Europace (2012) **14**, 942–947
doi:10.1093/eupace/eur389

Frequent premature atrial complexes predict new occurrence of atrial fibrillation and adverse cardiovascular events

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Received 20 June 2011; accepted after revision 23 November 2011; online publish-ahead-of-print 19 December 2011

Aims To investigate the relation between baseline frequency of premature atrial complexes (PACs) and new atrial fibrillation (AF) and adverse cardiovascular events.

Method and results Four hundred and twenty-eight patients without AF or structural heart disease undergoing 24 h electrocardiography monitoring for palpitations, dizziness, or syncope were recruited. One hundred and seven patients with number of PACs at the top quartile (i.e. >100PACs/day) were defined to have frequent PACs. After 6.1-year follow-up, 31 patients (29%) with frequent PACs developed AF compared with 29 patients (9%) with PACs ≤100/day ($P < 0.01$). Cox regression analysis revealed that frequent PACs [hazard ratio (HR): 3.22 (95% confidence interval (CI): 1.9–5.5; $P < 0.001$)], age >75 years (HR: 2.3; 95% CI: 1.3–3.9; $P = 0.004$), and coronary artery disease (HR: 2.5; 95% CI: 1.4–4.4; $P = 0.002$) were independent predictors for new AF. Concerning the composite endpoint (ischaemic stroke, heart failure, and death), patients with frequent PACs were more at risk than those without (34.5 vs. 19.3%) (HR: 1.95; 95% CI: 1.37–3.50; $P = 0.001$). Cox regression analysis showed that age >75 years (HR: 2.2; 95% CI: 1.47–3.41; $P < 0.001$), coronary artery disease (HR: 2.2, 95% CI: 1.42–3.44, $P < 0.001$), and frequent PACs (HR: 1.6; 95% CI: 1.04–2.44; $P = 0.03$) were independent predictors for the secondary composite endpoint.

Conclusion Frequent PACs predict new AF and adverse cardiovascular events.

Keywords Premature atrial complexes • Atrial fibrillation and stroke

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice.[1] Irrespective of the pattern (paroxysmal, persistent, and permanent), AF is associated with an increased risk of ischaemic stroke, congestive heart failure, and death.[1–7] While prompt management of AF may avoid or reduce the incidence of these complications, AF is often not diagnosed until these complications occur: up to 25% of patients with AF-related stroke had AF first diagnosed at the time of stroke.[8] Early identification of patients at high risk of AF would enable more aggressive primary prevention and targeted intervention.

Premature atrial complex (PAC) is a common arrhythmia that is often considered a benign phenomenon.[9–11] The prevalence has been reported to be as high as 73% in young individuals,[9] and 100% in apparently healthy older subjects.[10,11] Despite its benign concept, PACs are more frequent in patients with underlying cardiac conditions such as coronary heart disease, chronic rheumatic heart disease, left ventricular dysfunction, hypertension, and hyperthyroidism.[12] In addition, in patients with paroxysmal AF, rapid runs of PACs originating from arrhythmogenic foci resident in the pulmonary veins often precede episodes of AF.[13–18]

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Premature atrial complexes can be readily identified and quantified by 24 h electrocardiography (ECG) recording, and may thus serve as a surrogate marker for paroxysmal AF. It nonetheless remains unclear whether frequent PACs can predict the new occurrence of AF, as well as other adverse cardiovascular events such as ischaemic stroke, heart failure, and death in patients with only mild symptoms like palpitation. The aim of this study was to investigate the relation between the baseline frequency of PACs and the new occurrence of AF as well as other adverse cardiovascular events in patients with mild symptoms.

Methods

Patients

Between July 2002 and December 2003, 743 consecutive patients with palpitations, dizziness, or syncope were referred to our non-invasive cardiology laboratory for elective 24 h ECG monitoring. Patients were excluded if they had previously documented AF or AF diagnosed during 24 h ECG monitoring, high-grade atrio-ventricular block, pacemaker or implantable cardioverter defibrillators, chronic rheumatic heart disease, history of congestive heart failure, or ischaemic stroke. The final analysis thus involved 428 patients. Patients with total number of PACs at the top quartile of the present cohort (i.e. more than 100 beats/day) were considered to have frequent PACs.

Study design

Demographic data, cardiovascular risk factors, indications for 24 h ECG monitoring, and medications were recorded. Hypertension was defined as resting systolic or diastolic blood pressure $\geq$140/90 mmHg on two occasions or prescription of anti-hypertensive drugs. Diabetes mellitus was defined as a serum fasting glucose $\geq$7.0 mmol/L or prescription of anti-diabetic medication. Smoking status was recorded as smoker (past and current) or non-smoker. A resting 12-lead ECG was recorded (paper-speed: 50 mm/sec) to provide baseline rhythm and 24 h ECG monitoring (GE Marquette SEER digital system) performed to assess frequency of PACs. All 24 h ECG recordings were reviewed and edited manually. Recordings had to exceed 20 h and be of good quality to be analysed by two independent cardiologists. Premature atrial complexes were quantified using the total number of PACs/day. Premature atrial complexes at the top quartile, i.e. PACs >100 beats/day in the present cohort, were classified as frequent. Patients were prospectively followed up in our medical and/or cardiac outpatient clinic. The new occurrence of AF, ischaemic stroke, and congestive heart failure or death within the follow-up period was retrieved from the medical records and discharge summaries of our hospital as well as other institutions. Patients who failed to attend the clinic were contacted by phone. The primary endpoint of new occurrence of AF was defined as AF documented by at least two standard 12 lead ECGs at least 4 h apart. The secondary endpoint was a composite of ischaemic stroke, congestive heart failure, or death during the follow-up period. Ischaemic stroke was defined as a neurological deficit of sudden onset that persisted for more than 24 h, and corresponded to a vascular territory in the absence of primary haemorrhage, and that could not be explained by other causes (trauma, infection, vasculitis). It was confirmed by computerized axial tomography or magnetic resonance imaging of the brain. Congestive heart failure was diagnosed according to the modified Framingham criteria.[19,20]

Statistical analysis

Continuous variables are expressed as mean $\pm$ SD. Statistical comparisons were made using Student's *t*-test, Pearson χ^2 test, as appropriate. As patients at the top quartile of total number of PACs/day were deemed to have frequent PACs, their clinical parameters were compared with those of the bottom three quartiles. Kaplan–Meier survival functions and the log-rank test were used to compare the survival distributions between groups, and the Cox proportional hazards regression model was used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) of new-onset AF, ischaemic stroke, and congestive heart failure between frequent PAC patients and non-frequent PAC patients. To adjust for some potential confounder effects like age and smoking status, Cox proportional hazards regression analyses were also performed by including other baseline demographic factors. Variables selections were performed by the forward selection method at which the variable with the smallest *P* value ($\leq$0.1) was entered into the model at each step until the *P* values of all other variables were greater than 0.1. Calculations were performed using SPSS software (version 18.0). A *P* value <0.05 was considered statistically significant.

Results

A total of 428 patients (66 $\pm$ 10.2 years, men: 43.7%) were recruited in this study. The mean number of PACs was 533.5 $\pm$ 2108.9 beats/day; the median number of PACs was 12 beats/day (range: 0–21 637 beats/day; inter-quartile range: 3–100 beats/day). One hundred and seven patients with total number of PACs/day at the top quartile of the present cohort (i.e. PACs >100 beats/day) were considered to have frequent PACs and were compared with patients of the three lower quartiles. *Table 1* summarizes the clinical characteristics of the study population. There were no significant differences in gender, prevalence of diabetes, hypertension, or coronary artery disease, indications for 24 h ECG monitoring, or cardiovascular medication. Patients with frequent PACs were nonetheless older (71.3 $\pm$ 9.8 vs. 65.1 $\pm$ 9.9 years, $P < 0.01$) and were more likely to be a smoker (36.4 vs. 24.6%, $P = 0.02$).

Prediction of new occurrence of atrial fibrillation

After a mean follow-up of 6.1 $\pm$ 1.3 years, 31 patients (29%, 48.3 per 1000 patient-years) with frequent PACs and 29 patients (9.0%, 14.3 per 1000 patient-years) without frequent PACs developed new-onset AF ($P < 0.001$) (*Table 2*). *Figure 1* depicts the Kaplan–Meier AF-free survival in patients with and without frequent PACs. Patients with frequent PACs had a higher incidence of AF than those without frequent PACs with an HR of 3.9 (95% CI: 3.2–11.1; $P < 0.001$). The 1- and 2-year incidence of AF were, respectively, 7.5 and 11.2% in patients with frequent PACs, both significantly higher than those of patients without frequent PACs (1.9 and 2.5%, $P < 0.001$). Cox regression analysis revealed the presence of frequent PACs (HR: 3.22; 95% CI: 1.9–5.5; $P < 0.001$), age >75 years (HR: 2.3; 95% CI: 1.3–3.9; $P = 0.004$), and coronary artery disease (HR: 2.5; 95% CI: 1.4–4.4; $P = 0.002$) to be independent predictors for the new occurrence of AF.

Table 1 Baseline characteristics

	All	Frequent PACs		
		No	Yes	
	(*n* = 428)	(*n* = 321)	(*n* = 107)	*P* value
Age (years)	66.7 ± 10.2	65.1 ± 9.9	71.3 ± 9.8	<0.01*
Age>75, *n* (%)	112 (26.2)	67 (20.9)	45 (42.1)	<0.01*
Male sex, *n* (%)	187	137 (42.7)	50 (46.7)	0.47
Hypertension, *n* (%)	194	142 (44.2)	52 (48.6)	0.43
Diabetes, *n* (%)	73	52 (16.2)	21 (19.6)	0.41
Cigarette smoker, *n* (%)	118	79 (24.6)	39 (36.4)	0.018*
Coronary artery disease, *n* (%)	75	55 (17.1)	20 (18.7)	0.71
Echocardiographic parameters				
Left atrial size, cm	3.8 ± 0.8	3.7 ± 0.8	4.0 ± 0.8	<0.01*
Left ventricular ejection fraction, %	65.8 ± 8.1	66.4 ± 8.3	64.0 ± 6.9	<0.01*
CHADS2				0.01*
0, *n* (%)	173 (40.4)	140 (43.8)	33 (30.8)	
1, *n* (%)	146 (34.1)	107 (33.4)	39 (36.4)	
2, *n* (%)	91 (22.0)	65 (20.3)	26 (24.3)	
3, *n* (%)	17 (4.0)	8 (2.5)	9 (8.4)	
Indications for 24 h ECG monitoring				0.16
Palpitation, *n* (%)	235 (54.9)	182 (56.7)	53 (49.5)	
Dizziness, *n* (%)	108 (25.2)	82 (25.5)	26 (24.3)	
Others, *n* (%)	85 (19.9)	57 (17.8)	28 (26.2)	
Medications				
Calcium channel blocker, *n* (%)	202 (47.2)	145 (45.2)	57 (53.3)	0.15
Beta-blocker, *n* (%)	190 (44.4)	142 (44.2)	48 (44.9)	0.91
ACEI, *n* (%)	168 (39.3)	121 (37.7)	47 (43.9)	0.25
ARB, *n* (%)	19 (4.4)	14 (4.4)	5 (4.7)	0.89
Aspirin, *n* (%)	107 (25.0)	88 (23.7)	19 (17.8)	0.05*

*$P < 0.05$.

Prediction of ischaemic stroke, congestive heart failure, and mortality

The secondary composite endpoint of ischaemic stroke, congestive heart failure, and death occurred during the follow-up period in 99 out of 428 patients (23.1%): 37 in 107 patients (34.5%) with frequent PACs, and 62 in 321 patients (19.3%) without frequent PACs (HR: 1.95; 95% CI: 1.37–3.50; $P = 0.001$) (*Figure 2A*). *Table 3* summarizes the clinical characteristics of patients with and without the secondary endpoint. Patients who reached this secondary endpoint were significantly older (72.5 ± 9.6 vs. 64.9 ± 9.7 years, $P < 0.001$), were more likely to be male (55.6 vs. 40.1%, $P = 0.007$), and have hypertension (55.6 vs. 42.2%, $P = 0.02$), or diabetes (25.3 vs. 14.6%, $P = 0.01$), be a smoker (39.4 vs. 24.0%, $P = 0.003$), or have coronary artery disease (33.3 vs. 12.8%, $P < 0.001$), or frequent PACs (37.4 vs. 21.3%, $P = 0.001$). Cox regression analysis showed that age >75 years (HR: 2.2; 95% CI: 1.47–3.41; $P < 0.001$), coronary artery disease (HR: 2.2; 95% CI: 1.42–3.44; $P < 0.001$), and frequent PACs (HR: 1.6; 95% CI: 1.042.44; $P = 0.03$) were independent predictors for the occurrence of ischaemic stroke, congestive heart failure, and death.

In the analysis of the sub-components of the secondary endpoint, there were 41 ischaemic strokes (15.4 per 1000 patient-years), 35 instances of congestive heart failure (13.1 per 1000 patient-years), and 60 deaths (22.5 per 1000 patient-years) during the follow-up period. In the 41 ischaemic strokes observed, 16 occurred in patients with frequent PACs, and 25 (7.8%) in those without (HR: 2.1; 95% CI: 1.1–4.8; $P < 0.001$) (*Figure 2B*). In addition, among these 41 ischaemic stroke patients, 8 developed new-onset AF prior to ischaemic stroke. Likewise, more patients with frequent PACs developed congestive heart failure (HR: 2.2; 95% CI: 1.2–5.6; $P = 0.02$), or died (HR: 1.8; 95% CI: 1.1–3.6, $P = 0.02$) (*Figure 2C* and *D*). For the 35 patients developed congestive heart failure, only 2 were preceded the development of AF.

Discussion

In this study, we compared the incidence, time course, and clinical predictors of new occurrence of AF and adverse cardiovascular events in patients with and without frequent PACs (>100 PACs/day). Our results showed that patients with frequent PACs were at greater risk of new occurrence of AF, and other adverse cardiovascular events including ischaemic stroke, heart failure, and

Table 2 Clinical characteristics of patients with and without new onset AF

	AF		
	No ($n = 368$)	Yes ($n = 60$)	*P* value
Age (years)	65.6 ± 9.9	73.3 ± 9.3	<0.001*
Age>75, *n* (%)	82 (22.3)	39 (50.0)	<0.001*
Male sex, *n* (%)	156 (42.4)	31 (51.7)	0.18
Hypertension, *n* (%)	158 (42.9)	36 (60.0)	0.01*
Diabetes, *n* (%)	62 (16.8)	11 (18.3)	0.78
Cigarette smoker, *n* (%)	94 (25.5)	24 (40)	0.02*
Coronary artery disease, *n* (%)	54 (14.7)	21 (35.0)	<0.001*
Echocardiographic parameters			
Left atrial size, cm	3.8 ± 0.8	4.0 ± 0.8	0.08
Left ventricular ejection fraction, %	66.1 ± 8.1	63.6 ± 7.1	0.02*
CHADS2			<0.001*
0, *n* (%)	163 (44.4)	10 (16.7)	
1, *n* (%)	121 (33.0)	25 (41.7)	
2, *n* (%)	68 (18.5)	23 (38.3)	
3, *n* (%)	15 (4.1)	2 (3.3)	
Frequent PACs, *n* (%)	76 (20.1)	31 (51.7)	<0.001*

*$P < 0.05$.

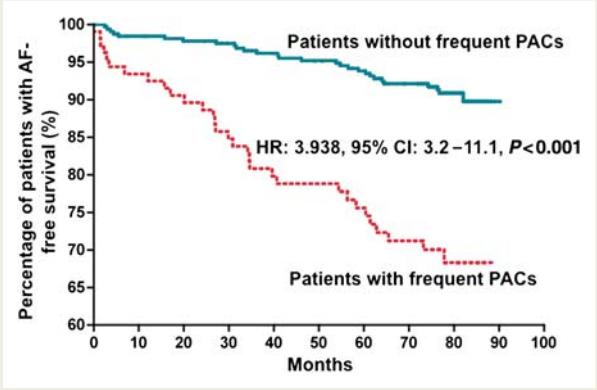

Figure 1 Kaplan–Meier estimate of percentage of new-onset AF-survival in patients with and without frequent premature atrial complexes.

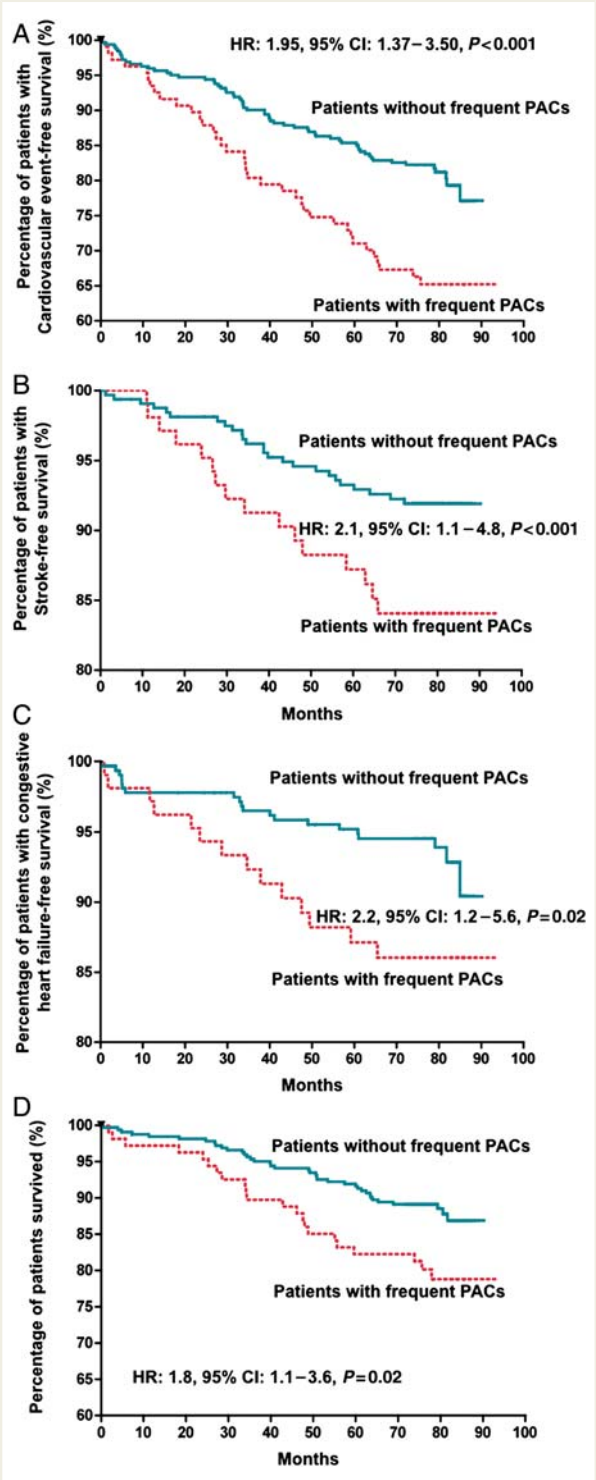

Figure 2 Kaplan–Meier estimate of percentage of cardiovascular event-free survival (*A*), ischaemic stroke free-survival (*B*), new-onset heart failure-free survival (*C*), and overall survival (*D*) in patients with and without frequent premature atrial complexes.

mortality. For patients with frequent PACs, more aggressive management including intense follow-up and risk factor control may allow early detection, and thus prompt management of AF.

Although the use of long-term anti-coagulants can effectively prevent 60% of AF-related ischaemic strokes, up to 25% of patients with AF-related stroke had AF diagnosed only at the time of stroke,[8] precluding them from any primary preventive therapy. Early identification of patients at risk of AF and ischaemic stroke may enable more timely intervention to prevent these complications.[21–23] Conventional risk factors for AF include male gender, advanced age, diabetes, hypertension, hyperthyroidism, and the presence of structural heart disease such as coronary heart disease, valvular heart disease, and congestive heart failure.[6,24,25] Recent advances in the understanding of the pathophysiology of AF suggest that rapid runs of PACs originating from atrial muscle

Table 3 Clinical characteristics of patients with and without secondary endpoints (ischaemic stroke, congestive heart failure, or death)

	Secondary endpoints		
	No ($n = 329$)	Yes ($n = 99$)	*P* value
Age (years)	64.9 ± 9.7	72.5 ± 9.6	<0.001*
Age>75, *n* (%)	66 (20.1)	46 (46.5)	<0.001*
Male sex, *n* (%)	132 (40.1)	55 (55.6)	0.007*
Hypertension, *n* (%)	139 (42.2)	55 (55.6)	0.02*
Diabetes, *n* (%)	48 (14.6)	25 (25.3)	0.01*
Cigarette smoker, *n* (%)	79 (24.0)	39 (39.4)	0.003*
Coronary artery disease, *n* (%)	42 (12.8)	33 (33.3)	<0.001*
Echocardiographic parameters			
Left atrial size, cm	3.8 ± 0.8	3.9 ± 0.8	0.16
Left ventricular ejection fraction, %	66.5 ± 7.9	63.5 ± 8.1	0.001*
CHADS2			<0.001*
0, *n* (%)	152 (46.3)	21 (21.2)	
1, *n* (%)	108 (32.9)	38 (38.4)	
2, *n* (%)	59 (18.0)	32 (32.3)	
3, *n* (%)	9 (2.7)	8 (8.1)	
Frequent PACs, *n* (%)	70 (21.3)	37 (37.4)	0.001*

*$P < 0.05$.

sleeves surrounding the pulmonary veins can initiate and perpetuate AF.[13–17,26,27] In the case of paroxysmal AF, the occurrence of PACs often precedes episodes of AF.[13–17] Successful electrical isolation of the pulmonary vein in patients with paroxysmal AF reduces the number of PACs.[28] More interestingly, an increased number of PACs after successful pulmonary vein ablation predicts AF recurrence in the case of paroxysmal AF.[28] This suggests that PACs may be a surrogate marker and/or portent for new AF. This possibility was first explored in patients with acute ischaemic stroke, in whom undiagnosed AF would likely be more prevalent and contribute to their strokes.[29,30] Wallmann *et al.*[29] studied the association between the frequency of PACs and the new occurrence of AF in 99 patients with acute ischaemic stroke and no pre-existing AF. After a mean follow-up of 22.4 months, 33% of patients with frequent PACs defined as the total number of PACs at the top quartile (PACs >70 beats/day in this cohort) developed new AF compared with only 5% in those without frequent PACs.[29] Consistently, a recent population-based study involving 687 apparently healthy individuals found a similar association between high frequency of PACs and the development of AF, albeit with a higher cut-off for the definition of frequent PACs (≥720 PACs/day).[31] In this study, after a median follow-up of 6.3 years, 7 out of 99 patients with ≥720 PACs/day (12.8 per 1000 patient-years) developed new AF compared with only 4.3 per 1000 patient-years in patients with <720 PACs/day ($P = 0.008$). More importantly, frequent PACs (≥720 PACs/day) was also associated with a higher risk of stroke (18.8 vs. 4.9%, $P = 0.0002$) as well as total mortality (37.2 vs.18.9%, $P = 0.005$).[31] Our study extends these observations to patients with symptoms suggestive of possible cardiac arrhythmias but without pre-existing AF that a high frequency of PACs was associated with a subsequent occurrence of AF. In stark contrast to this study, and despite a much lower cut-off for frequent PACs in our study (>100 PACs/day), the incidence of new AF in our cohort of symptomatic patients was nearly four-fold that reported among asymptomatic individuals. The most plausible explanation is that among symptomatic patients, the likelihood of developing clinical AF is much higher than in those without symptoms. This underlies the rationale that the frequency of PACs may offer an effective screening tool to identify patients at high risk of developing new AF.

While it is conceivable that the presence of frequent PACs predicts the development of new AF, the mechanisms by which frequent PACs result in an increased risk of other adverse events are not as clear. A previous population-based cohort documented that frequent PACs was an independent risk factor for ischaemic stroke. In a cohort of 402 men born in 1914 with no previously documented cardiovascular disease, Engstrom *et al.*[32] demonstrated that PACs more than 218 beats/day *per se* was associated with an increased incidence of stroke (relative risk = 1.9). The increased risk of these adverse events may be attributable to a higher proportion of patients with frequent PACs developing AF, but there may also be alternative explanations. For instance, PACs are more common in patients with underlying cardiac conditions including coronary heart disease, chronic rheumatic heart disease, left ventricular dysfunction, hypertension, and hyperthyroidism.[12] Any of these may increase the incidence of adverse cardiovascular events even in the absence of AF.

Taken collectively, our results indicate that frequent PACs (>100 PACs/day) among those with symptoms suggestive of cardiac arrhythmias, confers a significantly higher risk of new AF, ischaemic stroke, heart failure, and death. A more intense follow-up and repeated 24 h ECG monitoring may allow early detection of AF, and thus allow implementation of effective preventive measures including anti-coagulation in high-risk subjects.

Study limitations

This study had several limitations. First, the diagnosis of frequent PACs was arbitrary and lacked consensus. Our data suggested that a cut-off of >100 PACs/day (the top quartile) would allow better risk stratification of patients; apparently, different cut-offs have been found useful in different patient populations. Second, asymptomatic episodes of AF were not assessed routinely by ambulatory ECG monitoring. In fact, the lack of follow-up 24 h ambulatory ECG screening was one of the major shortcomings of our work. Third, although we have controlled the potential confounders using multivariate logistic regression, alternative strategy such as the use of case–control design may also be appropriate. Fourth, all patients had symptoms such as palpitation, dizziness, or syncope rather than being asymptomatic, and thus represent a sicker cohort. The extrapolation of our results to other patient populations might therefore be inappropriate. Nonetheless, the current study provides data that support the potential use of PACs in symptomatic patients to stratify their risks.

Conflict of interest: none declared.

Funding

This work was supported by the Small Project Fund from the University of Hong Kong (201007176180 to C.-W.S.).

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