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Original Article

# Programmed electrical stimulation for risk stratification of patients with ischemic cardiomyopathy

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ABSTRACT

*Background:* Patients with ischemic cardiomyopathy (ICM) are at an increased risk for sudden death. Although earlier trials used programmed electrical stimulation (PES) for risk stratification, more recent data demonstrate the benefit of implantable cardiac defibrillators (ICDs) in selected patients with reduced left ventricular ejection fraction (LVEF) without performing PES. However, little is known about the outcome of non-inducible patients. The purpose of this study was to evaluate the efficacy of PES for mortality risk stratification in patients with ICM.

*Methods:* All consecutive patients who met the inclusion criteria (history of coronary artery disease, LVEF $\leq$ 35%, and absence of documented spontaneous sustained ventricular tachycardia or aborted sudden cardiac death) were included in the study. The stimulation protocol involved up to three extrastimuli from two different sites in the right ventricle, with 180 ms as the shortest coupling interval. The primary endpoint was overall survival.

*Results:* A total of 198 patients were included in the study; of these, 60 exhibited negative (−)PES, and 138 had positive (+)PES and also underwent ICD implantation. The mean follow-up duration was 4.5 years. There was no difference in age or LVEF between the patient groups. We found a trend towards an increased 5-year survival rate in the (+)PES group in whom ICD implantation had been performed ($p=0.058$). Survival was significantly better in patients under 68 year olds in the (+)PES group in whom ICD implantation was performed (hazard ratio = 0.3, $p=0.01$). The survival rate of patients $\geq$ 68 years old was similar in both groups ($p=0.95$).

*Conclusions:* Non-inducibility during PES does not predict the prognosis of patients with ischemic cardiomyopathy.



## 1. Introduction

Patients with ischemic cardiomyopathy are at an increased risk for serious ventricular arrhythmias and sudden cardiac death (SCD). Epidemiological studies indicate that more than 50% of cardiac deaths are sudden [1,2]. Antiarrhythmic drugs (AAD) do not reduce mortality in these patients [3–7]. Although earlier trials used programmed electrical stimulation (PES) for risk stratification [6–8], more recent data demonstrate the benefit of implantable cardiac defibrillators (ICDs) to treat patients with severely reduced left ventricular ejection fractions (LVEF) without performing PES [7,9]. However, as many patients will never have any ICD treatment, further risk stratification is required. The MADIT I and II studies included PES before randomization to ICD or medical therapy (PES was not mandatory but encouraged in MADIT II and was performed in 80% of the patients). In the MUSTT study, a registry of all patients recruited was maintained, and included those patients who did not experience abnormal rhythms induced during PES (non-inducible patients). Buxton et al. showed that with no antiarrhythmic therapy, the non-inducible patients had better prognosis than inducible patients [10]. However, the mortality rate of both groups was still high, and the non-inducible patients might still benefit from ICD. The purpose of this study was to evaluate the efficacy of PES for risk stratification based on mortality for inducible patients treated with ICD vs. non-inducible patients in a "real-world" registry.

## 2. Materials and methods

### 2.1. Study cohort

We performed a retrospective analysis of all consecutive patients referred for PES between 1999 and 2009, who met the

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following inclusion criteria: 1. Presence of coronary artery disease (CAD); 2. time from the last myocardial infarction to PES > 40 days; and 3. LVEF ≤ 35%. Patients with documented sustained ventricular arrhythmias were excluded. During this period, criteria for ICD implantation in Israel for primary prevention were similar to those of the MADIT I study; hence, this was the common practice. Since 2009, MADIT II inclusion criteria have been gradually implemented. Patients enrolled at that time had LVEFs 31–35% and therefore needed to have positive PES to be eligible for an ICD. The study protocol was approved by the institutional review board of Carmel Medical Center (IRB protocol no. 0126-09-CMC; date of approval July 7th, 2010).

### 2.2. Definitions

The presence of CAD was determined based on a history of myocardial infarction. We included data regarding medications at the time of hospital discharge after the procedure. Mitral regurgitation (MR) grade (0 – normal, 3 – severe) was determined using echocardiography.

### 2.3. Electrophysiological study

The protocol included stimulation from two right ventricular sites (the apex and septum) and two different drive trains (600 ms and 400 ms) [6]. We used up to three extrastimuli, with the shortest coupling interval being 180 ms. No drug was administered to enhance inducibility. Induction of sustained ( ≥ 30 s) or unstable VT, or ventricular flutter (VFL), was considered positive PES, while induction of ventricular arrhythmias other than monomorphic VT was considered positive only if reproducibly induced with a single or double extra-stimuli. Monomorphic VT was defined as a VT with a uniform stable QRS morphology with a cycle length > 230 ms. VFL was defined as sustained monomorphic VT with a shorter cycle length ( ≤ 230 ms). Ventricular fibrillation (VF) was defined as a rapid disorganized rhythm without consistently identifiable complexes.

### 2.4. Device implantation

All patients with (+)PES underwent ICD implantation within the same week. The implantation and programming were not uniform but left to the discretion of the operator. However, programming was typically performed according to the PainFREE Rx II study protocol. Patients underwent dual-chamber ICD implantation if they had a history of atrial arrhythmias.

### 2.5. Patient follow-up

For patients who underwent ICD implantation, follow-up was conducted at our ICD clinic 3–6 months interval. Appropriate ICD therapy was defined as any therapy (anti-tachycardia pacing or DC shock) given for sustained ventricular arrhythmia. Inappropriate therapy was defined as therapy administered for supraventricular tachycardia. Survival status, record of hospitalization, and medical events were verified using the Health Maintenance Organization (HMO) database. Follow-up for all other patients utilized the HMO database.

### 2.6. Study endpoints

The primary study endpoint was overall survival. In addition, we evaluated complications related to the ICD implantation, such as infection, lead reposition, deep venous thrombosis, and inappropriate activation.

### 2.7. Statistical analysis

Analysis was performed according to an intention-to-treat model. Continuous variables were compared using Student's *t*-test or the Mann–Whitney *U* test, as appropriate. Continuous variables with a non-normal distribution are presented as median (interquartile range). Categorical variables are expressed as percentages and were compared using Chi-squared or Fisher's exact tests, as appropriate. Univariate and multivariate Cox proportional hazards models for survival with a stepwise procedure were performed. Hazards ratios with 95% confidence intervals were estimated from

**Table 1**
Baseline characteristics.

| | Inducible | Non-inducible | *p* Value |
|---|---|---|---|
| Number | 138 | 60 | |
| Age (years) | 66.3 ± 9 | 68.5 ± 8.6 | 0.14 |
| Females, *n* (%) | 51 (45.1) | 29 (51.8) | 0.41 |
| Mean follow-up (months), mean ± SD | 42.0 ± 19.0 | 43.3 ± 18.7 | 0.64 |
| LVEF, % | 27.7 ± 5.6 | 28 ± 4.7 | 0.65 |
| LVEDD, mm | 59.3 ± 6.9 | 58.2 ± 6.8 | 0.3 |
| Mitral regurgitation (0–4 scale), mean ± SD | 1.03 ± 0.8 | 1.1 ± 0.9 | 0.45 |
| Previous PCI, *n* (%) | 63 (46) | 28 (47) | 0.9 |
| Previous CABG, *n* (%) | 68 (49) | 45 (27) | 0.58 |
| Mean time from previous MI or revascularization (years) ± SD | 8 ± 6 | 8.1 ± 5.9 | 0.88 |
| Atrial fibrillation, *n* (%) | 21 (15.2) | 17 (28.8) | 0.027 |
| Diabetes, *n* (%) | 30 (50) | 50 (36.2) | 0.07 |
| Hypertension, *n* (%) | 81 (58.7) | 40 (66.7) | 0.29 |
| Creatinine (mg/dL), mean ± SD | 1.2 ± 0.5 | 1.2 ± 0.46 | 0.98 |
| Medications | | | |
| β-Blockers, *n* (%) | 136 (98.6) | 52 (86.7) | < 0.001 |
| ACE inhibitors, *n* (%) | 125 (90.6) | 56 (93.3) | 0.53 |
| Amiodarone, *n* (%) | 12 (8.7) | 7 (11.7) | 0.51 |
| Other antiarrhythmic drugs, *n* (%) | 13 (9.4) | 6 (10) | 0.9 |
| Aldospirone, *n* (%) | 19 (14) | 12 (20) | 0.27 |
| Digoxin, *n* (%) | 17 (12.3) | 12 (20) | 0.16 |

LVEF, left-ventricular ejection fraction; LVEDD, left-ventricular end diastolic diameter; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MI, myocardial infarction.