Ghrelin expression and significance in 92 patients with atrial fibrillation

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Abstract

Objective: Ghrelin is a polypeptide that is closely associated with many cardiovascular diseases, such as hypertension, atherosclerosis, and heart failure. This article aims to understand the expression of ghrelin in patients with atrial fibrillation (AF).

Methods: A total of 182 patients with non-valvular heart diseases were recruited, among whom 92 had AF and 90 had sinus arrhythmia (SA). The serum ghrelin amount was tested by the ELASA method. Moreover, blood sugar, lipids, liver function, and renal function were tested. All recruited patients underwent echocardiographic examination following admission. Three cardiac cycles were observed under continuous exhalation. The left atrial diameter (LAD) and the left ventricular ejection fraction (LVEF) were measured and averaged. Patients with AF received conventional treatment, and the aforementioned parameters were re-measured after 8 weeks. The results were statistically analyzed.

Results: The serum ghrelin level in the patients in the AF group (199.55±79.59 pg/mL) was lower than that in the patients in the SA group (313.89±71.13 pg/mL, $p<0.01$), whereas the serum ghrelin level in those in the paroxysmal AF group (224.44±72.33 pg/mL) was higher than that in those in the persistent AF group (176.00±79.88 pg/mL, $p<0.01$). There was a positive correlation between the serum ghrelin level and LVEF in the patients in the AF group ($r=0.704$, $p=0.046$). After treatment, the serum ghrelin level and LVEF in the patients in the AF group significantly increased, whereas LAD decreased.

Conclusion: The serum ghrelin level in patients with AF was reduced, and after treatment, it significantly increased. There was a positive correlation between the serum ghrelin level and LVEF in the patients in the AF group. *(Anatol J Cardiol 2017; 17: 000-00)*

Keywords: atrial fibrillation, ghrelin, paroxysmal atrial fibrillation, persistent atrial fibrillation

Introduction

Atrial fibrillation (AF) is a common clinical arrhythmic condition and a threat to health. Prolonged AF can result in a series of complications, such as stroke and heart failure. AF not only affects the quality of life but also significantly increases the rate of hospitalization and mortality. The estimated number of individuals with AF globally in 2010 was 33.5 million (1).

Ghrelin is a polypeptide that consists of 28 amino acids and is widely found in the cardiovascular system. Ghrelin can improve many cardiovascular functions, such as increasing endothelial function, myocardial contractility, and vasodilation and alleviating ischemia–reperfusion injury. Therefore, studies on ghrelin are gaining attention. As previous studies have shown that ghrelin can improve malignant arrhythmia, this study aims to explore the role of ghrelin expression and its clinical significance in patients with AF.

The study protocol was approved by the Ethics Committee, and all participants provided written informed consent.

Methods

Research subjects

A total of 182 patients with non-valvular heart diseases from the Department of Cardiology, hospitalized between June 2011 and August 2015, were recruited for this study. Among these, 92 patients had AF and 90 had sinus arrhythmia (SA). The AF group was further divided into two groups: paroxysmal AF (45 patients) and persistent AF (47 patients). Patients with persistent AF were defined as those having a manifestation of AF for more than 7 days and requiring either electrical or pharmacologic cardioversion to return to normal heart pulses. Patients with paroxysmal AF were defined as those whose AF self-terminated within 7 days. The following conditions were excluded from this study: (i) valvular heart disease, congenital heart disease, myocardial disease, and myocarditis; (ii) acute coronary syndrome; (iii) severe liver and kidney dysfunctions, as well as acute and chronic inflammatory diseases; (iv) malignant tumor; (v) and hyperthyroidism; and (vi) age more than 80 years and younger than 50 years.

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In the full understanding on admission patient and medical history, in accordance with strict exclusion criteria selected the patient, if they does not accord with the standard, they cannot enter the group without exception. If hospitalization-related inspection found that the condition did not conform to the standard or existing the problems in the exclusion criteria, and the patient dropped out of the study after we explained it to them.

The study protocol was approved by the Ethics Committee, and all participants provided written informed consent.

Treatment method

AF treatment was carried out in accordance with the AF management guidelines by the American Heart Association/American College of Cardiology/Heart Rhythm Society. In accordance with their guidelines, AF patients were given appropriate medication, such as aspirin, clopidogrel, or warfarin, to prevent thromboembolism. They were also given β-blockers (metoprolol and bisoprolol), non-dihydropyridine calcium channel blockers, or amiodarone to control the ventricular rate. The entire course of treatment lasted 8 weeks.

Ghrelin and biochemical indicator tests

Blood samples were obtained from all patients the morning following admission for various biochemical tests, such as ghrelin, blood sugar, lipids, liver function, and renal function. All patients fasted for 12 h prior to blood collection. Blood samples were collected from patients with AF after 8 weeks to test for serum ghrelin levels. The serum ghrelin level was tested by ELASA method. In this study, we measured the total ghrelin level, and the detection range was 62.5–4000 pg/mL.

Echocardiography

All recruited patients underwent echocardiographic examination following admission. During the examination, the left lateral position, left ventricular long-axis view, and apical four-chamber and five-chamber views were imaged. Three cardiac cycles were observed under continuous exhalation. The left atrial diameter (LAD) and left ventricular ejection fraction (LVEF) were measured and averaged. All patients with AF underwent echocardiographic examination again after 8 weeks.

Echocardiography was not performed by the same physician, but those who performed echocardiography were senior ultrasound doctors and have the same inspection standards.

Statistical analysis

Statistical analysis of all data was performed using SPSS l7.0, and data were represented as mean±standard deviation (±s). Data from two groups that were normally distributed were compared using t-tests. Data that were not normally distributed were compared using non-parametric tests. The comparison of data was performed using chi-square tests. Numerical correlation analysis was performed using Pearson's correlation coefficient. The Kolmogorov–Smirnov test was used to identify whether the data were normally distributed.

For all statistical outcomes, $p<0.05$ was considered to be statistically significant, whereas $p<0.01$ was considered to be highly statistically significant.

Table 1. Clinical data of the patients in the AF and SA groups

	AF (n=92)	SA (n=90)	*P*
Age, years	69.93±8.64	67.95±7.59	0.281
Male, %	68	59	0.241
SBP, mmHg	136.52±35.06	130.82±33.72.	0.245
DBP, mmHg	72.18±23.56	69.91±22.85	0.302
FPG, mmol/L	6.22±0.81	6.03±0.79	0.521
TC, mmol/L	4.62±0.67	4.39±0.78	0.734
Creatinine, mmol/L	95.41±30.06	87.65±28.67	0.413
HBP, %	69	66	0.635
CHD, %	67	61	0.515
Diabetes, %	14	16	0.759
Hyperlipidemia, %	31	26	0.521
Stroke, %	21	14	0.306
BMI, kg/m^2	23.93±3.55	22.19±3.41	0.699
ACEI/ARB, %	58	56	0.753
β-blockers, %	82	46	<0.001

Data are presented as mean±SD, unless otherwise stated. ACEI/ARB - angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker; AF - atrial fibrillation; BMI - body mass index; CHD - coronary heart disease; DBP - diastolic blood pressure; FPG - fasting plasma glucose; HBP - high blood pressure; SA - sinus arrhythmia; SBP - systolic blood pressure; SD - standard deviation; TC - total cholesterol

Results

General information

There was no significant difference between the patients with AF and SA in terms of age, sex, systolic blood pressure, diastolic blood pressure, fasting glucose level, total cholesterol level, creatinine level, hypertension, diabetes, coronary heart disease, hyperlipidemia, stroke, body mass index, and angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker consumption. However, there was a significant difference in the consumption of β-blockers between the two groups, with a higher number of patients with AF consuming β-blockers than those with SA (Table 1).

Ghrelin levels

The serum ghrelin level in patients with SA was 313.89±71.13, whereas that in patients with AF was 199.55±79.59. The serum ghrelin level in the patients in the AF group was significantly lower than that in the patients in the SA group ($p<0.001$) (Fig 1). The serum ghrelin level in patients with paroxysmal AF was 224.44±72.33, whereas that in patients with persistent AF was 176.00±79.88. Among the patients in the AF group, the serum ghrelin level in patients in the paroxysmal AF group was sig-

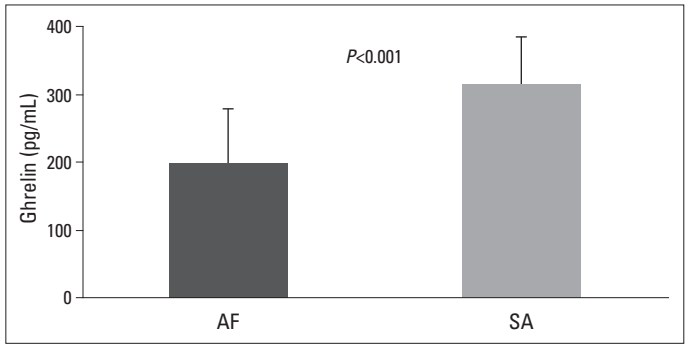

Figure 1. Comparison of serum ghrelin levels between the AF and SA groups (+s)
AF - atrial fibrillation; SA - sinus arrhythmia

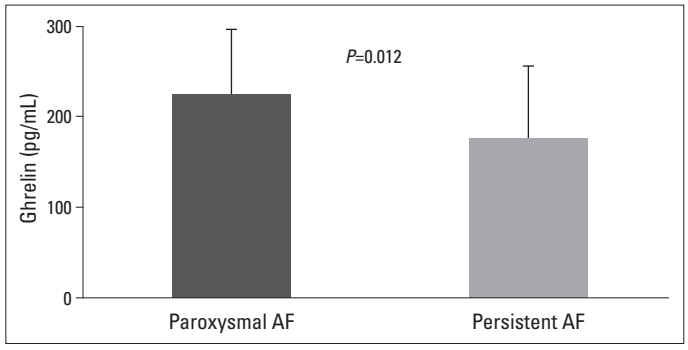

Figure 2. Comparison of serum ghrelin levels within the AF group (+s)
AF - atrial fibrillation

Table 2. Comparison of ultrasound indices of the patients in the AF and SA groups (+*s*)

	AF (n=92)	SA (n=90)	*P*
LAD, mm	39.99±5.96	36.86±5.96	0.006
LVEF, %	49.53±10.27	55.41±8.84	0.004

AF - atrial fibrillation; LAD - left atrium diameter; LVEF - left ventricular ejection fraction; SA - sinus arrhythmia

nificantly higher than that in those in the persistent AF group (p=0.012) (Fig. 2).

Comparison of echocardiography indices

In terms of LAD and LVEF, LAD in the patients in the AF group was significantly larger than that in those in the SA group, whereas LVEF in the patients in the AF group was significantly lower than that in those in the SA group. The differences in both indices were statistically significant (Table 2).

Correlation between the serum ghrelin level, LAD, and LVEF in the patients in the AF group

There was a positive correlation between the serum ghrelin level and LVEF in the patients in the AF group (r=0.704, p=0.046). The serum ghrelin level and LAD were not significantly correlated (Table 3).

The serum ghrelin levels, LAD, and LVEF before and after treatment in the patients in the AF group were tested. After treatment with medication, the serum ghrelin level and LVEF were significantly higher than those before treatment, whereas LAD significantly decreased. These differences were statistically significant (Table 4).

Table 3. Correlation between serum ghrelin levels, LAD, and LVEF in the patients in the AF group (+*s*)

	LVEF (%)	LAD, mm
Test indicator	49.53±10.27	39.99±5.96
Ghrelin, pg/mL	199.55±79.59	199.55±79.59
r value	0.704	0.442
P value	0.046	0.092

AF - atrial fibrillation; LAD - left atrium diameter; LVEF - left ventricular ejection fraction

Table 4. The serum ghrelin level, LVEF, and LAD in patients with AF before and after treatment (+*s*)

	Ghrelin, pg/mL	LVEF, %	LAD, mm
Before treatment	199.55±79.59	49.53±10.27	39.99±5.96
After medication treatment	223.57±73.60	53.02±9.26	38.09±6.24
P value	0.040	0.040	0.026

AF - atrial fibrillation; LAD - left atrium diameter; LVEF - left ventricular ejection fraction

Discussion

In the present study, the serum ghrelin levels in the patients with SA were significantly higher than those in the patients with AF, and the serum ghrelin levels in patients with paroxysmal AF were significantly higher than those in patients with persistent AF. These results may suggest that the serum ghrelin level may be an independent risk factor for the onset of AF.

The connection between ghrelin and AF could be established through the following conditions. First, atrial structural remodeling through atrial fibrosis will result in differences in atrial conduction and repolarization by interfering with atrial excitement and pulse transfer. These events are conducive for the occurrence and persistence of AF. AF is closely associated with the apoptosis of atrial myocytes (2). In chronic AF, apoptosis of atrial myocytes could aggravate atrial fibrosis and decrease myocardial contractility, which further leads to atrial structural remodeling. Ma et al. (3) found that ghrelin might act on the growth hormone secretagogue receptor (GHS-R) to suppress the apoptosis of myocytes after reperfusion following acute myocardial infarction. Hence, ghrelin might play a protective role for myocardial cells. Ghrelin also prevented ischemia–reperfusion injury and enhanced myocardial contractility, which are beneficial for maintaining the robustness and contractility of normal myocardia (4). Second, atrial electrical remodeling is the basis of AF and its persistence (5). Ghrelin might act on GHS-R to maintain the electrophysiological stability of myocardial cells after reperfusion (6). When injected into mice with ischemia–reperfusion injury, ghrelin could sustain the action potential through the

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functioning of calcium and sodium channels. As changes occur in the ion channel during atrial electrical remodeling, studies have further shown that a decreased ghrelin level might cause changes in atrial ion channels, which in turn might increase the possibility of repolarization and promote the onset of AF. Third, inflammation plays an important role in myocardial fibrosis, and the hypoxic and ischemic conditions caused by AF would further intensify inflammatory responses. It has been shown that ghrelin has strong anti-inflammatory effects and can inhibit the expression of interleukin-1β, interleukin-6, and tumor necrosis factor-α (TNF-α) (7). Another study demonstrated that ghrelin could inhibit the growth of chemotactic cytokines and the adhesion of monocytes, as well as inhibit TNF-α-induced activity of NF-KB (8). Therefore, we consider ghrelin to be a possible anti-inflammatory compound. Fourth, oxidative stress also plays a role in the development of AF. Ghrelin can inhibit oxidative stress (9). Suematsu et al. (10) showed that the levels of activated serum ghrelin and oxidative stress responses in obese patients were inversely proportional and that a reduced activated ghrelin level could increase oxidative stress.

The present study also found that the serum ghrelin levels in patients with persistent AF were lower than those in patients with paroxysmal AF and the differences were statistically significant. These results suggest a possible correlation between serum ghrelin levels and the onset of AF; however, the underlying mechanism is unclear and requires further confirmation.

The results of this study are consistent with those of previous studies, in which LAD in patients with AF was higher than that in patients without AF, whereas LVEF in patients with AF was significantly lower than that in patients with SA. These results further suggest the need to treat AF. In addition, it has been found that serum ghrelin levels in patients with chronic heart failure were significantly lower than those in the control group, and ghrelin levels varied in patients with different degrees of chronic heart failure. Similar to a positive correlation between the serum ghrelin level and LVEF (11), this study also showed a positive correlation between serum ghrelin level and LVEF in patients with AF. The present study also found that the ghrelin levels in patients with AF after treatment with medication were significantly higher than those in patients with AF before treatment and the cardiac function significantly improved after treatment. It appears that the serum ghrelin level changes according to the changes in the cardiac function. Therefore, regular testing of the serum ghrelin level in patients with AF will help to determine the progression of AF, which is of great significance for evaluating its clinical treatment.

Study limitations

The research only involved 182 patients, which is a limited number of patients in the research. We only limited to investigate the expression of ghrelin in patients with AF, but not the study of the correlative mechanism.

Conclusion

The serum ghrelin level in patients with AF was reduced and significantly increased after treatment. There was a positive correlation between the serum ghrelin level and LVEF in the patients in the AF group.

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References

1. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation 2014; 129: 837-47.
2. Chen YQ, Wang L, Su X, Tao L, Chen XF. Calpain-I, calpastatin, caspase-3 and apoptosis in the human left atrium in rheumatic atrial fibrillation. Zhonghua Xin Xue Guan Bing Za Zhi 2006; 34: 303-7.
3. Ma Y, Zhang L, Launikonis BS, Chen C. Growth hormone secretagogues preserve the electrophysiological properties of mouse cardiomyocytes isolated from in vitro ischemia/reperfusion heart. Endocrinology 2012; 153: 5480-90.
4. Ma Y, Zhang L, Edwards JN, Launikonis BS, Chen C. Growth hormone secretagogues protect mouse cardiomyocytes from in vitro ischemia/reperfusion injury through regulation of intracellular calcium. PLoS One 2012; 7: e35265.
5. Xu Y, Sharma D, Li G, Liu Y. Atrial remodeling: new pathophysiological mechanism of atrial fibrillation. Med Hypotheses 2013; 80: 53-6.
6. Iwamoto T, Terai S, Mizunaga Y, Yamamoto N, Omori K, Uchida K, et al. Splenectomy enhances the anti-fibrotic effect of bone marrow cell infusion and improves liver function in cirrhotic mice and patients. J Gastroenterol 2012; 47: 300-12.
7. Dixit VD, Schaffer EM, Pyle RS, Collins GD, Sakthivel SK, Palaniappan R, et al. Ghrelin inhibits leptin- and activation-induced proinflammatory cytokine expression by human monocytes and T cells. J Clin Invest 2004; 114: 57-66.
8. Li WG, Gavrila D, Liu X, Wang L, Gunnlaugsson S, Stoll LL, et al. Ghrelin inhibits proinflammatory responses and nuclear factor-kappaB activation in human endothelial cells. Circulation 2004; 109: 2221-6.
9. Sharma V, McNeill JH. The emerging roles of leptin and ghrelin in cardiovascular physiology and pathophysiology. Curr Vasc Pharmacol 2005; 3: 169-80.
10. Suematsu M, Katsuki A, Sumida Y, Gabazza EC, Murashima S, Matsumoto K, et al. Decreased circulating levels of active ghrelin are associated with increased oxidative stress in obese subjects. Eur J Endocrinol 2005; 153: 403-7.
11. Chen Y, Ji XW, Zhang AY, Lv JC, Zhang JG, Zhao CH. Prognostic value of plasma ghrelin in predicting the outcome of patients with chronic heart failure. Arch Med Res 2014; 45: 263-9.