Malignant Vasovagal Syncope: Pacemaker Therapy in Comparison to Medical Treatment

E. OCCHETTA, M. BORTNIK, C. VASSANELLI
Cardiology Department, University of Piemonte Orientale, Novara, Italy

R. AUDOGLIO
SRA, Linarolo (Pavia), Italy

Summary

This article provides an updated review of topics related to vasovagal syncope (VVS) and the efforts of the medical community and biomedical industry to find effective therapeutic solutions for the treatment of VVS. While the first part of this two-part review, which was published previously, addressed the clinical aspects and medical treatment of VVS, this second part analyzes the clinical benefit of conventional cardiac pacing, compares the efficacy of all available therapies, and draws several conclusions. In this context, Closed Loop Stimulation (CLS), whose rate response in driven by variations of myocardial contractility, is shown to be an optimal solution. All the clinical studies that have investigated syncopal recurrence with this pacing approach have yielded favorable results, even in long-term application. Patients paced with CLS did not exhibit a syncopal recurrence, and all were able to increase their quality of life. The introduction of new CLS-based devices is making this therapy available to patients with intrinsic activation of the ventricle. These factors are very important for the optimization of syncope therapy.

Key Words

Malignant vasovagal syncope, pacemaker therapy, Closed Loop Stimulation (CLS)

Introduction

The encouraging results from the "Inotropy Controlled Pacing in Vasovagal Syncope" (INVASY) Italian multicenter clinical trial – which demonstrated the effectiveness of pacing based on Closed Loop Stimulation (CLS, Biotronik, Germany) in preventing vasovagal syncope (VVS) [1,2], prompted us to prepare a review entitled "Malignant Vasovagal Syncope." The review provides an update on topics related to VVS and the efforts of the medical community and biomedical industry to find effective therapeutic solutions for the treatment of VVS.

The content of the review is divided into two parts. The first part addresses clinical aspects and medical treatment of VVS [3]. This article, which presents the second part of the review, analyzes the clinical benefits of conventional cardiac pacing (and of its special form CLS), compares the efficacy of all available therapies, and draws conclusions.

Conventional Pacing in VVS Prevention

For patients with cardioinhibitory VVS that is recurrent, refractory to tilt-table training and/or drug therapy, and is both physically and psychologically debilitating, the implantation of a pacemaker with dedicated response algorithms may be beneficial. The rationale for employing pacing to combat VVS is self-evident. Since it is known that in cardioinhibitory or mixed type VVS a decrease in the cardiac rate is always associated with the vasodepressive component, cardiac pacing – at a rate that is always higher than the intrinsic rhythm under basal conditions – should suppress the bradycardic effect on the evolution of syncopal spells.

The first studies on the use of cardiac pacing (conventional single- or dual-chamber) for preventing malignant VVS date back to the beginning of the 1990s. The results were promising from the beginning; they indicated that pacing could play an important role in the

prevention of VVS if certain pacing systems driven by algorithms dedicated to recognize and contrast the bradycardia associated to the VVS were to become available in the future [4]. Starting in the mid-1990s, a number of clinical studies were conducted with pacemakers equipped with a "dedicated" algorithm, or with a response properly programmed for the suppression or attenuation of symptoms related to syncopal recurrence. In 1998, the results of these studies induced the American College of Cardiology and American Heart Association (ACC/AHA) Task Force to include malignant VVS as an indication for permanent pacemaker implantation [5]. At present, the indication is Class IIa (weight of evidence/opinion is in favor of usefulness/efficacy), limited to "recurrent syncope without clear, provocative events and with a hypersensitive cardioinhibitory response," and Class IIb (usefulness/efficacy is less well established by evidence/opinion) for "neurally mediated syncope with significant bradycardia reproduced by a head-up tilt with or without isoproterenol or other provocative maneuvers"[6].
The following reviews the algorithms or programming modes that have yielded more concrete results in respect to conventional pacing. Table 1 presents an analysis of only those studies that did not include and/or allow the enrollment of patients with cardiac rhythm disturbances or neuromediated syncope of cardiovascular etiology (e.g., carotid sinus syndrome) with ACC/AHA Class I or IIa pacemaker indication. Currently, there are no other known approaches based on heart rhythm analysis for electrophysiologic therapy of VVS except algorithms based on monitoring variations of myocardial contractility, which will be discussed in the next section.

Rate Drop Response

Rate Drop Response (RDR) is the only true rhythm-based algorithm for the prevention of VVS. A simple description of this algorithm, which is included in some dual-chamber pacemakers (Medtronic, USA) is presented in the following. The patient's sinus rate is constantly monitored between two programmable rate levels (one maximum and one minimum). The speed of the sinus rate decrease from the maximum to the minimum level is evaluated within a programmable time window (T1 – T2 in Figure 1). The stability of the bradycardia, at a rate below the minimum level, is verified within a second time window (T2 – T3 in Figure 1).

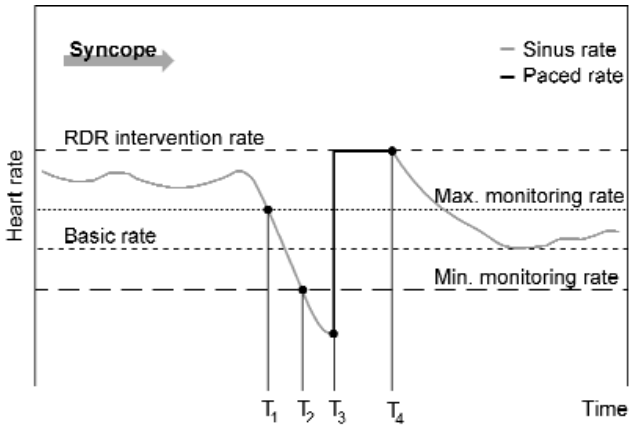

Figure 1. Illustration of the intervention mechanism of the DDD-RDR pacing mode during syncope.

The RDR interventional pacing rate (sufficiently high: up to180 bpm) and the time of pacing at RDR rate (T3 –T4 in Figure 1) are also programmed. When the sinus rate falls from the maximum to the minimum monitoring values in a time equal to or less than T1 – T2, the second monitoring window (T2 – T3 in Figure 1) is enabled. If the sinus rate remains at a value lower than the minimum monitoring level for a time at least equal to T2 – T3, then the RDR algorithm is started. At this point, the pacemaker begins dual-chamber pacing at the RDR interventional pacing rate for a period of time equal to T3-T4 (programmable: up to 15 min). At the end of this time period, the paced rate is gradually decreased back to the pacemaker's programmed basic rate.
The Vasovagal Pacemaker Study (VPS) [7] and the Syncope Diagnosis and Treatment (SYDIT) Study [8] seem to confirm that tiered dual-chamber pacing based on spontaneous heart rhythm variations is more effective than conventional drug treatment for preventing malignant VVS. However, the second Vasovagal Pacemaker Study (VPS II) [9] and the Vasovagal Syncope and Pacing Trial (SYNPACE) [10] have shown a relevant amount of syncopal recurrences in "paced" patients (compared to previous studies) and have indicated that the placebo effect of surgery in "control" patients has a statistically equivalent therapeutic effect to pacing. In essence, the final conclusion of the investigators is that RDR pacing is not effective in preventing VVS, limiting its efficacy to an extension of the time to first recurrence of syncope after device implantation.

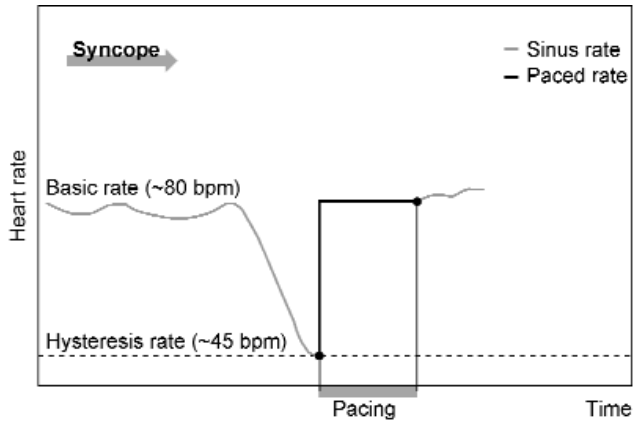

Figure 2. Illustration of the intervention mechanism of the DDI-HYST pacing mode during syncope.

DDI Pacing with Rate Hysteresis

DDI pacing with rate hysteresis (DDI-HYST) is a programming mode that mimics the RDR, although in a simpler manner (Figure 2). A conventional dual-chamber pacemaker is programmed to DDI mode. Its basic rate is set to about 80 bpm, while the rate hysteresis is set to about 45 bpm (always lower than the patient's minimum sinus rate at basal conditions). When the cardioinhibitory component of the VVS spell forces the heart rate below the value of the rate hysteresis, the device start to pace at the programmed basic rate in DDI mode. Pacing continues until the sinus rate is once again higher than the paced rate. The results from the Vasovagal Syncope International Study (VASIS) [11] are similar to those of VPS and SYDIT [7,8] with respect to preventing malignant VVS.

Contractility-based Pacing in VVS Prevention

The cardiovascular system is controlled by a highly specialized system operating in closed loop control, which reacts to external or pathologic influences in order to maintain a mean arterial blood pressure sufficient to perfuse all body organs in accordance with metabolic needs (Figure 3). When baroreceptors detect variations in the blood pressure, this information is transferred to the cardiovascular control centers located in the spinal medulla. Responding to this metabolic request, these control centers adjust the cardiac output, modulating the three parameters that regulate cardiac contraction: inotropy, chronotropy, and dromotropy. If

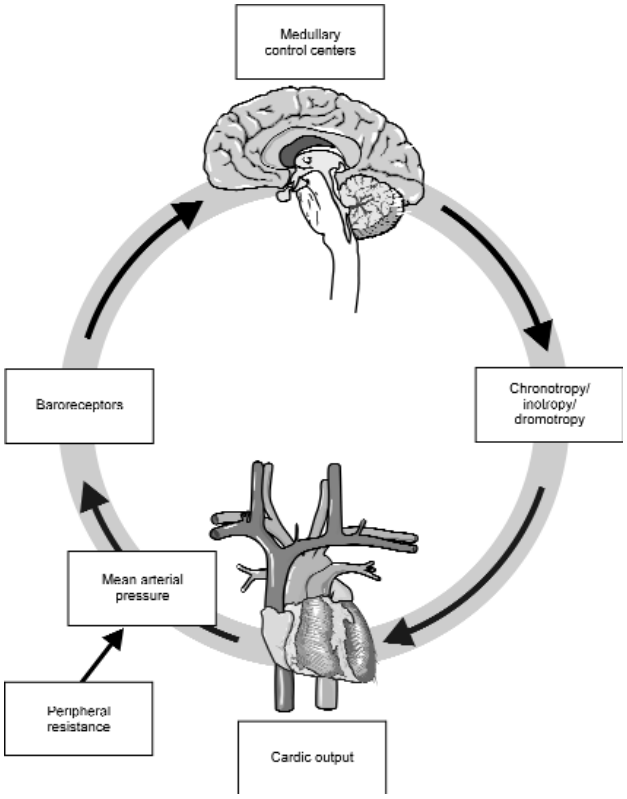

Figure 3. Illustration of the cardiovascular control closed loop system.

the arterial pressure is too low, the cardiac output is increased; if the pressure is too high, the cardiac output is decreased. Since the mean arterial blood pressure is determined by the ratio between the cardiac output and the total peripheral resistance, its variation following the regulation is transferred again to the circulatory control centers through the baroreceptors, verifying whether the cardiovascular equilibrium has been re-established.

As explained in the first part of this review [3], during vasovagal syndrome the diminished venous backflow stimulates a sympathetic compensatory tone that causes an increase of the inotropic effect. Since ventricular filling in not sufficient, the pressure in the left ventricle increases and, for the mechanism described above, the baroreceptors send a message that reduces heart rate. In other words, a paradoxical situation is established: an increase in the inotropic effect is associated with a decrease in the chronotropic state. This anomalous condition inhibits sympathetic activity and facilitates the vagal effect that, by increasing a peripheral vasodilatation with an associated reflexed bradycardia,

	VPS	VASIS	SYDIT	VPS II	SYNPACE
Objective	Investigation whether DDD-RDR pacing reduces symptoms and recurrence of VVS when compared with no pacing, i.e., optimized drug therapy	Investigation whether DDI-HYST pacing reduces symptoms and recurrence of VVS when compared with no pacing, i.e., optimized vasoconstrictor drug therapy (ethylephrine)	Investigation whether DDD-RDR pacing reduces symptoms and recurrence of VVS when compared to no pacing, i.e., optimized beta-blocker drug therapy (athenolol)	Investigation whether DDD-RDR pacing reduces symptoms and recurrence of VVS when compared to a "placebo," i.e., pacemaker programmed in ODO mode	Investigation whether DDD-RDR pacing reduces symptoms and recurrence of VVS when compared to a "placebo," i.e., pacemaker programmed in ODO mode
Pacemaker implantation in control group	No	No	No	Yes	Yes
Design	Prospective, randomized, controlled	Prospective, randomized, controlled	Prospective, randomized, controlled	Prospective, randomized, placebo-controlled, double-blinded, crossover	Prospective, randomized, placebo-controlled, double-blinded, crossover
Inclusion: Age	No limitation	> 40 years	> 35 years	No limitation	No limitation
Inclusion: Progressed VVS	> 6	> 3 in the last 2 years	> 3 in the last 2 years	> 6 in lifetime and/or ≥ 3 in the last 2 years	> 6 in lifetime and/or ≥ 3 in the last 2 years
Inclusion: HUTT	Positive HUTT (even if potentiated) with cardioinhibitory (pre)syncope	Positive HUTT (basal) with cardioinhibitory (pre)syncope	Positive HUTT (even if potentiated) with cardioinhibitory (pre)syncope	Positive HUTT (even if potentiated) with cardioinhibitory (pre)syncope	Positive HUTT (even if potentiated) with cardioinhibitory (pre)syncope[4]
Inclusion: Drug refractoriness	Yes	Yes	No	Yes	Yes
Inclusion: Other cause of syncope	None	None	None	None	None
Primary endpoint	First recurrence of VVS	First recurrence of VVS	First recurrence of VVS	First recurrence of VVS	First recurrence of VVS
No. of patients	54 (19 male)	42 (24 male)	93 (38 male), 2 patients died during the study	100 (40 male)	29 (10 male)
Mean age	43 years	Pacing: 64 ± 11 years, reference: 56 ± 14 years	58.1 ± 14.3 years	Pacing: 50.8 years, placebo: 47.8 years	53 ± 6 years
No. of VVS episodes	4.5 in the last year	3 in the last 2 years	3 – 130 in lifetime	4 in the last year.	12 in lifetime
Randomization	Pacing: 27, reference: 27	Pacing: 19, reference: 23	Pacing: 45, reference: 46	Pacing: 48, placebo: 52	Pacing: 16, placebo: 13
Mean follow-up per patient	Not available, bul probably 1 year	44.4 ± 36.4 months	17.3 ± 8.7 months	6 months	23.4 months (median)
No. of patients with recurrence of VVS during follow-up	Pacing: 5 (19%), reference: 16 (60%)	Pacing: 1 (5%), reference: 14 (61%) with a mean of 2 episodes per patient during follow-up	Pacing: 2 (4%)[1], reference: 12 (26%)[2] with a mean of 2 episodes per patient during follow-up	Pacing: 16 (33%), placebo: 22 (42%)	Pacing: 50%, placebo: 38%
Mean time to first recurrence of VVS	Not available	Not available	Pacing: 390 days (at first at 360 days), reference: 135 days (at first ar 15 days)	Not available	Pacing: 97 days, placebo: 20 days
Positive HUTT during follow-up	Not available	Pacing: 59%, reference: 61%	Not available	Not available	Not available

Table 1. Study characteristics regarding the treatment of vasovagal syncopes (VVS). Vasovagal Pacemaker Study (VPS) [7], the Vasovagal Syncope International Study (VASIS) [11], the (Syncope Diagnosis and Treatment (SYDIT) [8] Vasovagal Pacemaker Study (VPS II) [9], and the Vasovagal Syncope and Pacing Trial (SYNPACE) [10] in chronological order of publication. HUTT = head-up tilt test.

causes the VVS [12,13]. In this context, it was hypothesized that a paced rate, with a response based on variations of myocardial contractility, may play an important role in preventing VVS. Since contractility is a cardiac control element integrated in the cardiovascular closed loop system, a pacemaker operating with messages that correlate with the course of inotropism will become an integral part of such a control system and will respond to the hemodynamic needs of the patient (and not to algorithms that are simply based on the appropriateness and/or evenness of the cardiac rhythm). Atrioventricular sequential pacing at a sufficiently high rate, induced by the increase of contractility that always happens during the first stage of vasovagal syndrome, may prevent exhaustion of the sympathetic tone and counterbalance the increase of vagal tone, preventing arterial hypotension, bradycardia, and even syncope.

Closed Loop Stimulation

The concept of Closed Loop Stimulation (CLS, Biotronik, Germany) [14] offers a therapy for rate-variable stimulation of the heart on the basis of the closed loop principle with a negative feedback. The pacemaker achieves the variations of intracardiac impedance on a beat-to-beat basis during the systolic phase of the cardiac cycle at the apex of the right ventricle. This happens through unipolar rheometry between the ventricular distal electrode (tip) of a standard pacing lead and the pacemaker housing (indifferent electrode). These variations are then converted into pacing rates. During ventricular systole, the blood/myocardium ratio in the volume around the tip changes. Since the specific resistance of the blood is about one-third of that of the myocardium, the impedance trend mirrors the ventricular contraction dynamics, which is expressed by the changes in myocardial contractility. Some clinical studies have demonstrated that variations of intracardiac impedance, as measured by CLS, are closely correlated to both the right and left ventricular maximal pressure gradient (dP/dt_{max}) [15,16]. Previous realizations of the CLS concept in the Inos^2 CLS and Inos^{2+} CLS pacemakers required persistent ventricular pacing. This limitation no longer applies to the new Protos DR/CLS dual-chamber and Protos VR/CLS single-chamber pacemakers (all Biotronik), thus also optimizing CLS therapy in order to avoid long term anatomical and electrical remodeling to the ventricles caused by their artificial activation.

The very promising results obtained after the first implantation of a CLS pacemaker in a patient suffering from malignant VVS (78 years, male, 2 positive HUTTs at basal conditions with Type 2A VVS), at the

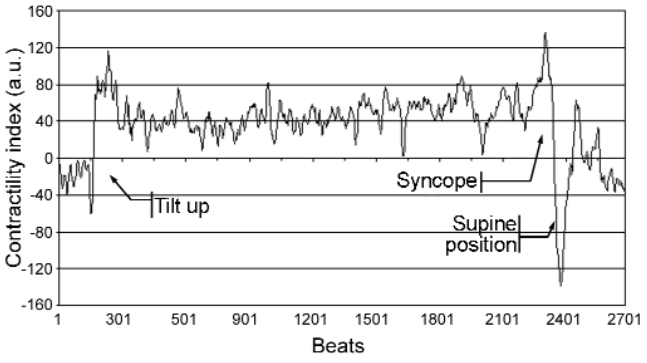

Figure 4. Myocardial impedance (contractility) monitored through telemetry of a CLS pacemaker programmed to DDD mode in a syncopal patient undergoing a positive head-up tilt test. At the beginning of the head-up tilt test the contractility increases, then vacillates around a stable, but still high value. Immediately before syncope, the contractility further increases and then suddenly drops at the time of syncope. It reverts to the basal value when the patient is placed in supine position. a.u. = arbitrary units.

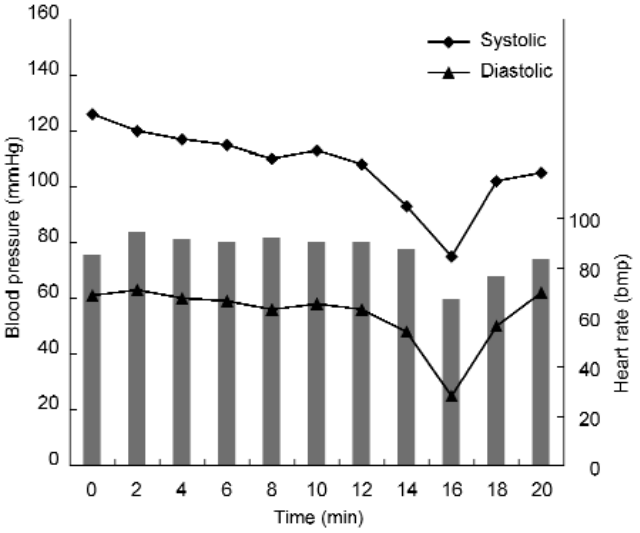

Figure 5. Systolic and diastolic blood pressure trends and heart rate histogram during head-up tilt test in a syncopal patient (same as in Figure 4) with the pacemaker programmed in the DDD mode.

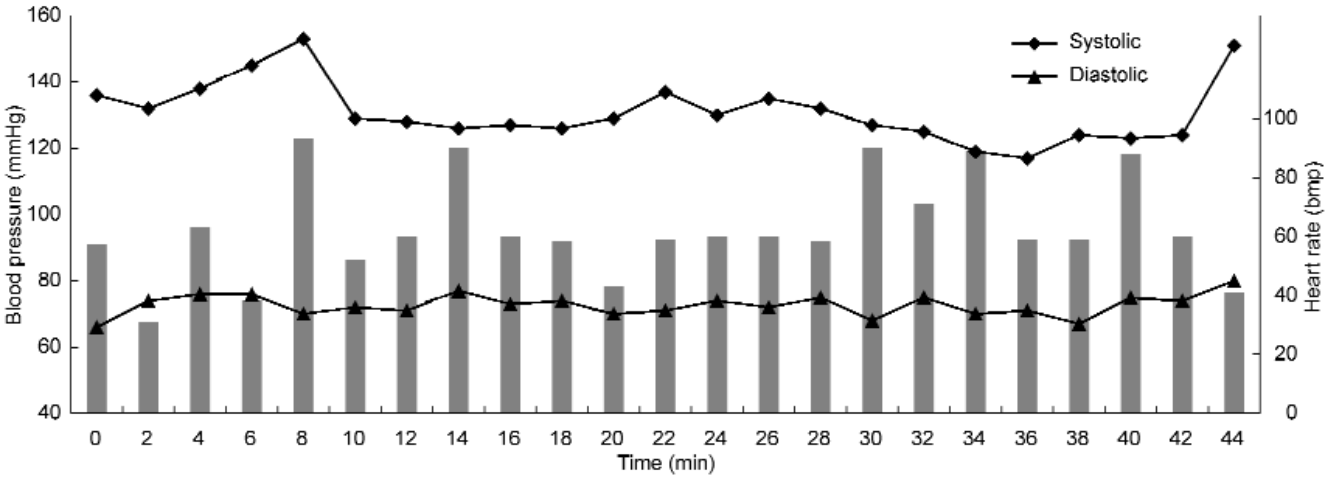

Figure 6. Systolic and diastolic blood pressure trends and heart rate histogram during head-up tilt test in a syncopal patient (same as in Figure 4) with the pacemaker programmed to DDD-CLS mode.

Cardiology Division of the Piemonte Orientale University in Novara, Italy [17] prompted the INVASY multicenter clinical investigation (Figures 4-6). The objective of this investigation was to verify the effectiveness of this new therapeutic approach on a wide population of patients suffering from recurrent VVS. The INVASY investigation took place in two separate and consecutive phases: first the Pre-INVASY registry [1] and then the INVASY study [2], all with similar characteristics for patient selection/inclusion and follow-up (Table 2). In July, 2001 the Steering Committee of the INVASY study decided to discontinue randomization due to the high clinical recurrence of VVS in the "placebo" arm.

Another "CLS in VVS" study was recently conducted by Griesbach, et al. [18] on a group of 22 patients suffering from malignant VVS. The authors concluded that CLS, which intervenes with a rate increase at the onset of a type 2A or 2B vasovagal spell, inhibits the syncopal episode. However, in type 3 VVS, in which the vasodepressive component is dominant, CLS can only limit the symptomatology to a presyncopal syndrome without loss of consciousness.

Peak Endocardial Acceleration in VVS Prevention

The Peak Endocardial Acceleration (PEA, Sorin, Italy) is an electric signal that reflects the maximum acceleration reached by the portion of the cardiac wall that is in contact with the ventricular tip electrode of a special pacing lead during the isovolumetric phase of cardiac contraction. To detect the PEA signal, the distal electrode has an integrated miniature accelerometer sensor located in a hermetically sealed chamber. The PEA corresponds to the mechanical vibration associated with the stress that the ventricular cardiac mass develops during the isovolumetric phase of contraction, known in phonocardiography as the "first heart sound." Clinical studies have demonstrated a close correlation between PEA and myocardial contractility (dP/dt_{max}) in both ventricles [19,20]. Consequently, the rationale of its use in preventing VVS is the same as that for CLS. The pacemaker records the amplitude of PEA on a beat-to-beat basis, and a dedicated algorithm converts these variations into pacing rates. In contrast to CLS pacing, which automatically adapts its response to patient needs, the PEA algorithm requires accurate programming of several parameters in order to supply a rate response suitable for each patient. The results of the "PEA in VVS" study using a PEA-VVS pacemaker (Sorin) in VVS [21] are shown in Table 2.

Discussion

The previous chapters provided a review of all the currently available therapeutic approaches and their effectiveness in the treatment of malignant VVS. To compare these methods, each therapeutic (or diagnostic) topic and its effectiveness in the various conditions will be discussed.

	Pre-INVASY	INVASY	PEA-VVS
Objective	Investigation whether DDD-CLS pacing reduces symptoms and recurrence of VVS	Investigation whether DDD-CLS pacing reduces symptoms and recurrence of VVS when compared to a "placebo" (DDI mode at a basic rate of 40 bpm)	Investigation whether DDDR driven by PEA reduces symptoms and recurrence of VVS compared to conventional pacing (DDI pacing at a basic rate of 70 bpm with 20 bpm rate hysteresis)
Pacemaker implantation	Yes	Yes	Yes
Design	Prospective registry	Prospective, randomized, controlled, single-blinded, crossover after the 2nd VVS recurrence or > 1 year "placebo."	Prospective, randomized, controlled, single-blinded, crossover (6 months)
Inclusion: Age	> 18 years	> 18 years	No limitation
Inclusion: Pregressed VVS	> 2 in the last year	> 2 in the last year	> 6 (> 1 in the last 6 months)
Inclusion: HUTT	2 positive HUTTs (at 15-day intervals) with cardioinhibitory (pre)syncope	Positive HUTT (basal or potentiated) with cardioinhibitory (pre)syncope	Positive HUTT with bradycardia
Inclusion: Drug refractoriness	Yes	Yes, no drug therapy during the study	
Inclusion: Other cause of syncope	None	None	None
Primary endpoint	Recurrence of VVS	Second recurrence of VVS	Recurrence of VVS or presyncope
No. of patients	34 (26 male), 5 had a previously implanted dual-chamber pacemaker that proved to be ineffective	50 (27 male), 2 had a previously implanted dual-chamber pacemaker with dedicated response that proved to be ineffective	23 (19 male)
Mean age	65 ± 10 years	Pacing: 59.0 ± 18.5, placebo: 58.3 ± 16.3 years	61.8 ± 15.2 years
No. of VVS episodes	6 (median) in lifetime (range from 3 to 20)	1.9 ± 0.9 in the last year (range from 2 to 10)	1.7 (pre)syncopes per month
Randomization	None	Pacing: 41, placebo: 9 randomization interrupted earlier	DDDR: 15 DDI: 8
Mean follow-up per patient	47.3 ± 8.0 months (range from 32 to 67)	Pacing: 18.9 ± 4.2 months, placebo: 12 months	6 months in each pacing mode
No. of patients with recurrence of VVS during follow-up	1 (2.9%) in a patients with chronic atrial fibrillation, 2 (5.8%) reported sporadic presyncopal symptoms	Pacing: 0 (0%)*, placebo: 7 (78%) 4 (2 VVS), 3 (1 VVS) * sporadic presyncopal symptoms: 4 (9.7%), occasional light dizziness: 2 (4.9%)	DDDR: 0 (0%) (0 VVS, 2 presyncopes) DDI: 4 (17%) (6 VVS and 4 presyncopes)
Mean time to first recurrence of VVS	Not available	Placebo only: 4 months (at first at 15 days)	Not available
Positive HUTT during follow-up	Not available	Pacing: 75%, placebo: 100%	Not performed

Table 2. Study characteristics regarding the treatment of vasovagal syncopes (VVS). Pre-INVASY registry [1], Inotropy Controlled Pacing in Vasovagal Syncope (INVASY) study [2], PEA-VVS study [21].

Syncopal Recurrences During Therapy

The reduction or suppression of syncopal recurrences is the main target of each therapeutic approach:

- Tilt training (TT) [22]
- Isometric arm-counter pressure maneuvers (IACPM) [23]
- Pharmacological treatment [4,8,24]
- Conventional pacing [7-11]
- Physiological pacing [1,2,18,21]

From Table 3 it is evident that only dual-chamber pacing driven by contractility variations allows the total suppression of recurrent malignant VVS. This is particularly relevant because this phenomenon was observed in a total of 92 patients in the three studies with CLS pacing listed in the table and in the 23 patients in the PEA study. To emphasize this result, the following should be pointed out:

- Drug therapy was not allowed in conjunction with pacing in the INVASY study;
- At the time of inclusion in the INVASY registry and study, seven out of 75 patients (9.3%) had an implanted dual-chamber pacemaker with a dedicated interventional algorithm that was ineffective in preventing VVS.

Pacing represents the last available solution for a patient suffering from malignant VVS, when psycho-physical training and/or pharmacological therapy has failed. It is almost impossible to compare the patients included in the various studies aimed at verifying TT, IACPM, or drug efficacy and the patients included in studies on pacing, because they differ substantially in age, baseline conditions, syncopal history, associated diseases, etc. As previously said, patients evaluated with TT were younger on average than those who were treated with pacing. IACPM patients were predominantly selected based on premonitory symptoms, while in pharmacological studies, the lack of control and, sometimes, the little evidence about the type of the treated syncopal recurrence, did not allow an appropriate meta-analysis of the data. In all cases, pacing driven by contractility has demonstrated its superior therapeutic benefit when compared to the other non-invasive approaches.

Studies conducted on conventional pacing [7-11], i.e., based on heart rhythm variations, have yielded controversial results in which it is unclear where the border lies between the benefit achieved by pacing and that caused by the placebo effect of surgery. This is because in type 2A and 2B VVS [11,25] the bradycardia/asystole and the associated hypotension develop very close together. Since the pacemaker must "see" the beginning and the stability of the bradycardia (DDD-RDR) or else it must wait until it reaches a hysteresis rate of 45 bpm (DDI-HYST), pacing may be insufficient to impede the syncope if the hypotension has become too high in the meantime. Conversely, CLS detects the variation of myocardial contractility that is known to occur at the beginning of the Bezold-Jarisch reflex and reacts with a rate increase after a mean time of 4 min from the onset of the HUTT, while the time required for syncope to occur is in between 19 [1,2] and 8.5 min [18]. This timely intervention suppresses the bradycardic effect and, thanks to the early increase of cardiac rate, counterbalances the hypotension induced by the decreased venous backflow with increased cardiac output. In cases in which the hypotensive component is abnormal and dominant, the patient may show presyncopal symptoms and dizziness at the peak of the neuromediated syndrome even if treated with CLS or PEA-based pacing.

DDDR pacing driven by PEA has been proven to have a response similar to that of CLS, because the guiding parameter (contractility) is the same in both systems. The only clinical investigation conducted with this pacing method shows that the PEA response is timely, but may at times allow presyncopal recurrence, as CLS pacing does.

The "placebo" effect caused by the positive psychological feeling a patient experiences from the mere implantation of a pacemaker has become a burning question in the expert community after the publication of the results of the VPS II study and the presentation of the SYNPACE study data. Because VVS is a neuromediated syndrome, it is logical to foresee that its occurrence in some patients may be influenced by psychological factors, and this effect should be taken into account. The SYNPACE study has shown that the placebo effect may influence up to 50% of patients implanted with an RDR device, while in a 12-month follow-up ("placebo" arm), CLS pacing has evidenced that this effect can be assessed in only 22% of treated patients. This is an additional demonstration of the superior efficacy of contractility-based versus rate-drop-based devices in preventing VVS.

Therapy	No. of patients	Follow-up (months)	VVS recurrence (%)		Author or study name
Tilt Training	38	43	18		Reybrouck, et al.
Isometric arm counter-pressure maneuvers	19	9	0.5		Brignole, et al.
Pharmacological	525	18.5	9		Benditt, et al.*
Pharmacological	23	44.4	60.9		VASIS (vasoconstrictors)
Pharmacological	46	17.3	26.1		SYDIT (beta-blockers)
DDD-RDR pacing	54	> 12	18.5		VPS
DDD-RDR pacing	45	17.3	4.3		SYDIT
DDD-RDR pacing	48	6	33		VPS II
DDD-RDR pacing	n.a.	23.5	50		SYNPACE
DDI-HYST pacing	19	44.4	5.2		VASIS
DDI pacing	23	6	17.4		Deharo, et al., PEA-VVS
DDD-CLS pacing	41	18.9	0	(9.7 presyncope)	INVASY
DDD-CLS pacing	34	47.3	2.9	(5.9 presyncope)	Pre-INVASY
DDD-CLS pacing	17	12.1	0		Griesbach, et al., CLS-VVS
DDDR-PEA pacing	23	6	0	(8.7 presyncope)	Deharo, et al., PEA-VVS
Placebo pacemaker	9	12	78		INVASY
Placebo pacemaker	52	6	42		VPS II
Placebo pacemaker	13	23.5	38		SYNPACE

Table 3. Possible typology of vasovagal syncope (VVS) recurrence during various therapeutic approaches: tilt training [22], isometric arm-counter pressure maneuvers [23], pharmacological treatment [4,8,24], conventional pacing [7-11], physiological pacing [1,2,18,21]. VVS classification type I, IIa, IIb, III according to [25].

Therapy	Type of VVS before therapy	Type of VVS during Therapy	Reasons for variation
Tilt training / isometric arm counter-pressure maneuvers	1, 2A, 2B, 3	1, 2A, 2B, 3	None, except orthostatic adaptation (reduction of vasodepressive component)
Pharmacological	1, 2A, 2B, 3	1, 2A, 2B, 3	None if the syndrome is drug-resistant (reduction of the vasodepressive or cardioinhibitory component depending on type and effectiveness of the drug)
DDD-RDR pacing	2A or 2B	1 or 3	Pacemaker intervention suppresses the cardioinhibitory component, and then recurrence is mostly of Type 3. If the algorithm takes to much time to intervene, Type 1 may occur.
DDI-HYST pacing	2A or 2B	1 or 3	Pacemaker intervention suppresses the cardioinhibitory component when the intrinsic rate reaches 45 bpm. A Type 1 or 3 syncopal event is possible.
DDD-CLS and DDD-PEA pacing	2A o 2B	Possible presyncopal (hypotensive) episodes	Pacemaker intervention always suppresses the cardioinhibitory component early on and partially counterbalances the vasodepressive element. Occurrence of presyncope and dizziness should be ascribed to a residual, decompensated hypotension.
Placebo pacemaker	2A o 2B	2A o 2B	None, except cases in which vasovagal syndrome is triggered by psychological conditions.

Table 4. Possible typology of vasovagal syncope (VVS) recurrence during various therapeutic approaches presented in Tables 1 and 2.

Typology of Syncopal Recurrence During Therapy

The literature is often incomplete or unclear about the typology of VVS during control HUTT or of VVS recurrence during therapy follow-up. The most severe types of malignant VVS, i.e., those that are associated with all resuscitating procedures and the majority of severe trauma, are the cardioinhibitory types 2A and 2B [11,25]), due to the more or less prolonged associated deep bradycardia or asystole. VVS of mixed (type 1 [25]) or vasodepressive (type 3 [25])] type are usually better tolerated by the patient. Table 4 illustrates what happens when a simple, logical process and a deductive analysis are applied when ascertaining the possibility of a certain type of syncopal event occurring during a particular therapy. In essence, pacing in general always modifies the type of VVS, reducing its severity. Conversely, pacing driven by contractility suppresses the recurrence of VVS, but rare hypotensive presyncopal symptoms may persist in some patients.

Statistical Reliability of Clinical Study Results

Malignant VVS does not recur at steady intervals. Periods of time in which a large number of spells occur may be followed by long periods (> 1 year) during which the symptomatology is totally absent. This aspect of the pathology is very important, as it may significantly affect the reliability of the results of clinical studies.
The only reliable tool we may use for this kind of evaluation is Table 5, which shows the probability of VVS recurrence one and two years after the diagnostic HUTT, drafted by Sheldon, et al. and based on the observation of patients not subjected to any therapy [26]. We can roughly evaluate the statistical reliability of the cited studies (for those where all necessary data was available) using this table, assuming the following:

- Each patient who exhibited syncope had only one recurrence during follow-up;
- The control HUTT had no relevance to the possible recurrence (TT effect);
- The effect of drugs, if administered, has no influence on the observed therapy (if not purely pharmacological).

As we can see in Table 6, almost all the cited studies yielded reliable results. Doubts remain for pharmacological studies in general, which were excluded from this analysis. A follow-up period of less than 1 year may allows some concern in the full acceptance of the outcome VVS recurrence as a statistically reliable data. In the VPS II [9] and the PEA-VVS [21] studies, the follow-up period was shorter. However, in the VPS II, the VVS occurrence at 6 months was so close to the probability of recurrence calculated by Sheldon (Table 5) that it may be considered as reliable in the first instance; in the PEA-VVS study, the intra-individual comparison (crossing over of pacing modes) resolves the problem.

Costs of Malignant Syncope Therapy

As discussed in previous chapters, conventional therapy often decreases the recurrence of syncope and the severity of symptoms for patients suffering from malignant VVS but does not prevent the risk of recidivation, which is sometimes accompanied by severe physical injuries. Holding equal for each patient the costs to diagnose the nature of syncopal spells, the following presents a comparison of the costs of managing a patient treated with conventional therapy (drug therapy) and CLS pacemaker implantation in the year 2002 [27] based on the Italian Social Security reimbursements (Diagnosis Related Groups, DRG).

Pharmacological Treatment
For a patient who is being administered optimal drug therapy, we can forecast a single syncopal recurrence per year. We can estimate the costs related to regular and emergency medical care (specific to this pathology) over a period of 10 years. Table 7 provides a summary of these estimated costs.

Total no. of pregressed VVS before HUTT	Risk at 1 year	Risk at 2 years
1	0.10	0.10
> 2	0.36	0.49
> 3	0.40	0.54
> 4	0.43	0.59
> 5	0.41	0.57
> 6	0.43	0.60

Table 5. Probability of spontaneous vasovagal syncopal (VVS) recurrence after diagnostic head-up tilt test (HUTT) in patients with a history of syncope [26].

Study	Mean follow-up (years per patient)	VVS recurrence at 1 year (reference)		VVS recurrence at 2 years and beyond (reference)	
Tilt training	3.6	-	-	0.18	(0.54)
Isometric arm counter-pressure maneuvers	0.9	0.005	(0.40)	-	-
VPS (pacing)	> 1	0.185	(0.43)	-	-
VASIS (pacing)	3.7	-	-	0.052	(0.54)
VASIS (drug treatment)	3.7	-	-	0.608	(0.54)
SYDIT (pacing)	1.48	0.021	(0.40)	-	-
SYDIT (drug treatment)	1.48	0.261	(0.40)	-	-
VPS II (pacing)	0.5	> 0.33	(0.43)	-	-
VPS II (ODO placebo pacing)	0.5	> 0.42	(0.43)	-	-
SYNPACE (pace)	1.36	0.50	(0.40)	-	-
SYNPACE (placebo)	1.36	0.29 – 0.50	(0.40)	-	-
PEA-VVS (PEA pacing)	0.5	0	(0.43)	-	-
PEA-VVS (DDI pacing)	0.5	> 0.17*	(0.43)	-	-
INVASY (pacing)	2.3	-	-	0	(0.54)
INVASY (placebo)	1	0.78	(0.40)	-	-
CLS-VVS (CLS pacing)	1	0	(0.43)	-	-

*Table 6. Reliability of the studies cited in Table 3, in accordance with data in Table 4. Reference values in parentheses are the estimated recurrences of vasovagal syncopes (VVS) in the observation period determined from the patient inclusion criteria and Table 5. *Recurrence calculated for syncopal episodes only.*

Physiological Pacing Treatment

Now, consider the same patient implanted with a cardiac pacemaker set to optimally treat VVS (with CLS). In this case, syncopal recurrence is prevented, and drug therapy loses any relevance. The estimated costs for the patient's regular and emergency medical treatment (specific to this pathology) over a period of 10 years are shown in Table 8. Since pacemaker intervention is expected only for short periods of time for these patients (during syncopal spell occurrence), an expected service life of 10 years is reasonable. Comparing the totals of the two tables we can see that pacing therapy not only yielded more favorable results for the patient, but also amounted to a savings of 3,000 Euro for medical costs over a period of 10 years. In the U.S., experts in health services management consider an additional cost of up to 20,000 USD for additional therapy that increases the cost-benefit ratio (even in terms of quality of life) as "very attractive" [28]. Moreover, there are additional social costs – ones that cannot be ascribed a financial figure – linked to the material and psychological damage that malignant VVS causes to the community and to the patient, such as loss of productivity, inability to drive or in engage in daily activities, and limitation in functional and social activities.

Conclusion

For some time now, malignant vasovagal syncope has been of clinical interest due to its complex and sometimes unknown etiology as well as the great difficulty encountered in suppressing, or at least lessening, its often severe physical and psychological consequences. Mild forms of the disease can be treated with proper diet and psychological education, while moderate cases may be treated with psycho-physical training or drug therapy. In the last decade, cardiac pacing has been increasingly used to treat the most serious cases of VVS – those that are refractory to conventional therapy and are associated with protracted asystolic periods – which requires emergency medical intervention for resuscitation procedures or to repair physical traumas caused by the syncopal spell. In this context, CLS, whose rate response is driven by variations of myocar-

Medical treatment	Cost (€)
Full dosage of beta-blocker therapy (athenolol, 100 mg/day)	832.20
Routine in-patient follow-up (20 exams in 10 years)*	1,058.80
Emergency room visits (10 visits in 10 years)	206.60
Hospitalization for mild/light cranial or bone traumas (2 incidents in 10 years)**	4,662.51
Hospitalization for cranial trauma with coma (1 hospitalization in 10 years)	4,862.31
Total	**11,622.42**

*Table 7. Estimated costs for conventional treatment of malignant vasovagal syncope. *follow-up includes: cardiologic ambulatory check with surface ECG every 6 months and an annual control head-up tilt test; **cranial trauma without coma and/or a bone fracture of an appendage treated in out-patient surgery.*

Medical treatment	Cost (€)
Implantation of a dual-chamber CLS pacemaker	7,722.20
Routine pacemaker follow-up and surface ECG (12 in 10 years)	418.32
Unexpected in-patient exams (3 in 10 years)*	553.14
Total	**8,693.66**

*Table 8. Estimated costs for pacemaker treatment for malignant vasovagal syncope. *Including cardiological examinations, 24-hour Holter recording, ECG, and control head-up tilt test.*

dial contractility, seems to be an optimal solution. All the clinical studies that have investigated syncopal recurrence with this pacing approach have yielded very favorable results, even in long-term application. Patients paced with CLS did not exhibit a syncopal recurrence, and all were able to increase their quality of life and adopt a lifestyle appropriate to their age and abilities. The main disadvantage of CLS having a larger diffusion as the treatment of choice for these patients, who are often young and healthy from the cardiovascular point of view, was the need for persistent ventricular pacing to assure the full performance of the rate-control algorithm.

But new scientific and technological advances are continually offering new solutions. Presently, the disadvantage of CLS, i.e., the need for persistent ventricular pacing, is eliminated with the introduction of a new family of CLS-based devices, which are optimizing CLS therapy even in patients with intrinsic activation of the ventricle. These factors are very important for the improvement of syncope therapy.

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Contact
Dr. Eraldo Occhetta
Divisione Clinicizzata di Cardiologia
Azienda Ospedaliera "Maggiore della Carità"
Corso Mazzini 18
I-28100 Novara
Italy
Phone: +39 0321 373 34 13
Fax: +39 0321 373 34 07
E-mail: cardio1@maggioreosp.novara.it