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Eligibility of cardiac resynchronization therapy patients for subcutaneous implantable cardioverter defibrillators

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Abstract

Background Before subcutaneous implantable cardioverter defibrillator (S-ICD) implantation, the adequacy of sensing is required to be verified through surface ECG screening. Our objective was to determine whether S-ICD can be considered as a supplementary therapy in patients who are receiving biventricular (BIV) pacing.

Methods We evaluated 48 patients with BIV devices to determine S-ICD candidacy during BIV, left ventricular (LV), right ventricular (RV) pacing, and intrinsic conduction (left bundle branch block—LBBB) by using an automated screening tool. Eligibility was defined by the presence of at least one appropriate vector in the supine and standing positions.

Results Eligibility was verified during BIV pacing in 34 (71%) patients. In patients screened-out, QRS duration was longer ($p = 0.035$) and ischemic cardiomyopathy was more frequent ($p = 0.027$). LV-only pacing was associated with a lower passing rate (46%) ($p < 0.001$ versus BIV). The LBBB QRS morphology during inhibited ventricular pacing was acceptable in 51% of patients. The QRS generated by RV pacing was acceptable in 25% of patients. In patients who passed the screening test during BIV, the QRS was not acceptable in 76% during RV pacing (i.e., accidental loss of LV capture). The concomitant adequacy during inhibited ventricular pacing (i.e., possible intrinsic conduction) was not assessed in 40% of patients.

Conclusions S-ICD may be a supplemental therapy in the majority of CRT patients. Standard BIV pacing should be preferred to the LV-only pacing mode, as it is more frequently associated with adequacy of S-ICD sensing. Spontaneous LBBB and RV-paced QRS morphologies are frequently inadequate. Therefore, in patients selected for concomitant S-ICD and CRT implantation, accidental loss of LV capture or possible intrinsic conduction must be prevented.

Keywords ICD · Subcutaneous · Screening · CRT · Sudden death

Abbreviations

ICD	Implantable cardioverter-defibrillators
S-ICD	Subcutaneous ICD
CRT	Cardiac resynchronization therapy
ECG	Electrocardiogram

1 Introduction

Implantable cardioverter-defibrillators (ICDs) are an established therapy for the prevention of sudden cardiac death [1]. The recently introduced subcutaneous ICD (S-ICD) was designed to provide defibrillation therapy [2], while avoiding the risks involved in accessing the heart via the vascular system and overcoming possible complications related to transvenous leads [3, 4]. However, as the S-ICD does not provide pacing, it is not ideally suitable for patients who need pacing therapy for bradycardia support, cardiac resynchronization therapy (CRT), or anti-tachycardia pacing. Nonetheless, in patients who already have a pacemaker and meet criteria for an ICD, an S-ICD can be considered as long as the pacemaker is endowed with bipolar leads and programmed to a bipolar pacing configuration.

Before S-ICD implantation, the adequacy of sensing is required to be verified through surface electrocardiogram (ECG) screening based on a dedicated ECG morphology tool. In patients with a previously implanted pacemaker, screening should be based on both the intrinsic and paced ECG morphologies.

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In the present analysis, we sought to determine whether S-ICD can be considered as a supplementary therapy in patients who are receiving biventricular pacing for CRT.

2 Methods

2.1 Study population

Consecutive patients in whom a transvenous pacemaker or ICD for CRT (CRT-D) had previously been implanted were enrolled at the study center during routine follow-up visits. All patients provided written informed consent for data storage and analysis, as approved by the Institutional Review Board.

2.2 Study procedures

Baseline evaluation included demographics and medical history, clinical examination, and echocardiographic evaluation. All patients underwent the screening protocol with the Automated Screening Tool by means of the Model 3120 Programmer (Boston Scientific, Natick, MA). ECG electrodes were placed 1 cm left-lateral to the xiphoid process (proximal electrode, LA), 14 cm cranial to the proximal electrode on the left parasternal line (distal electrode, RA), and between the 5th and 6th ribs on the left mid-axillary line (active can, LL). After ECG lead connection, the system automatically assesses the acceptability of each of the three vectors. The procedure is performed in both supine and standing positions, and at the end of the acquisition process, a report is provided that summarizes screening results and allows users to check QRS complex morphology across postures (Fig. 1). A patient was judged suitable for S-ICD if at least one sensing vector passed in both supine and standing positions without changes in the R wave axis. In all patients, the screening procedure was carried out in the following pacing configurations: standard biventricular, left ventricular-only, and right ventricular-only. In patients with preserved intrinsic conduction, we also performed the screening procedure during inhibited ventricular pacing. All pacing channels were programmed in bipolar configurations, with atrioventricular and interventricular delays set to the permanently programmed values.

2.3 Study endpoints

The primary endpoint was the passing rate during standard biventricular pacing. Moreover, we compared the characteristics of eligible and non-eligible patients. In addition, among the patients who passed the S-ICD screening, we assessed the concomitant adequacy during right ventricular-only pacing, in order to simulate an accidental loss of left ventricular capture. The concomitant adequacy during inhibited ventricular pacing was measured in order to assess the performance of the S-ICD in the event of possible intrinsic conduction, e.g., due to rapidly conducted atrial fibrillation, inappropriate programming of atrioventricular pacing delay, etc..

2.4 Statistical analysis

Descriptive statistics are reported as means ± SD, and categorical variables are reported as percentages. Differences between mean data were compared by means of a *t* test for Gaussian variables and by Mann–Whitney non-parametric test for non-Gaussian variables. Differences in proportions were compared by means of Chi-square analysis or Fisher's exact test, as appropriate. A P value $< .05$ was considered significant for all tests. All statistical analyses were performed by means of STATISTICA software, version 7.1 (StatSoft, Inc., Tulsa, OK, USA).

3 Results

3.1 Study population

A total of 48 consecutive patients who had received a CRT system for symptomatic refractory heart failure and left bundle branch block were enrolled in the study. Of these, 47 had a previously implanted CRT-D and one had a CRT pacemaker. Table 1 shows baseline clinical variables. The screening protocol was implemented in all patients. In five patients, as intrinsic conduction was not preserved, the screening procedure was not performed during inhibited ventricular pacing. A total of 1122 ECG recordings were collected for automatic analysis of S-ICD eligibility.

3.2 Passing rate in different pacing configurations

At least one suitable vector in both postures was identified in 34 (71%) patients during standard biventricular pacing (Fig. 2). At least two vectors were appropriate in 19 (40%) patients and three vectors in 3 (6%). The characteristics of eligible and non-eligible patients during standard biventricular pacing are reported in Table 1. In patients screened-out, QRS duration was longer ($p = 0.035$) and ischemic cardiomyopathy was more frequent ($p = 0.027$).

At least one suitable vector was identified in 22 (46%) patients during left ventricular-only pacing ($p < 0.001$ versus biventricular pacing) and in 12 (25%) patients during right ventricular-only pacing (Fig. 2). At least one suitable vector was identified during standard biventricular or left ventricular-only pacing in 38 (79%) patients. Overall, 39 (81%) patients passed the S-ICD screening in both supine and standing positions with at least one of the three pacing configurations. Of the 43 patients with preserved intrinsic conduction, 22 (51%) passed the screening test during inhibited ventricular pacing.

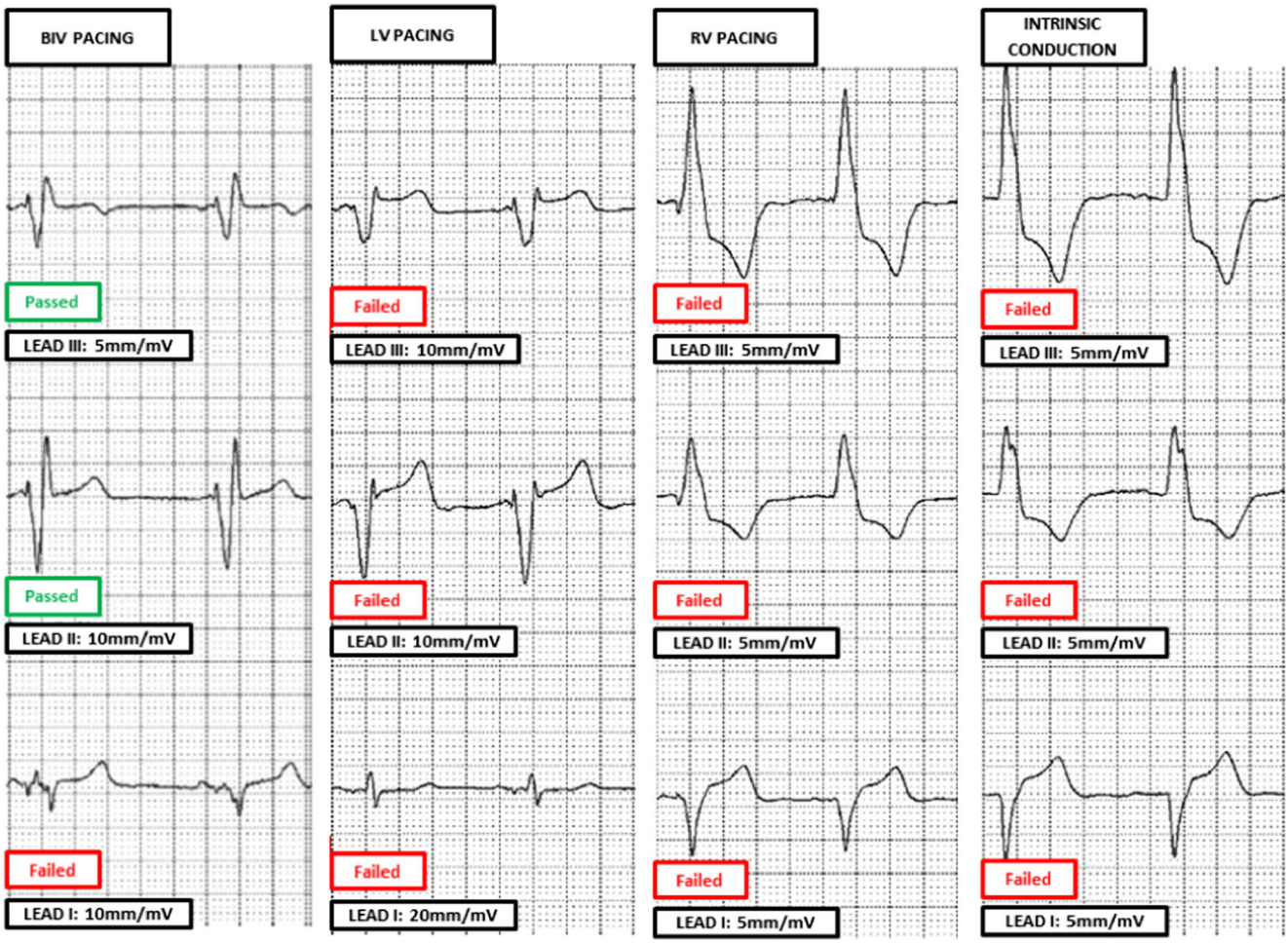

Fig. 1 Example of ECG recordings and screening results provided by the automated screening tool for the three vectors and four pacing configurations tested

Of the 34 patients who passed the screening test during biventricular pacing, the QRS was not acceptable in 26 (76%) during right ventricular-only pacing (i.e., simulated accidental loss of LV capture). Of the 30 patients with preserved intrinsic conduction who passed the screening test during biventricular pacing, adequacy during inhibited ventricular pacing (i.e., possible intrinsic conduction due to rapidly conducted atrial fibrillation or inappropriately long atrioventricular pacing delay) was not verified in 12 (40%).

During biventricular pacing, the primary vector (Lead III) was suitable in 20 (42%) patients, the secondary (Lead II) in 14 (29%), and the alternate (Lead I) in 22 (46%). The alternate vector was the most suitable also in the other pacing configurations (Fig. 3).

4 Discussion

In this analysis, we confirmed the S-ICD eligibility of 71% of patients with heart failure and left bundle branch block during biventricular pacing and the eligibility of 79% of patients during standard biventricular or left ventricular-only pacing. Therefore, S-ICD implantation may be a supplemental therapy in the majority of CRT patients.

According to the most recent guidelines [1, 5], the S-ICD is an alternative for patients with an ICD indication. The S-ICD does not require vascular access or permanent intravascular indwelling leads and was developed to overcome many of the limitations and complications (e.g., cardiac perforation, lead fracture, lead endocarditis, and venous thrombosis) associated with traditional transvenous ICD [3, 4]. However, the S-ICD does not provide pacing. Therefore, if the patient develops the need for bradycardia support, CRT, or anti-tachycardia pacing, the possibility of combining an S-ICD and a pacing system may be considered. In particular, the probability of developing CRT indications after implantation has been shown to be very low, i.e., 0.4% of patients over 3 years in the Evaluation of Factors Impacting Clinical Outcome and Cost Effectiveness of the S-ICD (EFFORTLESS S-ICD) Registry [6]. In these cases, two options are available: removing the S-ICD and implanting a CRT-D or simply adding a CRT pacemaker. The double-device approach may also be an option for

Table 1 Demographics and baseline clinical parameters of all patients and of eligible and non-eligible patients during standard biventricular pacing

Parameter	All patients (48)	Eligible patients (34)	Non-eligible patients (14)
Male gender, *n* (%)	40 (84)	27 (80)	13 (93)
Age, years	73 ± 8	73 ± 9	72 ± 7
Body mass index, kg/m^2	28 ± 6	27 ± 7	30 ± 5
LV ejection fraction, %	30 ± 6	30 ± 7	31 ± 6
NYHA III-IV, *n* (%)	24 (50)	14 (41)	10 (71)
Ischemic cardiomyopathy, *n* (%)	25 (52)	14 (41)	11 (79)*
Spontaneous QRS duration, ms	154 ± 27	147 ± 28	168 ± 22#
Chronic kidney disease, *n* (%)	9 (19)	7 (21)	2 (14)
Diabetes, *n* (%)	16 (33)	10 (29)	6 (43)
COPD, *n* (%)	7 (15)	5 (15)	2 (14)

LV left ventricle, *NYHA* New York Heart Association, *COPD* chronic obstructive pulmonary disease
*$p = 0.027$; #$p = 0.035$

patients in whom a CRT pacemaker is originally implanted or in patients with a dual-chamber pacemaker who develop heart failure and CRT/CRT-D indications. Indeed, the complications associated with transvenous device upgrade are well known [7]. Thus, the risk associated with the transvenous approach in order to upgrade a CRT pacemaker to a CRT-D should not be considered negligible, as the procedure requires the replacement of the generator and the implantation of a right ventricular defibrillator coil. The pacing lead may be left *in situ*, thus increasing the risk of venous thrombosis, or removed at the expense of higher procedural risks.

In our analysis, we found that S-ICD sensing was frequently adequate during biventricular pacing, confirming the feasibility of a double-device approach. In particular, S-ICD eligibility was more frequent in non-ischemic patients, although physicians' attitudes regarding ICD use in this group changed after the publication of the DANish randomized, controlled, multicenter study to assess the efficacy of implantable cardioverter defibrillators in patients with non-ischemic Systolic Heart failure on mortality (DANISH) [8].

Screening failure was more frequent with longer QRS duration. Similarly, owing to the longer duration of the paced QRS, failure occurred more frequently on left ventricular-only (54%) than on biventricular pacing (29%). In our analysis, we tested a single atrioventricular and interventricular delay for biventricular pacing. However, considering that optimized sequential biventricular pacing has been shown to be associated with a significant reduction in QRS duration [9], we can expect the passing rate to increase if delays are appropriately programmed. Moreover, the availability of multiple pacing options with modern quadripolar left ventricular leads may increase the probability of obtaining an eligible S-ICD configuration. The long QRS duration associated with left bundle branch block also resulted in a low passing rate during inhibited pacing (51%) and during right ventricular-only pacing (25%) in our series. By way of comparison, previous studies have reported failure rates of 4–10% in the general population [10–12] and 54% in patients paced at the right ventricular apex [13].

In the EFFORTLESS registry [6], the overall inappropriate shock rate was 8.1% at 1 year and appeared to be similar to the overall rate in historical transvenous ICD studies. Moreover, modeling studies showed that the latest S-ICD detection algorithms may reduce inappropriate shocks due to cardiac oversensing by 70 to 80% [14]. In this analysis, a patient was judged suitable for S-ICD if at least one sensing vector

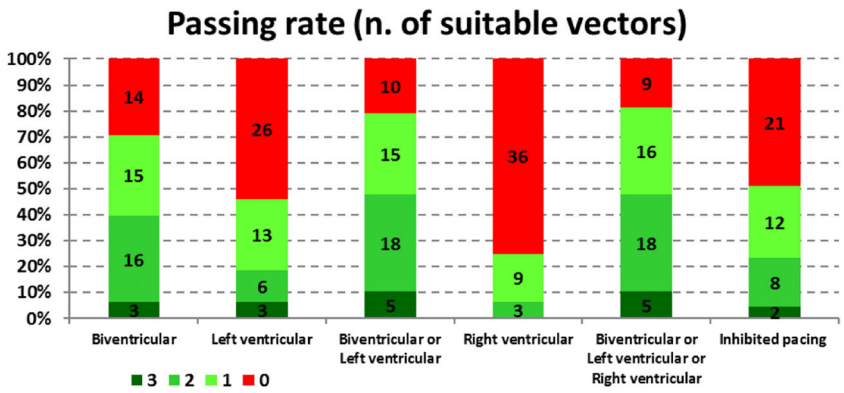

Fig. 2 Passing rate and number of suitable vectors for each pacing configuration tested

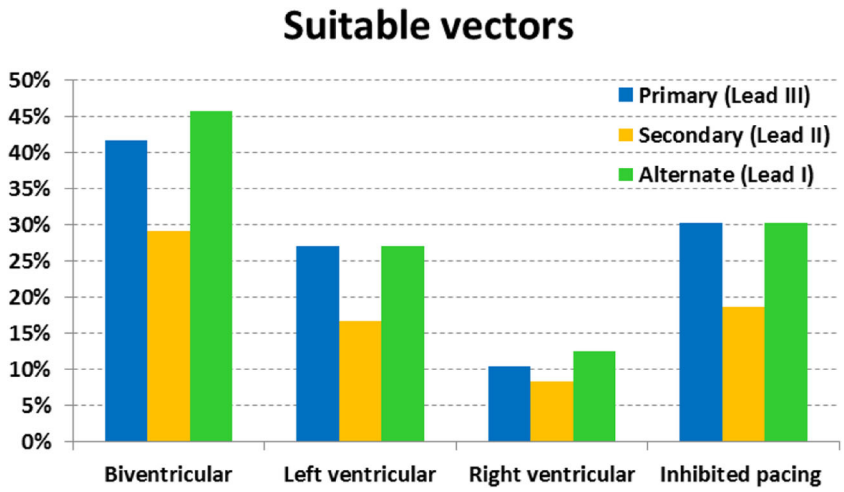

Fig. 3 Suitable vectors for each pacing configuration tested

passed in both supine and standing positions, in line with the manufacturer's recommendation. Although there is no evidence of an association between a greater number of adequate vectors at implantation and a lower rate of inappropriate events, the availability of a second suitable vector could be worthwhile. Indeed, previous follow-up studies showed that reprogramming, such as altering the sensing vector, storing a new template, or increasing the detection rate, after the first clinical event of inappropriate shock, was successful in preventing further inappropriate shocks [15]. In the present study, we also showed that at least two vectors were appropriate in 40% of patients in both postures during standard biventricular pacing and in 48% of patients during standard biventricular or left ventricular-only pacing.

In our analysis, the alternate vector was the most suitable during biventricular pacing and in the other pacing configurations. By contrast, in the EFFORTLESS Registry, the alternate vector was the least frequently programmed vector in a large population of S-ICD recipients with no conduction abnormalities or pacing [15].

The recommendations in the case of combined S-ICD and standard pacemaker implantation are to verify that the pacemaker is in the bipolar pacing mode, to select an adequate S-ICD sensing vector, and to ensure that the pacemaker does not pace faster than therapies are set on the S-ICD. If paced morphologies fail all vectors, the upper rate limit of the pacemaker should, if feasible, be set at < ½ the lower rate of the conditional shock zone. In this way, if the device does double count the QRS complex, it will still be below the conditional shock zone and no shock will be given [16]. With CRT pacemakers, additional considerations are required. According to our data, if the patient is receiving left ventricular-only pacing, probably he will require reprogramming to a biventricular pacing configuration to pass the screening test, with unknown consequences on the response to CRT. Moreover, S-ICD inadequacy due to spontaneous left bundle branch block and right ventricular-paced QRS morphologies may have practical implications. Indeed, accidental loss of left ventricular capture or possible intrinsic conduction can result in inappropriate sensing. For example, programming an inappropriately long atrioventricular delay may result in accidental loss of left ventricular or biventricular capture. Similarly, the occurrence of rapidly conducted atrial fibrillation will result in spontaneous left bundle branch block activation, with the risk of inappropriate shock due to over-sensing. According to our findings, the simultaneous verification of S-ICD adequacy during biventricular and right ventricular-only pacing was definitely rare (8 out of 48 patients, 17%), as well as the adequacy during biventricular and intrinsic conduction (22 out of 48 patients, 46%). Therefore, every effort must be made to prevent accidental loss of left ventricular capture or possible intrinsic conduction. Moreover, since previous studies showed unexpected significant variability in effective biventricular pacing during the day owing to spontaneous, fusion, or pseudo-fusion beats [17], a 24-h Holter recording should be also considered for the assessment of S-ICD eligibility of patients with CRT pacing systems.

4.1 Limitations

The clinical relevance of our findings is probably lessened by the small target population for a combined S-ICD and CRT pacemaker approach. Moreover, the present results should be interpreted within the constraints of the study limitations. Specifically, the number of patients in the present study was small. Moreover, we tested only the left parasternal position of the electrodes for S-ICD adequacy assessment, while it has been previously shown that the use of right parasternal placement may increase eligibility [18]. In addition, the actual detection performance of an implanted S-ICD is expected to be higher than that predicted by the screening tool. Indeed, although the automated screening tool mimics the S-ICD sensing scheme and applies the signal-processing filters currently used by S-ICD to analyze the ECG, the additional SMART

PASS algorithm has been recently incorporated into S-ICD, in order to reduce the amplitude of lower frequency signals, while maintaining an appropriate sensing margin [19].

5 Conclusions

S-ICD implantation may be a supplemental therapy in the majority of CRT patients. In these patients, standard biventricular pacing should be preferred to the left ventricular-only pacing mode, as it is more frequently associated with adequacy of S-ICD sensing. Spontaneous left bundle branch block and right ventricular-paced QRS morphologies are frequently inadequate. Therefore, in patients selected for concomitant S-ICD and CRT implantation, accidental loss of left ventricular capture or possible intrinsic conduction must be prevented.

When a system that combines a leadless pacemaker and an S-ICD [20] becomes available, the question of compatibility between pacing systems and S-ICDs will become even more relevant.

Compliance with ethical standards

All patients provided written informed consent for data storage and analysis, as approved by the Institutional Review Board.

Conflict of interest M. Lovecchio, S. Chiarenza and S. Valsecchi are employees of Boston Scientific, Inc. No other conflicts of interest exist.

Ethical approval The study was approved by the Local Ethics Committee.

Informed consent Informed consent was obtained from all individual participants included in the study.

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