CLINICAL INVESTIGATIONS

Sudden death and its risk factors after atrioventricular junction ablation and pacemaker implantation in patients with atrial fibrillation

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Background: Although sudden death (SD) is a rare complication after atrioventricular junction (AVJ) ablation and permanent pacemaker implantation, the risk factors leading to this SD remain unknown. The purpose of this study was to investigate SD and its risk factors after ablate-and-pace strategy for rate control in atrial fibrillation (AF) patients during long-term follow-up.

Hypothesis:

Methods: From January 2005 to December 2009, we enrolled into this study 517 AF patients with AVJ ablation and right ventricular pacemaker implantation. Patients were divided into 2 groups, SD and non-SD. Cox proportional hazards models were used to assess potential risk factors for overall mortality and SD.

Results: During a mean follow-up of 25.8 ± 18.6 months (range, 3 days to 63.8 months), 53 patients died (15 with SD). Cox proportional hazards models showed that the presence of congestive heart failure, New York Heart Association functional class, chronic renal failure, and nonsustained ventricular tachycardia were risk factors that predicted overall mortality. For SD, the presence of dilated cardiomyopathy and mitral stenosis were associated risk factors. SD was exclusively seen in patients who had narrow QRS complex or right bundle branch block prior to AVJ ablation and pacemaker implantation; SD was not seen in any patient with preexisting complete left bundle branch block.

Conclusions: Dilated cardiomyopathy, mitral stenosis, and baseline QRS morphology should be examined as potential risk factors for SD after AVJ ablation and pacemaker implantation.

KEYWORDS

Atrial fibrillation, Catheter ablation, Cardiac pacing, QRS morphology, Arrhythmia/all, sudden death

1 | INTRODUCTION

Atrial fibrillation (AF), the most common sustained arrhythmia in clinical practice, has become a major epidemic in cardiovascular medicine and is associated with increased morbidity and mortality.^{1,2} AF is often difficult to manage, especially in the elderly with persistent or permanent AF, because safe and effective antiarrhythmic drugs are

lacking.³ In AF patients with rapid ventricular rates and symptoms refractory to drug therapy, atrioventricular junction (AVJ) ablation and cardiac pacing is a proven effective therapeutic option.⁴⁻⁶ In appropriate patients, AVJ ablation followed by cardiac resynchronization therapy (CRT) has provided an excellent clinical outcome.⁷⁻⁹

Although ablate-and-pace is an effective therapeutic strategy, especially in elderly patients with permanent AF, sudden death

(SD) sometimes may occur postoperatively.¹⁰ However, it is often difficult to distinguish procedure-related SD from lethal ventricular arrhythmias and SD due to preexisting cardiovascular and other diseases. Hence, it is important to identify the risk factors for SD in these patients. In our recent report,¹¹ we have shown that a faster initial pacing rate immediately after AVJ ablation with subsequent gradual lowering of resting pacing rate is a plausible strategy to reduce the short-term risk of SD likely related to the procedure. However, SD remains a risk during long-term follow-up. In this retrospective study, we tried to determine the risk factors associated with SD in AF patients after AVJ ablation with right ventricular (RV) pacing.

2 | METHODS

2.1 | Patient Selection

We retrospectively searched and analyzed our database for the records of AF patients with AVJ ablation and pacemaker implantation between January 2005 and December 2009 at Mayo Clinic in Rochester, Minnesota. A history of documented AF in all patients was obtained by electrocardiogram (ECG) records in the hospital. AF was categorized as paroxysmal, persistent, and permanent. Paroxysmal AF was defined as self-terminating within 7 days; persistent AF was defined as lasting >7 days but <1 year, or requiring cardioversion or other intervention; and permanent AF was defined as failed cardioversion, or cardioversion was no longer attempted. The indications for AVJ ablation were drug-refractory and symptomatic paroxysmal, persistent, or permanent AF. The potential risks of the procedure were explained to the patients in detail. The protocol was reviewed and approved by the Mayo Clinic Institutional Review Board, and all patients gave verbal informed consent.

2.2 | AVJ Ablation With Subsequent Pacing

AVJ ablation with subsequent pacing was performed as we have previously reported.¹¹ Complete atrioventricular conduction block was achieved in all patients. Pacemakers with rate-responsive ventricular pacing (VVIR) were implanted in patients with permanent AF, or if the cardioversion failed to restore sinus rhythm and maintain it before the procedure. Pacemakers with rate-responsive dual-chamber pacing (DDDR) were implanted in patients with sinus rhythm or with a history of paroxysmal AF, but in whom sinus rhythm was maintained when the procedure was performed. Ten CRT pacemakers (CRT-P) and 45 CRT defibrillators (CRT-D) were implanted in patients with serious heart failure and/or ventricular arrhythmias. The timing of pacemaker implantation in relation to the ablation was variable, but most pacemakers were implanted prior to AVJ ablation: 337 were performed 1 to 3 days before ablation, 157 were 4 days before, 20 were on the same day, 2 were 2 days after, and 1 was within 2 days after ablation. Two patients (0.4%) required a left-sided ablation to achieve complete atrioventricular conduction block. The pacing rate in all patients was set at 90 bpm immediately after ablation, with 10-bpm monthly decrements to 60 bpm, unless the primary

physician decided on a different pacing rate because of the patient's clinical needs.

2.3 | Data Collection, Review, and Analysis

Complete records for all 517 patients were obtained from the Mayo Clinic centralized database. These records provided detailed patient information including histories, clinical manifestations, diagnoses, therapies, nursing care, and calls from nurses and family members, as well as the data recorded from patients' death certificates or autopsy reports.

The follow-up time was calculated from the day of AVJ ablation to May 2010 or the patient's death date. Follow-up evaluations of all patients were performed in the pacemaker clinic every 3 months for the first year and annually thereafter. The causes of patient death were established by reviewing patient records in hospitals or death certificates, or by talking to patients' families or their physicians. All patients had ≥ 1 follow-up data point from the outpatient pacemaker clinic, a survey, or both. SD was defined as "a natural, unexpected death, heralded by an abrupt loss of consciousness within 1 hour of the onset of acute symptoms."¹² Patients who died during follow-up were divided into 2 groups, the SD group and the non-SD group.

We reviewed and analyzed all baseline ECGs including rhythm, rate, P-R interval, atrioventricular conduction, QRS morphology, ST segment, and QTc interval, with special attention to pre-ablation QRS morphology. Comparison of baseline QRS morphology was performed respectively in the SD and non-SD groups.

2.4 | Statistical Analysis

Data were presented as mean $\pm$ standard deviation or as number of patients (percentage). Continuous variables were compared between the groups using the *t* test or rank-sum test, and categorical variables were compared using the χ^2 test or the Fisher exact test if the expected cell counts were low. Kaplan-Meier survival estimates were used to analyze overall survival and survival free of SD. Cox proportional hazards models were used to assess potential risk factors for overall mortality and SD. *P* < 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Patient Demographics

AVJ ablation with subsequent pacing was performed in 517 AF patients (235 males, 282 females) at Mayo Clinic from January 2005 to December 2009. The mean age was 73.6 ± 10.3 years (range, 23–94 years) at the time of procedure, and the mean follow-up period was 25.8 ± 18.6 months (range, 3 days to 63.8 months). VVIR pacemakers were implanted in 205 patients (39.4%), and DDDR pacemakers including 10 CRT-P and 45 CRT-D were implanted in 312 patients (60.6%). A detailed comparison of baseline characteristics of patients in the SD and non-SD groups is shown in Table 1.

TABLE 1 Comparison of patient demographics in the SD and non-SD groups

Characteristics	SD Group, n = 15 ^a	Non-SD Group, n = 502 ^a
Age at ablation, y	75.6 ± 8.7	73.6 ± 10.3
Male sex	6 (40.0)	229 (45.6)
Paroxysmal AF	3 (20.0)	226 (45.0)
Chronic AF	12 (80.0)	278 (55.0)
AF duration, y	5.8 (4.6)	4.5 (4.3)
Mean follow-up, mo	12.5 (12.8)	26.2 (18.6)
Mean no. of drugs	2.2 (0.6)	2.6 (1.1)
CHF	7 (46.7)	122 (24.3)
NYHA class	1.9 (1.0)	1.5 (0.9)
LVEF, %	44.9 (17.2)	49.9 (15.9)
DM	3 (20.0)	79 (15.7)
HTN	11 (73.3)	269 (53.6)
CHD	6 (40.0)	173 (34.5)
MI	2 (13.3)	40 (7.9)
DCM	4 (26.7)	38 (7.5)
Hyperlipidemia	9 (60.0)	204 (40.6)
CRF	0 (0)	39 (7.8)
Sleep apnea	3 (20.0)	77 (15.3)
Mitral stenosis	3 (20.0)	15 (3.0)
Aortic stenosis	1 (6.7)	16 (3.2)
Aortic regurgitation	2 (13.3)	26 (5.2)
SSS from arrhythmia data	1 (6.7)	70 (14.0)
NSVT/VT	1 (6.7)	26 (5.2)
QRS >120 ms or LBBB	0 (0.0)	103 (20.5)
CABG	2 (13.3)	72 (14.3)
PCI	1 (6.7)	32 (6.4)
LVEDD, mm	50.1 (11.9)	50.9 (8.4)
LAD, mm	62.7 (9.5)	61.8 (8.1)
QTc before ablation, ms	419.7 (81.8)	436.1 (66.2)
BMI, kg/m ²	28.7 (9.7)	29.3 (6.9)

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass graft surgery; CHD, coronary heart disease; CHF, congestive heart failure; CRF, chronic renal failure; DCM, dilated cardiomyopathy; DM, diabetes mellitus; HTN, hypertension; LAD, left atrial diameter; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; QTc, corrected QT interval; SD, sudden death; SSS, sick sinus syndrome; VT, ventricular tachycardia.

Data are presented as n (%) or mean ± standard deviation.

3.2 | Pre-ablation Baseline Characteristics of Patients Experiencing SD

Fifteen patients (9 females, 6 males; mean age, 75.6 ± 8.7 years) had SD after AVJ ablation and pacemaker implantation (Table 2). The time of death in these patients was 458.3 ± 319.7 days (range, 34–1166 days). All 15 patients had underlying cardiac diseases: 3 had paroxysmal AF, 6 had persistent AF, and 6 had permanent AF. The AF durations in 12 patients were 5.6 ± 4.6 years (range, 2–20 years) and were unknown in 3 patients. Seven patients had symptoms of

congestive heart failure (CHF) with New York Heart Association (NYHA) function class II to IV. The mean left ventricular (LV) ejection fraction was 35.0% ± 14.2% (range, 15%–68%). The mean LV end-diastolic diameter and left atrial diameter were 54.9 ± 12.1 mm (range, 37–79 mm) and 66.1 ± 7.8 mm (range, 45–78 mm), respectively. Eight patients received a VVIR pacemaker, 2 a single-chamber implantable cardioverter-defibrillator, and 5 a DDDR pacemaker, of which 3 were CRT-D devices. One patient was later upgraded to a CRT-D device from VVIR.

3.3 | Pre-ablation ECG Characteristics of Patients Experiencing SD

During AVJ ablation, 12 patients were in AF and 3 were in sinus rhythm. Fourteen patients had narrow QRS complexes and 1 patient had a right bundle branch block (RBBB) prior to ablation. Thus, SD was seen only in patients who had intact left bundle branch conduction (a narrow QRS complex or RBBB) prior to ablation. Of the 517 patients included in this study, 44 patients had LBBB prior to AVJ ablation; however, no SD was seen in any of these patients.

3.4 | Overall Survival, Survival Free of SD, and Potential Risk Factors for Overall Mortality and SD

In this study, 53 patients died during long-term follow-up. In addition to SD in 15 patients, the other causes of death were CHF (10), infection (4), chronic renal failure (2), cancer (6), chronic obstructive pulmonary disease (2), ventricular arrhythmia (1), natural (3), stroke (3), accident (1), CHF + chronic renal failure (1), cancer (1), and unknown causes (4). Results of Meier-Kaplan analysis for overall survival and survival free of SD are shown in the Figure.

Cox proportional hazards models showed that the presence of CHF, NYHA functional class, chronic renal failure, and nonsustained ventricular tachycardia (NSVT) are risk factors that predict overall mortality (Table 3). NSVT or ventricular tachycardia has a *P* value of 0.07, which has not reached significance. For SD, the presence of dilated cardiomyopathy (DCM) and mitral stenosis are the only risk factors identified. Furthermore, SD was exclusively seen in patients who had narrow QRS complex or RBBB prior to AVJ ablation and pacemaker implantation, and it was not seen in any patient with pre-existing complete LBBB, while the presence of coronary artery disease and history of myocardial infarction were not risk factors of SD in the study cohorts (Table 4).

Among the 15 patients with SD in long-term follow-up, 4 patients had CRT-D devices, including 1 patient upgraded to CRT-D due to serious heart failure and lethal arrhythmias during follow-up.

3.5 | Procedural Complications

Procedural complications include hematoma (5), pneumothorax (1), lead dislodgements (8), cardiac perforations (3), and failure to capture (7). There were no intraoperative deaths. Pacemaker malfunction was not detected at the last follow-up examination before death.

TABLE 2 Characteristics of patients with SD after AVJ ablation with subsequent pacing

Age, y	Sex	Day of Death	Structural Heart Diseases	AF Type	AF Duration, y	CHF	NYHA Class	LVEF, %	LVEDD, mm	LAD, mm	Baseline Rhythm	QRS Complex	AV Conduction	VRD	Device Type	PPM Mode/Rate, bpm	Upgrade to ICD or CRT
82	M	34	CAD, HTN	Perm	3	+	II	25	Unk	Unk	AF	Narrow	Normal	-	Single	VVIR/90	-
75	F	492	HTN, TR	Perm	6	-	I	68	37	62	AF	Narrow	Normal	-	Single	VVIR/90	-
83	F	236	HTN	Persi	Unk	-	II	40	49	62	AF	Narrow	Normal	-	Single	VVIR/90	-
77	M	125	CAD, MI, AR	Paro	Unk	-	I	57	46	63	SR	Narrow	AVB1	-	Single	VVIR/90	-
68	F	142	MS, TR, HTN	Perm	20	-	I	53	47	63	AF	Narrow	Normal	-	Single	VVIR/90	-
76	M	851	DCM	Persi	5	+	IV	15	64	74	AF	Narrow	Normal	-	Single	VVIR/90	CRT-D
66	F	466	CAD, HTN	Perm	Unk	+	II	49	56	59	AF	Narrow	Normal	-	Single	VVIR/90	-
84	F	1166	MR, TR	Perm	5	-	II	45	47	58	AF	Narrow	Normal	-	Single	VVIR/90	-
92	F	263	CAD, MI, HTN	Paro	2	-	I	58	44	53	AF	Narrow	Normal	-	Dual	DDDR/90	-
68	F	696	MS, MR, HTN	Paro	5	-	I	65	40	45	AF	Narrow	Normal	-	Dual	DDDR/90	-
65	M	410	HTN	Persi	3	-	I	55	44	60	SR	Narrow	AVB1	-	Single ICD	VVIR/90	-
83	M	695	CAD, MS, AS, TR, DCM, HTN	Persi	5	+	II	40	47	73	AF	RBBB	Normal	-	CRT-D	DDDR/90	-
74	M	390	CAD, AR	Persi	5	+	III	15	79	78	SR	Narrow	Normal	-	CRT-D	DDDR/90	-
80	F	751	DCM	Persi	5	+	III	35	56	65	AF	Narrow	Normal	-	CRT-D	DDDR/90	-
61	F	157	DCM, TR, HTN	Perm	5	+	III	53	41	60	AF	Narrow	Normal	+	Single ICD	VVIR/90	-

Abbreviations: AF, atrial fibrillation; AR, aortic regurgitation; AS, aortic stenosis; AV, atrioventricular; AVB1, grade 1 atrioventricular conduction block; AVJ, atrioventricular junction; CAD, coronary artery disease; CHF, congestive heart failure; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy defibrillator; DCM, dilated cardiomyopathy; DDDR, rate-responsive dual chamber pacing; F, female; HTN, hypertension; ICD, implantable cardioverter-defibrillator; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; M, male; MI, myocardial infarction; MR, mitral regurgitation; MS, mitral stenosis; NYHA, New York Heart Association; Paro, paroxysmal; Perm, permanent; Persi, persistent; PPM, permanent pacemaker; RBBB, right bundle branch block; SD, sudden death; SR, sinus rhythm; TR, tricuspid regurgitation; unk, unknown; VRD, ventricular rhythm disturbance; VVIR, rate-responsive ventricular pacing.

- signifies absence; + signifies presence.

FIGURE 1 Kaplan-Meier estimated (A) overall survival and (B) survival free of sudden death in patients who underwent atrioventricular junction ablation and device implantation.

4 | DISCUSSION

4.1 | Main Findings

In this retrospective study of 517 patients with drug-refractory AF, AVJ ablation with pacing was successfully performed in all patients. SD occurred in 15 patients during long-term follow-up. The main findings of this study are that (1) the presence of DCM and mitral stenosis were the only risk factors of SD; and (2) SD was exclusively seen in patients who had narrow QRS complex or RBBB prior to AVJ ablation and pacemaker implantation and was not seen in any patient with preexisting complete LBBB.

4.2 | Incidence of SD After AVJ Ablation and Pacing

It has been repeatedly reported that AVJ ablation followed by ventricular pacing is associated with a small (2%–4%) risk of SD.^{11,13–19} Gasparini et al¹³ reported that the 1-year SD mortality rate after AVJ ablation and pacing was 6.3% in a multicenter study of 585 patients. In a meta-analysis of randomized trials comparing AVJ ablation with pacemaker implantation and drug therapy, overall all-cause mortality was 3.5% with AVJ ablation and 3.3% with drug therapy in about 1 year of follow-up.¹⁴ In a recent meta-analysis, Chatterjee et al²⁰ reported that the incidence of procedure-related mortality (defined as death within 30 days of AVJ ablation with subsequent pacing) was 0.27% among 4886 patients from

TABLE 3 Potential risk factors for overall mortality

Characteristics	HR (95% CI)	P Value
Mean age at ablation, y	1.02 (0.992–1.05)	0.15
Male sex	1.06 (0.62–1.80)	0.84
Paroxysmal AF	0.70 (0.40–1.21)	0.20
AF duration, y	0.97 (0.90–1.05)	0.47
Mean no. of drugs	0.76 (0.57–1.01)	0.06
CHF	2.19 (1.28–3.75)	0.005
NYHA class	1.49 (1.17–1.91)	0.002
LVEF	0.99 (0.97–1.00)	0.08
DM	1.29 (0.65–2.57)	0.46
HTN	0.97 (0.57–1.65)	0.91
CHD	1.45 (0.85–2.47)	0.18
MI	2.07 (0.94–4.60)	0.07
DCM	1.59 (0.72–3.52)	0.26
Hyperlipidemia	1.10 (0.64–1.88)	0.74
CRF	2.53 (1.19–5.36)	0.02
Sleep apnea	1.11 (0.54–2.28)	0.77
Mitral stenosis	2.50 (0.90–6.97)	0.08
Aortic stenosis	1.12 (0.27–4.61)	0.87
Aortic regurgitation	2.28 (0.90–5.73)	0.08
SSS from arrhythmia data	1.37 (0.71–2.66)	0.35
NSVT or VT	2.35 (0.93–5.91)	0.07
QRS >120 ms or LBBB	0.58 (0.26–1.29)	0.18
CABG	1.01 (0.48–2.14)	0.98
PCI	1.04 (0.37–2.87)	0.95
LVEDD, mm	1.01 (0.98–1.05)	0.59
LAD, mm	1.00 (0.96–1.04)	0.96
QTc before ablation, ms	1.00 (0.99–1.00)	0.12
BMI, kg/m ²	0.99 (0.95–1.03)	0.54

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass grafting surgery; CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval; CRF, chronic renal failure; DCM, dilated cardiomyopathy; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; LAD, left atrial diameter; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; QTc, corrected QT interval; SSS, sick sinus syndrome; VT, ventricular tachycardia.

42 studies. At a mean follow-up of 26.5 months, the incidence of sudden cardiac death after AVJ ablation was 2.1%. In most of the above studies, it was difficult to distinguish the cause-and-effect relationship between the therapeutic procedure and SD because of the varying periods between SD and the procedure. In our previous report,¹⁰ the overall rate of SD after AVJ ablation and permanent pacemaker implantation was 2.1% when pacing at a lower rate limit of 60 bpm, whereas in our recent report,¹¹ the rate of SD was 0.2% when pacing at an initial lower rate of 90 bpm. These results suggested that AVJ ablation predisposed patients to bradycardia-dependent proarrhythmia. Changing the pacing rate algorithm improved outcome,¹¹ but a small residual incidence of SD exists. The concerns about SD on long-term pacemaker-associated complications may limit the effectiveness of the “ablate-and-pace” strategy.

TABLE 4 Potential risk factors for SD

Characteristics	HR (95% CI)	P Value
Mean age at ablation, y	1.02 (0.97-1.08)	0.44
Male sex	0.83 (0.30-2.34)	0.73
Paroxysmal AF	0.29 (0.08-1.03)	0.06
AF duration, y	1.04 (0.94-1.14)	0.45
Mean no. of drugs	0.60 (0.32-1.11)	0.10
CHF	2.59 (0.94-7.13)	0.07
NYHA class	1.49 (0.93-2.37)	0.10
LVEF	0.99 (0.96-1.02)	0.32
DM	1.46 (0.41-5.18)	0.56
HTN	2.32 (0.74-7.27)	0.15
CHD	1.11 (0.40-3.12)	0.84
MI	2.08 (0.47-9.25)	0.34
DCM	3.72 (1.18-11.68)	0.027
Hyperlipidemia	2.17 (0.77-6.09)	0.14
CRF	NA (no events in the group with CRF)	
Sleep apnea	1.38 (0.39-4.87)	0.62
Mitral stenosis	7.22 (2.02-25.82)	0.002
Aortic stenosis	1.97 (0.26-14.95)	0.51
Aortic regurgitation	3.42 (0.77-15.22)	0.11
SSS from arrhythmia data	0.38 (0.05-2.86)	0.35
NSVT/VT	1.58 (0.21-12.05)	0.66
QRS >120 ms or LBBB	NA (no events in the group with this)	
CABG	0.89 (0.20-3.93)	0.87
PCI	0.91 (0.12-6.90)	0.92
LVEDD, mm	0.99 (0.92-1.06)	0.70
LAD, mm	1.01 (0.94-1.08)	0.89
QTc before ablation, ms	1.00 (0.999-1.01)	0.57
BMI, kg/m ²	0.99 (0.91-1.06)	0.71

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass grafting surgery; CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval; CRF, chronic renal failure; DCM, dilated cardiomyopathy; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; LAD, left atrial diameter; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not applicable; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; QTc, corrected QT interval; SD, sudden death; SSS, sick sinus syndrome; VT, ventricular tachycardia.

4.3 | Plausible Mechanisms of SD After Ablate-and-Pace Strategy

The exact mechanism underlying SD after AVJ ablation remains elusive. It has been reported that the long-term right ventricular pacing can induce electrical and mechanical LV dyssynchrony in almost 50% of patients.²¹⁻²³ The development of inter- or intra-ventricular dyssynchrony is known to be associated with deterioration in heart failure symptoms, systolic LV function, and LV dilatation. In animal studies with LV dyssynchrony,²⁴ myocardial protein dysregulation in failing hearts was localized to the late-activated, high-stress lateral endocardium. Such molecular polarization within the left ventricle creates transmural and transchamber expression gradients of calcium

handling and gap junction proteins that may worsen chamber function and arrhythmia susceptibility. Yan et al²⁵ reported that ventricular dyssynchrony is associated with proarrhythmic repolarization dispersion. In addition, studies have also shown that acute mechanical dyssynchrony induced by single-site right ventricular pacing depresses systolic function, worsens myocardial efficiency, and leads to marked increases in wall stress heterogeneity.^{26,27} Chronic dyssynchrony leads to chamber remodeling of both early- and late-activated segments.²⁸ LV dyssynchrony is a strong independent predictor of major adverse events in idiopathic DCM, and the prognosis of patients with DCM is closely related to LV dyssynchrony. This may have implications for CRT and/or the use of implantable cardioverter-defibrillators in patients with idiopathic DCM.²⁹

Recently, we have reported that a faster pacing rate immediately after AVJ ablation, followed by a gradual decrease in the pacing rate, is a plausible strategy associated with the improved short-term clinical outcome¹¹; however, there were still 15 patients with SD among the 517 patients using this new pacing rate algorithm. In these 15 patients, 14 patients had a narrow QRS complex and 1 had RBBB prior to ablation. SD was not seen in any of the 44 patients with pre-existing LBBB. These observations suggest that the risk of SD after AVJ ablation and pacing during long-term follow-up could be related to new dyssynchrony imposed by RV pacing in patients without prior LV dyssynchrony (ie, a potential new arrhythmogenic substrate). In our recent report,¹¹ we concluded that SD is possibly procedure-related during short-term follow-up (<1 month), which could be alleviated by an initial faster pacing rate. However, a small risk of SD persisted long-term. Pacing-induced cardiac abnormality during long-term follow-up would be a plausible explanation. If our hypothesis is correct, prevention of ventricular dyssynchrony may be helpful in improving clinical outcome in patients undergoing AVJ ablation and pacing. Cox proportional hazards models were used to assess the potential risk factors for overall mortality and SD in this study. We found that the presence of CHF, NYHA functional class, chronic renal failure, and NSVT were risk factors that predict overall mortality. For SD, the presence of DCM and mitral stenosis were the only risk factors associated with SD. These findings suggest that the preexisting conditions and the patient's clinical status prior to ablation may lead to the increased risk of SD. More attention should be paid to patients with DCM, mitral stenosis, and baseline QRS morphology before and after AVJ ablation and pacemaker implantation to reduce or avoid SD.

4.4 | Sudden Death in Patients With CRT

The Cardiac Resynchronization Heart Failure (CARE-HF) study has demonstrated that in patients with heart failure, CRT leads to a 36% reduction in all-cause mortality³⁰; however, this study and a meta-analysis of randomized trials showed that CRT did not reduce the incidence of sudden cardiac death (35% in the CRT group vs 32% in the medical therapy group).^{30,31} Therefore, the underlying mechanism of SD after CRT remains uncertain. It has been suggested that CRT may enhance arrhythmogenicity by reversing the normal depolarization pattern from endocardium to epicardium, which enhances transmural dispersion of repolarization and propagation of early after-

depolarizations,³² and pacing-induced changes in QTc and QT dispersion may be related to the risk of sudden cardiac death in patients undergoing CRT.³³ These contentions were supported by experimental studies that LV pacing via the coronary sinus promotes arrhythmogenesis due to a pacing-induced increase in QTc and QT dispersion with increased transmural dispersion of repolarization involving the mid-myocardial M cells.³⁴

4.5 | Study Limitations

This study is limited by the retrospective, case-controlled, nonrandomized nature of its design and the overall low event rate. Although most of the factors were not related to SD, the SD group did appear "sicker." In the absence of autopsy data, it is difficult to retrospectively pinpoint the etiology of SD. The right ventricular pacing hypothesis is intriguing; however, the etiology of SD in these cases could also be multifactorial and based on the "selection of the substrate," as opposed to the ablation procedure itself. Also, adjudication of the occurrence of SD can be difficult retrospectively. The power of the statistical analysis is limited by the low event rate.

5 | CONCLUSION

The presence of CHF, NYHA functional class, chronic renal failure, and NSVT were risk factors that overall mortality in patients after AVJ ablation and pacemaker implantation, whereas the presence of DCM and mitral stenosis were the only risk factors associated with SD. SD was only seen in patients with intact left bundle branch conduction (either a narrow QRS complex or RBBB) prior to ablation, and it was not seen in any patient with preexisting left bundle branch block. To our knowledge, this is the first report that suggests DCM, mitral stenosis, and baseline QRS morphology should be examined as potential risk factors for SD after AVJ ablation and pacemaker implantation.

Conflicts of interest

The authors declare no potential conflicts of interest.

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