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Article

Effects of Short-Term Episodes of Atrial Fibrillation after Coronary Artery Bypass Grafting on the Long-term Incidence of Atrial Fibrillation and Ischemic Stroke

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Abstract

Background: To explore whether postoperative atrial fibrillation (POAF) has an impact on the incidence of late atrial fibrillation (AF) and late ischemic stroke after isolated coronary artery bypass grafting (CABG) compared to non-POAF patients. **Methods**: A total of 243 eligible patients were followed for five years, and divided into a POAF group (n = 69) and a non-POAF group (n = 174). The primary end point was the incidence of late AF, and late ischemic stroke. Kaplan-Meier analyses and Cox proportional hazards models were used to examine whether POAF is an independent risk factor for the occurrence of late AF and late ischemic stroke. **Results**: POAF patients were older than non-POAF patients. During the 5-year follow-up, the late occurrence of AF was significantly higher in POAF patients than in non-POAF (15.9% *vs.* 7.9% p = 0.006). There was no significant difference in the incidence of late ischemic stroke between POAF and non-POAF groups (p = 0.406). COX proportional regression analysis showed that POAF was independently associated with the late occurrence of AF (hazard ratio (HR) 3.27; 95% confidence interval (CI): 1.33–8.03, p = 0.01). **Conclusion**: POAF is an independent risk factor for the occurrence of late AF but not stroke after isolated CABG.

Keywords

atrial fibrillation; postoperative atrial fibrillation; coronary artery bypass graft

Introduction

New-onset postoperative atrial fibrillation (POAF) is the most common postoperative arrhythmia after cardiac surgery [1,2]. The reported incidence of POAF following coronary artery bypass grafting (CABG) is approximately 20–40% [3–5]. POAF usually occurs within one week after CABG. Although POAF is generally considered a transient and self-limiting event, it is linked to poor clinical outcomes and increased medical costs. Kosuma *et al*. [6] reported a 23% increase in medical costs of POAF patients compared with patients without POAF, and Auer *et al*. [7] showed that POAF patients had longer hospital stays than non-POAF patients. POAF is associated with increased perioperative morbidity and mortality [8]. Recent studies have demonstrated that the impact of POAF may extend far beyond the perioperative period, such as an increased risk of late ischemic stroke [9,10]. Long-term oral anticoagulation (OAC) has been proven very effective in reducing the incidence of stroke in nonsurgical atrial fibrillation (AF) patients, but whether POAF patients should be treated the same way remains unclear for the following reasons: First, it is unclear if POAF is an isolated event that will not occur in long term. If POAF is a temporary phenomenon, the risk of late ischemic stroke maybe overestimated, while OAC may result in a higher risk of bleeding during the postoperative period. Second, it is reported that POAF may have a lower long-term thromboembolic risk than that of nonsurgical AF patients [11]. A recent study by Hsu *et al*. [12] showed that POAF after CABG was not associated with late ischemic stroke in an Asian cohort. Therefore, POAF might not be regarded as equivalent to nonsurgical AF patients in terms of stroke risk. Consequently, it remains unclear if POAF should be treated with long-term oral OAC. Thus, whether POAF after CABG is associated with an increased occurrence of late AF and ischemic stroke needs further clarification.

In the present study, our primary objective was to determine if there is a correlation between POAF after CABG and the late occurrence of AF and late ischemic stroke.

Material and Methods

Patient Selection

The study protocol was approved by the Institutional Review Board of Beijing Anzhen Hospital and complied with the Declaration of Helsinki. Written informed consent was waived for this retrospective analysis. This study ret-

rospectively recruited patients who underwent isolated off-pump CABG surgery between 1 March 2017 and 31 December 2017. POAF was defined as newly developed AF of any duration at any time during the postoperative period before discharge, which was diagnosed by a physician [13]. Based on the presence or absence of postoperative POAF, patients were divided into two groups: a POAF group and a non-POAF group. Patients with one or more of the following conditions were excluded from this study: preexisting AF or flutter of any type, a history of thyroid disease, recent myocardial infarction, emergency surgery, concomitant vascular or valve surgery, anti-arrhythmia medications, mortality within 30 days after surgery, or repeat-CABG.

Data Collection

Demographic characteristics, medical history, and preoperative transthoracic echocardiographic parameters were retrospectively obtained using the patients' medical records. A $CHA_2DS_2VAS_C$ score (heart failure, hypertension, age $\geq$75, diabetes, stroke/transit ischemic attack (TIA), vascular disease, age 65–74 years, and sex was calculated.

Perioperative Management

Perioperative management, anesthesia, and surgical techniques were standardized according to hospital protocols. After surgery, routine electrocardiogram (ECG) monitoring was performed on all patients for at least 72 hours and prolonged when needed, and the nurses recorded patients' heart rhythm every 10 minutes. If the patient was suspected to have an arrhythmic event, a 12-lead ECG was recorded. POAF was managed to restore sinus rhythm using medication; when medication failed, POAF was managed by direct-current cardioversion. All POAFs were converted to sinus rhythm before hospital discharge and the antiarrhythmic treatments were terminated. No patient was treated with OAC after discharge.

Endpoints

The primary endpoint was the occurrence of late AF and late ischemic stroke. The occurrence of late AF was defined as AF occurring after 30 days following surgery during regular follow-up visits as detected by ECG or Holter monitoring [14]. Late ischemic stroke, was defined as stroke occurring 30 days following surgery [15].

Follow-up

All patients were followed for 5 years and follow-up was achieved in 97.2% (243/250) of patients. Patients were followed up with clinical examination, ECG, and Holter monitoring at 1 month, 3 months, and every 6 months thereafter.

Statistical Analysis

Normally distributed continuous variables are presented as mean $\pm$ standard deviation (SD), and non-normally distributed continuous variables are presented as median (25th–75th percentile), or percentages for categorical variables. Baseline characteristics of patients with and without POAF were compared using the Student's *t*-test, Mann-Whitney U-test, χ^2 test, and Fisher's exact test as appropriate. Late AF/ischemic stroke-free survival between POAF and non-POAF groups were compared using Kaplan-Meier analyses and log-rank tests. The association between POAF and the occurrence of late AF after adjustment for potential confounding variables was examined using Cox proportional hazards models. Variables that were significantly different ($p < 0.05$) were included as the covariates in the multivariable models. All p values were calculated based on 2-sided tests, and a $p < 0.05$ was considered statistically significant. All statistical analyses were performed using STATA 13.0 (Stata Corp., College Station, TX, USA).

Results

Comparison of Baseline Clinical Characteristics between POAF and Non-POAF Groups

A total of 243 patients were enrolled in this study and were assigned into two groups: a POAF group (n = 69) and a non-POAF group (n = 174). The demographic and baseline clinical characteristics of patients in these two groups are summarized in Table 1. POAF patients were older than non-POAF patients. In addition, there were no significant differences with regard to any of the other variables such as medical history, preoperative transthoracic echocardiography parameters, and medication between the two groups. All 69 POAF patients converted to sinus rhythm before discharge: 5 patients converted to sinus rhythm spontaneously, 63 converted to sinus rhythm by medication, and 1 converted to sinus rhythm by direct-current cardio-version.

The POAF Group Had a Higher Incidence of Late AF Compared to the Non-POAF Group

During the 5-year follow-up, late AF developed in 15.9% (n = 11) of POAF patients and in 7.9% (n = 9) of non-POAF ($p = 0.006$) (Table 2). Kaplan-Meier survival curve analysis with log-rank statistic showed that freedom from late AF was significantly lower for POAF patients compared to non-POAF patients (log-rank $p = 0.0041$) (Fig. 1). After adjustment for all potential confounding variables, COX proportional regression analysis showed that POAF remained independently associated with the development of late AF (hazard ratio (HR) 3.27; 95% CI: 1.33–8.03, $p = 0.01$).

Table 1. Comparison of demographic and baseline clinical characteristics between POAF and non-POAF groups.

Variables	POAF	Non-POAF	*p*
	N = 69	N = 174	
Age	63.5 ± 9.4	59.8 ± 9.2	0.005
Women (%)	17 (24.6)	35 (20.1)	0.438
Smoking (%)	29 (42.0)	93 (53.4)	0.108
Drinking (%)	8 (11.6)	30 (17.2)	0.274
BMI (kg/m^2)	25.7 ± 3.2	25.5 ± 2.9	0.751
Hypertension (%)	22 (31.9)	52 (29.9)	0.760
Diabetes mellitus (%)	45 (65.2)	99 (56.9)	0.234
Hyperlipidemia (%)	17 (24.6)	47 (27.0)	0.705
Myocardial infarction (%)	28 (40.6)	49 (28.2)	0.061
PCI (%)	11 (15.9)	17 (9.8)	0.174
Stroke/TIA (%)	7 (10.1)	8 (4.6)	0.105
Heart failure (%)	6 (8.7)	9 (5.2)	0.303
PAD (%)	32 (46.4)	77 (44.3)	0.764
LAD/mm	37.2 ± 4.0	36.5 ± 4.4	0.247
LVEF	59.8 ± 9.6	60.9 ± 9.2	0.397
Preoperative med			
Statins (%)	30 (43.5)	91 (52.3)	0.215
Beta-blocker (%)	54 (78.3)	134 (77.0)	0.834
ACEI/ARB (%)	18 (26.1)	43 (24.7)	0.824
CCBs (%)	21 (30.4)	33 (18.9)	0.055
Postoperative med			
Statins (%)	36 (52.2)	105 (60.3)	0.245
Beta-blocker (%)	64 (92.8)	158 (90.8)	0.626
ACEI/ARB (%)	10 (14.5)	30 (17.2)	0.602
$CHA_2DS_2VAS_C$	2 (1, 3)	2 (1, 3)	0.061

Note: BMI, body mass index; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; PAD, peripheral artery disease; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CCBs, calcium channel blockers; POAF, postoperative atrial fibrillation.

POAF and Non-POAF Groups Had Comparable Rates of Late Ischemic Stroke

During the 5-year follow-up, POAF and non-POAF groups had comparable rates of late ischemic stroke (5.8% *vs.* 3.4%, $p = 0.406$; Table 2). Kaplan-Meier survival curve analysis showed no significant difference in freedom from ischemic stroke between POAF and non-POAF groups patients (log-rank $p = 0.4131$) (shown in Fig. 2).

Discussion

CABG is associated with an increased risk of new onset POAF. POAF is often regarded as a less worrisome event because it is believed to be a self-limiting disorder secondary to surgery [16]. Patients who have POAF converted to sinus rhythm prior to discharge are rarely monitored for the occurrence of late AF and therefore are unlikely to be anticoagulated [17]. Hence, it is imperative to better understand the impact of POAF on the occurrence of late AF and late ischemic stroke after discharge to help develop appropriate management, including necessary surveillance and treatment approaches.

In the present study, we found that POAF was a significant risk factor for late AF following CABG, supported by

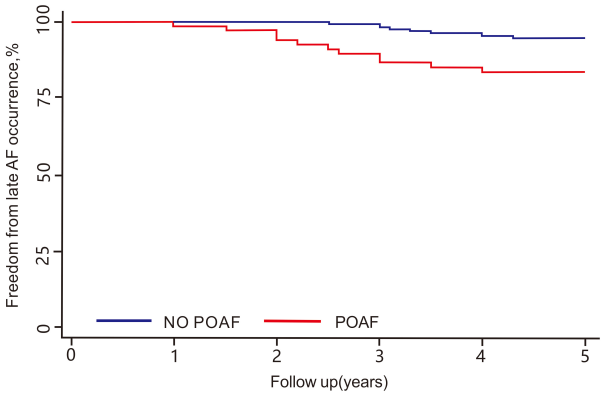

Fig. 1. Kaplan-Meier curves of time to the first episode of late AF in patients with (red line) or without (blue line) POAF. Note: POAF, postoperative atrial fibrillation; AF, atrial fibrillation.

Table 2. Differences in incidences of the occurrence of late AF and ischemic stroke between POAF and non-POAF groups.

End point	POAF	Non-POAF	*p*
	n = 69	n = 174	
Late AF	11 (15.9%)	9 (7.9%)	0.006
Ischemic Stroke	4 (5.8%)	6 (3.4%)	0.406

Note: POAF, postoperative atrial fibrillation; AF, atrial fibrillation.

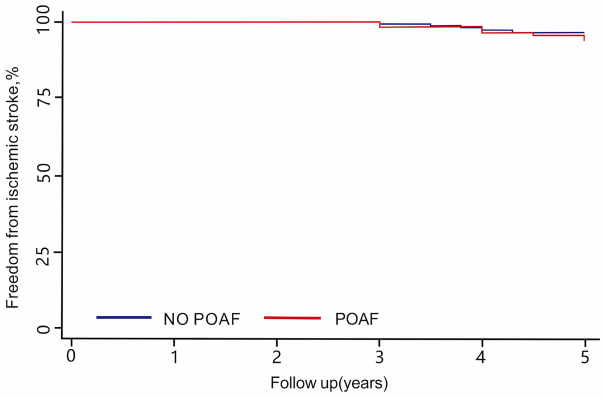

Fig. 2. Kaplan-Meier curves of ischemic stroke in patients with (red line) or without (blue line) POAF. Note: POAF, postoperative atrial fibrillation; AF, atrial fibrillation.

the finding that the POAF patients had a 3.27-fold higher risk of late AF compared to the non-POAF patients. Our results are consistent with several recent studies. Melduni *et al*. [14] reported that POAF after CABG and/or heart valve surgery occurred in 37.5% of patients, of whom 49.3% occurred during follow-up [14]. Lee *et al*. [18] showed that POAF after CABG occurred in 20.8% of patients, of whom 10.2% occurred during long-term follow-up. These POAF patients were at a 5-fold increased risk of late AF. Park-Hansen *et al*. [19] found that POAF after open-heart surgery occurred in 49% of patients, of whom 43.8% occurred during follow-up. Konstantino *et al*. [20] showed that POAF after CABG occurred in 27% of patients, of whom 30% occurred during follow-up. EI-Chami *et al*. [21] enrolled 23 POAF patients after CABG and used an implantable loop recorder to detect AF recurrence. They showed that 60.9% of POAF patients developed recurrent AF. These accumulating data challenged the general concept that POAF is a transient phenomenon secondary to surgery and suggests that patients who develop POAF should undergo surveillance and routine screening for late AF. Increased efforts have been made to identify patients at high risk for POAF in order to take due precautions during the preoperative period [22,23].

However, the mechanism for POAF and the occurrence of late AF remain poorly understood. Recently van Schie *et al*. [24] showed that patients who developed POAF had pre-operative atrial proarrhythmic substrates, such as lower conduction velocity, and larger low-voltage areas compared with those without POAF. Nevertheless, in patients without a history of AF, the pre-existing atrial proarrhythmic substrates is not sufficient to induce AF, but in the presence of surgery-related triggers, POAF may occur [25,26]. POAF might be the result of the interaction between surgery-related triggers and pre-existing atrial proarrhythmic substrates [26]. How does POAF progress to the occurrence of late AF? It has been shown that AF can give rise to AF [27]. Initiation of AF results in electrical remodeling within hours and structural remodeling, the latter of which takes months to develop. Electrical and structural remodeling forms a vicious cycle as one can exacerbate the other. Additionally, AF may also result in progressive autonomic remodeling, which plays an important role in the development of sustained AF in the first few hours after AF initiation [28,29]. As a result, AF can progress from paroxysmal to more persistent forms of AF. Therefore, although POAF is transient and secondary to surgery or acute medical disease, it may also cause vulnerable substrate progression that accelerate its progression to the occurrence of late AF.

Previous studies showed that POAF was closely associated with an increased long-term risk of ischemic stroke. A meta-analysis revealed that POAF was correlated with an elevated risk of short- and long-term stroke and mortality [15]. A more recent study suggested that POAF patients had an increased 5-year risk of stroke and TIA compared with age- and gender-matched non-POAF patients [30]. However, in the present study, we found no significant difference in the incidence of late ischemic stroke during follow-up between POAF and non-POAF groups. This observation was in line with a recent report showing that there was no correlation between POAF and late stroke in an Asian cohort [12]. It is possible that race and/or the limited number of patients contributed to the discrepant findings among the previous studies and our own. Therefore, further studies are warranted to clarify these conflicting observations.

Some limitations of this study should be noted. First, patients with undetected paroxysmal or asymptomatic AF before surgery might not have been excluded from the study, which may affect the results. Second, this study might have sampling bias and other confounders due to its retrospective nature. Third, the rate of absence of late AF after discharge might be overestimated because of the possibility of missing an asymptomatic occurrence of AF. Fourth, all patients underwent off-pump CABG in this study. Therefore, our study revealed a relationship between POAF and late AF occurrence after off-pump CABG. Extrapolation of our conclusions to all patients with different surgeries should be done with caution. Finally, this study had a relatively small sample size. Further studies using a larger sample size are needed.

Conclusion

We report that POAF is significantly associated with the occurrence of late AF but not stroke after CABG. Postoperative surveillance for the occurrence of late AF is recommended. The decision to start OAC should be left to cardiologist's discretion.

Abbreviations

POAF, postoperative atrial fibrillation; AF, atrial fibrillation; CABG, coronary artery bypass grafting; OAC, oral anticoagulation; TIA, transit ischemic attack; ECG, electrocardiogram; SD, standard deviation; BMI, body mass index; PCI, percutaneous coronary intervention; PAD, peripheral artery disease; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CCBs, calcium channel blockers.

Availability of Data and Materials

All data are available from the corresponding authors upon reasonable request.

Author Contributions

LC and WD conceptualized and designed the study. LC wrote the manuscript. WD revised the manuscript. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The study was approved by the Institutional Review Board of Beijing Anzhen Hospital (No. D11110700300000). The study was a retrospective study and did not require an informed consent form.

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Conflict of Interest

The authors declare no conflict of interest.

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