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Original article

Increased serum high mobility group box 1 protein in patients with atrial fibrillation

Xiaorong Hu , Wenjie Zhou , Qijun Bai , Jichun Wang , Xinhong Yang , Changwu Xu , Zhibing Lu , Hao Xia , Hong Jiang *

Department of Cardiology, Renmin Hospital of Wuhan University, Cardiovascular Research Institute of Wuhan University, 238 Jiefang Road, Wuchang, Wuhan, 430060, PR China

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ABSTRACT

Background: Inflammatory process has been associated with development and recurrence of atrial fibrillation (AF). High mobility group box 1 protein (HMGB1) has been proved to be as a novel pro-inflammatory cytokine in cardiovascular diseases. This study investigated whether the serum HMGB1 level was increased in AF patients.
Methods: A total of 88 consecutive AF patients were enrolled in this study. Thirty age- and sex-matched healthy people were considered as control group. Serum HMGB1 concentration in AF patients and healthy people was measured by ELISA.
Results: HMGB1 level in persistent AF group (8.62 ± 2.18 ng/ml) was higher than that in control group (2.22 ± 0.63 ng/ml) and paroxysmal AF group (5.29 ± 1.43 ng/ml) (both $P < 0.05$). HMGB1 level in paroxysmal AF group was higher than that in control group ($P < 0.05$). There was significantly positive correlation between HMGB1 and hs-CRP in AF patients ($n = 88$, $r = 0.629$, $P < 0.05$).
Conclusion: The present study showed that serum HMGB1 level was markedly increased in paroxysmal and persistent AF patients.

1. Introduction

AF is the most common sustained cardiac rhythm disturbance in clinical practice, increasing in prevalence with age. The estimated prevalence of AF is 0.4 to 1% in the general population, increasing with age to 8% in those older than 80 years [1,2]. In prospective studies, the incidence of AF increases from less than 0.1% per year in people younger than 40 years to over 1.5% per year among women and 2% among men older than 80 years [3]. Despite the extensive studies, the pathophysiological mechanisms underlying the genesis of AF remain unclear. More recently, the bulk of evidence suggests that inflammatory process is associated with development and recurrence of AF [4]. Many studies showed that several pro-inflammatory cytokines, such as hs-CRP, CRP or interleukin-6 (IL-6) were significantly increased in patients with AF and may be associated with greater risk of AF recurrence after electrical cardioversion and catheter ablation [4–6]. These results suggest that pro-inflammatory cytokines may play an important role in development and recurrence of AF and be a possible pathogenic link to AF.

HMGB1, a nonchromosomal nuclear protein, could regulate gene transcription and maintain the nucleosome structure [7]. In 1999, Wang et al. [8] first demonstrated that HMGB1 functioned as a delayed mediator in inflammatory responses in sepsis and showed that the inhibition of HMGB1 confers significant protection against the lethal effects of endotoxin, indicating that the extracellular HMGB1 plays a important role in the pathogenesis of sepsis. Recent studies revealed that HMGB1 also functioned as a novel pro-inflammatory cytokine in cardiovascular diseases [9,10]. In addition, Salman et al. [11] showed that the incidence of paroxysmal AF is high in critically ill patients with sepsis (HMGB1 play the critical role in the pathogenesis of sepsis [8]), suggesting that HMGB1 may contribute to the genesis of paroxysmal AF in sepsis patients. However, whether serum HMGB1 was increased in AF patients remain unknown. In the study, we aimed to investigate whether the serum HMGB1 level was increased in patients with AF.

2. Materials and methods

2.1. Study subjects

This clinical protocol was approved by the institutional medical Ethics Committee and conducted according to the ethical

Abbreviations: AF, atrial fibrillation; hs-CRP, high-sensitive C-reactive protein; HMGB1, high mobility group box 1 protein; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; BMI, body mass index; WBC, white blood count; ROS, reactive oxygen species.

* Corresponding author. Tel.: +86 027 88041911; fax: +86 027 88040334.
E-mail address: jianghwurm@163.com (H. Jiang).

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guidelines outlined in the Declaration of Helsinki. A total of 88 consecutive AF patients were enrolled from Renmin Hospital of Wuhan University, P.R. China. Another 30 age- and sex-matched healthy people who agreed to participate in this study were considered as control group. Detailed medical history, physical examination, routine biochemical testing, 12-lead electrocardiograms were performed both in AF patients and control group. Valvular functions, left ventricular size (LVEDD) and functions (ejection fraction, EF), and LAD were evaluated by transthorasic echocardiography. The diameter of the left atrium was measured in parasternal long axis view. AF duration was determined by the patient's description of a well-defined and abrupt onset palpitation with subsequent electrocardiograms evidence of AF at the time of presentation. Exclusion criteria were as follows: coronary artery disease, valvular heart disease, LVEF less than 45%, other types arrhythmias, surgery or stroke within 6 months, a history of infection, chronic inflammatory, hepatic or malign disease, chronic renal failure, autoimmune diseases, abnormal thyroid function, imbalance of electrolytes, use of anti-inflammatory drugs such as corticoids, nonsteroidal anti-inflammatory drugs excluding aspirin.

2.2. AF classification

AF lasting less than or equal to 7 days is defined as new onset. After two or more episodes, AF is considered recurrent. If the arrhythmia terminates spontaneously, recurrent AF is designated paroxysmal; when sustained beyond 7 days, it is termed persistent which may include permanent AF. First-detected AF may be either paroxysmal or persistent. Lone AF was defined as AF occurring in the absence of structural heart disease and hypertension [12].

2.3. Sample collection and biochemical investigation

Peripheral venous blood was drawn from the antecubital vein after a 12 h fasting period between 7:00 and 8:00 AM in the morning. Serum samples were aliquoted and stored at −70 °C until being used. All samples were thawed only once. Serum hs-CRP was measured with standard laboratory techniques on a Hitachi 912 Analyzer (Roche Diagnostics, Germany). Serum HMGB1 level was determined with a commercially available ELISA kit (HMGB1 ELISA kit II; Shino-Test Corporation, Tokyo, Japan) according to its protocol.

2.4. Statistical analysis

Statistical analysis was performed with the SPSS 16.0 s (SPSS Inc., Chicago, IL, USA). Data was presented as mean ± SD or the percentage of incidence. Chi^2 test or Fisher's exact test was used to compare proportions. One-way ANOVA or Welch was used for comparisons among groups and the Student-Neuman-Keuls or Dunnett T3 was used for post-hoc multiple comparisons. Pearson correlation coefficient was used to assess the relationship between serum HMGB1 concentrations and other parameters. Statistical significance was defined as $P < 0.05$.

3. Results

3.1. Clinical characteristics of patients

As shown in Table 1, there were no significant differences in percentages of sex, smoking, drinking, hyperlipemia, hypertension, diabetes and mediations (except digoxin which may be used it for controlling ventricular rate), age, BMI, LVEDD, EF and WBC among three groups. However, significant differences in HMGB1 and hs-CRP were found (both $P < 0.05$). HMGB1 level in persistent AF group (8.62 ± 2.18 ng/ml) was higher than that in control group (2.22 ± 0.63 ng/ml) and paroxysmal AF group (5.29 ± 1.43 ng/ml) (both $P < 0.05$). HMGB1 level in paroxysmal AF group was higher than that in control group ($P < 0.05$). Hs-CRP level in persistent AF group (4.20 ± 1.04 mg/ml) was higher than that in control group (0.98 ± 0.32 mg/ml) and paroxysmal AF group (2.11 ± 0.94 mg/ml) (both $P < 0.05$). Hs-CRP level in paroxysmal AF group was higher than that in control group ($P < 0.05$). The LAD and AF duration in persistent AF group were larger or longer than those in control group and paroxysmal AF group (both $P < 0.05$). The AF duration in paroxysmal AF group was longer than that in control group ($P < 0.05$). The LAD in paroxysmal AF group was larger than that in control group, but no statistical significance was found ($P > 0.05$).

Table 1
Characteristics of AF patients and controls.

Controls ($n = 30$)	Paroxysmal AF ($n = 55$)	Persistent AF ($n = 33$)	
Male (%)	50	51.0	51.5
Smoking (%)	33.3	38.2	39.4
Drinking (%)	26.7	23.6	27.3
Hyperlipemia (%)	16.7	16.4	18.2
Hypertension (%)	13.3	29.1	27.3
Diabetes (%)	6.7	7.3	9.1
Mediations (%)			
Aspirin	3.3	12.7	15.2
Digoxin	0	12.7#	18.2#
β-blocker	6.7	9.1	12.1
Calcium blocker	10.0	12.7	12.1
ACEI	6.7	7.3	6.1
Propafenone	0	7.3	9.1
Aminodarone	0	10.9	12.1
Statins	13.3	16.4	15.2
Age (year)	55.6 ± 8.5	57.5 ± 9.6	59.8 ± 11.2
BMI (kg/m^2)	23.7 ± 3.2	24.8 ± 3.9	25.1 ± 4.2
LAD (mm)	31.8 ± 3.9	35.8 ± 4.6	41.8 ± 5.3#*
LVEDD (mm)	46.9 ± 3.6	47.8 ± 4.0	49.2 ± 4.8
LVEF (%)	64.3 ± 4.1	60.5 ± 6.0	59.7 ± 9.3
AF duration (day)	0	163 ± 179#	347 ± 396#*
hs-CRP (mg/L)	0.98 ± 0.32	2.11 ± 0.94#	4.20 ± 1.04#*
WBC (×10^9)	6.08 ± 1.42	7.14 ± 1.93	7.06 ± 2.05
HMGB1 (ng/ml)	2.22 ± 0.63	5.29 ± 1.43#	8.62 ± 2.18#*

Data were presented as mean ± SD or the percentage of incidence. AF: atrial fibrillation; ACEI: angiotensin converting enzyme inhibitor; BMI: body mass index; LAD: left atrial diameter; LVEDD: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction; hs-CRP: high-sensitivity C-reactive protein; WBC: white blood count; HMGB1: high mobility group box 1 protein. #$P < 0.05$, compared to the controls; *$P < 0.05$, compared to paroxysmal AF.

3.2. Association of HMGB1 levels of cardiovascular risk factors

As shown in Table 2, there was significant correlation between HMGB1 and hs-CRP in AF patients ($n = 88$, $r = 0.629$, $P < 0.05$). There

Table 2
Pearson corrections of HMGB1 level with cardiovascular risk factors.

Variable	r	P
Age	0.298	< 0.05
BMI	0.223	> 0.05
LAD	0.352	< 0.05
LVEDD	-0.105	> 0.05
LVEF	0.092	> 0.05
AF duration	0.231	> 0.05
hs-CRP	0.629	< 0.05
WBC	0.102	> 0.05

AF: atrial fibrillation; BMI: body mass index; LAD: left atrial diameter; LVEDD: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction; hs-CRP: high-sensitivity C-reactive protein; WBC: white blood count; HMGB1: high mobility group box 1 protein