Journal of Cardiovascular Diseases & Diagnosis
ISSN: 2329-9517

Cha et al., J Cardiovasc Dis Diagn 2017, 5:2
DOI: 10.4172/2329-9517.1000261

Research Article OMICS International

Vasospastic Angina, Especially Involving Coronary Arteries Supplying Atria, is a Predictor for Atrial Fibrillation

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Abstract

Background: Atrial ischemia is a known risk factor of non-valvular atrial fibrillation (AF). However, relationship between coronary vasospasm and AF has not yet been determined.

Methods: We investigated consecutive patients with normal sinus rhythm without AF history who underwent coronary angiography with ergonovine provocation test to evaluate vasospastic angina (VA). Patients with spasms over 50% and either typical chest pain or electrocardiogram changes during provocation test were diagnosed as vasospastic angina (VA group).

Results: Out of total 683 patients investigated, nine (4.6%) patients in VA group (n=195) and seven (1.4%) patients in control group (n=488) developed new-onset AF (follow-up duration, median 56 months; range, 6-263 months). Annual AF incidence rate was higher in VA group (0.63%/y) than in control group (0.23%/y). In univariate and multivariate analysis adjusted for age, VA was an independent predictor of AF (HR 2.93, p=0.021). In subgroup analysis of 195 patients with VA, there were no cases of AF in patients with spasm observed only in the left anterior descending artery. All nine patients with new onset AF had spasm in the right coronary artery or left circumflex artery.

Conclusions: Vasospastic angina could be an independent predictor of new-onset AF.

Keywords: Atrial fibrillation; Vasospastic angina; Coronary spasm

Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia and prevalence of AF rises with age but, there is a lack of information concerning the mechanism causing and sustaining AF [1]. Atrial ischemia is one of determinant for the development of AF. An increased risk of atrial tachyarrhythmia has been observed in patients with atrial infarction [2]. In another study, experimental atrial ischemia creates a substrate for AF maintenance, apparently by causing local conduction slowing that promotes reentry [3]. These results suggest that atrial ischemia could promote AF, and relevant to AF mechanisms in association with coronary artery disease.

Vasospastic angina (VA) is one aspect of coronary ischemia [4]. However, data on association between AF and VA induced ischemia is limited. Thus, we sought to determine the contribution of vasospasm in promoting new-onset AF. We hypothesized that ischemia due to VA might have a role in AF development.

Materials and Methods

Our study protocol was approved by the institutional review board in Seoul National University Hospital, and is in accordance with the Declaration of Helsinki. Patient consent was waived, because it was not practical to obtain consents from large numbers of patients for a retrospective review study. The data was analyzed anonymously.

Study population

We investigated consecutive patients who underwent coronary angiography (CAG) with ergonovine provocation test for vasospastic angina evaluation between June 1991 and December 2013. All screened patients had no fixed stenosis ≥40% in major epicardial coronary arteries or their branches and normal sinus rhythm at electrocardiogram. Patients with prior AF, any abnormal echocardiographic finding (left ventricular dysfunction ≤50%, any valvular heart disease, atrial chamber enlargement, hypertrophic/dilated cardiomyopathy, or any regional wall motion abnormality) or follow-up duration <180 days were excluded from the study before enrollment.

Vasospastic angina

No patient had been on vasodilators at least 14 days within provocation test. During CAG with ergonovine provocation test, stepwise administration of intracoronary ergonovine was performed [5] and we continuously monitored patients via arterial pressure and 12-lead ECG (electrocardiography). The arterial spastic lesions were assessed by repetitive CAG. We defined coronary artery spasm as diameter reduction of >50% as compared with diameter after administration of nitroglycerine. Patients with coronary artery spasm and either typical chest pain or ECG changes were diagnosed as VA. ECG changes were considered ischemia when a transient ST segment elevation of >0.1 mV at 80 ms after the J point was noted in at least two leads. After spasm of the coronary artery had been confirmed, intracoronary nitroglycerin was administered.

Study design

Patients who diagnosed as VA were classified into VA group. The other patients who did not fulfill diagnostic criteria were defined as control group. We compared the incidence of AF in VA group to control group (Figure 1). All enrolled patients were followed up at least over 6 months and observed for progression to AF. Follow up duration

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Received March 03, 2017; **Accepted** March 08, 2017; **Published** March 15, 2017

Citation: Cha M, Ki Y, Choi E, Oh S (2017) Vasospastic Angina, Especially Involving Coronary Arteries Supplying Atria, is a Predictor for Atrial Fibrillation. J Cardiovasc Dis Diagn 5: 261. doi: 10.4172/2329-9517.1000261

was defined as the time interval from the initial CAG to one of the following events: ECG-documented AF diagnosis or the last record of follow-up visit. Follow up information was obtained from the inpatient and outpatient electronic medical record system. Subjects who die are treated as censored observation. Patients had undergone regular clinic follow up with ECG every 3-6 months. Additional unscheduled ECG tests were performed when patient complaint palpitation or chest discomfort.

Statistical analysis

Baseline characteristics are provided as 'mean ± standard deviation' for continuous variables and percentage for discrete variables. Potential covariates with clinical relevance, such as VA and age, were selected by examining their significance in univariate models. Cox regression survival analysis was performed to assess independent predictors of AF. A *p*-value of <0.05 was used to indicate statistical significance. All statistical tests were performed with SPSS for Windows version 22 (SSPS Inc., Chicago, IL).

Results

Baseline characteristics

Consecutive 1086 patients with normal CAG results and ergonovine provocation test were screened, and 403 patients (prior AF, n=41; follow-up less than 180 days, n=282; any abnormal echocardiographic finding, n=80) were excluded. Total 683 patients (307 women) were enrolled. 195 patients were diagnosed as VA. The baseline characteristics are shown in Table 1.

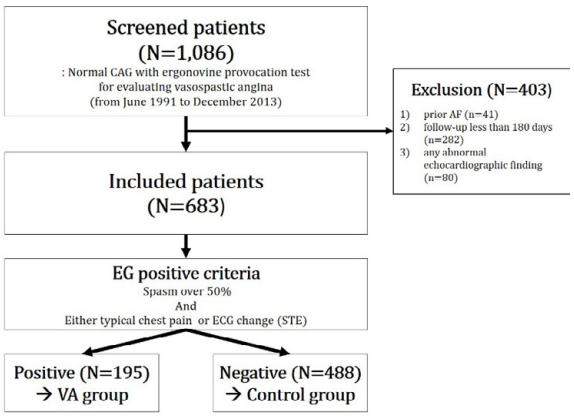

Figure 1: Patient enrolment: Among 683 study-included patients, there were 195 patients diagnosed with variant angina. Annual AF incidence rate was higher in VA group (0.63%/y) than in control group (0.23%/y).

	Total (N=683)	VA group (N=195)	Control group (N=488)	*p*-value
Age	56.4 ± 11.2	57.7 ± 10.0	55.8 ± 11.6	0.034
Female	307 (44.9%)	48 (24.6%)	259 (53.1%)	<0.001
Body mass index (kg/m²)	25.3 ± 3.0	24.2 ± 3.1	26.6 ± 2.5	0.119
Hypertension	200 (29.3%)	69 (48.3%)	131 (40.3%)	0.128
Diabetes mellitus	50 (7.3%)	20 (14.0%)	30 (9.2%)	0.144
Congestive heart failure	3 (0.4%)	0 (0.0%)	3 (0.6%)	0.457
Previous stroke	14 (2.0%)	5 (2.6%)	9 (1.8%)	0.344
Chronic kidney disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
LVEF (%)	62.4 ± 6.8	62.9 ± 6.0	62.2 ± 7.1	0.257
Follow-up duration (years)	6.3 ± 6.8	6.7 ± 7.9	6.2 ± 6.3	0.457
LVEF: Left ventricular Ejection Fraction; VA: Vasospastic Angina				

Table 1: Baseline characteristics.

Univariate Analysis	Hazard ratio	95% CI	*p*-value
Vasospastic angina	3.17	1.18-8.50	0.022
Age	1.07	1.01-1.13	0.019
Female	1.08	0.66-1.78	0.749
Body mass index	0.94	0.78-1.14	0.537
Hypertension	1.58	0.59-4.25	0.363
Diabetes mellitus	2.87	0.92-8.94	0.069

Table 2: Univariate Cox regression analyses for clinical predictors of AF development.

Multivariate Analysis	Hazard ratio	95% CI	*p*-value
Vasospastic angina	2.93	1.09-7.89	0.033
Age	1.06	1.01-1.12	0.025

Table 3: Multivariate Cox regression analyses for clinical predictors of AF development.

Incidence of new-onset AF

Patients were monitored for an average period of 79.5 ± 58.9 months per patient (median 56 months; range 6 to 263 months). AF was documented in 16 patients during follow-up. Nine patients (4.6%) among the 195 patients in VA group and seven patients (1.4%) among the 488 patients in control group developed new-onset AF. Annual AF incidence rate was higher in VA group (0.63%/year) than in control group (0.23%/year). Average time interval from CAG to AF was 43 ± 36 months (median, 32, range 1-125 months), and there was no significant difference between VA and control group (p=0.168). Nine of 16 VA patients (4 in VA group and 5 in control group) had no symptoms and were diagnosed with AF on a routine ECG, while the other 7 patients (5 in VA group and 2 in control group) were diagnosed via an unscheduled ECG due to palpitation or chest discomfort.

Risk factors for new-onset AF

In univariate analysis, advanced age (HR 1.07, p=0.019) at VA diagnosis and presence of VA were univariate predictors of AF. The presence of VA was associated with a 3.17-fold increase in risk of AF (p=0.022). Sex, body mass index, hypertension and diabetes mellitus were not associated with the increased risk of new-onset AF (Table 2).

In multivariate analysis in Table 3, VA and age were independent predictors for new-onset AF. Patients with VA showed 3 times higher AF incidence than control group.

Subgroup analysis of VA group according to spastic coronary arteries

In the subgroup analysis of 195 VA patients, spasm observed at left anterior descending (LAD) coronary artery in 56 patients (28.7%), left circumflex artery (LCx) in 60 patients (30.8%), and right coronary artery (RCA) in 131 patients (67.2%). There were no cases of AF in patients with spasm observed only in the LAD. All 9 patients with new onset AF had spasm in either or both RCA or LCx. The detailed data are described in Table 4.

Discussion

The new finding of the present study is that VA, especially involving coronary arteries supplying atria, was the independent predictors for

Vasospastic artery	Total	AF development	
	(N=195)	YES (N=9)	NO (N=186)
LAD	56	5	51
LCx	60	4	56
RCA	131	7	124
LAD only	42	0	42
LCx only	7	0	7
RCA only	52	4	48
LCx or RCA	153	9	144
LAD, LCx and RCA	15	5	13

LAD: Left Anterior Descending Artery; LCx: Left Circumflex Artery; RCA: Right Coronary Artery

Table 4: Subgroup analysis of VA group according to spastic coronary arteries.

AF development. To the best of our knowledge, this is the first report showing the association between new-onset AF and VA.

Atrial ischemia and atrial fibrillation

Hung et al. reported a case of paroxysmal atrial fibrillation described in a patient that was consistent with the clinical history developed after induction of coronary artery spasm [6]. In a canine model, isolated atrial ischemia induced by occlusion of an atrial branch caused localized atrial conduction slowing and promotes the maintenance of AF, and increased the duration of AF induced by burst pacing [7]. In the study of autopsied patients with atrial arrhythmia and myocardial infarction history, a coronary occlusion was found proximal to the origin of the sinus node artery and there was infarction of the sinus node [8].

The sinus node artery mainly from RCA or LCx is known to supply almost the entire atrial myocardium [9]. Thus, repeated impairment of coronary flow caused by spasm in the RCA or LCx could lead to atrial ischemia. In previous studies, coronary ischemia in atrial supplying arteries (RCA and LCx) was a cause of early atrial arrhythmia in acute myocardial infarction [10], and the other study showed that coronary occlusion to the origin of severe RCA stenosis was a powerful predictor of AF after coronary artery bypass surgery [11].

Coronary spasm and atrial fibrillation

We hypothesized that myocardial ischemia due to coronary spasm might also have a role in AF development. In the present study, we enrolled total 683 patients with normal coronary artery and VA diagnosed strictly by provocation test with CAG. Overall sixteen patients developed AF and among them nine AF developed patients in VA group had spasm in either RCA or LCx, supplying atrial myocardium. There were no cases of AF in patients with spasm in the LAD only, supplying territory of which is not atria.

Risk factor of atrial fibrillation development

Risk factors for AF are diverse and include advanced age, male sex, diabetes mellitus, hypertension, valvular heart disease, myocardial infarction, heart failure, and obesity [12]. We excluded patients with structural heart disease at enrollment, and all patients had normal coronary angiograms without evidence of myocardial infarction. One interesting point of our study is that our results showed that hypertension, diabetes mellitus, sex and body mass index had no significance in predicting AF development. This might be because the baseline characteristics of enrolled patients had less risk than the study population of previous studies. The causal relation between diabetes or sex and AF is still a debatable issue [13]. In our study cohort, patients with diabetes composed only 7.3%, compared to the prevalence of diabetes without AF in the general population of about 12% [14]. In a previous study of hypertensive patients, those who subsequently developed atrial fibrillation had a higher mean systolic blood pressure during follow-up. All patients in the study cohort were regularly followed in the out-patient clinic, and we confirmed that there were no cases of uncontrolled hypertension through review of the electronic medical records. Lastly, among 16 patients who developed AF, there was only one patient with body mass index over 30 kg/m^2 (criteria for obesity). In summary, our study patients had low risk for AF development, and this could be a statistical limitation.

There is no evidence of spasm resolving with time, and anti-anginal management has to be continued for VA patients [15]. In our study, patients diagnosed with VA were treated with nitrates and calcium antagonists to prevent coronary spasm. Despite treatment with anti-anginal medication, persistent or recurrent episodes of angina are frequently reported [16]. Therefore VA group patients may have a higher risk of atrial ischemia compared to the control group. Medical treatment could reduce exposure to ischemia, and AF incidence might be higher in untreated VA patients.

The vasospastic arteries do not directly relate to atrial ischemia itself. The missing link between coronary spasm and atrial fibrillation is the main limitation of this study. We thought that it was impossible to confirm atrial ischemia with data from already performed tests. This study is retrospective in design, and we could not obtain the data needed to prove atrial ischemia. We attempted to analyze P wave morphology and PR segment changes on patients' electrocardiography pre, during and post-ergonovine administration, but we could not acquire meaningful results. Next, we considered that there was potential for selection bias in this study, which enrolled just those patients who have undergone coronary angiography and echocardiography and study cohort is composed almost exclusively of Korean, which may limit the generalization of our findings to other ethnic groups. However, VA prevalence is reported to be higher in the Asian population than Caucasians [17], and we believe that study data of this size, confirmed by provocation test is rare and valuable in itself. Furthermore, patients diagnosed with VA through provocation test receive proper vasodilator therapy. As this result in lower risk of atrial ischemia, it appears that the incidence of new-onset AF in our group of patients with VA may be lower than in the actual VA population.

Conclusion

VA could be a novel independent predictor of new-onset non-valvular AF. Its mechanism might be atrial ischemia, but further investigation is needed.

Conflict of interest: None

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