Clin Auton Res
DOI 10.1007/s10286-017-0441-7

REVIEW

Vasovagal syncope with asystole: the role of cardiac pacing

Michele Brignole[1] · Marco Tomaino[2] · Alessio Gargaro[3]

Received: 31 March 2017 / Accepted: 19 June 2017

Abstract Whereas cardiac pacing has a very limited role overall in patients with vasovagal syncope (VVS), there are three reasons which support pacing efficacy in tilt-induced asystolic VVS. These are: (1) contrary to mixed and vasodepressor forms, an asystolic tilt response is specific, i.e., diagnostic, of VVS and is unlikely to occur in control patients without history of syncope and in patients with cardiac syncope; (2) contrary to mixed and vasodepressor forms, an asystolic tilt response predicts a similar asystolic event during prolonged ECG monitoring with a positive predictive value of 86%; (3) the available evidence from trials supports the efficacy of dual-chamber pacing with a low recurrence rate of syncope after pacing ranging from 6% up to 23% during 3 years of follow-up. The latter results should be confirmed by an ongoing double-blind randomized controlled trial before cardiac pacing becomes an established indication. It is commonly believed that the most frequent cause of recurrence of syncope in patients treated with a pacemaker is an associated hypotensive reflex. In these cases additional measures should be used to counteract hypotension. Recognizing prodromal symptoms, avoiding triggers, and performing counterpressure maneuvers are the well-known first steps. There are two additional useful measures when these fail: stopping/reducing hypotensive drugs and (in selected cases) adding fludrocortisone.

Keywords Syncope · Pacemaker · Tilt table test · Vasovagal syncope · Cardioinhibitory reflex · Asystolic pause

Introduction

According to the classification of the guidelines on syncope of the European Society of Cardiology [1], the term vasovagal syncope (VVS) is used to identify one of the three clinical forms which constitute reflex (neurally mediated) syncope, the other two forms being situational and carotid sinus. In a broader definition, VVS also includes those atypical forms with suspected vasovagal mechanism which lack a confident diagnosis after the initial assessment. In these last forms a positive response to tilt testing can be useful for confirming the initial suspicion and giving information on the underlying mechanism of syncope. VVS is the most frequent cause of syncope, its real prevalence depending on the clinical setting and the diagnostic accuracy required for its diagnosis. In one cohort study [2], which utilized a standardized diagnostic approach, VVS was certain at initial evaluation in 24% of patients, increasing to 63% after including the highly likely diagnoses; in another study [3] of patients referred to syncope units, VVS was diagnosed at initial evaluation in

This invited article follows the structure of the lecture given at the European Federation for Autonomic Societies (EFAS) meeting held in Innsbruck, February 17, 2017.

✉ Michele Brignole
mbrignole@asl4.liguria.it

Marco Tomaino
marcotomtrial@gmail.com

Alessio Gargaro
alessio.gargaro@biotronik.com

[1] Department of Cardiology, Arrhythmologic Centre, Ospedali del Tigullio, Via Don Bobbio, 25, 16033 Lavagna, Italy

[2] Central Hospital, Bolzano, Italy

[3] BIOTRONIK Italy S.p.A., Vimodrone, Italy

Published online: 01 July 2017

15% and by means of tilt testing in a further 26% of patients.

Vasovagal syncope can be caused by a decrease in cardiac output and or vasodilatation. In the elderly a decrease in cardiac output is by far the most important factor. On average systemic vascular resistances remain higher than supine control up to the actual faint [4, 5]. Typically, the vasovagal reflex is both vasodilation and bradycardia. In its extreme manifestation, vagal reflex gives rise to an asystolic pause. Patients with asystolic forms have a higher baroreflex gain than those without asystole [6]. When VVS is induced during tilt testing, a variety of responses are found which have been classified in the Vasovagal Syncope International Study (VASIS) classification shown in Table 1 [7].

In typical VVS populations, pacing seems to have marginal efficacy. The explanation is that the heart can never pump out more blood than flows in. In most cases of vasovagal orthostatic syncope in adult and elderly subjects, the dominant mechanism is a decrease in central blood volume due to pooling of blood in capacitance vessels in the splanchnic region and lower limbs, with consequent reduced venous return, cardiac filling, and low cardiac output resulting in hypotension [8]. As a logical consequence, two randomized double-blind studies, which enrolled mainly patients without an asystolic tilt response, reported a non-significant 17% reduction in syncope [9–11]. In patients with a clinical diagnosis of neurally mediated syncope the benefit of pacemaker therapy was greater when tilt test—passive and potentiated with nitroglycerin—was negative [12]. Tilt-table testing may be considered to identify patients with a pronounced decrease in central blood volume who would be less likely to respond to permanent cardiac pacing [12–14]. For the above reasons, in patients with tilt-induced VVS cardiac pacing is not considered indicated by American guidelines [15] and consensus document [14] and has a weak Class IIb (evidence B) indication in the European guidelines for cardiac pacing [16].

Nevertheless, recent data suggest that the cardioinhibitory (CI) reflex may play a major role in causing syncope in patients with tilt-induced asystolic VVS and therefore there is the rationale for cardiac pacing to be effective in this particular form of VVS. This review will provide the reasons in support and will give the correct indication for cardiac pacing therapy.

Reasons supporting pacing efficacy in tilt-induced asystolic (VASIS 2B) vasovagal syncope

Three main reasons support the efficacy of cardiac pacing in patients with tilt-induced asystolic vasovagal syncope, but not in the other groups; these reasons are described below.

Asystolic (VASIS 2B) tilt response is specific for vasovagal syncope

An asystolic tilt response with a pause greater than 3 s (VASIS 2B type) according to the New VASIS classification shown in Table 1 [4] was unlikely to occur in control patients without history of syncope [17–19], in patients with cardiac syncope [20, 21], and in patients with unexplained syncope [22]; thus, contrary to mixed and vasodepressor forms, this type of response is specific, i.e., diagnostic, of VVS with a rate ranging from 10% to 44% depending on clinical features and age of patients [21, 22] (Fig. 1).

Asystolic (VASIS 2B) tilt response predicts asystolic spontaneous syncope

In the International Study of Syncope of Uncertain Etiology (ISSUE-3) trial [12] an asystolic response greater than

Table 1 The modified VASIS classification [7]

Type 1 mixed	Heart rate falls at the time of syncope, but the ventricular rate does not fall to less than 40 bpm or falls to less than 40 bpm for less than 10 s with or without asystole of less than 3 s. Blood pressure falls before the heart rate falls
Type 2A, cardioinhibition without asystole	Heart rate falls to a ventricular rate less than 40 bpm for more than 10 s, but asystole of more than 3 s does not occur. Blood pressure falls before the heart rate falls
Type 2B, cardioinhibition with asystole	Asystole occurs for more than 3 s. Heart rate fall coincides with or precedes blood pressure fall
Type 3 vasodepressor	Heart rate does not fall more than 10%, from its peak, at the time of syncope
Exception 1, chronotropic incompetence	No heart rate rise during the tilt (i.e., less 10% from the pre-tilt rate)
Exception 2, excessive heart rate rise	Excessive heart rate rise both at the onset of the upright position and throughout its duration before syncope (i.e., greater than 130 bpm)

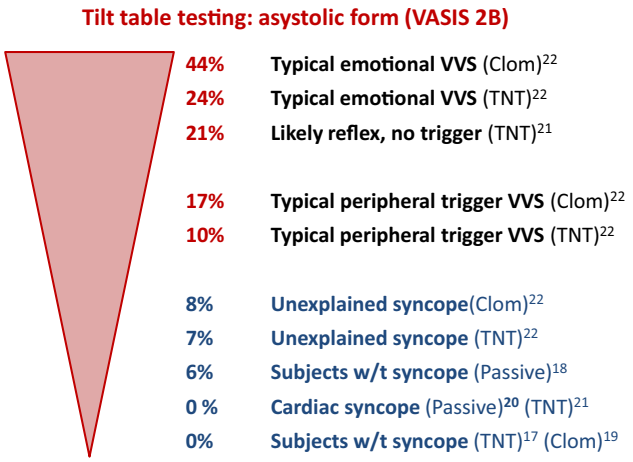

Fig. 1 Asystolic (>3 s) responses observed during tilt table test performed in different clinical conditions. The studies reported in the figure used the Westminster protocol for passive tilt [18], the Italian protocol for glyceryltrinitrate tilt [17], and the clomipramine protocol [19] for a total of 553 syncope patients and 411 control subjects without syncope. Studies using other tilt protocols, e.g., isoproterenol challenge, were not included. *VVS* vasovagal syncope, *Clom* clomipramine, *TNT* glyceryltrinitrate

3 s predicted a similar asystolic event during prolonged ECG monitoring with implantable loop recorder with a positive predictive value of 86% (95% CI 70–95%). On the contrary, mixed and vasodepressor forms and negative tests were unable to predict the spontaneous outcome.

Results from controlled pacemaker trials

In a small randomized trial [23], performed in the 1990s in 42 selected patients affected by severely recurrent (median 6 episodes) asystolic tilt-positive VVS, syncope recurred in 1 patient (5%) in the group treated with DDI pacemaker with rate hysteresis and in 14 patients (61%) in the no-pacemaker arm during a mean follow-up of 37 months ($p = 0.0006$); the actuarial 3-year recurrence rates were 6% and 50%, respectively.

In the multicenter Syncope Unit Project (SUP) 2 trial [24], patients affected by asystolic tilt-induced VVS, patients affected by carotid sinus syncope, and patients who had a documentation of asystolic syncope during loop recorder monitoring were treated with dual-chamber pacemaker and were compared with a control group of unpaced patients and followed up to 3 years (Table 2); the actuarial syncope recurrence rate was significantly lower in VVS than in controls with a hazard ratio of 0.43 and was similar to the recurrence rate observed in patients with carotid sinus syncope and those with spontaneously documented asystolic events. Apart lower age, the patients with asystolic tilt had similar clinical characteristics to those of the other subgroups. In SUP 2 [24] asystolic tilt patients had a better outcome than similar patients in the ISSUE-3 trial [12] that showed a recurrence rate of tilt-asystolic patients of 35% at 12 months. There are important differences between the two studies. In ISSUE- 3 the inclusion criterion was a pause documented by implantable loop recorder and not tilt test response which was a complementary test, not performed in all patients. In addition, a type II error due to the small populations (only 14 VASIS 2B patients were included in ISSUE-3) and important differences in inclusion criteria (age, prodromes) might explain such apparent different results.

In the most recent multicenter randomized controlled cross-over trial performed in Spain in 46 patients, aged over 40 years, affected by severely recurrent (more than five episodes during life) CI–VVS [25], during 12 months of follow-up, syncope recurred in 4 (9%) patients treated with a dual-chamber pacemaker with closed loop stimulation compared with 21 (46%) patients who had received a sham pacemaker programmed off ($p = 0.0001$).

In conclusion, the available evidence from small trials support the efficacy of dual-chamber pacing even though syncope can recur in a minority of patients with a rate similar to that observed in other forms of reflex syncope. In the era of evidence-based medicine, the above results must be confirmed by a double-blind randomized controlled trial before cardiac pacing becomes an established indication for CI–VVS.

Need for a double-blind randomized trial

The above considerations form the rationale for a randomized controlled trial. The benefit of dual-chamber pacing with closed loop stimulation (CLS) in tilt-induced cardioinhibitory reflex syncope (BIOSync CLS) trial (http://clinicaltrials.gov/ct2/show/NCT02324920) is a multicenter, patient- and outcome-assessor-blinded, randomized, parallel-arm, placebo-controlled trial with the objective of assessing the clinical benefit of dual-chamber rate-adaptive cardiac pacing in patients older than 40 years, with tilt-induced type VASIS 2B asystolic response [26]. The primary endpoint is the time to the first post-implant recurrence of syncope; the secondary endpoint is the time to the first recurrence of pre-syncope or syncope, whichever comes first. Patients receive the implantation of a dual-chamber cardiac pacing with CLS; the pacemaker is randomized to on or off after pacemaker implantation; the patients are followed up until the first adjudicated primary endpoint event for a maximum of 2 years. An important original characteristic of the study design is that patients are asked to self-report syncopal symptoms at least every 3 months with self-administered questionnaires addressed to an independent adjudication

Table 2 Estimated recurrence rate of syncope, analyzed by means of Kaplan–Meier survival curves, in paced and in control patients in SUP 2 trial [24]

Characteristics	Pacing: asystolic (VASIS 2B) tilt testing, $n = 38$	No pacing (control group), $n = 142$	p value (pacing vs. no pacing)	Pacing: CSS, $n = 78$	Pacing: ILR-documented asystolic episodes, $n = 21$
1-year recurrence rate (95% CI)	3 (0–9)	21 (13–29)	$p = 0.037$ HR = 0.43 (95% CI 0.27–0.96)	9 (3–15)	11 (0–25)
2-year recurrence rate (95% CI)	17 (3–31)	33 (23–43)		16 (6–26)	24 (2–46)
3-year recurrence rate (95% CI)	23 (5–41)	43 (29–57)		16 (6–26)	24 (2–46)

CSS carotid sinus syncope, *ILR* implantable loop recorder

committee. This solution allows patients and members of the adjudicating board to be blind to randomization. The self-administered questionnaire had been previously validated in a cohort of 77 patients and showed a Cohen concordance kappa of 0.90 ($p < 0.0001$) between the answer provided by the patients and those collected by an expert physician [26]. The study is designed to detect a 40% relative reduction of the 2-year incidence of syncopal recurrences with 80% statistical power. The study flow is shown in Fig. 2. Since the study is a comparison between DDD and CLS vs no pacing, it is not intended to assess the relative contribution of DDD and CLS.

Who are the candidates for cardiac pacing?

The fact that pacing may be effective does not mean that it is also always necessary. It must be emphasized that the decision to implant a pacemaker needs to be made in the clinical context of a benign condition that frequently affects young patients. Thus, cardiac pacing should be limited to a highly selected small proportion of adult patients affected by severe reflex syncope.

The clinical presentation is probably as important as tilt-test positivity when selecting patients who can benefit from cardiac pacing. The SUP 2 study population was characterized by age over 40 years, history of recurrent and severe syncopes beginning in middle or older age, and frequent injuries, probably due to presentation without warning [27]. In particular, the patients with asystolic tilt-induced VVS had a mean age of 65 years, were mostly female, and had a history of both pre-syncopes and syncopes; the longest pause induced during tilt test was on average of 21 s.

Also the temporal relationship between asystole and blood pressure drop observed during index tilt table test is of value for a proper patient selection. This point was not considered among the inclusion criteria of the trials mentioned above that limited inclusion to the presence of an asystolic pause during tilt test. The ideal candidate for pacemaker therapy is probably the patient in whom there is still normotension or mild hypotension at the time that asystole occurs and cardiac pacing starts (Fig. 3). Conversely, if asystole occurs—and cardiac pacing starts—when blood pressure is already very low, cardiac pacing is more likely to be ineffective. The exact timing of asystole in relation to that of loss of consciousness is valuable. Adding video recording to tilt table testing, Saal et al. [28] recently showed that asystole occurred at least 3 s before syncope in approximately two-thirds of patients who had an asystolic tilt response, suggesting that CI primarily caused syncope, whereas it occurred too late to have been the primary cause of loss of consciousness in the other third. Interestingly, in patients with early asystole, blood pressure was significantly higher than in those with late asystole.

In practice, how many potential candidates are there who can benefit from a pacemaker? The exact figure is uncertain. On the basis of the sample size calculation in the BioSync study [26], we estimate that 12% of patients over 40 years and a history of three or more syncopal episodes in the previous 2 years undergoing tilt test could potentially benefit from a pacemaker.

How to counteract hypotensive susceptibility?

In general, we may expect that, after pacemaker implantation, syncope will recur in up to 23% of patients during 3 years of follow-up [24]. It is commonly believed that the most frequent cause of recurrence is an associated hypotension at the time of syncope. In these cases additional measures should be used to counteract hypotension. Recognizing prodromal symptoms, avoiding triggers, and performing counterpressure maneuvers are the well-known first steps. There are two additional useful measures when

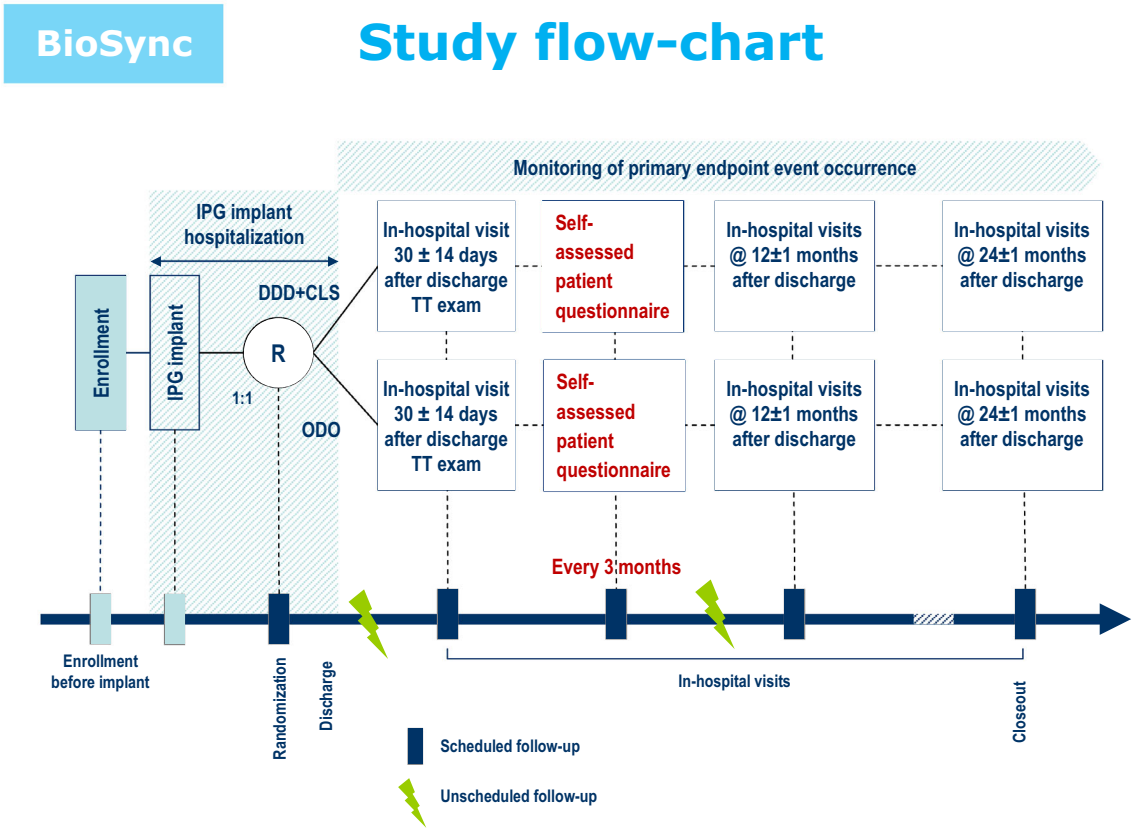

Fig. 2 Flow chart of the BioSync trial [26]. After the written informed consent and enrolment, patients undergo dual-chamber pacemaker implantation according to standard procedures. Before being discharged, patients are randomized to the active group (dual-chamber pacing with close loop stimulation feature on) or to placebo (pacing off). After the implant, patients are visited in hospital at 12 and 24 months unless earlier termination occurs. At 1-month visit, tilt table test is repeated. A special method for blinding is implemented in the study design. Patient and outcome assessor blinding is ensured by the patient and the independent adjudication committee who are both blinded to random assignments. Although investigators are not blind to randomization, they are not be involved in the collection and assessment process of study endpoints. Indeed, syncope and pre-syncope study endpoints are collected by means of a specifically designed validated self-administered patient questionnaire. *IPG* implantable pulse generator, *TT* tilt test

these fail: these are stopping/reducing hypotensive drugs and (in selected case) adding fludrocortisone.

Stop/reduce hypotensive drugs

The association of VVS syncope with comorbidities requiring chronic vasoactive drug therapy is a frequent clinical problem in the elderly. In the multicenter randomized prospective STOP-VD trial [29], 73% of elderly patients with reflex syncope were taking one or more vasoactive drug (antihypertensive, antidepressant, L-dopa antagonist). In the active arm, the hypotensive therapy was modified in order to achieve "not too high, nor too low" systolic BP value of 140 mmHg. Compared with the control arm of patients who continued therapy, the recurrence of syncope was safely reduced from 42% to 10% with a hazard ratio of 0.22 (95% CI 0.07–0.65) during a mean follow-up of 13 months.

Fludrocortisone

Fludrocortisone, by increasing renal sodium re-absorption and expanding plasma volume, may counteract the physiological cascade leading to the orthostatic vasovagal reflex. The prevention of syncope trial II (POST 2) [30] enrolled 210 patients with recurrent syncopal spells and randomized them to receive fludrocortisone at highest tolerated doses from 0.05 to 0.2 mg daily or placebo. The trial demonstrated a modest reduction in vasovagal syncope recurrences in young (median age 30 years) patients with low–normal values of arterial BP and without comorbidities. On the other hand some patients have to discontinue fludrocortisone therapy owing to side effects (ankle edema, hypokalemia), and in others with comorbidities (e.g., patients with hypertension or heart failure, etc.) fludrocortisones is contraindicated because of increased risk of end-target organ damage and cardiovascular events, thus

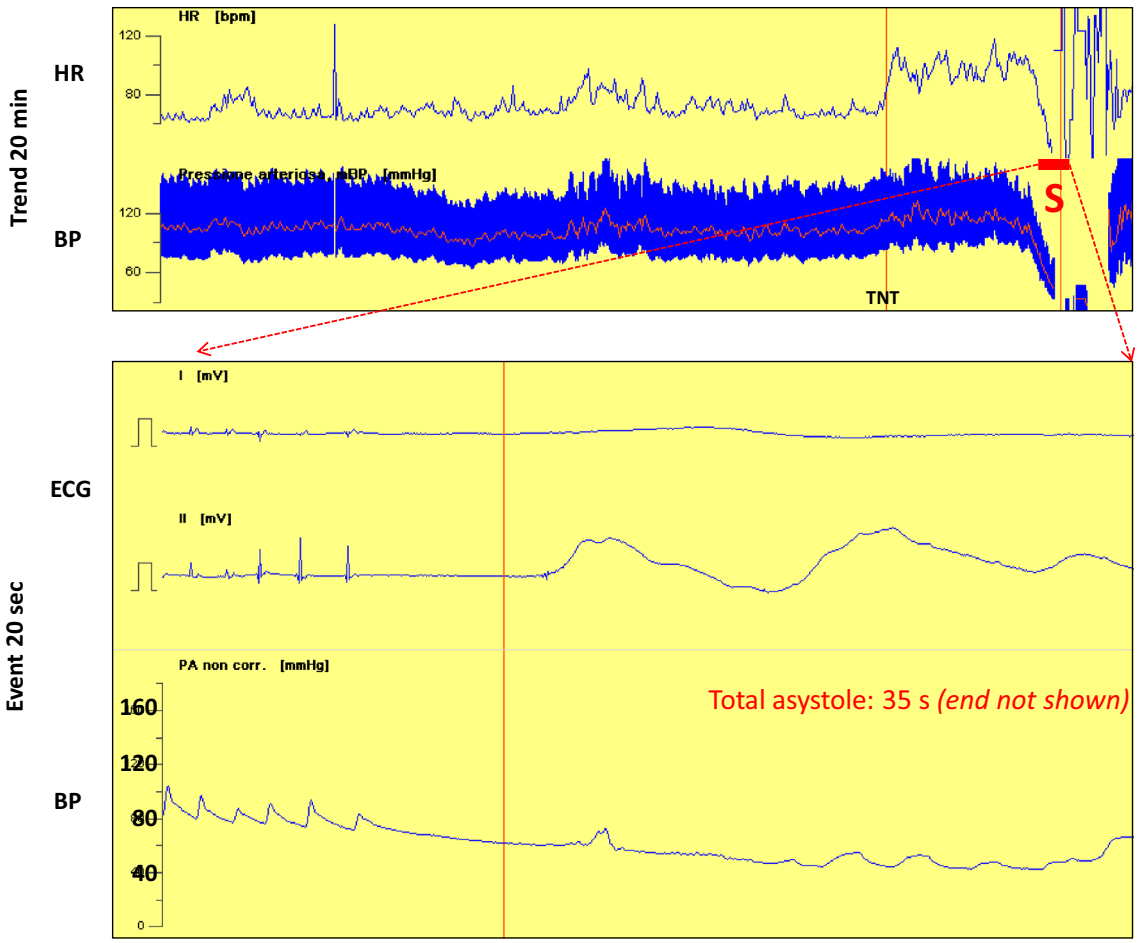

Fig. 3 Case of a 58-year-old woman with tilt-induced CI VVS suitable for cardiac pacing therapy. *Top panel* 20 min heart rate (*HR*) and blood pressure (*BP*) trend. HR and BP fall coincide; the fall is sudden, rapid, and of short duration before syncope occurs. *Botton panel* expanded tracing, at the time of syncope, a 35-s-long asystolic pause is recorded; note that in the beats immediately preceding the pause, BP is still approximately as high as 90 mmHg, suggesting that the main determinant of loss of consciousness is a CI reflex and not a hypotensive reflex. *TNT* glyceryltrinitrate, *S* syncope

equating the benefit/risk ratio. However, fludrocortisone may be useful in selected patients when the previous measures failed.

Conclusion

Cardiac pacing is reasonably effective in tilt-induced asystolic VVS. Since the vasovagal reflex is both vasodilation and bradycardia, antihypotensive measures should be added to cardiac pacing when hypotensive syncope coexists.

References

1. Moya A, Sutton R, Ammirati F et al (2009) Guidelines for the diagnosis and management of syncope (version 2009). Eur Heart J 30:2631–2671
2. van Dijk N, Boer KR, Colman N (2008) High diagnostic yield and accuracy of history, physical examination, and ECG in patients with transient loss of consciousness in FAST: the Fainting Assessment Study. J Cardiovasc Electrophysiol 19:48–55
3. Brignole M, Ungar A, Casagranda I et al (2010) Prospective multicentre systematic guideline-based management of patients referred to the syncope units of general hospitals. Europace 12:109–118
4. Verheyden B, Liu J, van Dijk N, Westerhof BE, Reybrouck T, Aubert AE, Wieling W (2008) Steep fall in cardiac output is main determinant of hypotension during drug-free and nitroglycerine-induced orthostatic vasovagal syncope. Heart Rhythm 5:1695–1701
5. Nigro G, Russo V, Rago A, Iovino M, Arena G, Golino P, Russo MG, Calabrò R (2012) The main determinant of hypotension in nitroglycerine tilt-induced vasovagal syncope. Pacing Clin Electrophysiol 35:739–748
6. Chaddha A, Wenzke KE, Brignole M, Wasmuns SL, Page RL, Hamdan MH (2016) The role of the baroreflex in tilt table testing: outcome and type of response. JACC Clin Electrophysiol 2:812–817
7. Brignole M, Menozzi C, Del Rosso A, Costa S, Gaggioli G, Bottoni N, Bartoli P, Sutton R (2000) 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 2:66–76
8. Wieling W, Jardine DL, de Lange FJ, Brignole M, Nielsen HB, Stewart J, Sutton R (2016) Cardiac output and vasodilation in the vasovagal response: an analysis of the classic papers. Heart Rhythm 13:798–805
9. Connolly SJ, Sheldon R, Thorpe KE et al (2003) Pacemaker therapy for prevention of syncope in patients with recurrent severe vasovagal syncope: second Vasovagal Pacemaker Study (VPS II): a randomized trial. JAMA 289:2224–2229
10. Raviele A, Giada F, Menozzi C et al (2004) 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 25:1741–1748
11. Sud S, Massel D, Klein GJ, Leong-Sit P, Yee R, Skanes AC, Gula LJ, Krahn AD (2007) The expectation effect and cardiac pacing for refractory vasovagal syncope. Am J Med 120:54–62
12. Brignole M, Donateo P, Tomaino M et al (2014) 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 7:10–16
13. Sutton R, Brignole M (2014) Twenty-eight years of research permit reinterpretation of tilt-testing: hypotensive susceptibility rather than diagnosis. Eur Heart J 35:2211–2212
14. Sheldon RS, Grubb BP, Olshansky B et al (2015) 2015 Heart Rhythm Society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. Heart Rhythm 12:e41–e63
15. Shen WK, Sheldon RS, Benditt DG et al (2017) 2017 ACC/AHA/HRS guideline for the evaluation and management of 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. Circulation. doi: 10.1161/CIR.0000000000000498
16. Brignole M, Auricchio A, Baron-Esquivias G et al (2013) 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy. Eur Heart J 34:2281–2329
17. Bartoletti A, Alboni P, Ammirati F et al (2000) 'The Italian Protocol': a simplified head-up tilt testing potentiated with oral nitroglycerin to assess patients with unexplained syncope. Europace 2:339–342
18. Petersen ME, Williams TR, Gordon C, Chamberlain-Webber R, Sutton R (2000) The normal response to prolonged passive head up tilt testing. Heart 84:509–514
19. Theodorakis G, Livanis EG, Leftheriotis D, Flevari P, Markianos M, Kremastinos D (2003) Head-up tilt test with clomipramine challenge in vasovagal syndrome—a new tilt testing protocol. Eur Heart J 24:658–663
20. Brignole M, Gianfranchi L, Menozzi C, Raviele A, Oddone D, Lolli G, Bottoni N (1993) Role of autonomic reflexes in syncope associated with paroxysmal atrial fibrillation. J Am Coll Cardiol 22:1123–1129
21. Ungar A, Sgobino P, Russo V et al (2013) Diagnosis of neurally mediated syncope at initial evaluation and with tilt table testing compared with that revealed by prolonged ECG monitoring. An analysis from the third International Study on Syncope of Uncertain Etiology (ISSUE-3). Heart 99:1825–1831
22. Furukawa T, Maggi R, Solano A, Croci F, Brignole M (2011) Effect of clinical triggers on positive responses to tilt-table testing potentiated with nitroglycerin or clomipramine. Am J Cardiol 107:1693–1697
23. Sutton R, Brignole M, Menozzi C, Raviele A, Alboni P, Giani P, Moya A (2000) 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 102:294–299
24. Brignole M, Arabia F, Ammirati F et al (2016) 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 18:1427–1433
25. Baron-Esquivias G et al (2017) The SPAIN trial. Presented at late breaking trials, ACC17, American College of Cardiology Annual Scientific Session, Washinghton, March 19
26. Brignole M, Tomaino M, Aerts A, Ammirati F, Ayala-Parades F, Deharo JC, Del Rosso A, Hamdan M, Lunati M, Moya A, Gargaro A (2017) 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 18:208. doi:10.1186/s13063-017-1941-4
27. Brignole M, Ammirati F, Arabia F et al (2015) Assessment of a standardized algorithm for cardiac pacing in older patients affected by severe unpredictable reflex syncopes. Eur Heart J 36:1529–1535
28. Saal DP, Thijs RD, Bootsma M, Brignole M, Benditt DG, van Dijk JG (2017) Temporal relationship of asystole to onset of transient loss of consciousness in tilt-induced reflex syncope. JACC Clin Electrophysiol (in press)
29. Solari D, Tesi F, Unterhuber M, Gaggioli G, Ungar A, Tomaino M, Brignole M (2016) Stop vasodepressor drugs in reflex syncope: a randomised controlled trial. Heart 103:449–455
30. Sheldon R, Raj SR, Rose MS et al (2016) Fludrocortisone for the prevention of vasovagal syncope: a randomized, placebo-controlled trial. J Am Coll Cardiol 68:1–9