CLINICAL STUDY

Prediction of Atrial Fibrillation Being Asymptomatic at First Onset by Cardiac Pacing

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Summary

Asymptomatic or silent atrial fibrillation (AF) has long been a clinical problem due to the incidence of ischemic stroke. A method is needed to predict the development of silent AF before the occurrence of ischemic stroke. This study was focused on the symptoms of AF, especially palpitation, in pacemaker patients. We assessed the hypothesis that absence of palpitation during rapid ventricular pacing could be a predictor of future onset AF being asymptomatic.

In this study, we assessed the presence of symptoms during RV pacing and AF symptoms on 145 pacemaker patients at the outpatient clinic by VVI pacing at 120 ppm. The relationship between symptoms during RV pacing and symptom during AF was assessed. The predictive value of absence of symptom during RV pacing on AF being asymptomatic was assessed.

Of 145 patients, 74 had previous AF episode. Among the AF patients, absence of symptom during VVI pacing was associated with AF being asymptomatic.

Of 145 patients, 71 had no previous AF events. There were 14 patients who had new-onset AF or atrial flutter (AFL) after the device implantation. Four of the 14 patients (28.6%) were symptomatic during first AF/AFL episode, and 10 (71.4%) were asymptomatic during first-onset AF. All ten patients who were asymptomatic during cardiac pacing test were asymptomatic during their initial episodes of AF as well.

This study showed that absence of symptoms during rapid ventricular pacing was associated with first-onset AF being asymptomatic.

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Key words: Pacemaker, Cardiogenic strokes, Asymptomatic atrial fibrillation

Asymptomatic or "silent" atrial fibrillation (AF) has long been a clinical problem due to the incidence of ischemic stroke.[1-3] Mortality in patients with ischemic stroke provoked by AF is high. A method is needed to predict the development of silent AF before the occurrence of ischemic stroke, especially in patients with higher $CHADS_2$ or CHA_2DS_2-VASc score.[3-6]

Pacemaker-implanted patients have a high incidence of AF episodes, and these AF episodes were detected by a remote monitoring system or routine pacemaker check at the pacemaker clinic.[1,2] At the pacemaker check, we found completely asymptomatic patients during RV pacing to measure pacing threshold, and most of those patients seemed to be asymptomatic during AF episodes. Thus, we hypothesized that if the patients were completely asymptomatic during cardiac pacing, those patients' AF could be asymptomatic. The relationship between symptoms during cardiac pacing and AF symptoms is unknown. Since now, there is no prediction method for silent AF before AF documentation. This study was focused on AF symptoms in pacemaker patients to reveal the characteristics of silent AF patients and the predictor of AF being silent. This study aims to determine the risk factor of first-onset AF being asymptomatic.

Method

In this study, we conducted a retrospective, medical record-based study to research the relationship between symptoms during RV pacing and AF symptoms. The observation period was from 2014 April to 2020 December. The presence of the patient's symptoms was surveyed through reviewing the medical record, especially the interview of doctors who engaged in the pacemaker clinic. A total of 145 pacemaker-implanted patients interviewed in detail about their symptoms during routine pacemaker check-ups were included. Patients who did not have a definite description of the presence or absence of palpitation in the medical record were excluded.

During routine pacemaker check at our institute, RV

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Table I. Characteristics of Whole Patients

	Palpitation (+) (n = 85)	Palpitation (-) (n = 60)	P-value
Age	73 ± 12	78 ± 13	0.0088
Male	43 (50.6%)	36 (60.0%)	0.26
MVP mode	15 (17.6%)	12 (20.0%)	0.72
DDD mode	51 (60.0%)	31 (51.7%)	0.32
VVI mode	16 (18.8%)	17 (28.3%)	0.18
SSS	42 (49.4%)	32 (53.3%)	0.64
AVB	44 (51.8%)	31 (51.7%)	0.99
PVC or NSVT	17 (20.0%)	16 (26.7%)	0.35
$CHADS_2$ score	2 ± 1	3 ± 1	< 0.0001
$CHA2DS_2$-VASc score	3 ± 1	4 ± 2	0.0015
Vp > 40%	40 (47.1%)	35 (58.3%)	0.18
EF < 50%	8 (9.4%)	6 (10.0%)	0.91
IHD	15 (17.6%)	16 (26.7%)	0.19
HF	10 (11.8%)	17 (28.3%)	0.012
Valvular disease	17 (20.0%)	8 (13.3%)	0.30
HT	58 (68.2%)	49 (81.7%)	0.07
DM	21 (24.7%)	29 (48.3%)	0.0032
DL	46 (54.1%)	32 (53.3%)	0.93
CKD	35 (41.2%)	33 (55.0%)	0.10
HD	2 (2.4%)	2 (3.3%)	0.72
HUA	21 (24.7%)	20 (33.3%)	0.26
Ischemic stroke	10 (11.8%)	16 (26.7%)	0.021
Smoking	29 (34.1%)	31 (51.7%)	0.035
Alcohol	11 (12.9%)	14 (23.3%)	0.10
Obesity	27 (31.8%)	19 (31.7%)	0.99
β blocker	31 (36.5%)	19 (31.7%)	0.55
ACE inhibitor	12 (14.1%)	10 (16.7%)	0.67
ARB	37 (43.5%)	29 (48.3%)	0.57
Statin	34 (40.0%)	17 (28.3%)	0.15

MVP indicates managed ventricular pacing; SSS, sick sinus syndrome; AVB, atrioventricular block; PVC, premature ventricular contraction; NSVT, non-sustained ventricular tachycardia; Vp, ventricular pacing; IHD, ischemic heart disease; HF, heart failure; HT, hypertension; DM, diabetes mellitus; DL, dyslipidemia; CKD, chronic kidney disease; HD, hemodialysis; HUA, hyperuricemia; ACE, angiotensin-converting enzyme; and ARB, angiotensin receptor blockade.

threshold measurement was conducted at 120 pacing per minute (ppm) in order to achieve complete RV pacing state to avoid fusion beats. According to the past report, hemodynamic change during VVI pacing seems to resemble AF hemodynamic state.[7] RV pacing was conducted at least eight beats in each patient for threshold measurement, and sudden alteration of cardiac rhythm was occurred by mandatory pacing. The pacing was stopped when the threshold was measured, and the pacing duration was less than 10 s. Palpitation felt on the neck or chest during RV pacing was defined as a positive result of the pacing test.

AF episodes were determined by routine pacemaker check or remote monitoring. AF was confirmed by checking the EGM records of the pacemaker and more than 6 min AF burdens were regarded as AF episodes. We interrogate patients who had AF episodes whether they had a symptom or not. The patient had palpitation or chest discomfort during daytime, regarded as symptomatic. If the episode was detected at night, we asked patients if they had palpitation or chest discomfort or nocturnal urination. If patients had no such episodes, including daytime, these patients were regarded as asymptomatic.

Statistical analysis: Statistical analysis was conducted by Prism 9 (GraphPad Software, San Diego, CA, USA). Student's t-test was conducted to normally distributed numbers, and Mann-Whitney test was adopted to non-normally distributed numbers. Chi-square test was adopted for analyzing numerical factors. The P-value below 0.05 was adopted as a statistically significant difference.

Results

In 145 patients, 60 (41.4%) had no apparent symptom or completely no symptom during RV pacing. The patients' character is shown in Table I. Asymptomatic patients during RV pacing were older (73 ± 12 versus 78 ± 13, P = 0.0088) and had higher $CHADS_2$ (2 ± 1 versus 3 ± 1, P < 0.0001) and CHA_2DS_2-VASc score (3 ± 1 versus 4 ± 2, P = 0.0015) than patients who had palpitation during RV pacing. Asymptomatic patients also had high incidence of heart failure (P = 0.012), diabetes mellitus (P = 0.0032), history of ischemic stroke (P = 0.021), and smoking habits (P = 0.035) as shown in Table I.

There were 74 patients who had previously documented AF [42 paroxysmal AF (PAF), 1 persistent AF

Table II. Characteristics of Patients with Previous Atrial Fibrillation

	Symptom (+) (n = 26)	Symptom (-) (n = 48)	P-value
Age	77 ± 9	77 ± 10	0.82
Male	16 (61.5%)	33 (68.8%)	0.61
Pacing palpitation	21 (80.8%)	15 (31.3%)	< 0.0001
MVP mode	4 (15.4%)	9 (18.8%)	0.72
DDD mode	9 (34.6%)	21 (43.8%)	0.44
VVI mode	13 (50.0%)	18 (37.5%)	0.30
SSS	21 (80.8%)	26 (54.2%)	0.023
AVB	5 (19.2%)	27 (56.3%)	0.0036
PVC or NSVT	6 (23.1%)	14 (29.2%)	0.57
$CHADS_2$ score	2 ± 1	3 ± 1	0.1
$CHA2DS_2$-VASc score	3 ± 1	4 ± 2	0.18
Vp > 40%	12 (46.2%)	29 (60.4%)	0.24
EF < 50%	2 (7.7%)	6 (12.5%)	0.52
IHD	4 (15.4%)	10 (20.8%)	0.57
HF	5 (19.2%)	16 (33.3%)	0.20
Valvular disease	7 (26.9%)	10 (20.8%)	0.55
HT	20 (76.9%)	39 (81.3%)	0.66
DM	7 (26.9%)	19 (39.6%)	0.28
DL	12 (46.2%)	26 (54.2%)	0.51
CKD	16 (61.5%)	29 (60.4%)	0.92
HD	1 (3.8%)	1 (2.1%)	0.66
HUA	8 (30.8%)	21 (43.8%)	0.27
Ischemic stroke	4 (15.4%)	16 (33.3%)	0.097
Smoking	12 (46.2%)	23 (47.9%)	0.88
Alcohol	4 (15.4%)	12 (25.0%)	0.34
Obesity	6 (23.1%)	15 (31.3%)	0.46
β blocker	15 (57.7%)	20 (41.7%)	0.19
ACE inhibitor	4 (15.4%)	12 (25.0%)	0.34
ARB	11 (42.3%)	22 (45.8%)	0.77
Statin	8 (30.8%)	14 (29.2%)	0.89

MVP indicates managed ventricular pacing; SSS, sick sinus syndrome; AVB, atrioventricular block; PVC, premature ventricular contraction; NSVT, non-sustained ventricular tachycardia; Vp, ventricular pacing; IHD, ischemic heart disease; HF, heart failure; HT, hypertension; DM, diabetes mellitus; DL, dyslipidemia; CKD, chronic kidney disease; HD, hemodialysis; HUA, hyperuricemia; ACE, angiotensin-converting enzyme; and ARB, angiotensin receptor blockade.

(PeAF), and 31 long-standing persistent AF (LSAF) patients]. Of these patients, the total number of silent AF patients was 48: 28 in PAF, 1 in PeAF, and 19 in the LSAF were asymptomatic. The factors associated with being asymptomatic during RV pacing such as age, $CHADS_2$ score, CHA_2DS_2-VASc score, incidence of heart failure, diabetes mellitus, history of ischemic stroke, and smoking habits were not associated with AF being asymptomatic in these patients. On the other hand, the absence of pacing palpitation and atrioventricular block (AVB) were associated with AF being asymptomatic (Table II). The relative risk of absence of pacing palpitation was 2.084 (95% CI 1.447-3.244) and 1.639 (95% CI 1.186-2.338, P = 0.0036) for AVB. The positive predictive values of AF being asymptomatic were 86.8% for absence of pacing palpitation and 83.9% for AVB. The sensitivity and specificity were 68.8% and 80.1% for absence of pacing palpitation and 54.2% and 80.1% for AVB, respectively.

The rest of the 71 patients had no previous AF or atrial flutter (AFL) episodes at the time of pacemaker implantation. Of these patients, 22 (31.0%) had new-onset AF/AFL after the pacemaker implantation, and more than 6 min episodes were documented in 14 patients. One patient was common atrial flutter (AFL). The median follow-up period to AF detection was 3.4 ± 1.4 years. There were four symptomatic AF/AFL patients (28.6%) and ten asymptomatic AF patients (71.4%). The characteristics of those 14 patients are shown in Table III. The median duration of first-onset AF episode were 447 ± 345 min and 526 ± 1401 min (symptomatic AF/AFL versus asymptomatic AF, P = 0.9157). Pacing palpitation and ARB administration were associated with AF being asymptomatic in those patients (pacing palpitation P = 0.04, ARB P = 0.018). Asymptomatic during RV pacing at 120 ppm correlated with AF being asymptomatic with 100% of the positive predictive value (Figure). The relative risk was 2.000 (95% CI 1.045-3.502), and the sensitivity and specificity of this method were 60.0% and 100%, respectively. The positive predictive value, the relative risk, sensitivity, and specificity of ARB were 100%, 2.333 (95% CI 2.160-3.913), 70.0%, and 100%, respectively. The risk factor associated with AF being asymptomatic was only absence of pacing palpitation in both previous and new-onset AF group.

Table III. Characteristics of Patients with New Onset Atrial Fibrillation

	Symptom (+) (n = 4)	Symptom (-) (n = 10)	P-value
Age	68 ± 14	75 ± 13	0.38
Male	3 (75%)	5 (50%)	0.39
Pacing palpitation	4 (100%)	4 (40%)	0.04
MVP mode	1 (25%)	2 (20%)	0.84
DDD mode	3 (75%)	8 (80%)	0.84
VVI mode	0 (0%)	0 (0%)	
SSS	2 (50%)	5 (50%)	> 0.999
AVB	2 (50%)	5 (50%)	> 0.999
PVC or NSVT	1 (25%)	1 (10%)	0.47
$CHADS_2$ score	1 ± 2	2 ± 1	0.07
$CHA2DS_2$-VASc score	2 ± 1	4 ± 2	0.06
Vp > 40%	1 (25%)	3 (30%)	0.85
EF < 50%	0 (0%)	0 (0%)	
IHD	0 (0%)	3 (30%)	0.22
HF	0 (0%)	3 (30%)	0.22
Valvular disease	0 (0%)	2 (20%)	0.33
HT	1 (25%)	8 (80%)	0.052
DM	1 (25%)	5 (50%)	0.39
DL	0 (0%)	4 (40%)	0.13
CKD	1 (25%)	5 (50%)	0.39
HD	0 (0%)	1 (10%)	0.51
HUA	0 (0%)	2 (20%)	0.33
Ischemic stroke	0 (0%)	1 (10%)	0.51
Smoking	2 (50%)	4 (40%)	0.73
Alcohol	0 (0%)	3 (30%)	0.22
Obesity	0 (0%)	5 (50%)	0.078
β blocker	1 (25%)	1 (10%)	0.47
ACE inhibitor	1 (25%)	0 (0%)	0.1
ARB	0 (0%)	7 (70%)	0.018
Statin	0 (0%)	3 (30%)	0.22

MVP indicates managed ventricular pacing; SSS, sick sinus syndrome; AVB, atrioventricular block; PVC, premature ventricular contraction; NSVT, non-sustained ventricular tachycardia; Vp, ventricular pacing; IHD, ischemic heart disease; HF, heart failure; HT, hypertension; DM, diabetes mellitus; DL, dyslipidemia; CKD, chronic kidney disease; HD, hemodialysis; HUA, hyperuricemia; ACE, angiotensin-converting enzyme; and ARB, angiotensin receptor blockade.

Discussion

This study demonstrated that asymptomaticity during mandatory cardiac pacing correlated with first-onset AF being asymptomatic. One of our expectations was that mandatory cardiac pacing could induce sudden rhythm change and temporary irregular beats. We speculated that this rhythm change produced by rapid pacing during the threshold test might imitate AF onset, leading patients to feel palpitation during cardiac pacing.[8] However, the presence of palpitation during the pacing was not strongly associated with the presence of AF symptoms in patients who had already diagnosed at the timing of pacing test. On the other hand, our results also suggest that pacemaker patients with no symptoms during rapid ventricular pacing will be asymptomatic at the first onset of AF. Besides, the population was already determined even before the first onset of AF episode. The reason for being asymptomatic during cardiac pacing in patients without arrhythmic events is unclear, and further investigation is required.

In this study, we concluded that if patients are "impervious" to RV pacing, they are at risk for silent new-onset AF in the pacemaker-implanted patients. Hemodynamic change should occur during ventricular pacing due to non-physiological ventricular contraction. Furthermore, it was reported that the brain could detect hemodynamic instability via afferent fibers of cardiac neurons or carotid sinus baroreceptors.[8] Therefore, we speculated two possible mechanisms that made pacing palpitation asymptomatic.

The one is the mechanism by which the neural network from heart or carotid sinus to the brain was modified or damaged. Resemble putative mechanism was reported in catheter ablations for AF. For example, "symptomatic" AF patients after catheter ablation often recurrences as "asymptomatic" AF.[9] The symptom silencing after the ablation seems to be caused by nerve damage within the heart during catheter ablation.[9] Another mechanism might be neuronal changes in the brain. The afferent nerves from the heart to the brain finally reach the hypothalamus and the cortex.[8] These intracranial neural networks could be causative lesions for the silencing AF symptom. Therefore, we hypothesized that patients with asymptomatic AF who never received catheter ablations

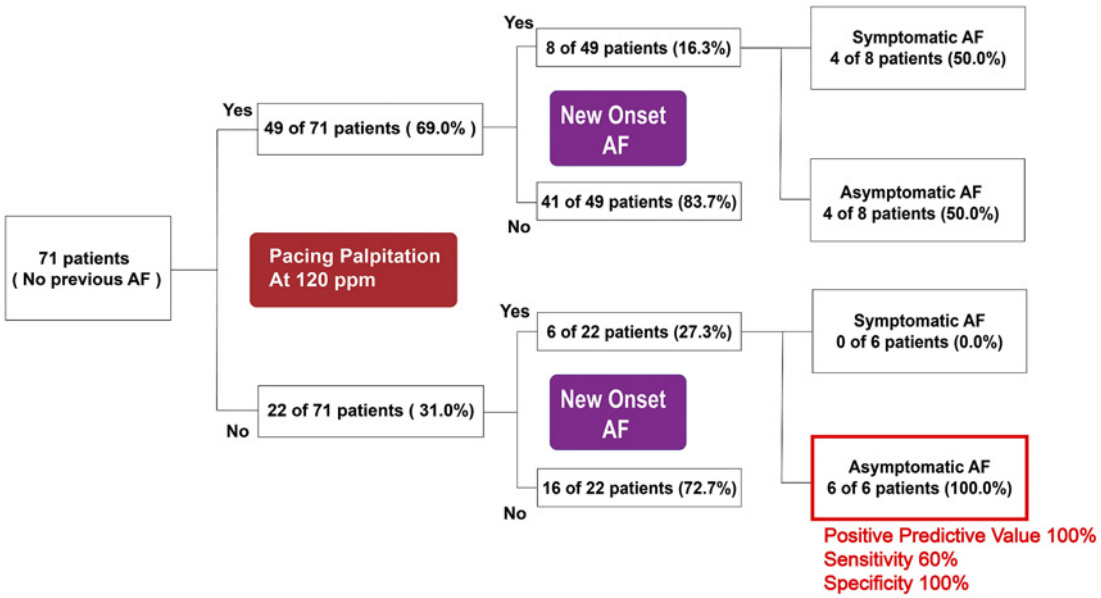

Figure. Relationship between the appearance of symptoms during RV pacing and new-onset AF. When patients were asymptomatic during pacing at 120 ppm, new-onset AF was also asymptomatic. The positive predictive value of this pacing method was 100%. Sensitivity and specificity were 60% and 100%, respectively (Chi-square analysis, $P = 0.04$). AF indicates atrial fibrillation; and RV, right ventricle.

might already have dysfunction between the peripheral cardiac nerve and the central brain.

In this study, we concluded that if patients are "impervious" to RV pacing, they are at risk for silent new-onset AF in the pacemaker-implanted patients. The results may suggest new clinical implications. For example, applying the pacing method to patients with a high risk of cerebral infarction such as no AF patients with a high $CHADS_2$ score who undergo catheter examination like coronary angiography might be reasonable. In such cases, a temporary pacing test at 120 ppm could be easily added to the catheter-based angiography. If the patient is asymptomatic during the pacing, preferential effort for early detection of AF would be recommended, including using wearable electrogram or pulse monitors or implantable cardiac electrogram monitor.[10-12)]

In addition, noninvasive extracorporeal cardiac pacing would be possible in the future.[13)] If it is realized, our pacing method with noninvasive technology would contribute to even the general population with high risks of cerebral infarction, such as $CHADS_2$ score above one through consecutive AF screenings.

Although the present pacing method has high PPV, we need to mention that our study has limitations in the patient population and methodology. Pacemaker patients have high incidents of AF and thus differ from the general population. Moreover, we cannot assume that patients had no previous AF episodes at the time of pacemaker implantation. Moreover, our method requires cardiac pacing, which limits its application to the general population at present.

Disclosure

Conflicts of interest: None.

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