$) groups, **Figure 3**.

Table 1: The main characteristics of the included subjects.

Characteristics	Control(n=23)	PaAF(n=24)	PeAF(n=25)	F/chi-square	p-value
Age(year)	57.2±9.7	62.4±10.8	66.9±8.7	5.92	0.004
Gender(n,%)				0.07	0.79
Male	11	11	11		
Female	12	13	14		
Weight(kg)	63.7±10.5	61.4±9.8	59.5±10.6	0.99	0.37
Height(cm)	166.7±8.2	164.2±7.9	163.5±9.2		
Hypertension(n,%)				7.64	0.006
Yes	3	11	13		
No	20	13	12		
Diabetes(n,%)				0.15	0.69
Yes	2	2	3		
No	21	22	22		
Scr (μmol/L)	61.4±18.3	66.2±22.7	64.9±24.1	0.30	0.74
TC(mmol/L)	4.42±1.23	4.56±1.04	4.24±1.43	0.41	0.67
TG(mmol/L)	1.33±0.65	1.56±0.68	1.49±0.72	0.69	0.50

PeAF=Persistent atrial fibrillation

PaAF=Paroxysmal atrial fibrillation

TC= total cholesterol

TG= total glyceride

Table 2: The main measurement values of echocardiography for the 3 groups.

Echocardiography	Control	PaAF	PeAF	F	p-value
LAD(mm)	33.2±4.8	35.9±6.8	40.7±9.2	6.68	0.002
LVSD(mm)	31.2±4.2	31.8±5.1	32.9±5.1	0.77	0.47
LVDD(mm)	45.6±6.2	44.8±7.6	46.3±8.4	0.25	0.78
LVEF(%)	65.3±4.8	60.3±9.1	57.8±8.7	5.65	0.005
LAVI(ml/m ²)	30.96±4.73	35.30±7.61	39.76±7.53	10.07	0.0001

LAD :left atrial diameter

LVSD :left ventricular end systolic diameter

LVDD :left ventricular end diastolic diameter

LVEF :left ventricular ejection fraction

LAVI :left atrial volume index

Table 3: Serum Hcy, Galectin-3 concentration for the 3 groups.

Characteristics	Control	PaAF	PeAF	F	p-value
Hcy(μmol/L)	8.43±2.79	10.91±4.28	14.08±5.00	5.91	0.004
Galectin-3(ng/ml)	1.44±0.18	1.59±0.26	1.81±0.33	11.66	<0.0001

Figure 2: Scatter plot of serum Hcy, Galectin-3 concentration for different groups(A: Serum Hcy for control, PaAF, PeAF groups; B: Serum Galectin-3 for control, PaAF, PeAF groups).

Figure 3: The correlation between serum Hcy, Galectin-3 concentration and LVI in different groups(A: Correlation between LVI and Hcy in control group; B: Correlation between LVI and Hcy in PaAF group; C: Correlation between LVI and Hcy in PeAF group; D: Correlation between LVI and Galectin-3 in control group; E:Correlation between LVI and Galectin-3 in PaAF group; Correlation between LVI and Galectin-3 in PeAF group).

Serum Hcy and Galectin-3 as biomarker for diagnosis of PeAF

Using serum Hcy as reference, diagnostic sensitivity and specificity values were determined to be 72.00 (95%CI:50.61-87.93) and 62.50 (95%CI:40.59-81.20), respectively, with an AUC of 0.68 between PaAF and PeAF.

For serum Galectin-3, the sensitivity and specificity values were 64.00 (42.52-82.03) and 66.67 (95%CI:44.68-84.37), respectively (Table 5), with an AUC of 0.68, Figure 4.

Table 4: Correlation between serum Hcy, Galectin-3 concentration and LAVI.

Correlation	r_{pearson}	95%CI	R square	p
LVAI vs Hcy				
Control	-0.067	-0.47 to 0.36	0.005	0.76
PaAF	0.49	0.10 to 0.74	0.24	0.016
PeAF	0.51	0.14 to 0.75	0.26	0.009
LAVI vs Galectin-3				
Control	0.21	-0.31 to 0.51	0.014	0.58
PaAF	0.54	0.18 to 1.78	0.29	0.006
PeAF	0.60	0.27 to 0.80	0.36	0.001

Table 5: The diagnostic efficacy of serum Hcy and Galectin-3 as biomarker for diagnosis of PeAF.

Reference	Sen(%)	Sep(%)	AUC(95%CI)	LR	p	Cut off
Hcy	72.00(50.61-87.93)	62.50(40.59-81.20)	0.68(0.54-0.84)	2.16	0.023	12.24
Galectin-3	64.00(42.52-82.03)	66.67(44.68-84.37)	0.71(0.56-0.85)	1.92	0.013	1.67

Figure 4: Roc curve for serum Hcy and Galectin-3 as biomarker for diagnosis of PeAF(A:serum Hcy in diagnosis of PeAF; B: serum Galectin-3 in diagnosis of PeAF).

Discussion

In the present work, we found that LAD ($p=0.002$), LVEF ($p=0.005$) and LAVI ($p=0.0001$) are significantly higher in the AF group in comparison to controls. This indicates atrial structural remodelling in AF patients. The results also indicate that LAVI is positively correlated with both serum Hcy and Galectin-3 in AF patients. This may be evidence that Hcy and Galectin-3 acts as import serological markers for atrial structural remodeling. Therefore, as serum Hcy and Galectin-3 are elevated in AF patients,

they may represent a potential marker of atrial structural remodeling.. However, the diagnostic efficacy of PeAF from PaAF was limited by low AUC.

Mihm and colleagues [23] found that oxidative damage in human AF alters myofibrillar energetics and contributes to atrial contractile dysfunction. Kim et al. [24] also found that expression of both monoamine oxidase B and tyrosinase related protein-1 is up-regulated in the right auricles of patients with atrial fibrillation; furthermore, expression of the antioxidant gene glutathione peroxidase-1 is down regulated, while active oxygen in

vivo is up regulated. Lin and colleagues [25] found that evidence of oxidative injury and deletion of mtDNA in cardiac muscle is increased in the patients with AF, which may impair of bioenergetic function of mitochondria and ultimately induce the oxidative vicious oxidative cycle involved in the pathogenesis of atrial myopathy in AF. The aforementioned reports suggest that oxidative stress plays a role in the process of AF. Hcy an amino acid containing a sulfhydryl group, and is thus able to participate in various important redox reactions in vivo, in addition to being a marker of oxidative stress in vivo. Hcy produces a large number of oxygen free radicals and peroxides by its own oxidation [26]. This active oxygen directly affects calmodulin, causing intracellular calcium overload and inducing changes to atrial ion channels that ultimately lead to atrial electrical remodeling and promote the occurrence of atrial fibrillation. In a large prospective study, Cai et al. [27] found that high Hcy level is a risk factor for the occurrence of atrial fibrillation, potentially due to the fact that long-term high Hcy levels can interfere with the potassium channel currents of atrial myocytes and cause electrical remodeling of the atrium. Nasso et al. [28] found that Hcy levels in peripheral blood are an independent predictor of recurrence in patients with atrial fibrillation (including paroxysmal and persistent atrial fibrillation) after epicardial ablation.

However, the model that oxidative stress mediates the pathological consequences associated with elevated homocysteine remains controversial [29]. For example, lowering elevated homocysteine levels does not decrease pathological consequences associated with elevated homocysteine [30]. Therefore, the relationship between oxidative stress, hyperhomocysteinemia and the pathological consequences of heart disease requires further exploration. Hcy is an intermediate metabolite in the metabolic pathway of cysteine and methionine. It may undergo remethylation to methionine in a reaction catalyzed by ethylenetetrahydrofolate homocysteine methyltransferase [29]. Hcy also can be recognized and activated by methionyl-tRNA synthetase to produce Hcy-thiolactone, which can react with the ϵ -amino group of a protein lysine residue. The N-hcy-linked protein carrying a free thiol group can influence protein structure and function, thus leading to severe diseases [31].

Goktekin [32] selected 52 patients with nonvalvular atrial fibrillation and 33 age- and gender-matched control participants for his study, in which he detected markers of fibrosis and inflammation in their serum, including galectin-3, matrix metalloproteinase-9, MMP-9, apolipoprotein-2, Lcn2 and type III procollagen N-terminal protein of type III proco. The results showed that levels

of galectin-3, MMP-9, PIIINP, NLR and hs CRP were higher in the AF group than in the control group. Additionally, levels of galectin-3, MMP-9, PIIINP and NLR were positively correlated with left atrial volume index.

Our work is consistent with these findings. Moreover, we also determined that galectin-3 is not only related to the occurrence of AF, but also implicated in its development and maintenance. Yalcin et al. [33] found that serum galectin-3 levels in patients with paroxysmal atrial fibrillation with left ventricular ejection fraction retention were higher than those of the control group, and galectin-3 levels were positively correlated with the degree of atrial fibrosis shown by 3D delayed enhanced MR imaging. Gurses et al. [34] found that the level of serum galectin-3 in patients with AF with preserved ejection fraction was higher than that of the age-matched control group, in addition to being positively correlated with left atrial volume index. Both of the above studies indicate that galectin-3 is related to left atrial fibrosis, participates in the process of left atrial structural remodeling and promotes the development of atrial fibrillation.

In conclusion, serum Hcy and Galectin-3 are elevated in AF patients and may be a potential marker for atrial structural remodeling. However, due to low AUC, the diagnostic efficacy of PeAF from PaAF is currently limited.

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