RESEARCH ARTICLE

Serum macrophage migration inhibitory factor is correlated with atrial fibrillation

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Objective: Macrophage migration inhibitory factor (MIF) is a proinflammatory cytokine secreted by macrophages. This study is performed to investigate whether serum MIF is correlated with atrial fibrillation (AF).

Methods: Totally, 186 AF patients and 103 healthy controls were enrolled in this study. AF patients were then divided into paroxysmal AF, persistent AF, and permanent AF subgroups.

Results: There were higher serum MIF concentrations in AF patients than in healthy subjects. Logistic regression analysis demonstrated that serum MIF was associated with AF. Permanent AF patients exhibited higher serum MIF concentrations than persistent and paroxysmal AF subgroups. Elevated serum MIF concentrations were found in persistent AF patients compared with paroxysmal AF patients. Moreover, serum MIF concentrations were associated with left atrial diameter after Spearman correlation analysis.

KEYWORDS

atrial fibrillation, inflammation, left atrial diameter, macrophage migration inhibitory factor

1 | INTRODUCTION

Atrial fibrillation (AF), a common cardiac arrhythmia, has a prevalence of 1%-2% in the population.¹ AF patients show an increased risk of mortality, stroke, and cardiac failure.² AF brings a huge public health fee to the whole world. The exact mechanism underlying AF is complex and unclear. Recently, atrial inflammation is thought to account for the most of these physiopathological changes.³

Macrophage migration inhibitory factor (MIF) is a soluble factor initially identified in activated T lymphocytes. MIF is released by macrophages including T lymphocytes by the stimulation of lipopolysaccharide, tumor necrosis factor- α (TNF- α), and interferon- γ (IFN- γ).⁴ In addition, MIF induces the production of a proinflammatory cytokines including TNF- α , IFN- γ , interleukin (IL)-1 β , and IL-6.⁵ Serum MIF were shown to be correlated with some diseases associated with inflammatory mechanism including rheumatoid arthritis,⁶ diabetes,⁷ and coronary artery disease (CAD).⁸ Inflammation is also involved in AF pathogenesis. Therefore, serum MIF is hypothesized to be correlated with AF development.

This study is performed to investigate whether serum MIF is correlated with AF.

2 | MATERIALS AND METHODS

2.1 | Subjects

This cross-sectional study enrolled 186 patients with AF and 103 healthy subjects. AF patients were diagnosed according to the guidelines established by the European Society of Cardiology in 2010.⁹ We excluded the patients with cardiomyopathy, congenital heart disease, valvular heart diseases, and hyperthyroidism from this study. AF patients were then divided into three subgroups: paroxysmal AF (n=66), persistent AF (n=68), and permanent AF (n=52). The definition of paroxysmal AF was AF episodes lasting <7 days and which terminated spontaneously. AF episodes lasting more than 7 days and/or requiring termination with pharmacologic or direct current cardioversion were defined as persistent AF. Permanent AF was defined as AF lasting more than 6 months in duration and more than one attempt of unsuccessful cardioversion to restore normal sinus rhythm.⁹ One hundred and three healthy subjects who underwent routine medical check-ups in our hospital were enrolled in as the controls. The study plan was approved by the Research Ethics Committee of our hospital, and all patients provided informed consent.

	The controls	AF patients	P value
N	103	186	
Age (yr)	59.54±10.73	61.14±10.08	.209
Gender (M/F)	61/42	114/72	.731
BMI (Kg/m ²)	24.15±2.36	23.89±2.96	.446
SBP (mmHg)	123.79±13.49	138.47±14.98	<.001
DBP (mmHg)	81.83±8.30	86.10±11.17	.001
TG (mmol/L)	1.07±0.50	1.65±0.94	<.001
TC (mmol/L)	4.94±0.94	5.08±1.05	.204
HDL-C (mmol/L)	1.33±0.17	1.18±0.20	<.001
LDL-C (mmol/L)	3.19±0.43	3.27±0.75	.334
LAD (mm)	29.54±3.10	38.23±3.98	<.001
MIF (ng/mL)	6.26 (5.05-7.00)	15.37 (12.35-18.71)	<.001

TABLE 1 Clinical and biochemical characteristics of the case and control groups

2.2 | Measurements

Fasting venous blood was collected for further study. Serum MIF concentrations were assessed by an enzyme-linked immunosorbent assay kit (R&D Systems, Minneapolis, MN, USA) [sensitivity: 0.068 ng/mL; assay range: 0.2-10 ng/mL; coefficient of variations (CVs) of intra-assay: 4.5%-6%; CVs of inter assay: 8.4%-9.4%].

2.3 | Statistical analysis

We used Power and sample size calculators to determine the sample size by a level of α of 0.05 and power of 90%. A minimum sample of seven subjects in the AF and control groups are needed. Data normal distribution was analyzed using the Kolmogorov-Smirnov test. The data differences between case and control groups were analyzed by unpaired *t* test, Chi-square tests, or Mann-Whitney *U* test. Chi-square tests, one-way ANOVA, or Kruskal-Wallis test were used to compare the data differences between AF subgroups. Logistic regression model was performed to determine the risk factors for AF. The correlation of serum MIF concentrations with left atrial diameter (LAD) was analyzed by Spearman correlation analysis. *P* value <.05 was statistically significant.

3 | RESULTS

3.1 | Baseline clinical characteristics

AF patients showed higher systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides, and LAD, as well as lower high-density lipoprotein cholesterol (HDL-C) compared with the controls (Table 1).

3.2 | Serum MIF concentrations in AF patients

There were relatively higher serum MIF concentrations in the case group than in the control group (*P*<.001) (Table 1). Both simple and multivariate logistic regression analysis indicated the correlation of

serum MIF concentrations with AF development (Table 2). Permanent AF patients had higher serum MIF concentrations than in paroxysmal and persistent AF groups (Table 3). Furthermore, significant higher serum MIF concentrations were observed in persistent AF patients compared with paroxysmal AF subjects (Table 3).

3.3 | Serum MIF concentrations with atrial remodeling

Serum MIF concentrations were found to be positively correlated with LAD ($r=.315$, *P*<.001) (Figure 1).

4 | DISCUSSION

Obesity is a risk factor for AF. Obesity and structural heart disease independently predicted AF recurrence in a 5-year follow-up study.¹⁰ Bariatric surgery group showed a lowered risk of developing AF by 29% compared with the control group.¹¹ Weight loss by bariatric surgery decreased the risk of AF among severe obesity subjects.¹¹ Wong et al.¹² reported that abdominal and overall adiposity, as well as epicardial fat were associated with AF development. MIF regulated the differentiation of 3T3-L1 preadipocytes. Knockdown of MIF expression inhibited the adipogenesis in 3T3-L1 cells.¹³ Promoter polymorphisms of MIF gene were shown to be associated with obesity.¹⁴ Circulating MIF concentrations were higher in overweight adolescents compared with the controls.¹⁵ In addition, Median plasma MIF concentrations in severely obese subjects were significantly lowered after weight loss.¹⁶ It is suggested that MIF plays a role in AF development through the crossroad between obesity.

Inflammation is a clear mechanism of AF development. High-sensitivity C-reactive protein (CRP) was associated with the development of AF in patients presenting with ST elevation myocardial infarction.¹⁷ Treatment with soluble epoxide hydrolase inhibitor significantly reduced atrial Fibrosis, Atrial Fibroblast Activation, and atrial electric remodeling by inhibiting the activation of key inflammatory signaling molecules.¹⁸ MIF was produced by macrophages after the inflammatory stimulation.⁴ MIF was involved in the mechanism of

TABLE 2 Logistic regression Analysis for the presence of AF

	Simple regression		Multiple regression	
	OR (95%CI)	P	OR (95%CI)	P
Age (yr)	1.015 (0.992-1.040)	.209		
Gender (M/F)	0.917 (0.561-1.499)	.731		
BMI (Kg/m ²)	0.967 (0.887-1.054)	.444		
SBP (mmHg)	1.078 (1.055-1.102)	<.001	1.102 (1.032-1.177)	.004
DBP (mmHg)	1.044 (1.018-1.072)	.001	0.904 (0.805-1.015)	.088
TG (mmol/L)	3.352 (2.095-5.364)	<.001	2.077 (0.879-4.906)	.096
TC (mmol/L)	1.171 (0.918-1.494)	.204		
HDL-C (mmol/L)	0.017 (0.004-0.070)	<.001	0.037 (0.002-0.704)	.028
LDL-C (mmol/L)	1.200 (0.829-1.738)	.333		
MIF (ng/mL)	3.662 (2.495-5.375)	<.001	3.523 (2.319-5.351)	<.001

TABLE 3 Clinical and biochemical characteristics of AF subgroups

	Paroxysmal AF	Persistent AF	Permanent AF	P value
N	66	68	52	
Age (yr)	61.67±10.24	60.24±9.80	61.65±10.35	.652
Gender (M/F)	39/27	40/28	35/17	.576
BMI (Kg/m ²)	24.12±3.24	23.76±2.74	23.76±3.04	.737
SBP (mmHg)	133.86±15.06	140.01±14.56 ^a	142.31±14.19 ^a	.005
DBP (mmHg)	83.18±10.80	85.88±10.26	90.10±11.78 ^{ab}	.003
TG (mmol/L)	1.56±0.91	1.65±0.92	1.75±1.02	.559
TC (mmol/L)	5.12±1.11	5.10±1.13	5.07±0.87	.976
HDL-C (mmol/L)	1.17±0.21	1.16±0.19	1.21±0.21	.337
LDL-C (mmol/L)	3.23±0.78	3.33±0.79	3.25±0.66	.728
LAD (mm)	35.74±4.08	38.50±2.79 ^a	41.04±3.19 ^{ab}	<.001
MIF (ng/mL)	11.10 (8.87-14.19)	14.02 (11.28-17.07) ^a	19.84 (16.90-23.44) ^{ab}	<.001

^aP<.05 vs paroxysmal AF patients; ^bP<.05 vs persistent AF patients.

FIGURE 1 The correlation of serum MIF concentrations with LAD

cardiovascular disease. Diabetic apoE^{-/-} mice had significantly aggravated atherosclerotic lesions. MIF gene silencing inhibited atherosclerotic lesions and stabilized atheromatous plaque, decreased

macrophages and lipids deposition, depressed inflammatory cytokines production in apolipoprotein E-deficient mice.¹⁹ MIF expressed was found in atherosclerotic lesions. In addition, MIF expression was up-regulated during the progression of atherosclerosis in cultured human umbilical vascular endothelial cells.²⁰ Patients with acute coronary syndromes showed higher plasma MIF concentrations compared with patients with stable CAD and control subjects. Increased MIF concentrations were associated with CRP and IL-6 concentrations.²¹ Therefore, MIF is supposed to induce AF development by the upregulation of the production of inflammatory factors.

The present study indicated that serum MIF concentrations are elevated in AF patients. This suggests the possible role of MIF in AF pathogenesis. MIF played a role in the electrical remodeling of AF by decreasing L-type Ca²⁺ currents through the impairment of channel function and the activation of c-Src kinases in atrial myocytes.²² H₂O₂ induced increased MIF protein and gene levels in a dose-dependent manner in atrium myocytes, which indicates the possible mechanism of MIF in AF development.²³ In addition, our results demonstrated that serum MIF concentrations were correlated with LAD which is a parameter for atrial remodeling. This indicates that MIF is involved in the

mechanism of AF. Serum MIF concentrations may be utilized to assess the risk of AF development and atrial remodeling.

This study has several potential limitations. First, this is a cross-sectional study. The results may be confirmed by future longitudinal studies. Second, the sample is relatively small. We may perform this design again in a larger population.

In conclusion, serum MIF concentrations are correlated with the development of AF.

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