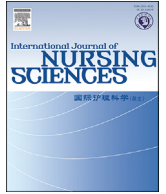


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Original Article

Preoperative P-wave duration as a predictor of atrial fibrillation after coronary artery bypass grafting: A prospective cohort study with meta-analysis

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ABSTRACT

Objectives: Reported prediction rules for postoperative atrial fibrillation (AF) have suffered from inconsistent results and controversy surrounding the predictive value of a preoperative P-wave duration (PreOPWD). This study examined PreOPWD as a predictor for AF after coronary artery bypass grafting (CABG).

Methods: Two-hundred-and-ninety-nine patients with sinus rhythm before off-pump CABG were recruited into the study. Patients' demographic and clinical data were evaluated prospectively. Patients were continuously monitored for the first seven postoperative days. Multiple logistic regression was used to determine significant predictors of AF. Findings were then combined with similar studies and a meta-analysis was performed.

Results: Postoperative AF was observed in 33.1% of 299 patients. Patients with AF were older, had a prolonged PreOPWD, higher incidences of hypertension, aortic regurgitation, and mitral regurgitation. A cut-off point of $\text{PreOPWD} \geq 105$ ms achieved a specificity of 74%, and a sensitivity of 65% for predictive of AF. Multivariate analysis showed that $\text{PreOPWD} \geq 105$ ms (odds ratio [OR] 4.63, 95% confidence intervals [CI] 2.66 to 8.03, $P < 0.001$), $\text{age} \geq 60$ years (OR 2.72, 95% CI 1.51 to 4.90, $P < 0.01$) and hypertension (OR 2.10, 95% CI 1.08 to 4.07, $P < 0.05$) independently predicted postoperative AF. A meta-analysis of this data combined with those of ten other studies showed that PreOPWD was greater in patients with POAF, with a weighted mean difference of 3.95 ms (95% CI 1.97 to 5.92, $P < 0.001$).

Conclusion: This study confirmed, among other predictive characteristics, that PreOPWD is a powerful independent predictor of POAF.

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1. Introduction

Atrial fibrillation (AF) is one of the most common arrhythmic complications following coronary artery bypass grafting (CABG) surgery, with an incidence varying from 20% to 36% [1–3]. Postoperative AF (POAF) is associated with significant morbidity, increased mortality, longer hospital stay and higher hospital costs [1,2,4–6]. In general, prophylactic medical therapies decrease the incidence of POAF, but the results in about 64%–84% of post-CABG

patients receiving unnecessary treatment [7,8]. Therefore, targeting POAF high-risk patients for prophylactic measures could reduce adverse effects and the associated costs significantly.

Numerous risk factors have been identified [9–11]. Only older age, however, has consistently shown to be associated with POAF, and its etiology is incompletely understood. Precipitating and predisposing factors such as structural changes of the atria resulting from hypertension, intraoperative atrial ischemia, and pericardial inflammation are thought to play a role in its pathogenesis [5,12]. Proposed mechanisms behind the occurrence of POAF include the preexistence of abnormal atrial tissue, electrophysiological abnormalities such as intra-atrial and inter-atrial conduction delay, as well as dispersion of atrial refractoriness in combination with other perioperative conditions [13,14]. P wave

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duration, which reflects the velocity and synchronization of atrial conduction, might be a potential predictor for POAF [14]. Although the predictive value of preoperative P-wave duration (PreOPWD) has been investigated extensively, the inconsistency results among difference studies necessitate further investigation. Therefore, in an effort to add to the evidence base, this study examines the predictive value of PreOPWD for POAF, then combines the results with similar studies and analyses the findings in a meta-analysis.

2. Methods

2.1. Study population

This study was conducted in two cardiac surgery centers in Beijing, China, between June 2010 and March 2012. All patients with normal sinus rhythm prior to undergoing first time isolated off-pump CABG were recruited consecutively. Patients needed to be older than 18 years of age and in normal sinus rhythm (SR) before surgery. Patients were excluded in the following cases: previous history of any kind of AF or atrial tachycardia; need for concomitant valvular surgery. The study was approved by the ethics committees of the university. Written informed consent was obtained from all patients. Patients' demographic data and clinical data were collected prospectively.

2.2. Surgical procedure

The patients underwent CABG in a standard fashion by the experienced surgical teams through median sternotomy. Briefly, after adequate stabilization, the procedure involved exposing and snaring the target vessel above the anastomotic site using a 4–0 prolene suture with a soft plastic snigger to prevent coronary injury. The coronary artery was then opened, and the anastomosis performed. Visualization was enhanced by the use of a surgical blower-humidifier. Conduits for bypass included the internal mammary artery, the saphenous vein and the radial artery, individually or in combination.

2.3. Postoperative care

All patients were followed up in the cardiac surgery ICU. Heart rate, central venous and arterial pressures were continuously monitored during the ICU stay. The fluid-management routine at ICU comprised 12 h infusion supplemented with potassium and magnesium to maintain electrolyte balance within normal range. Patients were weaned off mechanical ventilation when they demonstrated hemodynamic and respiratory stability, a peripheral temperature higher than 36 °C, and were cooperative and free of major bleeding. Chest tubes were removed within the second postoperative day.

All patients were continuously monitored in ICU using individual bedside monitors (PHILIPS, M8003A). After patients were transferred to the ordinary wards, they were monitored by telemetry (LENOVO, MB800) connected to a station monitoring system. The electrocardiographic data were stored for 24 h and reviewed on a daily basis by the cardiac surgery team. The printouts of all abnormal rhythms were also reviewed by the attending cardiologist who was blinded to the clinical outcomes.

The endpoint for the study was the onset of AF during the first week following CABG surgery. AF was defined as absent P wave before the QRS complex with irregular ventricular rhythm, which lasted 5 min or longer. Time of presentation, duration, and mode of conversion (spontaneous or pharmacologic) of each episode were recorded.

2.4. Preoperative P-wave duration

Preoperative standard 12-lead ECGs were obtained within 48 h of the scheduled surgery at a paper speed of 25 mm/s (Massachusetts 5500, General Electric Medial Systems, USA). All ECG tracings were calibrated to the standard 1 cm = 10mv. Following 10 min of rest in supine position, ECGs were recorded in a quiet room. Ten second samples of all 12 leads were recorded simultaneously. The PreOPWDs were measured on all simultaneously recorded 12 leads of the surface ECG using commercial software (Cardiosoft 6.5, General Electric Medial Systems, USA) by a nurse who was blinded to the patients' grouping. The mean P-wave durations for at least three complexes were calculated in each lead. The onset of the P-wave was defined as the junction between the isoelectric line and the beginning of P-wave deflection and the offset of the P-wave was defined as the junction between the end of the P-wave deflection and the isoelectric line [12]. P-wave duration was measured from the onset to the offset of the P-wave.

2.5. Meta-analysis

A meta-analysis of the association between PreOPWD and POAF was conducted according to “the guidelines of Meta-analysis of Observational Studies in Epidemiology Group (MOOSE)” [15]. Studies published prior to and including December 2017 were searched using PubMed, Web of Science, the Cochrane clinical databases, EMBASE, EBSCO, Elsevier, OVID, CINAHL, Springer, Proquest, CNKI (China National Knowledge Infrastructure) and Wanfang in English and Chinese. In addition, a manual search was performed using all review articles on this topic, reference lists of papers, and abstracts from conference reports. Key words and MeSH terms included in the search were related to “atrial fibrillation”, “atrial arrhythmia”; and “coronary artery bypass grafting”, “CABG”, “cardiac surgery”; and “predictor”, “risk factor”; and “P wave”, “electrocardiogram” and “signal average electrocardiogram”. Studies were included if they met the following criteria: (i) the patients had elective CABG surgery without concomitant cardiac or noncardiac surgical procedures; (ii) they were in sinus rhythm before surgery; (iii) the study was undertaken to evaluate the role of PreOPWD in the prediction of AF after CABG; and (iv) the primary endpoint was POAF lasting for ≥ 5 min. Twenty-two studies were considered suitable for review, however ten of these were missing control groups, two did not define AF as a primary outcome. Ten studies met the inclusion and exclusion criteria [9,12,14,16–22]. Because the data did not satisfy the heterogeneity test ($Q_2 = 38.41$, $P < 0.0001$), a random effects test was used, and the source of significant heterogeneity between studies was explored by sensitivity and subgroup analyses.

2.6. Statistical analysis

Continuous, normally distributed variables are expressed as mean \pm standard deviation and differences between groups were assessed using student *t*-test. Variables which are not normally distributed are expressed as medians (interquartile ranges) were compared by using the Mann-Whitney *U* test. Categorical data are presented as proportions and were analyzed with Chi-square or Fisher's exact test as appropriate. A multivariate logistical regression was used to identify the independent predictors of POAF. The best cutoff point for the PreOPWD and age in predicting the possibility of POAF were defined via a receiver-operating characteristic (ROC) curves analysis, then PreOPWD and age described as a categorical variable were entered multivariate model to evaluate its predictive value. The performance of the models was assessed by the ROC curve and the area under the curve (AUC). Accuracy of the

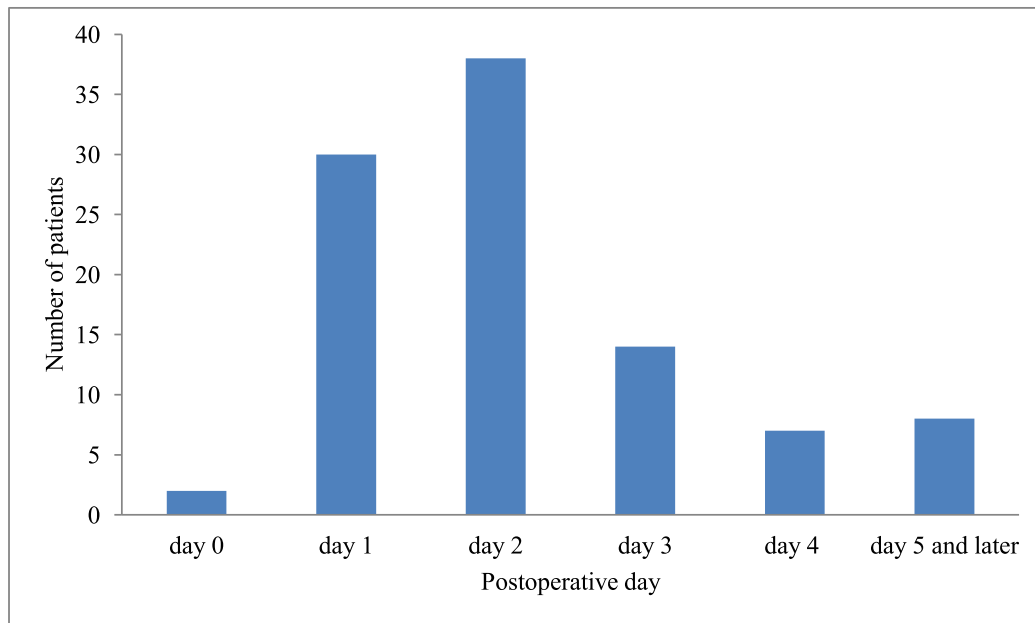


Fig. 1. Distribution of atrial fibrillation onset.

predictors was represented using the terms sensitivity and specificity. All statistical procedures were performed with SPSS for Windows version 16.0 (SPSS Inc, USA). The meta-analysis was performed with Review Manager version 4.2 (Revman, The Cochrane Collaboration, Oxford, United Kingdom). A two-tailed $P < 0.05$ was considered to indicate statistical significance.

3. Results

Of 328 eligible patients, 29 were excluded because of chronic AF ($n = 12$) or paroxysmal AF ($n = 8$), unwilling to participate ($n = 3$), and undergoing combined valve replacement and CABG ($n = 6$). Finally, 299 patients were analyzed. The mean age was 62.39 ± 9.37

Table 1
Preoperative patient characteristics.

Characteristics	AF ($n = 99$)	non-AF ($n = 200$)	t/χ^2	P value
Age (years)	65.94 ± 8.04	60.64 ± 9.50	-4.767	<0.001
Age ≥ 60 years	77(77.8)	105(52.5)	17.765	<0.001
Male	69(69.7)	157(78.5)	2.781	0.095
Mean body mass index (kg/m^2)	25.48 ± 3.29	25.56 ± 3.40	0.189	0.850
NYHA Classification			5.465	0.141
I	58 (58.6)	144 (72.0)		
II	32 (32.3)	42 (21.0)		
III	7 (7.1)	11 (5.5)		
IV	2 (2.0)	3 (1.5)		
Major comorbidities				
Hypertension	81 (81.8)	138 (69.0)	5.552	0.018
Diabetes mellitus	29 (29.3)	79 (39.5)	2.990	0.084
COPD	4 (4.0)	7 (3.5)	0.054	0.817
Myocardial infarction	57(57.6)	96 (48.0)	2.430	0.119
Cerebrovascular disease	21 (21.2)	30 (15.0)	1.806	0.179
Echocardiographic and ECG results				
Left atrial diameter (mm)	37.02 ± 6.70	36.51 ± 5.28	-0.722	0.471
LVEF (%)	62 ± 13	63 ± 12	0.485	0.628
Aortic regurgitation	16 (16.2)	12 (6.0)	8.056	0.005
Mitral regurgitation	26 (26.3)	31 (15.5)	4.971	0.026
P-wave duration (ms)	110.32 ± 13.13	102.28 ± 11.30	-5.483	<0.001
P-wave duration ≥ 105 ms	73(73.7)	71(35.5)	38.781	<0.001
Angiography results				
Triple vessel disease	93(93.9)	188(94.0)	0.001	0.983
Left main disease	38 (38.4)	72 (36.0)	0.162	0.687
Right coronary artery disease	95 (96.0)	193 (96.5)	0.054	0.817
Medication				
ACEI or ARB	63 (63.6)	137 (68.5)	0.707	0.400
Calcium channel blocker	38 (38.4)	72 (36.0)	0.162	0.687
β -blocker	88 (88.9)	179 (89.5)	0.026	0.872
Digoxin	3 (3.0)	8 (4.0)	0.009	0.926
Statins	86 (86.9)	174 (87.0)	0.001	0.975

Data are presented as n (%) or means \pm SD.

NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 2
Multivariate analysis of predictors of atrial fibrillation.

Variables	HR	95%CI	P value
Age (≥ 60 years)	2.72	1.51–4.90	0.001
Hypertension	2.10	1.08–4.07	0.028
P-wave duration (≥ 105 ms)	4.63	2.66–8.03	<0.001

HR, Hazard ratio; CI, confidence interval.

years, 33.1% developed AF, which occurred 2.30 ± 1.45 days after CABG. The majority (83.5%) had the first AF episode between postoperative days 1 and 3 (Fig. 1). The mean duration of AF was 4 (1–7) hours which were converted either spontaneously (10/99) or pharmacologically (89/99).

3.1. Univariate and multivariate analysis for predictor of POAF

Univariate analysis revealed that patients in the AF group were significantly older than non-AF group. PreOPWD was significantly longer among patients with POAF compared to those in non-AF. Patients with POAF were more likely to have a higher incidence of hypertension, aortic regurgitation, and mitral regurgitation (Table 1). Multivariate analysis showed that PreOPWD (odds ratio [OR] 1.05, 95% CI 1.03 to 1.08, $P < 0.001$), age (OR 1.06, 95% CI 1.03 to 1.09, $P < 0.001$), and hypertension (OR 2.60, 95% CI 1.29 to 5.25, $P < 0.01$) were independent predictors of POAF. A ROC curve was used to evaluate the sensitivities and specificities at different cut points. PreOPWD ≥ 105 ms had the best predictive value of the development AF with a sensitivity of 74% and specificity of 65%, respectively. The combination of PreOPWD ≥ 105 ms with age ≥ 60 years only increased specificity to 79%, but sensitivity decreased to 58%. Unadjusted PreOPWD ≥ 105 ms was significantly associated with POAF (OR 5.10, 95% CI 2.99 to 8.69; $P < 0.001$), this effect was still in existence after adjustment for age (OR 4.73, 95% CI 2.74 to 8.15; $P < 0.001$) and hypertension (OR 5.02, 95% CI 2.93 to 8.59, $P < 0.001$). Multivariate predictors were dichotomized on the basis of variable distribution, and a high-risk patient population was identified by age ≥ 60 years a PreOPWD ≥ 105 ms and hypertension (Table 2). The model discriminated between AF and non-AF under the AUC 0.76.

3.2. Meta-analysis

The meta-analysis that combined results from our study with 10 other similar studies and included a total of 3141 patients (Fig. 2). Characteristics of the eleven included studies were shown in Table 3. The prolonged PreOPWD was associated with a higher incidence of POAF. The heterogeneity test showed that there were significant differences between individual studies ($P < 0.0001$, $I^2 = 74\%$). Despite sensitivity and subgroup analysis were conducted, the heterogeneity was still significant. The weighted mean difference in PreOPWD between patients with AF and non-AF was 3.95 ms (Fig. 3).

4. Discussion

The main findings of this present prospective study were that a PreOPWD ≥ 105 ms predicted occurrence of POAF with a sensitivity of 74%, and a specificity of 65%. Although older age was also a predictor, when combined age ≥ 60 years with PreOPWD ≥ 105 ms, only increased specificity to 79%, but sensitivity decreased to 58%. In addition, the meta-analysis included in this study confirmed that prolonged PreOPWD was associated with greater risk of POAF.

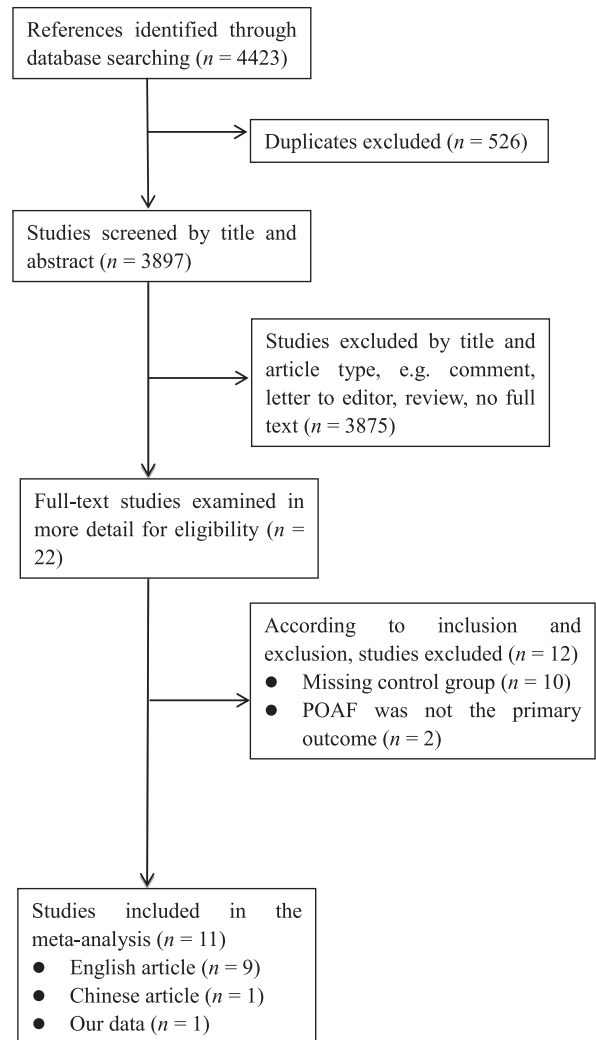


Fig. 2. Study selection process. POAF, Postoperative atrial fibrillation.

4.1. The preoperative P-wave duration

Although the underlying mechanisms of POAF remain unclear, animal and clinical studies shown that both substrate and trigger factors are mandatory for the initiation and maintenance of AF [23–26]. A structural substrate might be the consequence of an association of multiple predisposing factors (advanced age, hypertension, obesity, and left atrial enlargement). These factors might alter the atrial refractoriness and slow atrial conduction, which predisposes the occurrence of multiple re-entry wavelets [27]. A prolonged PreOPWD might indicate a delayed intra- and inter-atrial conduction or increased inhomogeneous conduction velocity of the atria [14,16–20]. Therefore, P-wave duration on the standard ECG could serve as a noninvasive marker of intra- and inter-atrial conduction disturbances.

Surgical procedures on the heart can produce atrial ischemic and damage, which will result in atrial and pericardial inflammation that may act as a triggering factor of POAF [28]. In patients with pre-existed AF substrate indicated by prolonged PreOPWD on the standard ECG may prolong atrial refractoriness leading to slow conduction and regions of block, a triggering factor could set up local areas of functional blocks resulting in the depolarising wavefront faces both refractory and excitable myocardium. This

Table 3
Characteristics of studies included in the meta-analysis.

First author(Ref#)	Year	Sample size(n, AF/non-AF)	The incidence of POAF(%)	Measurement of P wave duration
Klein M [16]	1995	16/29	36	Lead II P wave duration measurement was performed manually by three independent observers.
Stafford PJ [17]	1997	51/138	27	Lead II P wave duration measurement was performed manually by two independent observers.
Dimmer C [19]	1998	16/75	17.5	Lead I, II and III P wave duration was calculated by three independent blinded observers.
Aytemir K [18]	1999	19/34	35.8	Lead II P wave duration measurement was performed manually by two independent observers.
Chang CM [14]	1999	37/83	31	Lead II, III, aVF and V ₂ P wave duration in three consecutive beats was confirmed by an experienced cardiologist.
Caravelli P [20]	2002	56/73	43	One lead of lead I, II and III P wave duration was performed manually by two independent observers.
Amar D [9]	2004	508/1045	33	Lead II P wave duration was measured manually according to previously defined values for prolonged P wave duration (>110 ms) or PR interval (>180 ms)
Chandy J [12]	2004	81/219	27	Lead II P wave duration was measured manually.
Tongtong S [22]	2007	103/209	30	Lead II P wave duration was measured manually by two independent observers.
Sovilj S [21]	2010	14/36	28	Lead II P wave duration mean value and the standard deviation were calculated over all subsequent episodes of 15 min of the recorded data.
The present study	2017	99/200	33.1	The mean P-wave durations for at least three complexes were calculated in each lead by a blinded nurse with commercial software

POAF, postoperative atrial fibrillation.

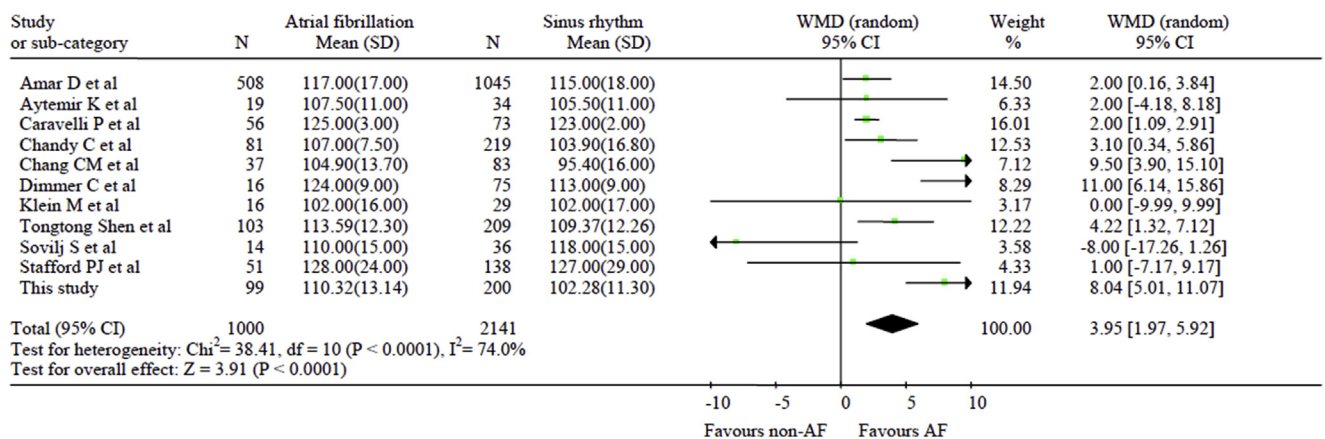


Fig. 3. Preoperative P-wave duration and the risk of atrial fibrillation after CABG with WMDs and 95% CIs.

makes the reentrant circuits possible to form leading to the initiation and maintenance of POAF [29].

4.2. Age and hypertension

Both advanced age and hypertension were found to be independent predictors of POAF in present study. Age-related structural changes, such as increased atrial fibrosis and atrial dilation, might result in alteration in the atrial refractory and conduction velocity, leading to increased incidence of POAF [30]. This is supported by the findings of Goette et al. [31], in which, right atrial appendage of 259 patients taken during cardiac surgery and atrial fibrosis, including interstitial and perivascular fibrosis, was quantitatively analyzed with point counting on stained paraffin section. They found that age was correlated positively with the amount of atrial fibrosis and P-wave duration. It is also confirmed in our study that patients' age correlated positively with PreOPWD, although the correlation was weak. After adjusted age, a PreOPWD ≥ 105 ms still was associated with significantly higher incidence of new-onset POAF.

Similarly, hypertension-related structural changes may have a significant role in the genesis of associated arrhythmias. A number of pathological changes such as fibrosis, resulting from chronic elevation of left ventricle filling pressures in a hypertrophic heart may contribute to the prolongation of atrial activation time [32]. It has been demonstrated that maximum P-wave duration was longer in patients with hypertension compared with controls [33]. However, information available in the study is not enough to explain this finding, further studies are required.

The present results confirm the high incidence of AF in patients undergoing CABG (33.1%) and the majority of the initial episodes of AF occurred within the first 3 days after surgery [1,9,10]. An increasing incidence of POAF in recent years that may be attributed, at least in part, to the frequent use of continuous postoperative rhythm monitoring. The rapid improvements of surgical and anesthetic technology, and major advances in the practice of percutaneous coronary revascularization procedures resulted in referral of significantly older and sicker patients to cardiac surgery compared to patients referred to open-heart surgical procedures about 20 years ago [1].

4.3. Study limitations

Firstly, continuous monitoring was conducted for only one week post-surgery, a higher incidence of POAF was likely. However, AF was rarely observed after the seventh postoperative day in previous studies [1,2]. Secondly, our data was collected five years ago, but it was a prospective study, and combined with a meta-analysis to further conform the results. Thirdly, the present study mainly focused on the PreOPWD, but surgical factors may play a role in the occurrence and maintenance of POAF. We will consider intra-operative and postoperative precipitating factors including examining the postoperative P-wave characteristics for POAF in future work to determine additional POAF prevention strategies.

5. Conclusions

This study confirmed that PreOPWD, among other predictive characteristics, is a powerful independent predictor of POAF. By using PreOPWD cutpoint of 105 ms or greater on standard ECG, patients might benefit from implementation of POAF prevention strategies.

Conflicts of interest

The authors declare that there are no any actual or potential conflicts of interest including any financial, personal or other relationships with other people or organizations.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.ijnss.2018.04.003>.

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