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Original Article

Risk factors for the development of incident atrial fibrillation in patients with cardiac implantable electronic devices

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ABSTRACT

Introduction: Cardiac implantable electronic devices (CIEDs) can detect atrial fibrillation (AF) early and accurately. Risk factors for the development of new-onset AF in patients with CIEDs remains uncertain.
Methods: Patients with CIEDs who visited Chiba University Hospital between January 2016 and December 2016 were enrolled. We only included patients without single chamber CIEDs or a known history of AF.
Results: Of 371 patients with CIEDs, 78 (21.0%; median age 61.0 years, 65.5% male) developed new-onset AF. Multivariate analysis demonstrated that independent predictors for the development of new or incident AF were age ≥65 years (odd ratio [OR] 2.76, 95% confidence interval [CI] 1.54–4.96, P = 0.001), diabetes mellitus (OR 2.24, 95% CI 1.20–4.19, P = 0.011), congestive heart failure (OR 1.94, 95% CI 1.06–3.54, P = 0.031), and left atrial volume index > 34 ml/m^2 (OR 3.51, 95% CI 1.96–6.25, P < 0.001). Based on these 4 clinical factors (age ≥ 65, diabetes mellitus, congestive heart failure, left atrial volume index > 34 ml/m^2) there was a good predictive ability for new AF development (AUC 0.728) and clinically usefulness using decision curve analysis.
Conclusions: A substantial number of patients with CIEDs develop new-onset AF. Four clinical factors (age ≥ 65, diabetes mellitus, congestive heart failure, left atrial volume index > 34 ml/m^2) independently predicted new-onset AF and may provide an approach to clinically useful risk assessment for incident AF.

1. Introduction

Atrial fibrillation (AF) is associated with an increased risk of stroke, heart failure, and mortality [1]. Therefore, early detection of new-onset incident AF may allow the timely initiation of treatment to prevent not only from progression of AF, but also from the consequences of AF. However, a substantial number of patients has no symptoms regarding AF [2], and are often under-diagnosed by conventional diagnostic methods such as physical examinations, 12-lead electrocardiogram (ECG), and 24-hour Holter ECG [3]. Unfortunately, asymptomatic and short-term AF is sometimes newly diagnosed after admission following an acute stroke or transient ischemic attack (TIA) [4].

Cardiac implantable electronic devices (CIEDs) can automatically record all spontaneous episodes of arrhythmia using programmable detection criteria, and continuous ECG monitoring allows the detection of intermittent and short-term AF regardless of the presence of symptoms. Previous studies demonstrated that atrial high rate episodes (AHREs) detected by CIEDs have a high correlation with clinically documented AF [5], and are independently associated with an increased risk of ischemic stroke and systemic embolism [6–8].

Risk factors for the development of new-onset AF in patients with CIEDs remains uncertain. In the present study, we investigated incident AF in a cohort of patients with CIEDs, and determine clinical risk factors that were independently associated with the development of new-onset AF. Second, we tested a risk factor cluster that was associated with a good probability of new-onset AF development amongst CIED patients.

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2. Material and methods

We enrolled the patients receiving pacemakers, implantable cardioverter defibrillator (ICD), and cardiac resynchronization therapy (CRT) with or without defibrillation, who visited Chiba University Hospital between January 2016 and December 2016. Patients were eligible for inclusion if they had at least 1 follow-up visit and device interrogation after CIED implantation. Patients who had a prior history of AF or had single-chamber CIED implanted were excluded. If pacing mode of VVI or AAI was set even in patients with dual-chamber CIEDs, we excluded these patients. Of the total number of CIED patients (n = 504) attending our unit, total of 371 patients (73.6%) were included in the present analysis. The present study was conducted with the approval of the Ethics Committee of Chiba University Hospital.

We retrospectively reviewed the patients' medical records, and collected clinical information on age, gender, body surface area, systolic/diastolic blood pressure, alcohol consumption, indication for CIEDs (sick sinus syndrome, atrioventricular block, ventricular tachycardia (VT) or fibrillation (VF), and chronic heart failure), past history of stroke or TIA, underlying heart disease (coronary artery disease, hypertrophic cardiomyopathy, dilated cardiomyopathy, and valvular heart disease), comorbidity (hypertension, diabetes mellitus, peripheral artery disease, and chronic obstructive pulmonary disease), and medication (beta-blocker, ACE inhibitor/ARB, statin, diuretics, and class I and III antiarrhythmic agent) at the CIEDs implantation. Furthermore, data on 12-lead ECG, laboratory data (estimated glomerular filtration rate (eGFR), brain natriuretic peptide (BNP), thyroid stimulating hormone (TSH), and free thyroxine (FT4)), and transthoracic echocardiography (left ventricular ejection fraction (LVEF) and left atrial volume index (LAVI)) were also collected. Echocardiographic images were acquired in the standard parasternal and apical views. LVEF was assessed by Simpson's biplane method of disks, left atrial (LA) volume by the formula; LA volume = $\pi / 6$ ($D_1D_2D_3$); where D1 was the antero-posterior LA dimension in parasternal long axis view, D2 and D3 was short- and long-axis in the apical 4 chamber view. LAVI was also calculated as LA volume / BSA [9]. Prior history of AF was defined as a documented AF on 12-lead ECG or Holter ECG monitoring, and such patients were excluded from our study cohort. Patients attended for follow-up every 3 to 6 months, at which time the device diagnostic information was interrogated and stored. All of the CIEDs were programmed to the nominal setting, which detected any episodes of arrhythmia. We defined the CIEDs-detected AF as the AHREs lasting at least 5 min with atrial rate ≥180 beats/min. AHREs with the longest duration of < 5 min were excluded from the CIEDs-detected AF given that previously published studies suggested that the 5 minute cut-off value excluded most episodes of over-sensing due to mechanical problems and appropriately detected clinical AF [5,10]. Device diagnostic information on AHREs was reviewed by at least 1 experienced electrophysiologist, blinded to clinical outcomes.

We calculated the $CHADS_2$ and CHA_2DS_2-VASc scores, which are well established clinical risk scores for predicting stroke and thromboembolism in patients with AF [11,12]. The HATCH score, which is a risk score for predicting the clinical progression of paroxysmal to persistent AF, was also calculated [13]. One recent study suggested that the HATCH score was useful in estimation and stratification of the development of new AF [14]. The study population was initially categorized into the two groups according to whether the CIEDs-detected AF was recorded or not. The former was defined as the 'New-onset AF' group, and the latter as the 'No AF' group.

Furthermore, a subanalysis was performed to assess the relationship between risk factors for new-onset AF and duration time of AHRE. Duration time of AHRE was divided into 3 groups; 5 min ≤ AHRE < 1 h, 1 h ≤ AHRE < 24 h, and 24 h ≤ AHRE, and was compared with score of risk factors for development of new-onset AF.

Continuous variables are presented as the mean ± standard deviation or median with interquartile range (IQR), and categorical variables as frequency (percentage). Continuous variables were compared using Student's *t*-test or Mann-Whitney *U* test, as appropriate. Categorical data were analyzed using the Chi-square test. To assess risk factors for the development of new-onset AF, we used logistic regression model by adding variables that were significant (P value < 0.10) from the univariate analysis.

Receiver-operating characteristic (ROC) curve analysis was performed to estimate continuous variables with the risk scores for the development of new AF based on an estimated area under the curve (AUC), which was used as an indicator of predictive value of the risk scores (often referred to as c-indexes). Comparisons of ROC curves were performed according to DeLong et al. [15]. To assess the risk scores for clinical utility, we also performed decision curve analysis, which was established by Vickers and Elkin for evaluating and comparing the clinical net benefit of prediction models [16]. The clinical net benefit is calculated by summing the benefits (true positive) and subtracting the harms (false positive). The result of this analysis is presented with the selected probability threshold plotted on the x-axis and the benefit of the evaluated model on the y-axis. SPSS Statistic ver. 24 (IBM, New York, NY, USA) and STATA 13 (STATA Inc., USA) were used for the analysis. P values < 0.05 were considered statistically significant.

3. Results

Baseline clinical characteristics of the 'New-onset AF' and the 'No AF' group are shown in Table 1. Mean age of the included patients was 61.0 ± 14.9 years old, and 243 (65.5%) were male. Overall median follow-up period was 55.0 (IQR 29.0–90.0) months. Of the 371 patients with CIED, 35.0% had pacemakers, 47.2% ICD, and 17.8% CRT. Indication for CIEDs included sick sinus syndrome (7,3%), atrioventricular block (29.1%), and VT/VF or chronic heart failure (63.6%).

Seventy-eight patients (21.0%) developed new-onset CIEDs-detected AF during the follow-up period (New-onset AF group), and 293 (79.0%) had no CIEDs-detected AF (No AF group). Compared to the No AF group, the New-onset AF patients were older with more prevalent hypertension, diabetes mellitus, and heart failure. The eGFR was significantly lower and left atrial diameter was significantly higher in the New-onset AF group, compared to the No AF group. We assessed cut-off value of eGFR ≤65 ml/min/1.73 m^2 and left atrial volume index > 34 ml/m^2 using ROC curve analysis. The proportion of pacemaker, ICD, and CRT was not significantly different between New-onset AF group and No AF group. In addition, atrial and ventricular pacing rate was also not significantly different between two groups.

Using a multivariate logistic regression analysis (Table 2), adjusting for age ≥65, hypertension, diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease, hypertrophic cardiomyopathy, eGFR ≤65 ml/min/1.73 m^2, left atrial volume index > 34 ml/m^2, and Class I and III antiarrhythmic agent, independent predictors for the development of new-onset AF were age ≥65 (odd ratio [OR] 2.76, 95% confidence interval [CI] 1.54–4.96, P = 0.001), diabetes mellitus (OR 2.24, 95% CI 1.20–4.19, P = 0.011), congestive heart failure (OR 1.94, 95% CI 1.06–3.54, P = 0.031), and left atrial volume index > 34 ml/m^2 (OR 3.51, 95% CI 1.96–6.25, P < 0.001).

Based on these 4 clinical factors (age ≥ 65, diabetes mellitus, congestive heart failure, left atrial volume index > 34 ml/m^2), each component of the score was assigned 1 point, giving a score range from 0 to 4 points; mean number of clinical factors was higher in the New-onset AF group (2.2 vs. 1.3, P < 0.001). The mean $CHADS_2$, CHA_2DS_2-VASc and HATCH scores were also higher in the New-onset AF group than the No AF group (Table 3). ROC curve analysis showed a good predictive ability of our 4 risk factor cluster (age ≥ 65, diabetes mellitus, congestive heart failure, left atrial volume index > 34 ml/m^2) for the development of new-onset AF, with an AUC of 0.728 (95% CI; 0.680–0.773, P < 0.001), whereby ≥2 risk factors had the best predictive value with 74.4% sensitivity and 58.7% specificity.

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