Rev Esp Cardiol. 2018;71(5):320–322

Editorial

Definitive Pacing Therapy in Patients With Neuromediated Syncope. Lessons From the SPAIN Study

La estimulación definitiva en el paciente con síncope neuromediado. Lecciones del estudio SPAIN

Gonzalo Baron-Esquivias[a,*] and Carlos A. Morillo[b,c]

[a] Servicio de Cardiología y Cirugía Cardiaca, Hospital Universitario Virgen del Rocío, Universidad de Sevilla, Sevilla, Spain
[b] Department of Cardiac Sciences, Libin Cardiovascular Institute of Alberta, University of Calgary, Calgary, Canada
[c] Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada

Article history:
Available online 30 December 2017

The prevalence of syncope in the general population is 6.2 per 1000 population/y, while the cumulative lifetime incidence is 35%, being higher in women (41%) than in men (28%). In patients with syncope, although 36% have only 1 event, the median number of syncope episodes in a lifetime is 2 [interquartile range, 1-5].[1] When referring specifically to the population with neurally mediated syncope and particularly vasovagal syncope (VVS), which is the most common cause of syncope in all published studies, the median number of episodes in a lifetime is 3 [2-6], with a recurrence rate of 30% at 30 months.[2]

Currently there is no gold-standard diagnostic tool for VVS, but there are 2 that are invaluable: one is a provocation test, the tilt table test (TTT), which provides evidence on the likelihood of having a VVS in patients with syncope of unknown etiology.[3] The TTT shows that 3 types of vasovagal response may occur, but the clinical relevance of the test has been questioned because it has been shown to have low reproducibility when multiple TTTs are performed in the same patient, and the relationship between the TTT-induced response and clinical recurrence is unknown.[4] The TTT, being a provocation test, as with many other tests in cardiology, aims to reproduce what occurs spontaneously, so its usefulness could certainly be questioned; however, a TTT-induced cardioinhibitory response and, in particular, asystole, are reported in up to 17.5% of patients with a positive TTT.[5]

The other invaluable tool in the diagnosis of VVS is the implantable Holter (IH), which records the spontaneous changes in heart rhythm that occur during syncope. On the electrical tracings of patients with spontaneous VVS and an IH, asystole/bradycardia is found to be a key component that occurs in 56% to 58% of patients. In addition, although there are few data, the reproducibility of IH findings appears to be much higher when there is a second syncopal episode.[6]

The first studies on pacing in patients with a cardioinhibitory reponse were based on TTT findings and used pacemakers (PM) with ventricular pacing only, which were not effective. However, efficacy was demonstrated in studies using a dual-chamber (DDD) PM, and also in those randomizing patients to receive DDD PM vs no therapy or drug therapy, including specific analyses with rate drop reponse (RDR) algorithms.[7,8] However, there is one main criticism of these studies, as presumably PM implantation could have a placebo effect that cannot be avoided when comparisons are made against a population without an implant. Therefore, there was a need for studies in which all study participants received PM implantation and subsequent double-blind randomization to either pacing "on" or pacing "off". Two randomized studies were conducted, one with 100 and another with 29 patients who received a DDD-RDR PM. Both had negative results showing that DDD-RDR pacing did not significantly reduce the risk of syncope recurrence.[9,10] These findings indicated that, as with drugs, DDD-RDR PM does not have a place in the therapeutic arsenal against VVS even if patients have recurrent syncope and asystole during the TTT.

In addition to those studies, a number of studies have been carried out since 1998 using a DDD PM with a closed-loop stimulation (CLS) sensor, which monitors the changes in intracardiac impedance that occur during the systolic phase of the cardiac cycle. The CLS sensor detects increased right ventricular contractility during the early stage of VVS, and can activate atrioventricular pacing, which can preempt and counteract a reduction in sympathetic tone, thereby avoiding hypotension, bradycardia, and possibly syncope. There are only 6 prospective studies (most of them observational) that have included patients with a cardioinhibitory response during TTT and all of them showed that DDD-CLS pacing was useful in reducing VVS recurrence. Five were conducted in Italian centers and 1 in the United States. None of them had a double-blind design, but all coincided in demonstrating a reduction in syncope or presyncope compared with controls at patient follow-up. The last study that used the CLS sensor was a multicenter, prospective, randomized single-blind study and included 30 patients with a cardioinhibitory response during TTT. All the participants received PM implantation and went on to have 2 more TTTs 1 week apart: 1 during DDD-CLS pacing and the other during DDD pacing. DDD-CLS pacing reduced the incidence of TTT-induced syncope significantly more than DDD pacing (76.7% vs 30.0%; $P < .001$). In addition, in patients that did experience

* Corresponding author: Av. de Portugal 19, 41004 Seville, Spain.
E-mail address: gonzalo.baron.sspa@juntadeandalucia.es (G. Baron-Esquivias).

http://dx.doi.org/10.1016/j.rec.2017.10.037

syncope, DDD-CLS pacing significantly prolonged the time to syncope during the TTT.[11] Although the study provides more evidence on the benefits of PM with CLS in VVS with asystole during TTT, there is a lack of evidence from double-blind trials on treatment with CLS vs no treatment.

Criticisms of the TTT and the negative results from clinical trials are in contrast to the reality that 63% of patients with VVS recurrence have spontaneous asystole demonstrated on IH.[6] This prompted the design of several studies to evaluate the usefulness of PM therapy when there is a spontaneous cardioinhibitory response. The most complete of these studies is the ISSUE-III trial, a multicenter prospective randomized double-blind study designed to evaluate the efficacy of DDD-RDR pacing therapy. Seventy-seven patients were randomized to DDD-RDR pacing or sensing only. At 2 years, the rate of syncope recurrence was calculated as 57% with pacemaker "off" and 25% with pacemaker "on", with a reduction in risk of recurrence of 57%.[12] Therefore, the RDR PM was effective in patients with VVS and cardioinhibitory response detected on IH.

In light of the negative results from the 2 clinical trials and the potential offered by PMs with CLS, in 2006 we designed the SPAIN study, a prospective, multicenter, randomized, double-blind study to compare the usefulness of the DDD-CLS PM vs DDI pacing, in the population with recurrent syncope and asystole during TTT. From the beginning, we knew that patient recruitment would be difficult, so we chose a crossover design to improve the statistical power. Participants were required to be older than 40 years, have a cardioinhibitory response on TTT (asystole $>$ 3 seconds or bradycardia $<$ 40 bpm for 10 seconds), at least 5 previous episodes of syncope, with 2 in the previous 12 months, have no heart disease or ECG changes and have normal ECG, echocardiogram, and 24 h Holter. Patients were randomized to receive DDD-CLS pacing (group A) or DDI pacing (group B), and at 12 months (or before if they had 3 syncopal episodes in 1 month) they crossed over to the opposite pacing arm, and were followed up for a further 12 months. The total follow-up time was 24 months. The primary outcome was a $\geq$ 50% reduction in the number of syncope episodes compared with the previous year and the coprimary outcomes were time to first recurrence of syncope in both treatment sequences and time to first syncope in each type of pacing.

Initially 25 Spanish centers and 1 Canadian center were invited to participate. We planned to include centers in Colombia, Mexico and Argentina, but this could not be done for administrative reasons, and in the end, 12 centers took part: 11 in Spain and 1 in Canada. The estimated sample size needed to demonstrate our hypothesis was 50 patients. The first patient was enrolled in April 2007 and the last in April 2014, showing the difficulty of completing this study.

Fifty-four patients were enrolled, but only 46 completed the protocol and were used in the final analysis; 22 were male (48%) and the mean age was 56 $\pm$ 10 years. Group A had 21 patients and group B had 25. The median number of previous syncope episodes was 12 [interquartile range, 9-20]. The primary objective of a $\geq$ 50% reduction in syncope episodes compared with the previous year was achieved in 29 of 46 patients; of them, in group A, 72% (95% confidence interval [95%CI], 47-90) met the primary objective with DDD-CLS pacing vs 28% (95%CI, 10-53) with DDI. In group B, 100% of the patients had a reduction $\geq$ 50% in syncope in the second period with DDD-CLS pacing (p = .0172). During the DDD-CLS pacing period, 4 patients (8.7%) had events vs 21 (46%) during the DDI period (hazard ratio = 6.72; 95%CI, 2-20). The time to first syncope recurrence was much longer in group A than in group B: 29 (95%CI, 15-29) vs 9.3 months (confidence interval could not be calculated due to low number of events; $P <$ .0158). In the total group of 46 patients, time to first event according to pacing mode was also much longer in DDD-CLS than in DDI: odds ratio = 0.11 (95%CI, 0.03-0.36; $P <$ .0001), representing an 89% relative risk reduction in favor of CLS, with an absolute risk reduction of 37% and a number needed to treat of 2.7 to prevent syncope recurrence with DDD-CLS treatment. The conclusion of our study was that DDD-CLS pacing reduces the burden of syncope and prolongs the time to first syncope up to 7 fold, prolonging the time to first recurrence in patients older than 40 years with recurrent syncope and cardioinhibitory response during TTT compared with DDI pacing.[13]

WHAT NEXT?

The European and the most recent American clinical guidelines (American College of Cardiology/American Heart Association/Heart Rhythm Society) have set a class IIb recommendation and level of evidence B for pacing with PM for patients older than 40 years old with recurrent syncope and cardioinhibitory response on TTT.[5,14] The SPAIN study demonstrated that pacing with DDD-CLS is highly effective in this population, which could lead to a change in the guidelines to a class IIa recommendation. The BYOSINC trial, which will randomize 128 patients to receive DDD-CLS with pacing on or off, will provide the definitive evidence, and it is highly likely the metanalyses of pooled data from these studies will reinforce these recommendations in the near future.[15]

The road to treatment advances for patients with recurrent VVS has been long and complex. However, in light of the new trials such as the SPAIN study, new therapeutic options are opening up. If we add together all the participants enrolled in the VPSII, SYNPACE, ISSUE-3 and SPAIN clinical trials, there are 252 patients. [9,10,12,13] It would therefore be wise to wait for more data to provide our patients with the best evidence-based recommendations.

FUNDING

The Research Agency of the Spanish Society of Cardiology received an unconditional grant from the company Biotronik España to fund the implantation of pacemakers in the centers where this were not otherwise covered. The collection and statistical analysis of data by an external company was essential in carrying out the SPAIN study.

CONFLICTS OF INTEREST

The investigators had no conflicts of interest in conducting this study. Furthermore, potential conflicts of interest were limited by having centralized administration and performance of the SPAIN study.

REFERENCES

1. Ganzeboom KS, Mairuhu G, Reitsma JB, Linzer M, Wieling W, Van Dijk N. Lifetime cumulative incidence of syncope in the general population: a study of 549 Dutch subjects aged 35-60 years. *J Cardiovasc Electrophysiol.* 2006;17:1172–1176.
2. Baron-Esquivias G, Errazquin F, Pedrote A, et al. Long-term outcome of patients with vasovagal syncope. *Am Heart J.* 2004;147:883–889.
3. Moya A, Sutton R, Ammirati F, et al. Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC). Guidelines for the diagnosis and management of syncope (version 2009). *Eur Heart J.* 2009;30:2631–2671.
4. Sagristà-Sauleda J, Romero B, Permanyer-Miralda G, Moya A, Soler-Soler J. Reproducibility of sequential head-up tilt testing in patients with recent syncope, normal ECG and no structural heart disease. *Eur Heart J.* 2002;23:1706–1713.
5. Baron-Esquivias G, Pedrote A, Cayuela A, et al. Long-term outcome of patients with asystole induced by head-up tilt test. *Eur Heart J.* 2002;23:483–489.
6. Brignole M, Vardas P, Hoffman E, et al. Indications for the use of diagnostic implantable and external ECG loop recorders. *Europace.* 2009;11:671–687.
7. Sutton R, Brignole M, Menozzi C, et al. Dual-chamber pacing in the treatment of neurally mediated tilt-positive cardioinhibitory syncope: pacemaker versus no therapy: a multicenter randomized study. The Vasovagal Syncope International Study (VASIS) Investigators. *Circulation.* 2000;102:294–299.

8. Sheldon R, Koshman ML, Wilson W, Kieser T, Rose S. Effect of dual-chamber pacing with automatic rate-drop sensing on recurrent neurally mediated syncope. *Am J Cardiol.* 1998;81:158–162.
9. Connolly SJ, Sheldon R, Thorpe KE, et al. VPS II Investigators, Pacemaker therapy for prevention of syncope in patients with recurrent severe vasovagal syncope: Second Vasovagal Pacemaker Study (VPS II): a randomized trial. *JAMA.* 2003;289:2224–2229.
10. Raviele A, Giada F, Menozzi C, et al. Vasovagal Syncope and Pacing Trial Investigators. A randomized, double-blind, placebo-controlled study of permanent cardiac pacing for the treatment of recurrent tilt-induced vasovagal syncope, The vasovagal syncope and pacing trial (SYNPACE). *Eur Heart J.* 2004;25:1741–1748.
11. Palmisano P, Dell'Era G, Russo V, et al. Effects of closed-loop stimulation vs, DDD pacing on haemodynamic variations and occurrence of syncope induced by head-up tilt test in older patients with refractory cardioinhibitory vasovagal syncope: the Tilt test-Induced REsponse in Closed-loop Stimulation multicentre, prospective, single blind, randomized study. *Europace.* 2017. http://dx.doi.org/10.1093/europace/eux015.
12. Brignole M, Menozzi C, Moya A, et al. Pacemaker therapy in patients with neurally mediated syncope and documented asystole: Third International Study on Syncope of Uncertain Etiology (ISSUE-3): a randomized trial. *Circulation.* 2012;125:2566–2571.
13. Baron-Esquivias G, Morillo CA, Moya-Mitjans A, et al. Dual-chamber pacing with closed loop stimulation in recurrent reflex vasovagal syncope. The SPAIN Study. *J Am Coll Cardiol.* 2017;70:1720–1728.
14. Shen WK, Sheldon RS, Benditt DG, et al. 2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Syncope: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2017;70:620–663.
15. Brignole M, Tomaino M, Aerts A, et al. Benefit of dual-chamber pacing with closed loop stimulation in tilt-induced cardio-inhibitory reflex syncope (BIOSync trial): study protocol for a randomized controlled trial. *Trials.* 2017;18:208.