# CLINICAL ANALYSIS OF ASSOCIATION OF CYSTATIN C AND ATRIAL FIBRILLATION

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Some studies have disclosed atrial fibrillation (AF) is associated with inflammation. Cystatin C is not only inflammatory markers but also an independent predictor of cardiovascular events.

**Aim.** We sought to investigate the relationship between serum levels of cystatin C and the occurrence and development of AF.

**Material and methods.** 134 paroxysmal and persistent AF (AF1 group) and 121 permanent AF (AF2 group) patients in AF group and 154 healthy people in control group were prospectively measured for cystatin C, other inflammatory markers, biochemical indicators, left atrial diameter (LAD), left ventricular diameter (LVD) and left ventricular ejection fraction (LVEF).

**Results.** (1) Compared with control and AF1 groups, AF2 group had higher values of cystatin C, high sensitivity C reactive protein (hsCRP), LAD and LVD whereas lower values of LVEF (P<0.05). (2) After adjust for age, gender and body mass index (BMI), correlation analysis showed that serum level of cystatin C was closely related to hsCRP, LAD, systolic blood pressure (SBP) and creatinine, the correlation coefficient were respectively 0.658, 0.502, 0.475 and 0.530 (P<0.01), but negatively associated with LVEF (P=0.011) in AF group. (3) Multivariate regression analysis showed the hsCRP, cystatin C, LAD and LVEF entered finally into the regression equation (cystatin C, OR: 3.41, 95%CI: 1.09–11.08, P=0.009).

**Conclusion.** The serum levels of cystatin C has significant correlation with AF, which indicates cystatin C may play an important role in the process of AF development.

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**Key words**: cystatin C, atrial fibrillation, inflammation, inflammatory markers.

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AF — Atrial fibrillation, BUN — Blood urea nitrogen, BMI — Body mass index, ECG — Electrocardiogram, EDTA — Ethylenediamine tetraacetic acid, FBG — Fasting blood glucose, GFR — Glomerular filtration rate, hsCRP — High sensitivity C reactive protein, HDL–C — High-density lipoprotein cholesterol, LAD — Left atrial diameter, LVD — Left ventricular diameter, LVEF — Left ventricular ejection fraction, LDL–C — Low-density lipoprotein cholesterol, Cr — Serum creatinine, SBP — Systolic blood pressure, DBP — Diastolic blood pressure, TC — Total cholesterol, TG — Triglycerides, WBC — White blood (cell) count.

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# КЛИНИЧЕСКИЙ АНАЛИЗ АССОЦИАЦИИ ЦИСТАТИНА С И ФИБРИЛЛЯЦИИ ПРЕДСЕРДИЙ

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В некоторых исследованиях было выявлено, что фибрилляция предсердий (ФП) связана с воспалением. Цистатин С является не только воспалительным маркером, но и независимым предиктором сердечно-сосудистых событий.

**Цель.** Мы попытались выяснить отношения между уровнем цистатина С в сыворотке крови и возникновением и развитием ФП.

**Материал и методы.** 134 пациента с пароксизмальной и персистирующей ФП (ФП1 группа), 121 пациент с постоянной ФП (ФП2 группа) и 154 здоровых людей в контрольной группе были под наблюдением для измерения цистатина С, других воспалительных маркеров, биохимических показателей, диаметра левого предсердия (LAD), диаметра левого желудочка (LVD) и фракции выброса левого желудочка (ФВ ЛЖ).

**Результаты.** (1) В сравнении с группой контроля, группы ФП1 и ФП2 имели более высокие значения уровня цистатина С, высокую чувствительность С реактивного белка (hsCRP), LAD и LVDб в тоже время — низкие значения ФВ ЛЖ (P<0,05). (2) После ранжирования по возрасту, полу и индексу массы тела (ИМТ), корреляционный анализ показал, что сывороточный уровень цистатина С тесно связан с hsCRP LAD, систолическим артериальным давлением (САД) и креатинином, коэффициенты корреляции были, соответственно, 0.658, 0.502, 0.475 и 0.530 (P<0.01), но отрицательно ассоциированы с ФВ ЛЖ (P=0,011) в группе с ФП. (3) Многофакторный регрессионный анализ показал, что hsCRP, цистатин С, LAD и ФВ ЛЖ в конечном счете входят в уравнение регрессии (цистатин С, OR: 3.41, 95%CI: 1.09–11.08, P=0.009).

**Заключение.** Уровень цистатина С в сыворотке крови имеет значимые корреляции с ФП, которая указывает на то, что цистатин С, может играть важную роль в процессе развития ФП.

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**Ключевые слова:** цистатина С, фибрилляция предсердий, воспаление, маркеров воспаления.

## Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and increases in prevalence with aging [1–3]. It has become one of the leading causes for hospitalized patients with AF because AF may induce stroke, heart failure and increases case fatality [1, 2, 4]. Unfortunately, its fundamental pathological mechanisms are not fully clear. Recent evidence is accumulating that AF may be closely interrelated with inflammation and inflammatory biomarkers [2, 4–6]. Some studies confirmed that diverse inflammatory factors participate in pathogenesis and development of AF [6–8].

Cysteine protease inhibitors-C (cystatin C) is a member of protease inhibitor superfamily. cystatin C is not only a relatively more sensitive indicator of evaluating renal function than creatinine but also an independent and strong predictor of cardiovascular events [7, 9]. Recently studies find cystatin C is closely related to the inflammatory process or other inflammation factors [7, 10]. However, it remains challenged whether or not there is correlation between cystatin C and AF. In this study, the correlation between cystatin C and AF was investigated and its possible pathogenesis was preliminarily discussed and elucidated.

## Materials and methods

*Subjects.* A total of 255 consecutively hospitalized patients with AF (assigned to group AF) were prospec-

tively recruited between June 2008 and December 2010 from the Second Hospital of Shandong University and Qilu Hospital of Shandong University, which included 134 cases of paroxysmal and persistent AF (placed to group AF1), 66 males and 68 females with mean age of 67.58±12.4 years old. There were 121 cases of permanent AF (put to group AF2), 58 males and 63 females, averaged (68.09±11.7) years old. All cases of AF diagnosed were verified by medical history, physical examination, electrocardiogram (ECG) or dynamic electrocardiogram. The control group had 154 cases of adults after health examination in the Second Hospital of Shandong University, selected from outpatients without diseases or with minor illnesses from cardiac or other departments following the same exclusion criteria. Of which, there were 71 male cases, 83 female cases with a mean age of 64.43±11.2 years old. ECG showed sinus rhythm in control group. There were not statistically significant differences (P>0.05) but comparability in comparison with age, sex and etiological composition among the three groups.

AF was defined and classified according to the management of atrial fibrillation of the European Society of Cardiology (ESC, 2010 edition) [11]. Paroxysmal AF is self-terminating usually within 48 hours, and may continue for up to 7 days. Persistent AF is present when an AF episode either lasts longer than 7 days or requires termination by cardioversion, either with drugs or by direct current cardioversion. Permanent AF is said to exist when the presence of the arrhythmia is accepted by the patient (and physician). Patients with any of the following conditions were excluded from the study: infectious diseases, malignant tumors; hyperthyroidism; hypokalemia, hypomagnesemia, hypocalcemia and acidosis; pneumonia and pulmonary embolism; moderate and severe anaemia; intracranial hemorrhage; liver and renal abnormal function and other organs dysfunction; immune system and endocrine metabolic diseases; pregnant women and breastfeeding women; taking some medicines such as statins and angiotensin-converting enzyme-inhibitors and/or angiotensin II receptor blockers. This research was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki". The study protocol and written informed consent were approved by the Ethics Committee of Clinical Research, the Secondary Hospital of Shandong University.

*Methods.* Peripheral vein blood were obtained from all participants early in the day after a 12 h fast, immediately transferred into a glass tube containing disodium EDTA, and centrifuged for 10 min at 3000 round/min, separated in aliquots and then stored at −80 °C. Cystatin C and hsCRP were respectively measured by means of a particle-enhanced turbidimetric immunoassay with commercial kits (Serum cystatin C, Beijing Leadman Biochemistry Co., Ltd. Beijing, China; hsCRP, Diagnostic System Laboratory Inc, Webster, TX, USA). Its normal reference value is 0−3mg/L.

Fasting blood glucose (FBG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL−C), high-density lipoprotein cholesterol (HDL−C), triglycerides (TG), blood urea nitrogen (BUN) and serum creatinine (Cr) were measured in automatic biochemical analyzer (Hitachi 7600, Tokyo, Japan) with enzymic method in all subjects. Blood routine was tested in a Sysmex XE-2100 hematology analyzer (Sysmex corporation, Kobe, Japan). Every participant received the test of a 12-lead MAC1200 electrocardiogram system (GE Healthcare, Milwaukee, WI, USA). Left atrium diameter (LAD), left ventricular diameter (LVD) and left vetricular ejection fraction (LVEF) were recorded using a Philips iE33 ultrasonocardiograph (Philips Medical Systems, Bothell, WA, USA).

*Statistical treatment.* Continuous variables were expressed as mean ± SD and categorical variables were presented as percentages. Continuous variables were compared using one-way ANOVA, and categorical variables were compared with chi-square test. The relationship between variables was evaluated by significance calculation of partial correlation analysis after adjusting classical risk factors (age, sex and body weight). The overall influence of selected risk factors on the AF was assessed using binary logistic regression. Predictors of AF were determined by the multivariate regression analysis. The association between variables and the occurrence of AF was represented by odds ratio (OR) and their accompanying 95% confidence interval (95% CI). SPSS 17.0 (SPSS Inc., Chicago, IL, USA) was used for all calculations. P<0.05 was considered significant.

## Results

**Comparison of baseline data between AF and control groups**

Baseline characteristics are shown in Table1. Compared with control group, AF1 and AF2 groups did not have statistical significance in age, gender, TG, TC and HDL (P>0.05), but had higher values of BM, SBP, FBG and Cr (P<0.05 or P<0.01). Values of BUN and LDL were significantly higher whereas those of DBP were significantly lower in AF2 group than in control group, while there were not significant differences in the values of BP, BUN and LDL between AF1 group and control group (P>0.05). Furthermore there were not statistical differences in baseline datum between AF1 group and AF2 group (all P>0.05).

**Comparison of inflammatory indicators between AF and control groups**

As shown in Table 2**,** white blood cell counts were showed no significant difference (P>0.05) whereas there were significant difference in the values of cystatin C and hsCRP among these groups (P<0.05 or P<0.01). Compared with control group, AF1 and AF2 groups had higher values of cystatin C and hsCRP (P<0.05 or P<0.01). Furthermore AF2 group had higher values of cystatin C and hsCRP than those in AF1 group (P<0.05 or P<0.01).

**Table 1**

**Comparison of baseline data between AF and control groups**

| Variables | control group | AF1 group | AF2 group |
|---|---|---|---|
| Age (year) | 64.44±11.20 | 66.08±12.45 | 65.37±11.83 |
| Male (n,%) | 71 (46.10) | 66 (49.25) | 60 (47.93) |
| BMI | 26.32±4.42 | 28.40±4.78* | 28.95±5.07* |
| SBP | 132.36±13.26 | 143.59±14.05* | 144.18±15.63* |
| DBP | 82.94±10.70 | 79.66±11.32 | 78.80±11.05* |
| FBG (mmol/l) | 5.88±1.24 | 6.28±2.20* | 6.35±2.48** |
| BUN (mmol/l) | 5.95±2.26 | 6.30±3.07 | 6.57±3.12** |
| Cr (umol/l) | 60.79±12.58 | 87.65±25.84* | 88.19±26.36** |
| TG (mol/l) | 1.18±0.53 | 1.20±0.46 | 1.24±0.60 |
| TC (mol/l) | 4.46±0.95 | 4.29±0.74 | 4.51±0.70 |
| HDL (mol/l) | 1.32±0.33 | 1.26±0.26 | 1.20±0.30 |
| LDL (mol/l) | 2.59±0.63 | 2.63±0.58 | 2.70±0.68* |

Compared with control group, * P<0.05, **P<0.01.

**Table 2**

**Comparison of inflammatory indicators between AF and control groups**

| Variables | control group | AF1 group | AF2 group |
|---|---|---|---|
| WBC (×109/L) | 5.89±1.88 | 6.07±1.91 | 6.12±2.03 |
| hsCRP (mg/l) | 1.28±1.09 | 2.76±1.18** | 3.90±1.25**## |
| cystatin C (mg/l) | 0.84±0.17 | 1.05±0.28* | 1.35±0.41**# |

Compared with control group, * P<0.05, **P<0.01; Compared with AF1 group, # P<0.05, ## P<0.01

**Comparison of echocardiogram parameters between AF and control groups**

As outlined in Table 3**,** Echocardiogram showed AF1 and AF2 groups had higher values of LAD and LVD but lower values of LVEF than those of control group (P<0.05 or P<0.01). Compared with AF1 group, AF2 group had higher values of LAD and LVD but lower values of LVEF (P<0.05 or P<0.01).

**Analysis for correlation between cystatin C and high risk factors of AF**

As demonstrated in Table 4**,** after adjusting age, gender and body weight, cystatin C was closely related to hsCRP, LAD, SBP and Cr, and their correlation coefficient respectively were 0.658, 0.502, 0.475 and 0.53 (P<0.05 or P <0.01) whereas cystatin C was inversely related to LVEF (P=0.01).

**Multivariate Analysis of AF risk factors**

As presented in Table 5, all selected variables from AF and control groups were analysed by stepwise regression analysis and the related indicators were picked out. Finally, hsCRP, cystatin C, LAD and LVEF by turns entered the regression equation, showed in Table 4, included respectively hsCRP (OR: 3.76; 95% CI: 1.18–13.90; P=0.015), cystatin C (OR: 3.41; 95% CI: 1.09–11.08; P=0.008), LAD (OR: 1.84; 95% CI: 0.91–5.75; P=0.037), SBP (OR: 1.78; 95% CI: 1.05–4.32; P=0.006) and LVEF (OR: 1.26; 95% CI: 0.85–3.09; P=0.043).

## Discussion

Cystatin C is a cysteine protease inhibitor having a molecular weight of 13kD, synthesized in all nucleated cells at a constant rate and present in an unglycosylated protein form, which extensively exists in animals and plants tissue and participate in proteolytic regulation between the interior and the exterior of the cell [7,12]. Due to its free filtration in the glomerulus, nearly complete reabsorption and catabolism in the proximal tubule, and lack of tubular secretion, serum cystatin C concentrations are closely related to the glomerular filtration rate (GFR) reflecting renal function [7, 9, 12]. So cystatin C is thought to be a specific, accurate and more sensitive marker than creatinine clearance rate.

In recent years, a large number of studies have confirmed that cystatin C is likely to be an independent risk factor of cardiovascular disease [7, 12]. The close relationship between cystatin C and cardiovascular disease is not only involved to kidney function but also is mediated by inflammatory mechanism [7, 13, 14]. The unique association of AF with renal dysfunction could be explained by the fact that AF and renal dysfunction share a number of risk factors [15]. Although mechanical stress on atrium due to volume overload could be the mediating factor that

**Table 3**

**Comparison of ultrasound parameters of left heart between AF and control groups**

| Variables | control group | AF1 group | AF2 group |
|---|---|---|---|
| left atrial diameter (LAD, mm) | 33.67±3.40 | 43.54±10.61** | 47.09±11.75**# |
| Left ventricular diameter (LVD, mm) | 49.49±7.33 | 52.63±11.29* | 54.14±11.38**# |
| LVEF | 54.82±8.46 | 50.07±10.50* | 47.31±12.13**# |

Compared with control group, * P<0.05, **P<0.01; Compared with AF1 group, # P<0.05, ## P<0.01

**Table 4**

**Analysis for correlation between cystatin C and AF high risk factors**

| | hsCRP | LAD | LVD | LVEF | SBP | FBG | Cr | BMI | LDL |
|---|---|---|---|---|---|---|---|---|---|
| r | 0.658 | 0.502 | 0.246 | -0.353 | 0.475 | 0.213 | 0.53 | 0.153 | 0.164 |
| P | 0.00 | 0.000 | 0.044 | 0.010 | 0.035 | 0.048 | 0.009 | 0.057 | 0.036 |

leads to development of AF in patients with renal dysfunction, this may not be the case in earlier phases. One possible mechanism for a higher prevalence of AF in early stages of renal insufficiency could be relevant to inflammation [15]. In this study, only cystatin C among indicators reflecting renal function in multivariate analysis had strong connection with AF. It is explained that cystatin C is more sensitive than other markers to reflect renal function. Some researchers also disclosed that cystatin C is a more reliable marker of renal function compared to creatinine or estimated GFR as it is less affected by age, gender, and ethnicity [9].

Many researchers have verified that cystatin C has a linear positive interrelation with a variety of inflammatory cytokines such as hsCRP and reflects the severity of inflammatory activity in a renal function-independent manner [12]. Cystatin C and its fragments may also affect the phagocytic and chemotactic functions of granulocytes and participate in the inflammatory process [9, 12]. In atrial tissue of the patients with atrial fibrillation, inflammation results in inflammatory cell infiltration, oxidative stress and damage. Then fibrous tissue repairs the local tissue damage. As a result, the pathological process leads to the atrial remodelling [6–8]. It is worth mentioning that Targoński et al. found the serum concentration of hsCRP is closely positive correlation with the diameter size of left atrium [16]. This study result was consistent with Targoński 's conclusion and showed the serum concentration of cystatin C also coincided with LAD.

This study confirmed that atrial fibrillation groups had higher values of cystatin C, hsCRP and LAD than those in control group. Furthermore, persistent atrial fibrillation group had significantly higher values of cystatin C, hsCRP and LAD than those in paroxysmal AF and control groups. At the same time, correlation analysis showed that cystatin C is closely related to hsCRP and LAD of patients with atrial fibrillation. Therefore it is speculated that the inflammatory cytokines such as cystatin C and hsCRP should modulate process of inflammatory, participate in the hypertrophic degeneration of atrial muscle fiber, and induce atrial structural abnormalities in patients with atrial fibrillation, thus lead to atrial electrical remodelling [6–8]. Inflammation is closely associated to atrial fibrillation [6] and may be the important medium (such as high blood pressure and obesity, etc.), which links with known risk factors for atrial fibrillation and results in the occurrence and development of atrial fibrillation [1, 3, 17]. Even the atrial pathoanatomy in lone atrial fibrillation showed inflammatory infiltration, muscle cell necrosis and fibrosis [1, 17]. Modern research confirmed that chronic inflammation has arrhythmogenic effect giving rise to the development of AF in susceptible populations. Inflammatory markers could be the result of atrial fibrillation rather than the cause of atrial fibrillation [18]. Conen et al. found the augment of hsCRP increased the risk of AF by 31% in the elderly [18]. In this study, monofactorial analysis showed

**Table 5**

**Multiple logistic regression analysis of predictive factors for AF**

| Variables | β | SE | OR | P | 95%CI |
|---|---|---|---|---|---|
| hsCRP | 0.73 | 2.90 | 3.76 | 0.015 | 1.18–13.90 |
| cystatin C | 0.60 | 2.35 | 3.41 | 0.009 | 1.09–11.08 |
| LAD | 0.34 | 1.12 | 1.84 | 0.037 | 0.91–5.75 |
| SBP | 0.58 | 0.91 | 1.78 | 0.006 | 1.05–4.32 |
| LVEF | 0.56 | 0.81 | 1.26 | 0.043 | 0.75–3.09 |

that the serum levels of hsCRP and cystatin C in 2 atrial fibrillation groups were higher than those in control group, and they were closely related to each other. Multifactor analysis showed that both cystatin C and hsCRP entered the regression equation and had higher OR values (3.41 and 3.76, respectively). It was demonstrated that atrial fibrillation is closely associated with inflammation regardless of the duration of atrial fibrillation. However, this study showed no significant relationship between white blood cell count and risk of incident atrial fibrillation, which differs from the result of the Framingham Heart Study [19].

Cystatin C is not only an independent risk marker of predicting cardiovascular risk but also is an independent risk factor of MetS [7]. As mentioned above, Cystatin C was not only related to inflammation but also was associated with the risk factors of atrial fibrillation, and these risk factors were properly the components of metabolic syndrome. Compared with no metabolic syndrome, the generating possibility of atrial fibrillation in patients of metabolic syndrome increased by 88% [3]. Atrial fibrillation and metabolic syndrome share common risk factors: obesity, hypertension, hyperglycemia and hyperlipidemia. The patients with higher level of cystatin C have higher metabolic state: higher BMI, blood pressure, blood sugar and lipid levels [12]. Researchers have shown that cystatin C is closely related to the metabolic syndrome [3, 7]. Insulin resistance is not only the pathogenesis of metabolic syndrome but also may be the pathological process that connects cystatin C with metabolic syndrome [7, 20]. Presumably, from another perspective, atrial filbrallation and the metabolic syndrome may have a common pathological relationship mediated by inflammtory biomakers such as cystatin C. This study confirmed that BMI, SBP, FBG and LDL in AF groups, especially in permanent atrial fibrillation group (AF2), were higher than those in the control group. Blood pressure is the most common risk factor of atrial fibrillation. Moreover SBP is the better predictor of atrial fibrillation than DBP [3]. This study also revealed that SBP closely correlated to cystatin C as showed in the univariate analyse. Linssen, et al. pointed out that AF facilitate the progression of HF in several ways. Due to rapid heart rates, an irregular ventricular rhythm, loss of atrioventricular synchrony, and an increase in mitral and tricuspid regurgitation, AF may further decrease cardiac

output and aggravate HF [21]. As shown in this study, LVEF was also independently aligned with AF. Some studies have validated that obesity is an independent risk factor for predicting atrial fibrillation [3]. But this study showed that BMI did not enter the regression equation in the multivariate analysis.

### Study limitations

There were several limitations in this study. Our sample size, although small, was sufficient to display differences between the control group and the AF group, however further studies with larger scale of cohorts are needed to confirmed these results. Additionally, some inflammatory indicators such as interleukin-6 and tumor necrosis factor -α were not applied in this study. Although these indicators maybe do not affect the conclusion of this study, which possibly made an impact on the estimate for action degree of hsCRP and cystatin C in this study. Furthermore, the relationship between cystatin C and atrial fibrillation was not verified by pathological and molecular biological methods. Finally, we did not progressively group the patients with paroxysmal and persistent atrial fibrillation into two parts according to AF duration.

### Conclusion

In summary, as a new inflammatory factor, cystatin C is intimately associated with atrial fibrillation, may play an important role in the occurrence and development of atrial fibrillation. However, the specific relationship and precise mechanism between cystatin C and atrial fibrillation will need to be verified by a lot of further basic and clinical study.

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