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Does cardiac pacing reduce syncopal recurrences in cardioinhibitory vasovagal syncope patients selected with head-up tilt test? Analysis of a 5-year follow-up database

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ABSTRACT

Purpose: Benefit of cardiac pacing in patients with vasovagal syncope (VVS) and cardioinhibitory response to head-up tilt test (HUTT) is still debated. We aimed at retrospectively assessing the long-term effect of cardiac pacing in a cohort routinely followed in our institutions.

Methods and results: From a cohort of 1502 patients who performed HUTT between 2008 and 2014, 181 (12%) patients had VASIS 2A (40) or 2B (141) response (median age 43 [interquartile range, 25–56] years, 59% male). Fifty patients (28%) received a dual-chamber pacemaker and 131 (72%) received training on physical maneuvers and medical therapy. The so-called 'Closed Loop Stimulation' (CLS) function was activated for at least 18 months in the pacing group. The 5-year recurrence rate of syncope of paced patients was compared with non-paced patients and with a subgroup of 18 propensity-score matched patients selected among non-paced patients. The 5-year Kaplan-Meier syncope free-rate was 81% (CI, 67%–90%) in the pacing group, 57% (47%–67%; $p = 0.004$) in the unmatched control group, 53% (27%–74%; $p = 0.005$) in the 18 propensity-matched patients. The hazard ratio of pacing versus non-pacing was 0.34 (CI, 0.18–0.70) when comparing with the whole non-pacing control group, and 0.25 (CI, 0.09–0.65) including only the propensity-score matched subgroup. No deaths were observed during the follow-up.

Conclusions: In the selected VVS population with HUTT-induced cardioinhibitory response, pacemaker therapy with CLS function was associated to 66% relative and 24% absolute risk reduction of 5-year syncopal recurrence rate. Benefit was confirmed after controlling variables affecting propensity for pacemaker therapy.

1. Introduction

Vasovagal syncope (VVS) is the most common cause of fainting. It is triggered by an inappropriate response of the autonomic nervous system, with excessive vagal tone and sympathetic withdrawal [1]. Significant bradycardia or prolonged asystole and concomitant hypotension in patients with recurrent severe cardioinhibitory VVS may result in serious physical injuries and psychological impairment, possibly leading to substantial limitations to social and working life [2–4].

Head-up tilt table test (HUTT) can reproduce neurally-mediated reflex in laboratory settings. Blood pooling and the decrease of venous inflow due to orthostatic stress and immobilization initiate the reflex [5]. Pioneering studies suggested that hypotension and bradycardia induced by tilt testing are similar to spontaneous episodes [6–8] and the HUTT response could therefore be used as a model for study hemodynamics during syncopal reflex [9, 10]. VVS is generally as a benign condition [5], although some authors have related neutrally-mediated hypotension-bradycardia to rare events of sudden death [11]. Benefit of pacemaker therapy in this population is not established yet as due to several positive and neutral studies [12–14]. According to the European Society of Cardiology (ESC) [15], cardiac pacing is a class IIB indication in the limited group of patients aged >40 with tilt-induced cardioinhibitory response (specifically, 2B according to VASIS classification [16]) with recurrent, frequent, unpredictable syncope. The uncertainty is likely at the origin of divergent opinions and different practices in current medical care. We therefore aimed at retrospectively evaluating the benefit of pacemaker therapy in routine medical practice by comparing long-term syncopal recurrence and outcome between paced and non-paced patients with VVS and cardioinhibitory response to HUTT by controlling for potential confounders.

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2. Methods

2.1. Study population

From a large cohort of 1502 patients (mean age 41 ± 16 years, 597 male, 39.7%) referred to the Syncope Unit of the Second University of Naples-Monaldi Hospital between October 2008 and December 2014 for the evaluation of episodes of transient loss of consciousness, we selected subjects who met the following requirements: (i) age ≥16 years; (ii) >1 syncopal episode of unknown origin within the previous year; (iii) absence of any structural cardiovascular diseases or arrhythmic episode potentially explaining transient loss of consciousness; (iv) no documentation of neurologic diseases, or varicose veins in the lower limbs; (v) negative response to orthostatic hypotension test and carotid sinus massage; (vi) cardioinhibitory response to HUTT with or without asystole (i.e., 2A or 2B according to the VASIS classification [16]).

As an additional selection criterion, complete report of anthropometric and clinical examination, 12 lead electrocardiogram (ECG), 24 h Holter recording monitoring and 2D color-Doppler echocardiogram, as performed per standard practice, had to be available in the institution archive. Data from first baseline visit until the last available follow-up date were analyzed.

The retrospective study was approved by the Ethics Committee and conducted in compliance with local regulations on data protection.

2.2. HUTT protocol and treatment

The HUTT was generally performed in the morning after an overnight fasting, in a quiet, slightly dimmed room. The procedure was carried out using a motorized tilt table with foot support according to the Italian Protocol [17]. After a 15-min supine control phase, patients were moved to the 60° upright position for 20 min (passive phase). In case of a negative result, 400 μg nitroglycerin was administered sublingually in the upright position and tilting was continued for a maximum of 45 min or until syncope. The syncope was defined as an abrupt, transient loss of consciousness and loss of postural tone. The HUTT was considered positive if the syncope developed in association with hypotension, bradycardia, or both. The syncopal phase was classified according to a modified VASIS classification [16].

Pharmacological therapy was started after HUTT in patients who did not receive a pacemaker. Patients without evidence of hypertension were treated with midodrine, from 2.5 mg three times a day up to 5.0 mg three times a day.

Pacemaker therapy was generally proposed to patients aged >40 years, HUTT-induced cardioinhibitory response, and unpredictable, recurrent syncope episodes unresponsive to alternative therapies. In patients who accepted the pacemaker therapy dual-chamber pacing was always activated after implant. Additionally the so-called 'Closed Loop Stimulation' (CLS) function [18] was activated for at least 18 months as a required procedure of a previously published study.

2.3. Statistical analysis

Continuous variable distributions were checked for normality with the Shapiro-Wilk test and were reported as mean ± SD if the normality hypothesis was not rejected. Median and interquartile ranges were used otherwise. Group comparisons were performed with the unpaired *t*-test or the Mann–Whitney test as appropriate.

Frequencies were compared with the chi-square or Fisher tests. Syncopal recurrence free-rates in the study groups during follow-up after HUTT were evaluated with the Kaplan-Meier method and compared with the log-rank test. Hazarad Ratio (HR) estimates were derived from Cox models.

Propensity for pacemaker therapy was evaluated with multivariate logistic models including several baseline variables automatically selected with a backward stepwise procedure (p to remove >0.1) and reporting odds ratios (OR) with 95% confidence interval (CI) for pacemaker decision. Basing on the results of this analysis, propensity score 2:1 matching was used to select subjects in the non-paced group with the nearest-neighbor method in order to obtain estimate of pacing effects while controlling for potential confounders.

Statistical significance was defined with a p value <0.05. Data were analyzed with version 11SE of the STATA software (StataCorp LP College Station, TX 77845 USA).

3. Results

3.1. Patient characteristics

A total of 181 patients with cardioinhibiltory HUTT response and cumulative follow-up of 740 patient-years (median, 48 (30–71) months) met the selection criteria. These were aged 43 (25–56), were men in most cases ($n = 106$; 58.6%) and prevalently presented with a VASIS 2B response to the HUTT (77.9%).

One hundred and thirty one patients of this cohort (72.4%) did not undergo pacemaker implantation. Physical maneuvers were recommended; midodrine was prescribed in 52 cases if not contraindicated for hypertension. Of this group, 28.2% had a VASIS 2A response to baseline HUTT (severe bradycardia without >3 s asystole), while the remaining 71.8% with a VASIS 2B response (>3 s asystole) had not received a pacemaker mainly due to age <40 (59.9%) or because the therapy was not considered or not accepted by the patient.

Fifty patients (27.6%, median age 54(45–63) years, 36 male) predominantly with VASIS 2B response (47, 94.0%) and frequent, unpredictable syncopal recurrences had received a pacemaker implantation within 2 months from baseline HUTT. The CLS function was activated in all devices.

Propensity for pacemaker therapy was evaluated with multivariate logistic models including automatically selected baseline variables. Pacemaker therapy was more frequently associated with older age (OR, 1.09 (CI, 1.04–1.15); $p = 0.001$), prodromes during HUTT (8.97 [2.10–38.24]; $p = 0.003$), hypertension (6.21 [1.57–24.52]; $p = 0.009$), smoking (3.79 [1.20–11.98]; $p = 0.023$), number of prior syncopal recurrences (1.35 [1.06–1.72]; $p = 0.013$), asystole duration during HUTT (1.10 [1.04–1.18]; $p = 0.002$). As expected, significantly older ages, higher number of prior syncopal recurrences, and longer heart rhythm pauses at baseline HUTT were observed in the pacing group, as compared to non-pacing group.

Further demographic and clinical details are reported in Table 1.

3.2. Syncope recurrence

During follow-up, 55 patients experienced one or more syncopal recurrences (median 2(2–4)): 9 patients were in the pacing group, 48 in the non-pacing group. The 5-year Kaplan-Meier syncope free-rate was 81.0% (CI, 66.5%–89.7%) in the pacing group, 57.1% (46.2%–66.6%; $p = 0.004$) in the unmatched non-pacing group, 53.5% (27.5%–73.8%; $p = 0.005$) in the propensity-score matched subgroup (Fig. 1). The HR of pacing versus non-pacing was 0.34 (CI, 0.18–0.70) when comparing with the whole non-pacing control group, and 0.25 (CI, 0.09–0.65) including only the propensity-score matched subgroup.

3.3. Adverse events

Nine out of 181 (4.9%) patients (4 subjects in the pacing group and 5 subjects in the non-pacing group) had syncope-related hospitalizations. No sudden cardiac death was reported and no patient underwent major medical/surgical intervention during the follow up.

Complications associated with pacemaker implantation were hematoma of the pacemaker pocket in two patients and a minor spontaneously reabsorbed pneumothorax in one patient.

4. Discussion

4.1. Main findings

In the selected cohort of VVS patients with cardioinhibitory (prevalently VASIS 2B) HUTT response, decision to implant a pacemaker was expectedly driven by age, male sex, prodromes and asystole duration at the baseline HUTT. It was also more frequently associated to hypertension and smoking. Patients who received a pacemaker had 66% relative and 24% absolute risk reduction of 5-year syncopal recurrence, corresponding to one abolished episode every 4.2 implanted pacemakers with 6% rate of minor device-related complications. After controlling for potential confounders with the propensity-score matching method, reduction of syncopal recurrences in the pacing group was greater.

4.2. Utility of the HUTT

Reflex syncope is the most frequent cause of syncope and VVS is responsible for 20% of all syncopal episodes [1]. According to the VASIS classification, cardioinhibitory VVS is the less frequent tilt-induced

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Table 1
Patient characteristics.

Baseline characteristics	Pacing group	Control group	*P**	Propensity matched control sub-group	*P***
N (%)	50 (27.6)	131 (72.4)		18 (9.9%)	
Follow-up (months)	72 (61–81)	39 (24–55)	<0.001	48 (36–55)	0.39
Age (years)	54 (45–63)	35 (21–48)	<0.001	43 (35–60)	0.015
Male gender (n, %)	36 (72.0)	70(53.4)	0.028	13(72.2)	0.99
Smoker (n, %)	33 (66.0)	31(23.6)	<0.001	9 (50.0)	0.27
Hypertension (n, %)	34 (68.0)	25(19.1)	<0.001	5 (27.8)	0.005
SD family history (n, %)	7 (14.0)	26(20.3)	0.395	3 (16.7)	0.72
Syncope family history (n, %)	11 (22.0)	10(7.7)	0.017	3 (16.7)	0.74
Ischemic HD (n, %)	3 (6.0)	5(3.8)	0.68	1 (5.6)	1.00
Structural HD (n, %)	12 (24.0)	26(19.8)	0.545	4 (22.2)	1.00
No. of prior syncopal events	5 (3–6)	3(2–5)	<0.001	3.5 (2–6)	0.20
Syncope-related injuries (n, %)	12(24.0)	18(13.7)	0.118	5 (27.8)	0.76
During HUTT					
HUTT reponse					
VASIS 2A (n, %)	3(6.0)	37(28.2)	0.001	0 (0.00)	–
VASIS 2B (n, %)	47(94.0)	94(71.8)		18 (100.0)	–
Asystole duration [*sec*]	14(10−20)	7(0–14)	<0.001	10 (5–20)	0.10
Pre-syncope (lipotimia) (n, %)	42(84.0)	82(62.6)	0.004	13 (72.2)	0.31
Pre-syncope minute [min]	27(25–33)	25(23–29)	0.010	24 (23–27)	0.05
Syncope minute [min]	30(28–37)	27(24–30)	<0.001	27 (26–34)	0.05
Nitroglycerine (n, %)	45(90.0)	105(80.1)	0.129	17 (94.4)	1.00

*Pacing vs. control groups.
Values are given as no. (%) for binary variables, median (interquartile range) for continuous variables HD = heart disease; HUTT = Head up tilt test; SD = sudden death.

syncopal form occurring in 20% of the patients undergoing HUTT for unexplained syncope [5].

Utility of HUTT in the diagnosis of syncope has been often questioned in the past [19] as due to complex classification of different syncopal forms, different responses to HUTT also within the same patients, and different protocols for HUTT conduct. More recently, secondary analyses of the ISSUE 3 study reported that subjects with negative HUTT response benefitted the most from pacemaker therapy, while VASIS 2B HUTT-response patients had a similar recurrence rate as compared to non-pacing control patients [20]. This result was however in contrast with the findings of the SUP 2 Registry [21] where syncopal recurrence rates were remarkably lower with 12% recurrence rate at 18 months. Small sample sizes and differences in study design and populations (particularly in terms of age, prevalence of prodromes and carotid sinus syndrome) may partially explain the discrepancy. However, the procedure for selecting patients undergoing pacemaker implantation in these two studies may have played an important role. The ISSUE 3 study enrolled patients with clinical asystole documented with an implantable loop recorder (ILR), performing the HUTT as an additional investigation procedure. Conversely, in the SUP 2 registry the HUTT was part of a standardized algorithm for a priori directing patients to pacemaker or ILR implantation. Data of the ISSUE 3 study

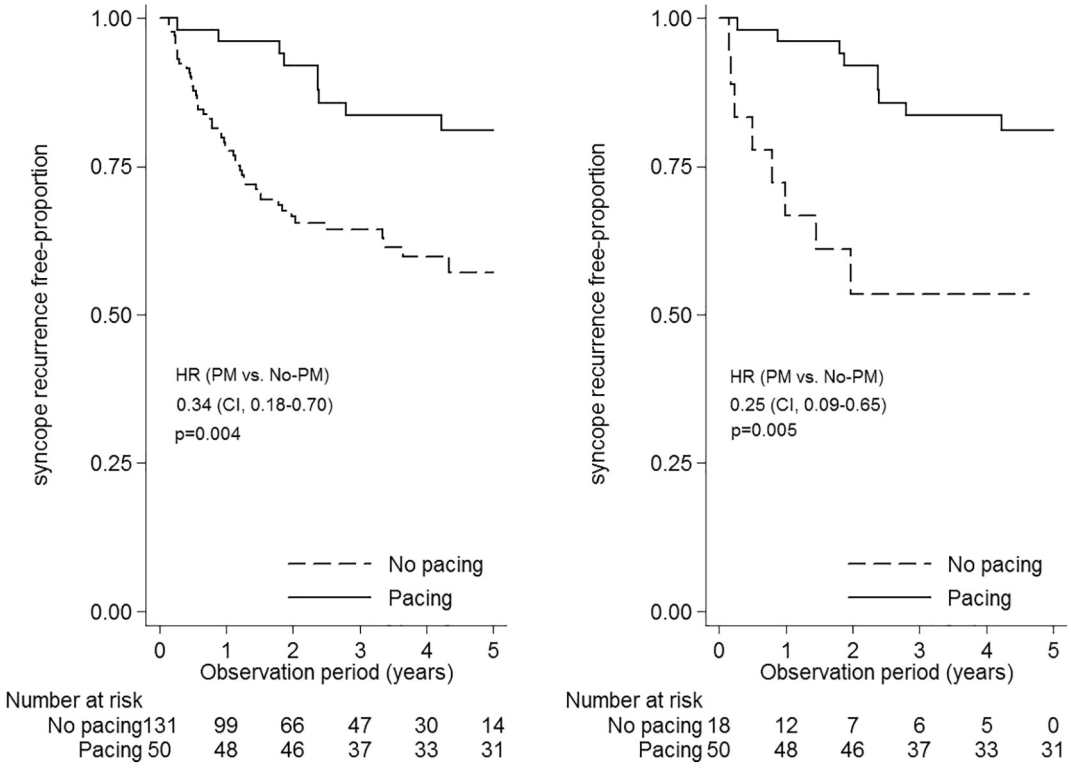

Fig. 1. Kaplan-Meier curves for syncope-recurrence-free survival in the pacing and no-pacing groups. (A) pacing group vs all non-pacing group; (B) pacing group versus propensity-score-matched non-pacing group. CI: 95% confidence interval; HR: hazard ratio; HUTT = Head-up tilt test; PM: pacemaker.

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confirmed that an asystolic response to HUTT was predictive of clinical ILR-recorded asystolic syncope during follow-up in 86% of the cases. Our results corroborate the clinical utility of the HUTT as an effective diagnostic tool and the VASIS 2B response as a marker for a priori identifying subjects who may benefit from pacemaker therapy. In our population, prevalently but not exclusively including VASIS 2B response patients, the cumulative recurrence rate was <15% in the pacing group at 5 years as compared to 43–47% in the non-pacing group. Considering the psychological impact of VVS and the related poor quality of life especially in patients with frequent recurrences, our data reinforce the body of evidence against a common practice based on a long-term ILR monitoring without preliminary performing the HUTT. Of course we still cannot draw definitive conclusions. A randomized, placebo-controlled trial is ongoing [22] to test the efficacy of pacing in patients selected by the HUTT for VASIS 2B response, challenging the current class IIB indication set forth by the most recent European guidelines [15].

4.3. Propensity for and actual efficacy of pacing

Efficacy of pacing in VVS has been discussed since several years, due to contrasting results of studies conducted so far and unclear or non-uniform patient selection criteria. Also a recent meta-analysis of 6 randomized trials reported no substantive evidence in favor of cardiac pacing in the reflex-mediated syncope beyond patients with recurrent VVS and asystole documented by implantable loop recorder [23]. HUTT-induced VVS is not considered an indication for cardiac pacing in the American guidelines [24], while it has a weak (Class IIb with level of evidence B) in age >40 and VASIS 2B response to HUTT in the European guidelines [15]. Medical decision about pacemaker implantation is often the result of the evaluation of individual clinical context and opinion. In our cohort of patients followed in one institution according to ordinary medical practice, propensity for pacemaker therapy was essentially influenced by age, burden of prior syncopal recurrences, and response to HUTT, namely prodromes and duration of asystolic pauses. Also other factors were statistically associated to pacing therapy, as hypertension (likely as a consequence of limited therapeutic options) and smoking. Very few data are available about the relation of smoking and HUTT response. It has been proposed that endothelial function and inappropriate peripheral vasomotion may have a significant role in the pathogenesis of neurally mediated syncope [25]. Smoking may influence peripheral vasomotion and in fact it has been shown to predict a negative response to HUTT [26]. We cannot provide evidence in favor of such hypothesis, even if we noted a trend to higher prevalence of symptom onset after nitrate administration at HUTT (88% in the smoker group versus 80% in non-smokers, but the difference did not reach statistical significance, probably due to limited available power). Nevertheless cardioinhibitory HUTT response despite smoking may be a marker of greater susceptibility to orthostatic stress.

Despite current uncertainty about indication to cardiac pacing in VSS, our data showed a benefit from cardiac pacing at least in patients aged >40 with asystolic response to HUTT as it was associated to a 5-year recurrence rate of 19.0% as compared to 42.9% in the non-pacing group, or 46.5% in the subgroup of 18 patients matched with the propensity-score nearest-neighbor method. Of note the significantly shorter follow-up available for the unmatched control group in our population may have led to underestimate the effect of pacing. This actually emphasizes the utility of the propensity-score analysis proposed here which has partially limited the bias although reducing the control sample-size.

Syncopal episode rates in the control group were in line with previous long-term observations [21], but lower than expected in the pacing group. Despite some differences in population characteristics, the SUP 2 Registry reported a 23% syncopal event rate at 3 years, the ISSUE 3 study a 25% rate at 2 years [13], the VPSII study a 31% rate at 6 months [14]. Our estimates were quite lower with 19.0% rate at 5 years with a relative 66% reduced risk for syncopal recurrences. On the one hand, patient selection may partially explain the result, as we systematically used the Italian protocol for HUTT with 60° angle, which may have contributed to identifying patients more sensitive to orthostatic stress. In a recent meta-analysis, 60° tilt in the active phase has been shown to be associated to increased specificity and decreased sensitivity when compared to 70° or steeper angles. [27]

On the other hand, the CLS function may have played a role in optimizing the effect of pacing. Previous small-sized studies [28, 29] and a retrospective analysis [30] using the CLS as pacing mode reported a syncope recurrence rate between 0% at 18 months and 4% at 4 years. The recently published results of the SPAIN study intra-individually comparing dual-chamber cardiac pacing with the CLS algorithm and DDI-sham control showed 38% absolute and 85% relative risk reduction of 1-year syncopal recurrence rate [31]. Available data therefore seem consistent with the hypothesis that the preventive effect of cardiac pacing might be maximized by the particular DDD-CLS mode used in these studies. It has been speculated that by monitoring intracardiac contractility, CLS may increase the pacing rate in an early stage of the vasovagal reflex preventing the increase in vagal tone [29]. However the hypothesis needs experimental confirmation as there is still no evidence that such mechanism may definitely explain these findings. Also the ongoing randomized BIOSync trial [22], which compares the effect of DDD-CLS mode versus the placebo ODO mode (sensing only), will not provide conclusive evidence in favor of the rationale for the use of CLS in VVS. Nevertheless results are awaited as they may provide indications on whether or not the hypothesis is worth further assessing.

5. Conclusions

Our retrospective analysis of 5-year follow-up data of a population with VVS selected for cardioinhibitory (prevalently VASIS 2B) response confirmed positive prognosis with no deaths and major injuries. Cardiac pacing with the addition of the CLS function remarkably reduced but did not completely abolish syncopal recurrence rate on the long-term. The benefit of cardiac pacing was confirmed and even increased after controlling for possible for confounders influencing propensity for pacemaker therapy.

Conflict of interest

AG is an employee of Biotronik Italy.
VR, AR, MDR, AAP, PG, IS, IP, NB and GN: nothing to disclose.

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References

[1] N. Colman, K. Nahm, K.S. Ganzeboom, et al., Epidemiology of reflex syncope, Clin. Auton. Res. 14 (Suppl 1) (2004) 9–17.
[2] J.D. Maloney, F.J. Jaeger, F.M. Fouad-Tarazi, H.H. Morris, Malignant vasovagal syncope prolonged asystolie provoked by head-up tilt, Cleve. Clin. J. Med. 55 (6) (1988) 542–548.
[3] K.A. Ellenbogen, C.A. Morillo, M.A. Wood, D.M. Gilligan, D.L. Eckberg, M.L. Smith, Neural monitoring of vasovagal syncope, Pacing Clin. Electrophysiol. 20 (1997) 788–794.
[4] M. Linzer, M. Pontinen, D.T. Gold, G.W. Divine, A. Felder, W.B. Brooks, Impairment of physical and psychosocial function in recurrent syncope, J. Clin. Epidemiol. 44 (10) (1991) 1037–1043.
[5] G. Barón-Esquivias, A. Pedrote, A. Cayuela, et al., Long-term outcome of patients with asystole induced by head-up tilt test, Eur. Heart J. 23 (6) (2002) 483–489.
[6] A. Almquist, I.F. Goldenberg, S. Milstein, et al., Provocation of bradycardia and hypotension by isoproterenol and upright posture in patients with unexplained syncope, N. Engl. J. Med. 320 (6) (1989) 346–351.
[7] A. Fitzpatrick, R. Sutton, Tilting towards a diagnosis in recurrent unexplained syncope, Lancet 1 (8639) (1989) 658–660.

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[8] A. Raviele, G. Gasparini, F. Di Pede, P. Delise, A. Bonso, E. Piccolo, Usefulness of head-up tilt test in evaluating patients with syncope of unknown origin and negative electrophysiologic study, Am. J. Cardiol. 65 (20) (1990) 1322–1327.
[9] G. Nigro, V. Russo, A. Rago, et al., The main determinant of hypotension in nitroglycerine tilt-induced vasovagal syncope, Pacing Clin. Electrophysiol. 35 (6) (2012) 739–748.
[10] V. Russo, A.A. Papa, C. Ciardiello, et al., Which hemodynamic parameter predicts nitroglycerin-potentiated head-up tilt test response? Pacing Clin. Electrophysiol. 38 (4) (2015) 507–513.
[11] S. Milstein, J. Buetikofer, J. Lesser, et al., Cardiac asystole: a manifestation of neurally mediated hypotension-bradycardia, J. Am. Coll. Cardiol. 14 (7) (1989) 1626–1632.
[12] R. Sutton, M. Brignole, C. Menozzi, et al., Dual chamber pacing in the treatment of neurally mediated tilt-positive cardio-inhibitory syncope: pacemaker versus no therapy: a multicenter randomized study. The Vasovagal Syncope International Study (VASIS) Investigators, Circulation 102 (2000) 294–299.
[13] M. Brignole, C. Menozzi, A. Moya, et al., International Study on Syncope of Uncertain Etiology 3 (ISSUE-3) Investigators. 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 125 (21) (2012) 2566–2571.
[14] S.J. Connolly, R. Sheldon, K.E. Thorpe, et al., Pacemaker therapy for prevention of syncope in patients with recurrent severe vasovagal syncope: Second Vasovagal Pacemaker Study (VPS II): a randomized trial, JAMA 289 (2003) 2224–2229.
[15] M. Brignole, A. Moya, F.J. de Lange, J.C. Deharo, P.M. Elliott, A. Fanciulli, A. Fedorowski, R. Furlan, R.A. Kenny, A. Martín, V. Probst, M.J. Reed, C.P. Rice, R. Sutton, A. Ungar, J.G. van Dijk, ESC Scientific Document Group, 2018 ESC guidelines for the diagnosis and management of syncope, Eur. Heart J. 39 (21) (2018) 1883–1948.
[16] M. Brignole, C. Menozzi, A. Del Rosso, et al., New classification of haemodynamics of vasovagal syncope: beyond the VASIS classification. Analysis of the pre-syncopal phase of the tilt test without and with nitroglycerin challenge, Europace 2 (2000) 66–76.
[17] A. Bartoletti, P. Alboni, F. Ammirati, et al., The Italian protocol: a simplified head-up tilt testing potentiated with oral nitroglycerin to assess patient with unexplained syncope, Europace 2 (2000) 339–342.
[18] M. Schaldach, H. Hutten, Intracardiac impedance to determine sympathetic activity in rate responsive pacing, Pacing Clin. Electrophysiol. 15 (11) (1992) 1778–1786.
[19] A. Raviele, Tilt-induced asystole: a useful prognostic marker or clinically unrelevant finding? Eur. Heart J. 23 (6) (2002) 433–437.
[20] M. Brignole, P. Donateo, M. Tomaino, et al., International Study on Syncope of Uncertain Etiology 3 (ISSUE-3) Investigators. Benefit of pacemaker therapy in patients with presumed neurally mediated syncope and documented asystole is greater when tilt test is negative: an analysis from the third International Study on Syncope of Uncertain Etiology (ISSUE-3), Circ. Arrhythm. Electrophysiol. 7 (1) (2014) 10–16.
[21] M. Brignole, F. Arabia, F. Ammirati, et al., Syncope Unit Project 2 (SUP 2) investigators. Standardized algorithm for cardiac pacing in older patients affected by severe unpredictable reflex syncope: 3-year insights from the Syncope Unit Project 2 (SUP 2) study, Europace 18 (9) (2016) 1427–1433.
[22] M. Brignole, M. Tomaino, A. Aerts, et al., BIOSync Study Steering Committee. 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 18 (1) (2017) 208.
[23] Evidence Review Committee Members, P.D. Varosy, L.Y. Chen, A.L. Miller, P.A. Noseworthy, D.J. Slotwiner, V. Thiruganasambandamoorthy, Pacing as a treatment for reflex-mediated (vasovagal, situational, or carotid sinus hypersensitivity) syncope: a systematic review for the 2017 ACC/AHA/HRS guideline for the evaluation and management of patients with syncope: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society, Heart Rhythm. 14 (8) (2017) e255–e269.
[24] Writing Committee Members, W.K. Shen, R.S. Sheldon, D.G. Benditt, M.I. Cohen, D.E. Forman, Z.D. Goldberger, B.P. Grubb, M.H. Hamdan, A.D. Krahn, M.S. Link, B. Olshansky, S.R. Raj, R.K. Sandhu, D. Sorajja, B.C. Sun, C.W. Yancy, 2017 ACC/AHA/HRS guideline for the evaluation and management of patients with syncope: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society, Heart Rhythm. 14 (8) (2017) e155–e217.
[25] B. Takase, T. Akima, A. Uehata, et al., Endothelial function and peripheral vasomotion in the brachial artery in neurally mediated syncope, Clin. Cardiol. 23 (11) (2000) 820–824.
[26] M. Iacoviello, C. Forleo, P. Guida, et al., Clinical predictors of head-up tilt test outcome during the nitroglycerin phase, Clin. Auton. Res. 20 (3) (2010) 167–173.
[27] C. Forleo, P. Guida, M. Iacoviello, M. Resta, F. Monitillo, S. Sorrentino, S. Favale, Head-up tilt testing for diagnosing vasovagal syncope: a meta-analysis, Int. J. Cardiol. 168 (1) (2013) 27–35.
[28] V. Russo, A. Rago, A.A. Papa, et al., The effect of dual-chamber closed-loop stimulation on syncope recurrence in healthy patients with tilt-induced vasovagal cardioinhibitory syncope: a prospective, randomised, single-blind, crossover study, Heart 99 (21) (2013) 1609–1613.
[29] E. Occhetta, M. Bortnik, R. Audoglio, C. Vassanelli, INVASY Study Investigators, Closed loop stimulation in prevention of vasovagal syncope. Inotropy Controlled Pacing in Vasovagal Syncope (INVASY): a multicenter randomized, single blind, controlled study, Europace 6 (2004) 538–547.
[30] P. Palmisano, M. Zaccaria, G. Luzzi, F. Nacci, M. Anaclerio, S. Favale, Closed-loop cardiac pacing vs. conventional dual-chamber pacing with specialized sensing and pacing algorithms for syncope prevention in patients with refractory vasovagal syncope: results of a long-term follow-up, Europace 14 (2012) 1038–1043.
[31] G. Baron-Esquivias, C.A. Morillo, A. Moya-Mitjans, et al., Dual-chamber pacing with closed loop stimulation in recurrent reflex vasovagal syncope: the SPAIN Study, J. Am. Coll. Cardiol. 70 (14) (2017) 1720–1728.

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