Internal Medicine: Open Access

Wang et al., Intern Med 2014, 4:3
DOI: 10.4172/2165-8048.1000151

Research Article Open Access

The Relationship between *Helicobacter pylori* Infection and Different Types of Atrial Fibrillation in a Chinese Population

De-zhao Wang[1], **Qing Tang**[2], **Shi-jing Li**[3], **Jun Wang**[3] **and Bu-xing Chen**[1]*

[1]*Department of Cardiology, Tiantan Hospital, Capital Medical University, Beijing, China*

[2]*Department of General Geriatrics, Beijing Haidian District Hospital, Beijing, China*

[3]*Department of Cardiology, Mentougou District Hospital, Beijing, China*

***Corresponding author:** Bu-xing Chen, Department of Cariology, Tiantan Hospital, Capital Medical University, No.6, Tiantanxili, Dongcheng District, Beijing, 100050, China, Tel: 86-10-67096572; E-mail: chbux@126.com

Received date: March 17, 2014, **Accepted date:** April 15, 2014, **Published date:** April 25, 2014

Abstract

Objective: To explore the relationship between *Helicobacter pylori* (Hp) infection and the different types of atrial fibrillation (AF).

Methods: Two hundred and eighty-five hospitalized patients with AF patients were enrolled. Patients were divided into five groups: Group 1, the initial-AF; Group 2, the paroxysmal-AF; Group 3, the persistent-AF; Group 4, the long-term persistent-AF; and Group 5, the permanent-AF. Patients in the first 3 groups were reclassified into the short-AF category and patients in the last 2 groups were reclassified into the long-AF category. All patients took the examination of ^{13}C urea breath test, high sensitive C-reactive protein (hs-CRP) and left atrial diameter (LAD), etc. tests and examinations. We analyzed the difference of these factors in all types of AF and explored the correlation between Hp infection and AF using logistic regression analysis.

Results: The Hp value and the hs-CRP level in patients with permanent AF were higher than those in the initial-AF, the paroxysmal-AF, and the persistent-AF groups (For Hp value: P=0.005, 0.012, and 0.038; for hs-CRP level: P=0.000, 0.025, and 0.006, respectively). The LAD of patients in the permanent-AF group was significantly larger than those in the other four groups (P=0.001, 0.010, 0.014, and 0.034, respectively). The values of Hp, hs-CRP, and LAD in the long-AF category were significantly higher than those in the short-AF category (all P<0.05). After controlling the potential confounders, Hp value ≥ 4‰, hs-CRP>5 mg/L, and LAD>36mm were significantly related to long AF.

Conclusion: The values of Hp in patients with long-term persistent or with permanent AF were significantly higher than those in patient with initial, paroxysmal or persistent AF. Hp δ value≥4‰ is an independent predictor for long AF.

Keywords: *Helicobacter pylori;* High sensitivity C-reactive protein; Left atrial diameter; Atrial fibrillation; ^{13}C urea breath test

Introduction

Atrial fibrillation (AF) is one of the most common clinical arrhythmias and easily complicated by cardiac insufficiency and thromboembolic complications, which seriously affects the patients' quality of life. The occurrence and maintenance mechanism of AF is not very clear at present. Some studies reported that the structural and electrophysiological basis of the occurrence of AF might be the left atrial reentrant micro ring and enlarged left atrium [1]. Some researchers found that elevated plasma high sensitive C-reactive protein (hs-CRP) level was an independent risk factor for AF, which indicated that chronic inflammation seemed to play an important role in the development of AF [2]. A study from the digestion department of internal medicine showed that the *Helicobacter pylori* (Hp) infection rate was as high as 50% in Chinese adults, and Hp was not only an important pathogenic reason to chronic gastritis and stomach cancer, but was also closely related to the occurrence of non-gastrointestinal diseases [3].

Some studies showed that chronic Hp infection was involved in AF and it played an important role in the development of AF [4-8], but others demonstrated that Hp infection was not correlated with AF [9-11]. However, these studies had relatively small sample sizes, and none of the patients have been classified into different AF-type categories in accordance with the guidelines to further explore the correlation between Hp infection and different types of AF. The purpose of this study was to clarify the relationship between Hp infection and the different types of AF, and to investigate the occurrence and maintenance mechanism of AF.

Materials and Methods

Subjects

This study consisted of a retrospective analysis of a single-site cohort. The consecutive hospitalized patients with AF (excluding cardiac insufficiency, acute coronary syndrome, thyroid dysfunction, and any infections) in Tiantan Hospital from January 1, 2007 to April 12, 2013 were selected. Subjects who had suffered gastrointestinal bleeding within 1 week; had a history of gastrectomy; or used

antibiotics, bismuth, or sucralfate within 1 month were excluded. There were 132 males (46.3%) and 153 females (53.7%). Patient history, physical examination, and laboratory results were recorded with chart abstraction. Their average age was 67.1 ± 13.5 years old. According to the 2012 ESC guidelines [12], patients were divided into 5 groups: Group 1, the initial-AF (firstly diagnosed regardless of the duration and symptoms); Group 2, the paroxysmal-AF (self-limited and terminated automatically in 48 hours); Group 3, the persistent-AF (lasting for more than 7 days, or less than 7 days but needed emergency or direct current cardioversion); Group 4, the long-term persistent-AF (lasting for more than or equal to 1 year with the rhythm of cardioversion treatment); and Group 5, the permanent-AF group, (lasting for more than 1 year without rhythm control or cardioversion failure. Based on the persistent time of AF, patients were classified into 2 categories: the short-AF, which persisted less than 1 year (including Groups 1, 2, and 3); and the long-AF category, which persisted more than 1 year (including Groups 4 and 5). Group 1 had 34 (11.9%) patients, Group 2 had 58 (20.4%) patients, Group 3 had 67 (23.5%) patients, Group 4 had 76 (26.7%) patients, and Group 5 had 50 (17.5%) patients. The baseline data of each group are shown in Table 1.

Group	Initial-AF group	Paroxysmal-AF group	Persistent-AF group	Long-term persistent-AF group	Pemernant-AF group	P value
Female, n	21（7.4%）	30（10.5%）	40（14.0%）	38（13.3%）	24（8.4%）	0.554
Smoke, n	14（4.9%）	17（6.0%）	18（6.3%）	32（11.2%）	18（6.3%）	0.281
Alcohol, n	9（3.2%）	15（5.3%）	18（6.3%）	29（10.2%）	20（7.0%）	0.278
Hypertention, n	17（6.0%）	38（13.3%）	27（9.5%）	47（16.5%）	34（11.9%）	0.010
Dyslipidemia, n	11（3.9%）	27（9.5%）	23（8.1%）	23（8.1%）	18（6.3%）	0.383
Diabetes Mellitus, n	8（2.8%）	18（6.3%）	17（6.0%）	23（8.1%）	12（4.2%）	0.847
Cerebral infarction, n	3（1.1%）	6（2.1%）	7（2.5%）	12（4.2%）	12（4.2%）	0.168
Hematencephalon, n	1（0.4%）	2（0.7%）	0（0.0%）	1（0.4%）	1（0.4%）	0.637
Family history of AF, n	3（1.1%）	5（1.8%）	6（2.1%）	2（0.7%）	2（0.7%）	0.424
Arteriosclerosis, n	21（7.4%）	28（9.8%）	44（15.4%）	46（16.1%）	30（10.5%）	0.381
Fudus abnormal, n	14（4.9%）	24（8.4%）	35（12.3%）	36（12.6%）	21（7.4%）	0.693
HP-IgG passitive	22（7.7%）	4（14.4%）	53（18.6%）	57（20.0%）	42（14.7%）	0.259
Mean age ± SD（years）	62.7 ± 13.81	66.1 ± 15.06	65.7 ± 11.72	69.8 ± 12.56	68.6 ± 14.28	0.076
Mean SBP ± SD (mmHg)	142 ± 20.0	142 ± 21.3	139 ± 21.1	144 ± 21.2	142 ± 16.5	0.556 0.076
Mean heart rate/ minute	77 ± 4.6	81 ± 3.0	85 ± 3.3	89 ± 3.3	88 ± 4.1	0.144 0.076
Mean WBC ± SD（10^9/L）	7.0 ± 2.64	6.8 ± 2.01	6.8 ± 1.85	7.2 ± 2.52	7.5 ± 2.72	0.448 0.076
Mean NEU ± SD (109/L)	4.8 ± 2.17	5.7 ± 2.58	5.4 ± 2.52	6.2 ± 2.66	6.25 ± 2.47	0.064 0.076
Mean LVEF ± SD（%）	62.2 ± 8.70	63.3 ± 8.12	64.0 ± 7.36	63.4 ± 9.52	63.4 ± 7.21	0.902 0.076
Mean BMI ± SD（kg/m^2）	29.0 ± 8.22	29.0 ± 8.72	26.5 ± 9.11	26.4 ± 8.35	28.6 ± 10.39	0.254 0.076

Table 1: Clinical data of 285 patients with AF

AF: Atrial Fibrillation; SD: Standard Deviation; NEU: Neutrophils; LVEF: Left Ventricular Ejection Fraction; BMI, body mass index.

Tests and examinations

Routine examination: All the patients underwent the following tests/examinations on the next day after admission: blood routine, biochemical items, glycosylated hemoglobin, hs-CRP, homocysteine (HCY), Hp-IgG antibody levels in serum, ^{13}C urea breath, blood coagulation, and ultrasonic cardiogram (UCG).

^{13}C urea breath test: The ^{13}C urea breath test was measured using the HCBT-01 breath test automatic instrument (Shenzhen Zhonghe Haidewei Biological Technology Co. Ltd) and the determination whether patients had Hp infection was calculated by $^{13}C/^{12}C$ isotope ratio (δ‰). Subjects were asked to be fasting more than 2 hours before blood tests. The positive value of Hp infection was defined as δ≥ 4 ± 0.4 ‰.

Hs-CRP and Hp antibody level: Hs-CRP was measured using particle enhanced immune transmission turbidimetry (DiaSys Diagnostic Systems of GmbH Company). Hp-IgG antibody was measured by the colloidal gold method (Shanghai Enterasys Biological Technology Co. Ltd).

UCG examination: UCG examination was performed using the United States GE Vivid 7 ultrasound heartbeat graph diagnosis system. Patients were asked to be in the left lateral position. The parasternal long axis, parasternal short axis, apical 4-chamber view, and apical 2-chamber view were used. Left ventricular end-diastolic diameter and left atrial diameter (LAD) were measured by using the parasternal long axis view. Biplane Simpson formula was used to quantify left ventricular ejection fraction (LVEF).

Statistical methods

Baseline characteristics of patients were compared using t-test for continuous variables and the chi-squared test for non-continuous variables. When continuous data were not normally distributed, groups were compared using nonparametric Wilcoxon rank sum test. The correlation between baseline characteristics and long AF was tested using a univariate logistic regression model. Clinically significant variables were entered into a multivariate regression model. P<0.05 was statistically significant. Statistical analysis was performed using the SPSS software (version 12.0).

Results

Comparison of Hp δ value, Hs-CRP, and LAD among five groups of AF

There was a significant difference in Hp δ value among the five groups of AF (P=0.034). Patients with permanent AF in Group 5 had a significantly higher Hp level than those in Group 1, 2, and 3(P=0.005, 0.012, and 0.038, respectively); there was also a significant difference in hs-CRP value among the five groups (P=0.014). The median hs-CRP value of Group 5 was significantly higher than those of Group 1, 2, and 3 (P=0.000, 0.025, and 0.006, respectively); The mean LAD value in Group 5 was significantly higher than those in Group 1, 2, 3, and 4 (P=0.001, 0.010, 0.014, and 0.034, respectively) (Table 2).

Group	Types of AF	n	Median Hp δ value (‰) (interquartile range)	Median hs-CRP (mg/L) (interquartile range)	Mean LAD ± SD (mm)
1	Initial AF	34	6.35(1.8-11.4)*	4.30(1.84-8.01)#	35.9 ± 3.80▲
2	paroxysmal AF	58	5.25(1.67-19.3)*	5.58(3.89-10.27)#	37.1 ± 4.64▲
3	Persistent AF	67	8.40(2.50-19.0)*	4.94(2.50-11.56)#	37.3 ± 4.54▲
4	Long persistent AF	76	8.10(2.43-30.4)	5.83(2.36-14.41)	37.6 ± 5.16▲
5	Permanent AF	50	14.9(4.13-31.0)*	6.81(5.25-16.68)#	39.5 ± 5.75▲

Table 2: Comaparing Hp δ value, hs-CRP, and LAD among five groups of AF

*Patients with permanent AF in Group 5 had a significantly higher Hp level than those in Group 1, 2, and 3

#The median hs-CRP value of Group 5 was significantly higher than those of Group 1, 2, and 3

▲The mean LAD value in Group 5 was significantly higher than those in Group 1, 2, 3, and 4

Hp: *Helicobacter pylori*; hs-CRP: high sensitive C-reactive protein; LAD: Left Atrial Diameter; AF: Atrial Fibrillation; SD: Standard Deviation.

Comparison of Hp δ value, Hs-CRP, LAD and other factors between Short-AF and Long-AF categories

There were significant differences in Hp value, hs-CRP, LAD, age, heart rate (HR), neutrophils (NEU), HCY, and high blood pressure (HBP) between Short-AF and Long-AF categories. Patients with Long AF were more likely to be older; have hypertension; and have a higher Hp value, hs-CRP, LAD, heart rate, NEU, and HCY level than those with short AF. There were no significant differences between the two groups about other chronic inflammation diseases (Table 3).

Variable	Short-AF category	Long-AF category	P value
Median Hp δ value (‰) (interquartile range)	6.40 (2.30-16.80)	11.45 (2.68-30.58)	0.008
Median Hs-CRP (mg/L) (interquartile range)	4.89 (2.81-10.00)	6.58 (3.38-15.56)	0.016
Mean LAD ± SD (mm)	36.9 ± 4.44	38.4 ± 5.46	0.013
Mean age ± SD (years)	65.2 ± 13.45	69.3 ± 13.23	0.010
Mean HR ± SD (bpm)	81.8 ± 25.54	88.6 ± 29.06	0.036
Mean NEU ± SD (10^9/L)	5.4 ± 2.48	6.2 ± 2.57	0.012
Mean HCY ± SD (umol/L)	9.5 ± 6.86	12.0 ± 9.09	0.008
HBP, n (%)	45 (15.8%)	81 (28.4%)	0.040

Table 3: Comparing Hp δ value, hs-CRP, LAD, and other factors between short-AF and long-AF categories

Hp: *Helicobacter pylori*; hs-CRP: high-sensitivity C-Reactive Protein; LAD: Left Anterior Descending; AF: Atrial Fibrillation; HR: Heart Rate; LEU: Leucocyte; HCY: Homocysteine; HBP: High Blood Pressure.

Logistic regression analysis in patients with long AF

In the multivariate logistic regression model, after adjusting for other important covariates, Hp δ value ≥ 4‰ remained an independent predictor for long AF (odds ratio [OR]: 1.81, 95% confidence interval [CI]: 1.055–3.106, p=0.031). Hs-CRP and LAD>36 mm were also found to be associated with long AF (OR: 1.713, 95% CI: 1.013-2.898, p=0.045; and OR: 2.331, 95% CI: 1.383-3.929, p=0.001). HBP, heart rates, NEU, HCY, and age were not significantly associated with long AF (Table 4).

Category	B value	SE	Wald X^2	P value	OR (95% CI)
LAD>36mm	0.846	0.266	10.100	0.001	2.331(1.383-3.929)
Hp δ value≥4%	0.594	0.275	4.646	0.031	1.81(1.055-3.106)
Hs-CRP>5mg/L	0.538	0.268	4.027	0.045	1.713(1.013-2.898)
HR>100bpm	0.594	0.326	3.333	0.068	1.812(0.957-3.430)
NEU>8×10^9/L	0.726	0.380	3.648	0.056	2.068(0.981-4.357)
Age ≥ 65 years	0.523	0.268	3.812	0.051	1.688(0.998-2.854)
HCY ≥ 15umol/L	0.468	0.320	2.134	0.144	1.596(0.852-2.990)
Hypertension	0.476	0.273	3.034	0.082	1.610(0.942-2.750)

Table 4: Logistic regression analysis in patients with long AF

SE: Standard Error; OR: Odds Ratio; hs-CRP, high-sensitivity C-Reactive Protein; LAD: Left Anterior Descending; AF: Atrial fibrillation; HR: Heart Rate; NEU: leucocyte; HCY: Homocysteine; HBP: High Blood Pressure.

Discussion

Research about AF began in the last century, but the mechanism of AF still has not been completely clarified to date. In recent years, with the continuous research of chronic Hp infection, the correlation between Hp and non-gastrointestinal diseases gradually entered people's field of vision, especially the relationship between Hp and AF. However, the researchers have not reached an agreement. For example, a case-control study from Montenero in showed that there was a strong correlation between chronic AF and Hp infection [6]; but Lunetta et al did not find an inevitable correlation between them in Korean population [9]. Furthermore, most of these studies were retrospective studies, had relatively small sample sizes, and no further classification for AF. Moreover, some studies only reported the relationship between Hp-IgG antibody and AF. There are great limitations to analyze the correlation between AF and plasma Hp-IgG antibody instead of Hp value, because the positive Hp-IgG antibody only shows that a patient has been infected with Hp previously and it does not reflect the situation in the patient with AF episode. Also, the sensitivity and specificity of Hp-IgG antibody for cardiovascular disease are poor because Hp-IgG antibody is unstable in the blood [10-12]. In our study, patients with AF were divided into 5 groups according to the classification of AF types in the 2012 (European Society of Cardiology)ESC guideline, and another classification was based on whether AF was persistent more than 1 year. The study adopted ^{13}C urea breath test to test situation of Hp infection, considering LAD, the level of hs-CRP and other relevant clinical data, and further analyzed the correlation between Hp infection and AF. Our study found that there was a significant correlation between Hp δ values in the five groups. Patients with permanent AF in Group 5 had a higher level of Hp value than those in other groups. Patients with long-AF had a higher Hp value than those with short AF. After adjusting for other important covariates in a multivariate regression model, Hp δ value ≥ 4% remained an independent predictor for long AF.

More and more evidence has shown that inflammation reaction has been closely related to AF since 1997. Inflammation and AF are inseparable and have interaction and reciprocal causation although whether the inflammation is the inducement or the secondary outcome of AF has not been determined [13]. CRP is recognized as one of the markers of inflammation. Some researchers have shown that CRP is one of the independent risk factors of AF; baseline CRP level can predict the risk of AF in the future; and CRP can reflect the degree of inflammation, which is closely related to the type and the duration of AF [14]. Our study found that hs-CRP significantly increased in patients with long AF, which was consistent with the results of previous researches.

The core part of the development of AF is atrial remodeling, which includes electrical remodeling, functional remodeling, and structural remodeling. Atrial electrical remodeling in patients with long AF is chronic and irreversible, which results in substantial calcium influx, calcium overload, atrial systolic dysfunction, atrial passive extension, and atrial enlargement; and further aggravates the functional remodeling and structural remodeling. The three different remodelings reinforce each other in a vicious cycle [13,14]. The longer the duration of AF, the atrial electrical remodeling and structural remodeling is more obvious. Therefore, the LAD of patients with long AF was significantly larger than those with short AF in our study.

Our study found that the Hp value was significantly increased in patients with long AF. Since inflammation is closely related to AF and Hp infection can lead to chronic inflammation, thus, it is reasonable to believe that there may be some internal relations between Hp infection and AF. On one hand, if patients are infected with Hp, their bodies will produce H^+/K^+-ATP enzyme autoantibodies that bind to the H^+/K^+-ATP enzyme and then damage the atrial cell pump that makes the ion environment imbalanced and the depolarization delayed, which will trigger attack of AF [15]. On the other hand, Hp will produce cytotoxin-associated protein A (CagA), which will stimulate gastric epithelial cells to produce interleukin-8, induce neutrophil infiltration, and result in a series of inflammatory reactions. The longer Hp infection lasts, the greater CagA toxicity will be sustained, and the more severe atrial muscle cells will be damaged [16]. This long-term chronic persistent inflammation is likely to be the foundation of permanent and long-term persistent AF. The current study also found that Hp-IgG antibodies (which only show that people were infected with Hp previously) had no correlation with the duration of AF, which also proved the important role of the continuing action of chronic inflammation in the development of AF.

However, the study is a retrospective research and has a small sample size. Large prospective studies are expected to confirm what we found in the relationship between Hp infection and long AF.

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