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Dual-Chamber Pacing With Closed Loop Stimulation in Recurrent Reflex Vasovagal Syncope

The SPAIN Study

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ABSTRACT

BACKGROUND Pacing in vasovagal syncope remains controversial.

OBJECTIVES The authors evaluated dual-chamber pacing with closed loop stimulation (DDD-CLS) in patients with cardioinhibitory vasovagal syncope.

METHODS This randomized, double-blind, controlled study included Canadian and Spanish patients age ≥40 years, with high burden syncope (≥5 episodes, ≥2 episodes in the past year), and a cardioinhibitory head-up tilt test (bradycardia <40 beats/min for 10 s or asystole >3 s). Patients were randomized to either DDD-CLS pacing for 12 months followed by sham DDI mode pacing at 30 pulses/min for 12 months (group A), or sham DDI mode for 12 months followed by DDD-CLS pacing for 12 months (group B). Patients in both arms crossed-over after 12 months of follow-up or when a maximum of 3 syncopal episodes occurred within 1 month.

RESULTS A total of 46 patients completed the protocol; 22 were men (47.8%), and mean age was 56.30 ± 10.63 years. The mean number of previous syncopal episodes was 12 (range 9 to 20). The proportion of patients with ≥50% reduction in the number of syncopal episodes was 72% (95% confidence interval [CI]: 47% to 90%) with DDD-CLS compared with 28% (95% CI: 9.7% to 53.5%) with sham DDI mode ($p = 0.017$). A total of 4 patients (8.7%) had events during DDD-CLS and 21 (45.7%) during sham DDI (hazard ratio: 6.7; 95% CI: 2.3 to 19.8). Kaplan-Meier curve was significantly different between groups in time to first syncope: 29.2 months (95% CI: 15.3 to 29.2 months) versus 9.3 months (95% CI: 6.21 months, NA; $p < 0.016$); odds ratio: 0.11 (95% CI: 0.03 to 0.37; $p < 0.0001$).

CONCLUSIONS DDD-CLS pacing significantly reduced syncope burden and time to first recurrence by 7-fold, prolonging time to first syncope recurrence in patients age ≥40 years with head-up tilt test–induced vasovagal syncope compared with sham pacing. (Closed Loop Stimulation for Neuromediated Syncope [SPAIN Study]; NCT01621464) (J Am Coll Cardiol 2017;70:1720–8) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Reflex vasovagal syncope (VVS) remains one of the most common causes of recurrent syncope. Despite multiple attempts with a variety of pharmacological options aimed at reducing the recurrence of VVS, less than a handful of evidenced-based options are currently recommended by guidelines (1). Pacemakers were initially met with enthusiasm and backed by several nonrandomized studies and 2 randomized trials, which suggested an almost 70% relative risk reduction (RRR) in the time to first recurrence of syncope (2,3). However, further well-designed randomized trials, in which all patients received a pacemaker and were randomly assigned to pacing versus no pacing, were unable to demonstrate a clinically significant reduction in syncope recurrence, evidencing a large placebo effect (4,5). Only 1 study that included older patients with an asystole recorded by an implantable cardiac monitor demonstrated a 50% RRR in the recurrence of syncope (6). Based on this evidence, recent guidelines provide a Class IIb recommendation (Level of Evidence: C), for pacemaker therapy in patients older than 40 years of age with cardioinhibitory response during head-up tilt testing (HUT) and with recurrent, frequent unpredictable syncope that was refractory to conventional therapy (1).

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Controversy remains regarding the most efficient pacing mode for the prevention of recurrent cardioinhibitory VVS; only 1 study using rate drop response showed superiority to placebo. The benefits of a physiological pacing algorithm with contractility sensor, known as closed loop stimulation (dual-chamber pacing with closed loop stimulation [DDD-CLS]), has been reported in 2 randomized and 3 observational studies that included patients with asystole during HUT (7–11). We carried out a randomized, prospective, double-blind, controlled, multicenter trial to determine the utility of DDD-CLS pacing in patients with cardioinhibitory refractory VVS.

METHODS

Ethics review committees in all 11 centers (10 in Spain and 1 in Canada) approved the protocol. Patients were eligible if they fulfilled all of the following inclusion criteria: 1) at least 5 previous VVS episodes (at least 2 occurring within the last year); 2) tilt-test with a cardioinhibitory response, defined as a heart rate <40 beats/min for at least 10 s or a >3-s pause; 3) age ≥40 years (based on recent guideline recommendations and previously published trials [1,4,5]); 4) absence of cardiomyopathy and normal 12-lead electrocardiogram; 5) no other indication for a permanent pacemaker; 6) geographical stability and availability to attend follow-up; 7) informed consent; and 8) any of the following contraindications: ß-blocker drug treatment, chronic polyneuropathy and any contraindication to DDD or DDDR pacing. Exclusion criteria included: 1) patients with syncope caused by carotid sinus hypersensitivity, or other cause of syncope; 2) participants in another concurrent trial; and 3) pregnant or breastfeeding women not using contraceptive methods. All patients underwent complete physical examination, including orthostatic test, carotid sinus massage, 12-lead electrocardiogram, 2-dimensional Doppler echocardiography, and 24-h Holter monitoring. HUT was performed using 2 previously reported protocols (12,13). For this trial, we only included patients with a cardioinhibitory response: bradycardia <40 beats/min during >10 s or asystole >3 s, as per the VASIS (Vasovagal Syncope International Study) classification (14).

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

DDD-CLS = dual-chamber pacemaker with closed loop stimulation

HUT = head-up tilt testing

IQR = interquartile range

RRR = relative risk reduction

sham DDI = dual-chamber pacemaker implantation but without pacing activity

VVS = vasovagal syncope

RANDOMIZATION AND STUDY TREATMENT. Randomization was performed by an automatic central phone system that allocated patients 1:1 to either group A (DDD pacemaker programmed to DDD-CLS mode for 12 months, after which patients crossed over to a sham DDI mode [30 pulses/min and subthreshold] for the remaining 12 months) or group B (DDI mode [30 pulses/min and subthreshold] for 12 months followed by crossover to active DDD-CLS pacing for the remaining 12 months). Patients in both arms crossed over after 12 months of follow-up or when a maximum of 3 syncopal episodes occurred within 1 month.

PACEMAKER IMPLANTATION AND PROGRAMMING. After inclusion and before randomization, all patients had a dual-chamber pacemaker that had the ability to be programmed in the DDD-CLS algorithm mode (Protos DR, Cylos DR, Cylos 990 DR, and Evia, Biotronik GmbH & Co., Berlin, Germany) implanted. In the active intervention arm (DDD-CLS pacing mode), the following programming was performed: lower rate (day/night) 45 pulses/min; upper rate 160 pulses/min; CLS rate 110 pulses/min with dynamic CLS set to "high" and dynamic rate limit set to "off"; atrioventricular interval fixed to 150 ms with atrioventricular hysteresis set to "high"; atrial refractory period 400 ms; pacing polarity set to unipolar and sensing polarity to bipolar; and output adjusted to double atrial and ventricular thresholds. In the "sham" DDI mode, programming was as