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Predictors of rate-adaptive pacing in patients implanted with implantable cardioverter–defibrillator and subsequent differential clinical outcomes

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Abstract

Purpose Patients with severe cardiomyopathy often have chronotropic incompetence, which is predominantly managed by activating rate-adaptive pacing in patients implanted with an implantable cardioverter–defibrillator (ICD) capable of atrial pacing. The purpose of this study was to determine predictors of rate-adaptive pacing activation, the cumulative incidence of activation, and the association of rate-adaptive pacing activation with subsequent clinical outcomes in an ICD population.

Methods The authors evaluated 228 patients implanted with an ICD between 2011 and 2015. Multivariable logistic regression was used to evaluate predictors of rate-adaptive pacing activation. Cox proportional–hazards regression was used to examine associations of rate-adaptive pacing activation and clinical outcomes.

Results Rate-adaptive pacing was turned on in 38.5% ($n = 88$) of patients during follow-up. Several statistically significant predictors of rate-adaptive pacing activation were found, particularly previous atrial fibrillation (odds ratio [OR] = 8.27, 95% confidence interval [CI] = 2.96–23.06, $p < 0.001$), previous myocardial infarction (OR = 4.17, 95% CI = 1.38–12.58, $p = 0.01$), and non-ischemic cardiomyopathy (OR = 3.83, 95% CI = 1.22–12.00, $p = 0.02$). In multivariable adjusted analyses, rate-adaptive pacing activation within 30 days of implantation was not associated with the risk of device therapy for tachyarrhythmias (hazard ratio [HR] = 1.52, 95% CI = 0.71–3.28, $p = 0.29$), atrial fibrillation (HR = 1.42, 95% CI = 0.71–2.87, $p = 0.32$), HF re-admission (HR = 1.39, 95% CI = 0.80–2.43, $p = 0.25$), nor all-cause mortality (HR = 2.34, 95% CI = 0.80–6.84, $p = 0.12$).

Conclusions During follow-up, more than one in three HF patients implanted with an ICD developed the need for rate-adaptive pacing. Atrial fibrillation, prior myocardial infarction, and non-ischemic cardiomyopathy were statistically significant baseline clinical predictors of rate-adaptive pacing activation. Rate-adaptive pacing activation was not associated with subsequent adverse clinical outcomes.

Keywords Cardiac resynchronization therapy · Cardiomyopathy · Chronotropic incompetence · Implantable cardioverter–defibrillator · Rate-adaptive pacing · Sick sinus syndrome

Abbreviations

ICD	Implantable cardioverter–defibrillator
HF	Heart failure
CI	Chronotropic incompetence
CRT-D	Cardiac resynchronization therapy defibrillator

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1 Introduction

It is well known that the use of an implantable cardioverter–defibrillator (ICD), as both a primary and secondary treatment of sudden cardiac death from ventricular arrhythmias in patients with heart failure (HF), is safe and effective [1–4]. It has also been shown that ICDs statistically improve survival in patients with HF and NYHA class II or III, when compared to antiarrhythmic medication [5].

Many patients with severe cardiomyopathy suffer from decreased exercise tolerance. Several studies have shown that chronotropic incompetence (CI) may contribute to this decreased exercise tolerance [6–8]. The etiology of CI is still

poorly understood, although antiarrhythmic medications, decreased ß-adrenergic receptor density, sinus node remodeling, and prolonged sinoatrial conduction have been suggested as contributing factors [9, 10]. In patients who have an atrial lead implanted, CI is predominantly managed by activating rate-adaptive pacing in a pacemaker or ICD. Patients who only have a right ventricular lead implanted rarely have their device programmed to pace the right ventricle, due to the risk of ventricular dyssynchrony induced by right ventricular apical pacing and the risk of worsened HF or death [11].

The prevalence of CI in a general HF population is roughly 30% [6, 7, 10]. However, the prevalence is unknown in a population undergoing novel ICD implantation. Furthermore, the prevalence of programming rate-adaptive pacing at implantation, as well as the incidence of development of CI necessitating rate-adaptive pacing, is also unknown in this population. Finally, it is unknown whether rate-adaptive pacing in this population will improve or worsen clinical outcomes, particularly the risk of ICD therapy, atrial fibrillation, heart failure readmission, and death.

Therefore, the aim of this retrospective analysis was to evaluate the prevalence of programming rate-adaptive pacing at implantation and the incidence of development of CI necessitating rate-adaptive pacing in subsequent follow-up, to identify specific clinical predictors for the activation of rate-adaptive pacing, and to correlate the use of rate-adaptive pacing with subsequent clinical outcomes, including ICD therapy for ventricular tachyarrhythmias, incidence of atrial fibrillation, heart failure readmission, and death, in a population with a novel ICD implant.

2 Methods

2.1 Data source

The National ICD Registry is a national registry in the USA, collecting data regarding ICD implantations from 1448 hospitals as of June 2008. It was developed in 2006 through a partnership between the Heart Rhythm Society (HRS) and the American College of Cardiology Foundation (ACCF), as a part of the National Cardiovascular Data Registry (NCDR) [12]. The registry data information from a single academic institution was used for data collection in conjunction with electronic medical records (EPIC, Madison, WI) at the University of California, San Diego (UCSD). The electronic medical records were used to collect specific information pertaining to clinical outcomes and patient characteristics not otherwise captured in the registry.

2.2 Study population

All UCSD patients implanted with an ICD with registry data available between March 1, 2011 and March 31, 2015 were considered for analysis ($n = 891$). Patients were included in the study regardless of the indication for ICD implantation, as the decision for implantation was at the discretion of the individual operator. Patients already implanted with an ICD or pacemaker ($n = 562$), patients implanted with a single chamber ICD ($n = 64$), patients with missing programmed mode at implant ($n = 25$), patients implanted with a subcutaneous ICD ($n = 10$), and patients undergoing lead revision or insertion only ($n = 2$) were excluded from the study, leaving a total of 228 patients included. A flowchart of the exclusion process is shown in Fig. 1.

2.3 Data collection and definitions

Variables were either collected in the registry or collected in the electronic medical record. Collectable data included demographics, implant indications, device settings at implant, and patient outcomes. Baseline heart rate was based on implantation day EKG or vital sign measurement. Rate-adaptive pacing activation was defined as programming rate-adaptive pacing on (versus off) based on the programmed mode of the device. Rate-adaptive pacing activation at implant was defined as turned on at the date of the procedure or the following day, usually during pre-discharge device check and programming. To correlate the use of rate-adaptive pacing with subsequent clinical outcomes, patients who had rate-adaptive pacing activated within 30 days after implantation were compared with patients who did not. The 30-day cutoff for activation of rate-adaptive pacing was chosen due to the clinical practice of programming and interrogation in conjunction with a wound-check within 30 days after implantation. Atrial fibrillation was defined as an episode of atrial tachyarrhythmia ≥ 30 s, with an atrial rate of ≥ 160 bpm [13]. The last date of follow-up was defined as the last face-to-face meeting with medical personnel recorded in the electronic medical record. Patients were censored on their last date of follow-up or on December 31, 2015.

2.4 Statistical analysis

Normally distributed continuous variables were expressed as the mean ± SD and compared by unpaired *t* tests. Categorical variables were expressed as simple proportions and compared by chi-squared tests. To identify statistically significant predictors of rate-adaptive pacing activation at any time during follow-up, multivariable logistic regression was performed using the backward stepwise elimination method (p value for entry = 0.20, p value for retention = 0.05). The multivariable regression models included the covariates presented in Table 1, which were selected based on the clinically plausible association of these predictor variables with rate-adaptive pacing activation or the outcomes of interest. Results were presented as odds ratios with 95% confidence intervals.

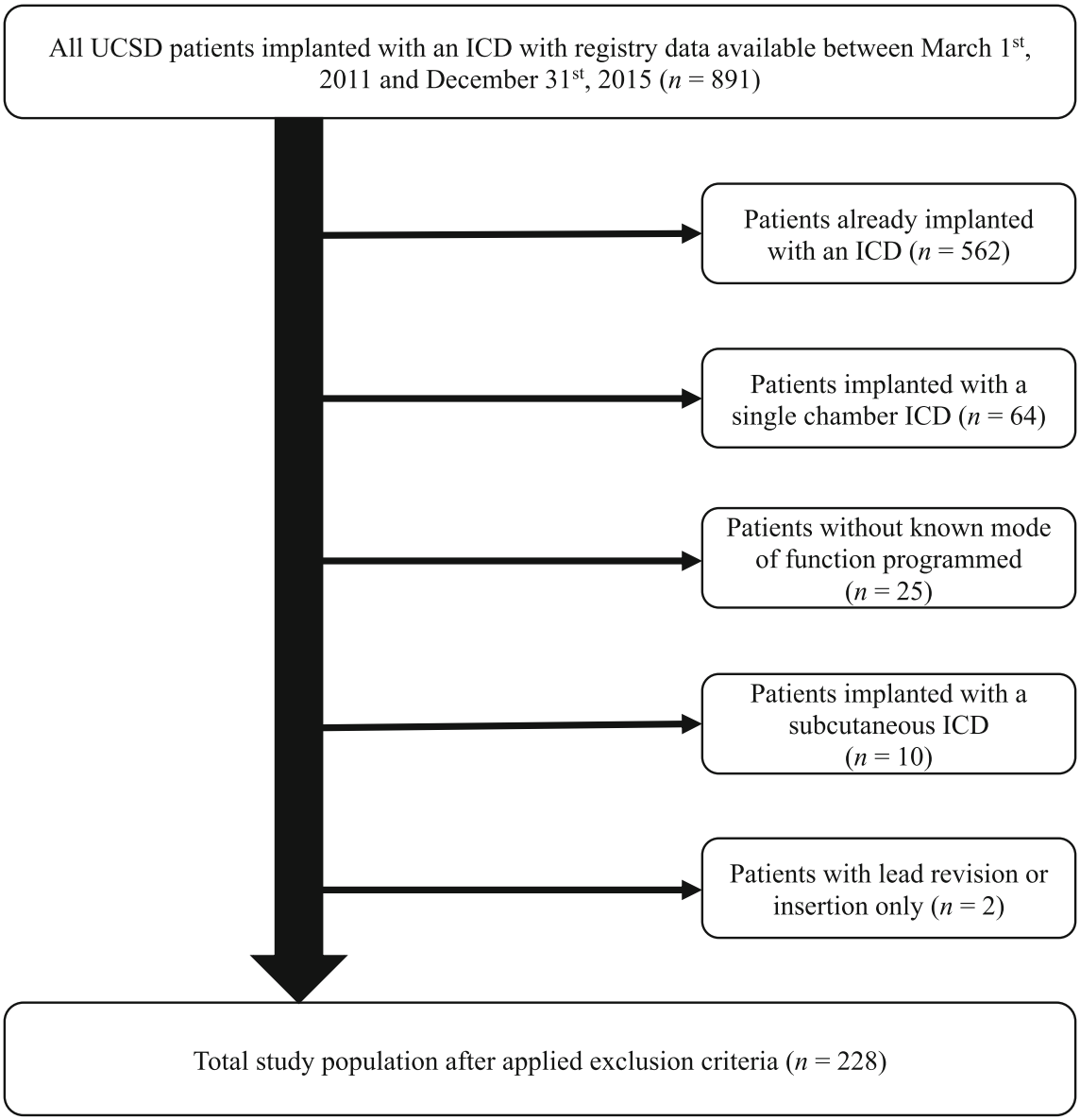

Fig. 1 Population selection—Flowchart showing how exclusion criteria were applied. ICD implantable cardioverter–defibrillator

In order to determine the association of rate-adaptive pacing activation within 30 days and subsequent clinical outcomes during follow-up, univariate time-to-event analysis was conducted by constructing Kaplan–Meier curves. Any difference between the two groups was evaluated with log-rank p values. Cox proportional hazard regression was used for multivariable adjustment, using the same covariates as in previous multivariable analyses in the models, as potential confounders. Hazard ratios were calculated for the two groups and presented with 95% confidence intervals.

Statistical analyses were carried out using SPSS (IBM SPSS Statistics for Macintosh, version 24.0, IBM Corp, Armonk, NY). All statistical tests were two-sided and considered significant if $p < 0.05$. Ethical approval for this study was granted by the UCSD Institutional Review Board.

3 Results

3.1 Baseline characteristics

A total of 228 patients undergoing an initial ICD implantation were analyzed. Patient demographic, clinical, and diagnostic data, stratified by rate-adaptive pacing activation (versus not) during follow-up, are shown in Table 1. The majority of the patients were male ($n = 159$, 69.7%), with a mean age of 62.0 ± 14.7 years. The two groups differed significantly in age and ethnicity ($p = 0.001$ and 0.01, respectively), with a higher age and a majority of non-Hispanic white race in patients with rate-adaptive pacing activated during follow-up. Significant clinical and diagnostic differences were also present between the two groups. Patients with a previous history of atrial

Table 1 Patient baseline characteristics

Characteristic	Rate-adaptive pacing activated during follow-up ($n = 88$)	Rate-adaptive pacing not activated during follow-up ($n = 140$)	p value
Demographic information			
Age, mean (SD) (years)	66.0 (13.7)	59.4 (14.7)	0.001
Height, mean (SD) (cm)	172.0 (11.8)	172.0 (12.2)	0.99
Weight, mean (SD) (kg)	81.4 (19.2)	83.6 (24.8)	0.47
Male gender	63 (71.6%)	96 (68.6%)	0.63
Ethnicity			0.01
Non-Hispanic white	58 (65.9%)	61 (43.6%)	
Black	2 (2.3%)	15 (10.7%)	
Hispanic	18 (20.5%)	46 (32.9%)	
Other	9 (10.2%)	16 (11.4%)	
Unknown	1 (1.1%)	2 (1.4%)	
Patient history and risk factors			
Heart failure	71 (80.7%)	113 (80.7%)	1.00
NYHA functional class			1.00
I	18 (20.5%)	29 (20.9%)	
II	24 (27.4%)	38 (27.4%)	
III	41 (46.6%)	64 (46.0%)	
IV	5 (5.7%)	8 (5.8%)	
Non-ischemic cardiomyopathy	39 (44.3%)	60 (42.9%)	0.83
Syncope	19 (21.6%)	25 (17.9%)	0.49
Atrial fibrillation/-atrial flutter	43 (48.9%)	28 (20.0%)	< 0.001
Ventricular tachycardia	28 (31.8%)	39 (27.9%)	0.52
Second degree AV block	0 (0.0%)	1 (0.7%)	0.43
Third degree AV block	9 (10.2%)	1 (0.7%)	0.001
Cardiac arrest	11 (12.5%)	18 (12.9%)	0.94
Ischemic cardiomyopathy	46 (52.3%)	60 (42.9%)	0.17
Previous myocardial infarction	36 (40.9%)	47 (33.6%)	0.26
Previous PCI	22 (25.0%)	37 (26.4%)	0.81
Previous CABG	15 (17.0%)	16 (11.4%)	0.23
Primary valvular heart disease	12 (13.6%)	12 (8.6%)	0.23
Cerebrovascular disease	7 (8.0%)	14 (10.0%)	0.60
Chronic lung disease	7 (8.0%)	17 (12.1%)	0.32
Diabetes mellitus	19 (21.6%)	53 (37.9%)	0.01
Obstructive sleep apnea	5 (5.7%)	8 (5.7%)	0.99
Current renal dialysis	1 (1.1%)	2 (1.4%)	0.85
Hypertension	59 (67.0%)	94 (67.1%)	0.99
Family history of SCD	4 (4.5%)	7 (5.0%)	0.88
Patient diagnostics			
LVEF (%)			0.55
< 20	7 (8.0%)	17 (12.1%)	
20 to 35	59 (67.0%)	86 (61.4%)	
> 35	22 (25.0%)	37 (26.4%)	
Heart rate, mean (SD) (bpm)	68.3 (17.4)	75.0 (15.5)	0.003
PR interval, mean (SD) (ms)	190.0 (42.0)	180.2 (38.6)	0.11
QRS duration, mean (SD) (ms)	130.6 (31.6)	123.5 (30.2)	0.10
SBP, mean (SD) (mmHg)	123.5 (22.4)	120.7 (20.0)	0.32
Hemoglobin, mean (SD) (g/dl)	13.0 (1.9)	12.7 (2.1)	0.35
Creatinine, mean (SD) (mg/dl)	1.1 (0.4)	1.1 (0.6)	0.67
Medications			
ß Blocker	77 (91.7%)	126 (93.3%)	0.65
Calcium channel blocker	1 (1.1%)	1 (0.7%)	0.75
Digoxin	13 (14.8%)	19 (13.8%)	0.83
Antiarrhythmic medications			
Amiodarone	14 (16.1%)	13 (9.4%)	0.13
Dofetilide	1 (1.1%)	0 (0.0%)	0.21
Mexiletine	0 (0.0%)	2 (1.4%)	0.26
Sotalol	6 (6.8%)	1 (0.7%)	0.01
Other	0 (0.0%)	1 (0.7%)	0.42
Device characteristics			
ICD type			0.01
Dual chamber	38 (43.2%)	84 (60.0%)	
CRT-D	50 (56.8%)	56 (40.0%)	
Device manufacturer			0.40
Biotronik	4 (4.5%)	12 (8.6%)	
Boston Scientific	27 (30.7%)	40 (28.6%)	
Medtronic	31 (35.2%)	57 (40.7%)	
Abbott	26 (29.5%)	31 (22.1%)	

Baseline characteristics of all implantable cardioverter–defibrillator recipients stratified by rate-adaptive pacing activated during follow-up versus not. Categorical variables are reported as proportions; continuous variables are reported as mean ± SD

AV atrioventricular, *CABG* coronary artery bypass graft, *CRT-D* cardiac resynchronization therapy defibrillator, *ICD* implantable cardioverter–defibrillator, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association, *PCI* percutaneous coronary intervention, *SBP* systolic blood pressure, *SCD* sudden cardiac death

fibrillation, third degree atrioventricular block, lower heart rate, and those prescribed sotalol were more likely to have rate-adaptive pacing activated during follow-up, while patients with diabetes mellitus were less likely to have rate-adaptive pacing activated during follow-up. Patients implanted with a cardiac resynchronization therapy defibrillator (CRT-D) were more likely to have rate-adaptive pacing

activated during follow-up than those implanted with a dual chamber ICD (see Table 1).

3.2 Rate-adaptive pacing activation

During a mean follow-up of 625.4 days, 88 patients (38.6%) had rate-adaptive pacing activated during follow-up. Rate-adaptive pacing was either activated within 1 day of implantation (n = 36, 15.8%), between 2 and 30 days after implantation (n = 12, 5.3%), or later than 30 days after implantation (n = 40, 17.5%). In multivariable logistic regression, there were several predictors of rate-adaptive pacing activation at any time during follow-up (Table 2). Predictors associated with greater odds of rate-adaptive pacing activation were non-ischemic cardiomyopathy, atrial fibrillation, myocardial infarction, a left ventricular ejection fraction between 20 and 35%, and higher concentration of hemoglobin. Predictors associated with lower odds of rate-adaptive pacing activation were greater height, heart failure, cerebrovascular disease, diabetes mellitus, and higher heart rate.

3.3 Clinical outcomes

During follow-up, a total of 38 patients in the cohort (16.7%) experienced device therapy for ventricular tachyarrhythmias (e.g., antitachycardia pacing or shocks), atrial fibrillation occurred in 79 patients (34.6%), 98 patients (43.0%) were readmitted for HF, and death occurred in 18 patients (7.9%). Absolute numbers of events, stratified by rate-adaptive pacing activated within 30 days (versus not), are shown in Table 3. In univariate Kaplan–Meier analyses (Fig. 2), there were no statistically significant differences in the cumulative risk of ICD therapy, atrial fibrillation, HF readmission, or mortality between patients who had rate-adaptive pacing activated within 30 days of implantation and patients who did not (p = 0.20, 0.09, 0.70, and 0.30, respectively). After multivariable adjustment, there continued to be no statistically significant difference in the aforementioned outcomes between the two groups (Table 4).

4 Discussion

4.1 Main findings

In this retrospective, single-center study of 228 first-time ICD recipients with ICDs capable of atrial pacing, rate-adaptive pacing was activated in more than 1 out of 3 patients at any time during follow-up. Several statistically significant

Table 2 Predictors of rate-adaptive pacing activation

Variable	Adjusted odds ratio	95% confidence interval	p value
Height	0.95	0.91–0.99	0.046*
Age	1.02	0.99–1.06	0.14
Weight	1.02	0.99–1.04	0.17
Heart failure	0.16	0.03–0.93	0.04*
Non-ischemic cardiomyopathy	3.83	1.22–12.00	0.02*
Atrial fibrillation/atrial flutter	8.27	2.96–23.06	< 0.001*
Myocardial infarction	4.17	1.38–12.58	0.01*
Cerebrovascular disease	0.09	0.01–0.69	0.02*
Diabetes mellitus	0.34	0.13–0.86	0.02*
LVEF (%)			
< 20	Reference		
20 to 35	6.08	1.16–31.84	0.03*
> 35	2.00	0.21–18.77	0.55
QRS	1.01	0.99–1.03	0.18
Hemoglobin	1.30	1.01–1.67	0.04*
Creatinine	2.05	0.88–4.78	0.10
ß Blocker	0.23	0.05–1.19	0.08
Calcium channel blocker	0.08	0.01–2.01	0.12
Amiodarone	3.25	0.91–11.60	0.07
CRT-D	2.90	0.82–10.22	0.10
Heart rate	0.95	0.92–0.98	< 0.001*

Predictors associated with rate-adaptive pacing activation during follow-up, after multivariable adjustment

CRT-D cardiac resynchronization therapy defibrillator, *LVEF* left ventricular ejection fraction

*Statistically significant predictors with a p value < 0.05

Table 3 Absolute numbers of events

Outcome	Entire cohort ($n = 228$)	Rate-adaptive pacing activated within 30 days of implantation ($n = 48$)	Rate adaptive pacing not activated within 30 days of implantation ($n = 180$)
Device therapy	38 (16.7%)	10 (20.8%)	28 (15.6%)
Atrial fibrillation	79 (34.6%)	20 (41.6%)	59 (32.8%)
Heart failure re-admission	98 (43.0%)	20 (41.6%)	78 (43.3%)
All-cause mortality	18 (7.9%)	5 (10.4%)	13 (7.2%)

Absolute numbers of events for clinical outcomes including device therapy, atrial fibrillation, heart failure re-admission, and all-cause mortality

predictors of rate-adaptive pacing activation were identified, including previous atrial fibrillation, myocardial infarction, a left ventricular ejection fraction between 20 and 35%, non-ischemic cardiomyopathy, and a lower heart rate. In both univariate and multivariable analyses, there were no statistically significant differences in clinical outcomes between ICD recipients who had rate-adaptive pacing activated within 30 days of implantation and patients who did not.

4.2 Rate-adaptive pacing activation

In our study, the incidence of activating rate-adaptive pacing within 30 days of implantation was 21.1% ($n = 48$). Hence, our data suggest that the prevalence of CI at baseline in an ICD population, as identified by the implanting practitioner, is one out of five patients, although this is lower than in a general HF population, where the

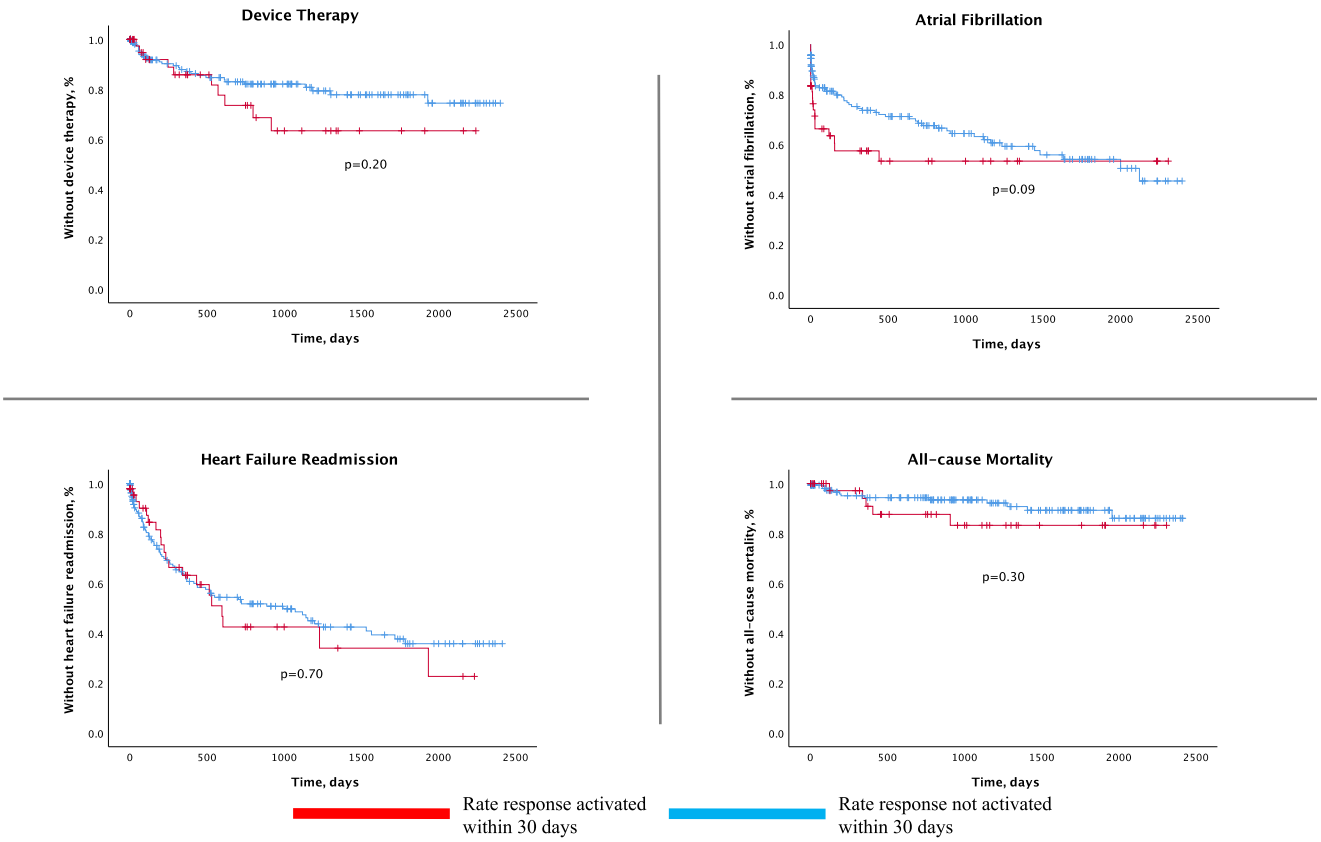

Fig. 2 Risk of clinical outcomes—Kaplan–Meier curves for clinical outcomes including device therapy, atrial fibrillation, heart failure readmission, and all-cause mortality

Table 4 Risk of clinical outcomes

Outcome	Adjusted HR	95% Confidence interval	*p* value
Device therapy	1.52	0.71–3.28	0.29
Atrial fibrillation	1.42	0.71–2.87	0.32
Heart failure re-admission	1.39	0.80–2.43	0.25
All-cause mortality	2.34	0.80–6.84	0.12

Hazard ratio (HR) of clinical outcomes in patients with rate-adaptive pacing activated within 30 days of implantation (versus not), after multivariable adjustment

prevalence has been reported to be approximately 30% or more [6, 7, 10]. This difference may be due to the fact that although rate-adaptive pacing and CI are closely linked, it cannot be excluded that rate-adaptive pacing was not activated in patients who in fact had CI but had yet to be identified as having this condition. Conversely, patients who had rate-adaptive pacing activated did not necessarily need to have CI, even though this connection has clinical importance.

To our knowledge, no previous studies have examined the cumulative incidence of rate-adaptive pacing activation in an ICD population after extended follow-up. Even though two previous studies by Nägele et al. and Fontenla et al. examined rate-adaptive pacing and subsequent clinical outcomes, the first study only examined patients implanted with a pacemaker, and the latter only investigated the incidence of rate-adaptive pacing activation at implantation [14, 15]. Over the total length of our study, with an average follow-up of 625.4 days, 88 patients (38.6%) had rate-adaptive pacing activated, indicating that the need for rate-adaptive pacing (and hence evidence for CI, as identified by the individual practitioner) in an ICD population may develop over time.

The etiology of CI is poorly understood, although many of the characteristics are associated with HF [10]. For example, the degenerative nature of myocardial ischemia has been linked to changes associated with CI (e.g., sinus node remodeling and prolonged sinoatrial conduction) [10]. Indeed, myocardial infarction was a predictor of rate-adaptive pacing activation during follow-up and is a well-known risk factor for the development of HF [3, 7], suggesting that rate-adaptive pacing activation is an indicator of CI. Furthermore, almost all of our patients had a ß-blocker prescribed, and a decreased ß-adrenergic receptor density has been described as an effect of both HF and ß-blocker therapy, eventually leading to the development of CI [9, 10]. Consequently, our data support those findings.

A common definition of CI is the inability to achieve 85% of the age-predicted maximum heart rate during exercise [7, 9, 16]. Consequently, a lower intrinsic heart rate is a characteristic of CI. In our study, a lower heart rate was a statistically significant predictor of rate-adaptive pacing activation during follow-up. Thus, our data have important clinical implications, suggesting that CI is an important predictor of rate-adaptive pacing activation in patients undergoing first-time ICD implantation, as well as suggesting that this syndrome needs further study in this population.

4.3 Clinical outcomes

Rate-adaptive pacing in patients implanted with an ICD or CRT-D has not been well investigated, with previous small studies indicating an improved response to exercise [7, 17, 18], as well as a potential for improved survival [19]. However, deleterious effects have also been described in one study which found that atrial rate-adaptive pacing increased the incidence of sustained atrial arrhythmias [15]. Overall, rate-adaptive pacing in this population is poorly understood and warrants further research.

Our data suggest that rate-adaptive pacing in an ICD population is not significantly associated with adverse events. However, although not significant, both univariate and multivariable survival analyses showed a trend towards an increased risk of the clinical outcomes of device therapy, atrial fibrillation, heart failure re-admission, and death, which may reflect a possible signal or residual confounding from covariates unable to be measured. These findings have implications for clinical practice as device therapy with rate-adaptive pacing is generally considered superior to device therapy without rate-adaptive pacing in patients who appear to have CI and warrant atrial pacing [17, 18]. Our findings indicate that it does not appear that activation of rate-adaptive pacing is associated with significant adverse clinical outcomes in an ICD population. As previously stated, the trend towards an increased risk of adverse events in the rate-adaptive pacing group is most likely due to residual confounding, as differences present at univariate analysis were attenuated after multivariable analysis. Even though there was no great difference at baseline between the two groups (see Table 1), it is possible that patients who had

rate-adaptive pacing activated during follow-up in fact suffered from more comorbidities that were otherwise not captured by our analysis.

In our study, patients who had rate-adaptive pacing activated during follow-up had a significantly lower heart rate. A lower heart rate is indicative of CI, thus providing the rationale for rate-adaptive pacing activation. However, with rate-adaptive pacing therapy, a patient's average heart rate is increased. Low heart rate has been proven to be beneficial in patients with HF or cardiovascular disease, and thus, a higher average heart rate may have negative consequences [14, 20, 21]. On the other hand, a good exercise tolerance is also beneficial for these patients, making it necessary for this population to increase their heart rate when needed [7, 22]. This poses an interesting problem for how to treat an ICD population with CI, as a low heart rate may increase the risk of decreased exercise tolerance, and a high heart rate may increase the risk for different adverse events. The relative importance of different heart rates is an area which needs further elucidation in future studies.

4.4 Limitations

Our study has several limitations. As with any retrospective database analysis, the possibility of selection bias cannot be excluded, thus making this a possible explanation of our results. The study sample is also relatively small, and therefore, the study may be underpowered to detect an association of rate-adaptive pacing activation with subsequent adverse clinical outcomes. Furthermore, this study was performed at a university hospital, and therefore, our results may not be applicable to a general population of ICD recipients. Due to the registry-based investigation method, our study relies heavily on the quality of the data collection for the registry. However, any measurement bias would be expected to be non-differential between the two groups. In our study, we found several statistically significant predictors of rate-adaptive pacing activation—making this particular type of bias unlikely. Changes in dosage of medications that may affect sinus node function (e.g., beta blockers, calcium channel blockers, and antiarrhythmic medications) were unable to be fully tracked; therefore, we were unable to study the association of medication dosage with activation of rate-adaptive pacing.

4.5 Conclusion

In conclusion, the incidence of rate-adaptive pacing activation over time in a population undergoing novel ICD implantation is one in three patients. Several statistically significant predictors of rate-adaptive pacing activation were identified. After multivariable adjustment, there were no significant differences in adverse events in patients with rate-adaptive pacing activated versus those without rate-adaptive pacing activated.

Compliance with ethical standards

Ethical approval for this study was granted by the UCSD Institutional Review Board.

Conflict of interest The UCSD Cardiac Electrophysiology Fellowship Training Program receives support from Medtronic, Inc., St. Jude Medical, Inc., Biotronik, Inc., Boston-Scientific, Inc., and Biosense-Webster, Inc.

Dr. Jonathan C. Hsu reports receiving honoraria from Medtronic, St. Jude Medical, Boston Scientific and Biotronik and research grants from Biosense-Webster and Biotronik.

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Research involving human participants and/or animals The UCSD Human Research Protection Program approved analysis of the data from our institution for this study.

Informed consent Owing to the retrospective and observational nature of this study, written informed consent was waived.

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