Malignant Vasovagal Syncope: Physiopathology, Diagnosis, Epidemiology, and Medical Treatment

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Summary

This review provides a brief summary of the physiopathology of vasovagal syncope, followed by a discussion of diagnostic methods, in particular the Head-up Tilt Test and the Implantable Loop Recorder. The epidemiology and management of syncope is discussed from the point of view of recently conducted by the Evaluation of Guidelines in Syncope Study (EGSYS) Italian group. The EGSYS data may be helpful for understanding the clinical relevance of neuromediated syncopal spells in Italy and how they are managed in variously structured hospital environments. In addition to the brief overview of the pharmacological options for the treatment of vasovagal syncope, the recent clinical experiences with alternative advanced therapeutical approaches such as tilt training and isometric arm counter-pressure maneuvers are briefly presented and discussed.

Key Words

Malignant vasovagal syncope, head-up tilt test, implantable loop recorder, drug therapy

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] – provided us incentive to prepare a review entitled "Malignant Vasovagal Syncope." The review provides an updated review of topics related to VVS and efforts made by the medical community and biomedical industry to find effective therapeutic solutions for it.

The contents of the review will be divided into two parts. This present first part addresses clinical aspects and medical treatment of VVS. The second part, to be published in the December issue of this journal, will analyze the clinical benefit of conventional cardiac pacing (and of its special form CLS), compare the efficacy of all available therapies, and draw conclusions.

Physiopathology of VVS

In susceptible subjects, the part of the autonomous nervous system that regulates the cardiovascular system may react in an uncoordinated manner when a sudden increase of efferent vagal activity is associated with an equally sudden decrease or block of the previously increased sympathetic flow. This results in a significant decrease of the heart rate (bradycardia) – induced by an increase of the vagal tone – and concomitant hypotension from arterial vasodilatation – caused by a decrease of the sympathetic tone. This phenomenon is called VVS (also referred to as neurocardiogenic or neuromediated syndrome, because the usual cause for the syncope stems from the nerves of the heart).

Although not all pathophysiologic mechanisms linked to this phenomenon are known, it is believed that the Bezold-Jarisch reflex, activated by inappropriate stimulation of the mechanoreceptors located inside the left ventricle, is primarily responsible for this phenomenon (Figure 1) [3,4].

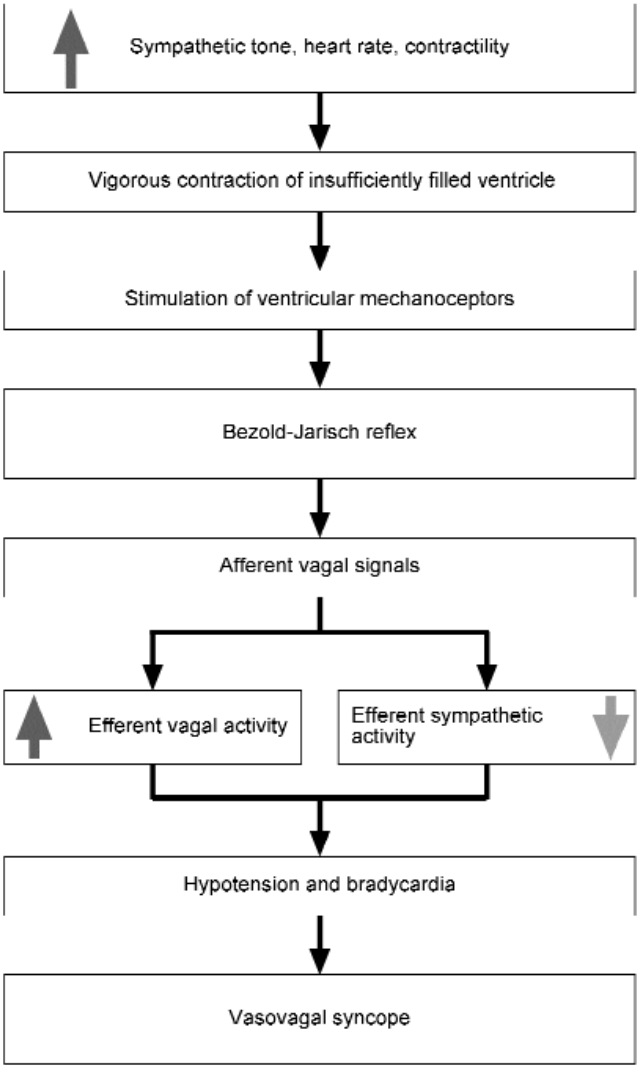


Figure 1. Activation mechanism of the Bezold-Jarisch reflex. Actually, this is a "clinical adaptation" of the true Bezold-Jarisch reflex, which is induced by a coronary chemoreceptor and baroreceptor reflex with vagal afferent and efferent activity (bradycardia and hypotension) caused by a drug infusion (veratridine or nicotine) in the coronary arteries of the left ventricle. It is believed that the Bezold-Jarisch reflex is triggered by a chemical stimulation of the mechanoreceptors located in the wall of the left ventricle.

There are two types of VVS, central and peripheral VVS. In the central type, the medullary centers controlling the cardiovascular system are directly influenced by efferent signals coming from the hypothalamus and generated by emotional stress, pain, fear, or dehydration. In these cases there is an increase of vagal activity, which induces hypotension, bradycardia, and lypotimia, which consequently triggers the syncopal spell. Conversely, in the peripheral type the central blood volume is reduced by a paradoxical dilatation of peripheral vessels, with a blood sequestration inside the venous network. The reduced central venous backflow activates an increase of the compensatory sympathetic tone and consequently of the heart rate and the contractile status (inotropy) of the left ventricular myocardium. The vigorous contractions of the insufficiently filled ventricle cause an increase of the intracavity blood pressure, which activates the mechanoreceptors located in the basal portions of the ventricle. These conditions, which mimic those observed during hypertension, inhibit sympathetic activity and induce vagal effects with resulting peripheral vasodilatation and reflex bradycardia. The VVS spell has three subsequent symptomatologic phases:

- Presyncope, or aura, with premonitory symptoms (dizziness, mental confusion, weakness, sweating).
- Loss of consciousness, with possible convulsions caused by the disinhibition of cerebral cortex activity caused by anoxia (oxygen deprivation).
- The post-syncopal period, usually characterized by the recovery of consciousness and orientation, but with persistent weakness for the entire day, nausea, cephalea (edema of the head), and seizures.

In some patients, the presyncopal phase is almost absent, with a fast loss of consciousness without a warning aura (drop attack). In patients with a mild pathology, the symptoms are limited to presyncope without loss of consciousness. The majority of patients rarely experience VVS. In exceptional circumstances (with central type VVS), the symptoms can be intense but of short duration. In these cases, the VVS is benign, and medical therapy is not necessary. These symptoms can be remedied with diet, exercise, and psychological training.

A different picture is presented by recurrent and severe VVS that is accompanied by significant hypotension and bradycardia, which may cause prolonged asystole (from 3 s to more than 60 s). In these cases, the VVS is malignant, and can cause a serious physical injury (e.g., cranial trauma or bone fractures following a fall or an accident) and psychological impairment, including a substantial limitation of the patient's social and working life. For these cases medical therapy is mandatory, which can take the form of physical training, medication, or cardiac pacing.

In general, VVS is a common pathology found in all ages of the population. However, its recurrence and incidence increase with age due to physiological changes in the neuro-cardiovascular, endocrine, and renal systems caused by the aging process.

Diagnosis of Syncope

Syncope is the result of several phenomena connected to underlying functional pathologies or anomalies. The origin (etiology) of syncope may be one of the following: cardiac (arrhythmic, caused by obstruction of blood flow or serious pumping defect); neuromediated or reflexed (vasovagal, situational, or visceroreflexed, carotid sinus, orthostatic, idiopathic, secondary); cerebrovascular; neuropsychiatric; metabolic; or of unknown origin [5]. When a patient is hospitalized for a syncopal episode whose origin is unknown, a battery of examinations and tests must be conducted. These include the following:

- Neurological examination (supra-aortic trunk Doppler ultrasonography, electroencephalogram, cranial computed tomography, neurological/psychiatric tests) to exclude a central origin of the syncope;
- Cardiological examination (vagal stimulation mainly using carotid sinus massage, 24-hour Holter ECG recording, echocardiogram, transesophageal stimulation, and electrophysiologic study/EPS) to exclude disturbances of cardiac conduction pathways or vasodepressive and/or cardioinhibitory syncopes of a non-neuromediated nature.

In the majority of cases, a blood and urine analysis and accurate evaluation of disease history exclude all behavioral, toxicological, and metabolic causes.

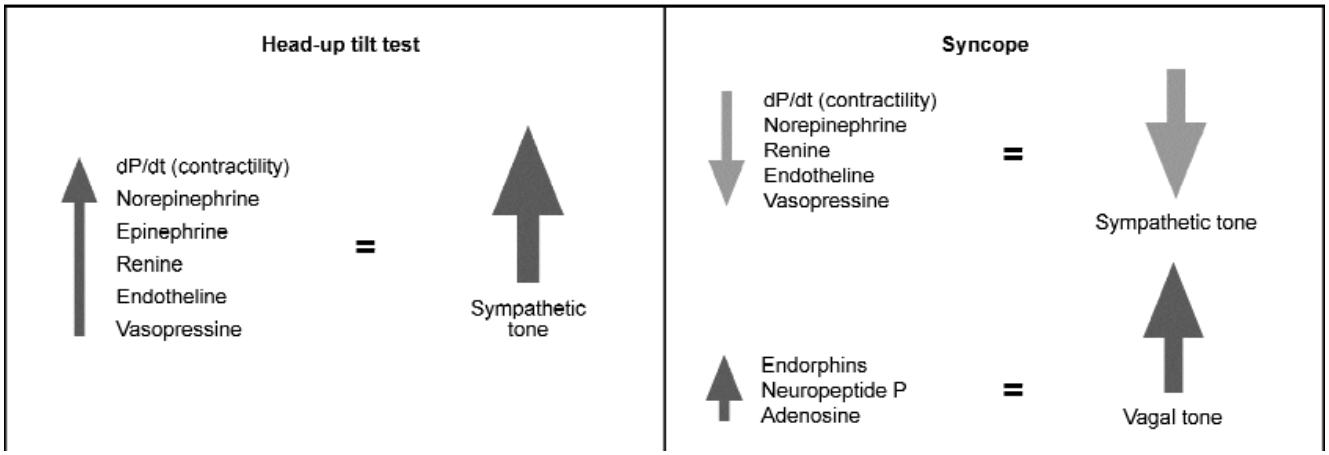
Head-Up Tilt Test

If the results of all the above-mentioned tests are negative, then the neuromediated origin of syncope can be assessed by means of the head-up tilt table test (HUTT) [6], or orthostatic test at the tilt table. During the HUTT, the patient is placed on a tilt table in the supine position and the heart rate and arterial blood pressure are measured. Then the patient is rapidly brought to the upright position by rotating the table to an angle of 60°, and the heart rate and blood pressure are monitored for 45 min, or until syncopal symptoms appear. At this point the table is returned to the horizontal position. When the HUTT is performed under the conditions described above, it is defined as a basal tilt test (Westminster protocol). If the basal HUTT is negative, its sensitivity can be increased by administering 300 μg of nitroglycerin by sub-lingual spray (Italian protocol) to promote peripheral vasodilatation [7], or by administering isoproterenol (infusion of 1 – 5 μg/min) to increase the contractile response and induce the Bezold-Jarisch reflex. This type of HUTT is defined as a potentiated tilt test. The HUTT is positive when a syncopal or presyncopal episode follows hypotension (associated with bradycardia/asystole for malignant VVSs or syncopes caused by alteration of the conduction system of the heart).

Studies that measured the variation of circulating cathecolamines during HUTT have shown that the symphatetic system reacts differently in patients with abnormal vagal reflex than in patients with normal vagal response (control group). During HUTT, the level of norepinephrine (vasoconstrictor properties) increases equally in the two groups. However, the level of epinephrine (vasoconstrictor and antiarrhythmic properties) in pathologic subjects increases until it reaches five times the basal value during syncope. During the first minutes of the test and before syncope, the simultaneous increase of renine (hypertensive properties), endotheline (vasoconstrictor properties), vasopressine (antidiuretic and hypotensive properties), and of myocardial contractility testifies to an increase of the symphatetic tone. The total amount of epinephrine and norepinephrine, which are essentially secreted by the adrenal medulla, promotes the inhibition of sympathetic neuronal activity. Therefore, the following occurs:

- A sudden decrease of the sympathetic tone at the time of syncope, as shown by a decrease of myocardial contractility, norepinephrine, renine, endotheline, and vasopressine); as well as an
- An increase of vagal tone, evidenced by the increase of the level of endorphins (analgesic properties), neuropeptide-P (properties similar to those of endorphins), and adenosine (Figure 2).

The VVS is later classified based on its response to the HUTT, in terms of variations in heart rate and arterial blood pressure [8]. This classification is summarized in Table 1.



a b

Figure 2. Course of cathecolamine concentration at the beginning of head-up tilt test, a) and during syncope, b).

Classification	Heart rate	Arterial blood pressure
Mixed (Type 1)	Rises during HUTT; falls at the time of syncope, but stays > 40 bpm or falls < 40 bpm for an interval < 10 s; with or without asystole for < 3 s	May rise during first part of HUTT; falls before the heart rate falls
Cardioinhibitory without asystole (Type 2A)	Rises during HUTT; falls to < 40 bpm for a period > 10 s; possible asystole, but for < 3 s	May rise during first part of HUTT; falls before the heart rate falls
Cardioinhibitory with asystole (Type 2B)	Rises during HUTT; asystole occurs for > 3 s	Falls at the time or before the heart rate falls
Vasodepressive (Type 3)	Rises during HUTT; falls at the time of syncope by ≤ 10% in respect to its peak level	Decreases by > 60% in respect to basal value

Table 1. Classification of vasovagal syncope versus response to head-up tilt test (HUTT) [8].
Exception 1: Chronotropic incompetence. No rise of HR during HUTT or rise < 10% from pre-tilt rate.
Exception 2: Excessive HR rise. HR rises at > 130 bpm both at the onset and throughout duration of HUTT before syncope.

Implantable Loop Recorder

The Implantable Loop Recorder (ILR, Medtronic, USA) is a relatively new diagnostic tool that can help assess the causes of syncope whose origin cannot be diagnosed using conventional approaches. This device is implanted in the subcutaneous pectoral region and monitors the rate and rhythm of the heart. The ILR can record and store in its memory several ECGs of anomalous cardiac rhythm episodes. Recording may be started automatically (using a programmable algorithm) or manually by the patient (based on symptomatology). The stored information can be telemetrically interrogated using an external programmer for purposes of a data analysis. The following two studies illustrate the usefulness of the ILR.

The first study is a combined Spanish/Dutch study, presented at the last European Society of Cardiology congress [9]. Between 1998 and 2000, 26 patients with syncope of unknown origin were implanted with ILR and instructed about its manual activation. All patients had shown negative results in cardiological tests (ECG, carotid sinus massage, 24-hour Holter recording, echocardiogram, and EPS). Five patients had recently experienced physical trauma following a syncopal episode. Due to the high incidence of syncopal symptoms, the investigators did not consider the HUTT results in their decision of whether or not to implant the device. During the follow-up (14 ± 5 months), 16 of the 26 patients activated the device for a total of

44 events. True syncope was verified in 10 patients (38% of events). The ILR showed that in 5 of the patients the heart rate decreased and was followed by asystole and syncope, suggesting neuromediated syncope. In these patients, who were later all implanted with a pacemaker, the preliminary cardiological tests showed the following: previous inferior myocardial infarction (1 patient), chronic AF (1 patient), right bundle-branch block, left anterior fascicular block (1 patient), Holter recorded nocturnal pauses < 2 s (1 patient), and a normal screening (1 patient). In the remaining 5 patients with syncope, no recurrence of cardiac arrhythmia was documented. Of these 5 patients, 2 had epilepsy (documented during an additional neurological screening) while in the remaining 3 patients the origin of syncopal spells remained unknown after all diagnostic tests had been conducted. It is interesting to note that the HUTT had positive results for 5 of the 16 patients who did not report syncopal recurrence during the follow-up, but had negative results for 9 of the 10 patients who experienced true syncopal episodes during the follow-up. The EPS was normal for all patients, and arrhythmia could not be induced in anyone, despite the structural cardiac diseases affecting some of the patients.

The second multicenter study is the ISSUE (International Study on Syncope of Uncertain Etiology) [10-12]. Between November 1997 and July 2000, 164 patients with syncopes of unknown origin were investigated with the aid of an ILR. There were three patient sub-groups:

- 82 patients without structural cardiopathy, with normal ECG and negative conventional diagnostic tests, including HUTT;
- 29 patients without structural cardiopathy and negative conventional diagnostic tests, but positive HUTT;
- 53 patients with bundle branch block and EPS evaluation of subnodal conduction within normal limits.

The diagnostic results of the ILR were very similar in the first two sub-groups, with a 34% incidence of syncopal recurrence (28/82 patients with negative HUTT and 10/29 patients with positive HUTT). Almost one half of the patients who experienced a syncopal recurrence (46% in the first sub-group and 62% of the second sub-group) exhibited a neuromediated pattern: one or more prolonged asystolic pauses, preceded by a few minutes of progressive bradycardia or tachy-bradycardia. A small percentage of patients (8% – 12%) experienced only sinus bradycardia, while about one-third of them presented a normal rhythm or sinus tachycardia during syncope. It is interesting to note that, as with all presyncopal episodes whose recording was activated by the patient, there were no asystolic pauses. In the patients without structural cardiopathy and with negative diagnostic tests, the ILR confirmed a neuromediated origin of about one-half of the syncopal recurrences and an extra-cardiac origin of the other half. In these cases, the predictive capability of the HUTT seems to be quite limited, as substantially similar results were found in the first and second sub-group of patients. In the sub-group with intraventricular conduction disturbances, the incidence of syncopal recurrence was 37% (19/53 patients). In almost all of the cases of recurrence (17/19 patients) the event could be attributed to a total AV block. In these cases, the ILR confirmed that the EPS performed to evaluate the subnodal conductive system has a poor predictive capability for patients with a clear intraventricular conduction disturbance and syncope. Prophylactic pacemaker implantation may be the best therapeutic option for such patients.

Epidemiology and Management

The clinical investigators of the Evaluation of Guidelines in Syncope Study (EGSYS) Italian group conducted some demographically-oriented pilot studies to determine guidelines for the management of patients admitted to the hospital emergency room due to a neuromediated syncopal spell [13,14]. The data collected during these recent studies may be helpful for understanding the clinical relevance of this pathology in Italy and how it is managed in variously structured hospital environments.

The first study (a prospective observational registry conducted between 11/5 and 12/7, 2001) provides an epidemiological picture about the cases seen at the emergency rooms of 28 major Italian hospitals [13]. All patients experienced a temporary loss of consciousness as the primary symptom. The occurrence of syncope was proven in 0.95% (996/105,173) of the admitted patients; 46% of these patients were hospitalized, mostly in the Internal Medicine Department. The mean in-patient period was 8.1 ± 5.9 days, with a mean of 3.48 diagnostic procedures per patient. Exact diag-

nosis was possible in 80% of cases, with neuromediated syncope being identified as the most frequent cause of loss of consciousness. An individual data analysis for each of the 28 hospitals indicated great dishomogeneity in terms of emergency room admission statistics, hospitalization department, diagnostic screening, and final diagnosis. For example, the percentages of carotid sinus massage ranged from 0% at one hospital to 58% at another (mean 12.5%); the HUTT ranged from 0% to 50% (mean 5.8%); the final diagnosis of neuromediated syncope ranged from 10% to 78.6% (mean 43.3%). The investigators' conclusion was that there is no standard procedure for syncope management at Italian hospitals.

The second study tested the hypothesis that syncope management may be influenced by the existence or lack of a "dedicated" Syncope Unit (SU) in hospitals [13]. Data obtained from 6 hospitals with a dedicated SU (as a sector of the Cardiology Department), were compared with data collected from another 6 hospitals without a dedicated SU. The methods, enrolment criteria, and observation period were the same as those of the first study (previous paragraph). There were 279 patients admitted at hospitals with an SU and 274 patients admitted at hospitals without an SU. At the "SU hospitals," 30 patients (11%) were referred to the SU for clinical evaluation. There were 12% fewer hospitalized patients at the SU hospitals than at the non-SU hospitals (43% vs. 49%), and the amount of diagnostic tests performed was 8% less (3.23 vs. 3.59 per patient). In particular, fewer laboratory tests (75% vs. 86%) were performed at SU hospitals, as were fewer cerebral CAT scans (17% vs. 24%), fewer echocardiograms (11% vs. 16%), more carotid sinus massages (13% vs. 8%), and more HUTT testing (8% vs. 1%). At these hospitals, the rate of diagnosis for neuromediated syncope was greater than at non-SU hospitals (56% vs. 36%). The investigators' conclusion was that standardized diagnostic procedures performed at the SU can substantially influence the screening and management of syncopal patients.

The third study carefully analyzed data collected from three SUs [13]. The investigators analyzed the data of 308 patients (mean age 61 ± 20 years; mean of 3 syncopal episodes per patient) admitted to SUs that all followed standardized procedures for diagnostic testing and final diagnosis (the guidelines for the diagnosis of syncope suggested by the ESC). In short, all patients underwent an initial evaluation based on their anamnesis, a physical examination, their arterial blood pressure (in supine and upright positions), and a surface ECG (this last test was performed for patients who were over the age of 45 or who had a history of cardiac disease). Any subsequent tests were based on the results of the initial evaluation. Priority was assigned to cardiological screening (ECG, Holter recording, stress test, EPS) and neuromediated tests (carotid sinus massage, HUTT, adenosine thriphosphate/ATP test); a neuropsychiatric evaluation was only performed if necessary. The initial evaluation alone proved a correct diagnosis in 72 patients (23%). One additional test was necessary to accurately diagnose 65 patients (21%), two additional tests were necessary for 64 patients (21%), and three additional tests were needed for 50 patients (16%). The diagnostic yield was 10% for the ECG, 3% for the echocardiogram, 16% for the Holter recording, 5% for the stress test, 27% for the EPS, 57% for the carotid sinus massage, 52% for the HUTT, and 15% for the ATP test. At the end of the diagnostic procedure, the cause of syncope still remained unknown in 57 patients (18%). The investigators concluded that a few simple tests are sufficient for a correct diagnosis of syncope, if a proper standardized procedure is used.

Medical Therapy

At present, the therapeutic approach to HUTT-induced VVS with vasodepressive response is influenced by the rate of reoccurrence and seriousness of symptoms. For patients whose syncopal recurrence is sporadic and caused by physical or emotional situations, therapeutic measures are mostly behavioral and include the following:

- Correct information about the benign nature of the syncope to reassure the patient;
- Avoidance of triggering factors, such as staying in an upright position for a prolonged period of time (especially in humid environments), dehydration, and stressful situations;
- Timely recognition of prodromes, with the patient immediately lying down to promote termination of the syncope, thus avoiding serious physical injuries;
- Diet (abundant consumption of liquids and salts) and exercise (moderate physical exertion);
- Use of elastic stockings;
- Specific physical exercises (isometric muscular activity of the superior and/or inferior limbs) done

by the patient when in upright position or during risky situations (e.g., coughing, minction, defecation, stressful situations, etc.).

In cases where VVS occurs more frequently and is highly symptomatic, the problem must be addressed with great care. In particular, the following patients should receive therapy:

- Patients with frequent recurrence of syncope, with early syncopal recurrence following the HUTT;
- Patients with so-called "malignant VVS," i.e., syncope without prodromes, which frequently causes serious trauma;
- Patients with professions where syncope poses a serious problem (taxi and bus drivers, pilots, etc.);
- Patients with syncopes occurring when they are seated, but who need to drive a car;
- Patients with serious forms of ischemic cardiopathy or cerebral vasculopathy, which may be worsened by frequent syncopal spells.

An advanced therapeutic approach may include psycho-physical training, and/or drug therapy.

Tilt Training

Tilt training (TT) is a therapeutic approach first proposed in 1997 by a team of cardiologists at the University of Leuven in Belgium [15]. TT is based on a simple procedure that helps the patient get accustomed to assuming a sudden upright position; the objective is to progressively decrease the intensity of the autonomous nervous system's abnormal response to the Bezold-Jarisch reflex. This procedure consists of two phases:

- During hospitalization, the patient undergoes a daily HUTT under basal conditions, and remains in an upright position until the symptoms of a syncopal spell or severe orthostatic intolerance become evident.
- Upon discharge, the patient is instructed to continue his exercises on a daily basis (or at least 3 times per week). The exercise consists of the patient standing up and remaining in an upright and static position, with shoulders leaning against a wall and feet placed 15 – 30 cm apart (simulated HUTT) for a period of at least 30 min. This exercise should be performed one or two times during the same session, depending on severity of the syncope. TT should be done for a period of at least one year. If a syncopal recurrence occurs after the end of the training period, TT must be repeated for another year period.

During TT, the patient's syncopal response is periodically tested by means of an ambulatory HUTT. To avoid possible risks during at-home training, it is advisable to invite members of the patient's family to attend TT sessions while the patient is in the hospital, so that they can be educated about how to help the patient perform his exercises. The ability to engage in such a long and complex therapeutic procedure mostly depends on the physical and psychological attitude of the patient. Young patients, even those with a strong symptomatology but who have never experienced physical injuries during a syncopal spell, will have a more positive attitude and will be more motivated to perform TT than elderly patients who have undergone surgery or who have sustained injuries due to falls or incidents caused by loss of consciousness following a syncopal event.

It may be of interest to report the results of a recent study conducted by the Leuven cardiology team on syncopal patients who engaged in TT for a long period of time [16]. In total, 38 patients (mean age 35.8 ± 20.5 years, range 6 – 76) were studied. The types of syncopes observed during HUTT were as follows: vasodepressive in 17 patients, cardioinhibitory in 13 patients, and mixed types in 8 patients. The study inclusion criteria were recurrent neurocardiogenic syncope and positive HUTT response under basal test conditions. The number of syncopal spells before hospitalization varied from > 10 per day in 1 patient, > 3 per day in 2 patients, > 1 per week in 6 patients, > 3 per month in 5 patients, > 1 per month in 4 patients, and > 2 in a total of 20 patients. The adopted TT procedure during the study was the same as the one previously described in this review. The mean follow-up time was 43 ± 7.8 months with a control ambulatory HUTT performed at 6 weeks, 3, 6, and 12 months after discharge. During hospitalization, the diagnostic HUTT was positive after 21.4 ± 13.4 min. In patients with vasodepressive VVS, positive results occurred after 24.5 ± 14.0 min, in patients with cardioinhibitory VVS, after 15.5 ± 9.4 min, and in patients with mixed VVS, after 25.1 ± 15.4 min. After 43 months of mean follow-up, 29 patients (76%) had abandoned TT, with only 9 (24%) continuing to exer-

cise on a regular basis. During follow-up, a total of 7 patients (18%) showed at least 1 syncopal recurrence. Thirty-one patients (82%) did not experience any further syncope; of those patients, 25 were asymptomatic, whereas 6 (19%) still experienced presyncopal symptoms. Further investigation proved that 6 of the 7 patients who exhibited syncopal recurrence had abandoned TT after one year. Investigators wish to stress that 19 of the patients (50%) who had abandoned the TT after one year did not experience syncopal spells during daily life activities.

The results of this study are very interesting, but two other relevant pieces of information should be stressed. First, the majority of patients included in the above study were relatively young (66% < 45 years), and second, a similar study performed in Italy by the "Task Force on Syncope" reported a 35% syncopal recurrence in patients observed for a follow-up of 3 years.

Isometric Arm Counter-Pressure Maneuvers

Isometric Arm Counter-Pressure Maneuvers (IACPM) [17] is a recent therapeutic approach to impede VVS and prevent the patient from losing consciousness. The basic concept is that a hypotensive status is always present during the prodromal phase preceding the syncope and is caused by peripheral vasodilatation due to the inhibition of sympathetic vasoconstrictive activity. This status can be experienced by most patients during the "aura" of a spontaneous vasovagal spell. IACPM is a combination of exercises, including handgrip (HG) and arm-tensing movements, that increase blood pressure (at least in healthy subjects) due to a sympathetic nerve discharge and an increase of vascular resistance; this contrasts the hypotension associated with the vasovagal spell and prevents loss of consciousness, i.e., aborts the syncope.

The IACPM procedure is simple to execute. When the patient perceives the onset of prodromal symptoms of VVS he should start an arm muscle tensing exercise. The arm tensing consist of the maximum tolerated isometric contraction of the two arms achieved by gripping one hand with the other and simultaneously pushing away the arms. This exercise should be performed continuously for two minutes or more. For VVS associated with orthostatic hypotension, the IACPM procedure should involve the leg muscles (leg pumping and tensing, leg crossing) to increase orthostatic blood pressure by mechanical compression of the venous bed in the legs and increase the systemic vascular resistance. The IACPM procedure is simple, does not require the use of any equipment, needs no external monitoring or assistance, and can be performed during daily life activities to abort spontaneous VVS attacks. An acute, single-blind, placebo-controlled, randomized, crossover, tilt-table efficacy study was conducted in Italy between August 2001 and April 2002 [18]. The study was conducted on 19 tilt-induced syncopal patients (12 male, mean age 55 ± 20 years, mean of three syncopal events before enrolled in the study), all with clear prodromal symptoms. The IACPM was administered for 2 min starting from the onset of VVS symptoms. In the arm in which IACPM was active (HG at 50% of maximum voluntary contraction), it caused an increase of systolic BP from 92 ± 10 mmHg to 105 ± 38 mmHg, whereas in the control arm (simulated IACPM - HG without contraction) the systolic BP decreased from 91 ± 11 mmHg to 73 ± 21 mmHg. The HR behavior was the same in the two arms. Patients who became asymptomatic were 63% vs. 11% and patients who developed syncope were 5% vs. 47%, in the active and control arms respectively. All patients were trained to self-administer the IACPM procedure at the occurrence of prodromal symptoms after hospital discharge. During the 9 ± 3-month follow-up, the treatment was performed in 95/97 (98%) episodes of impending VVS, and it was successful in 94/95 (99%) episodes. The IACPM procedure seems to be simpler and achieve more effective results than tilt training, but there is a relevant limitation that will reduce its application in patients suffering from malignant VVS. To be effective, IACPM requires that the patient clearly recognize the onset of syncopal prodromes, i.e., the vasovagal spell must present the symptomatologic phase of presyncope, or aura. Unfortunately, a large amount of attacks of malignant VSS are of the sudden onset type, thus not giving the patient a chance to initiate countermeasures before losing consciousness.

Pharmacological (Drug) Therapy

The most common option for treating malignant VVS is pharmacological therapy [19]. A wide range of drugs is presently being used to prevent neuromediated syncope, especially VVS, which is the more common and most often investigated form of syncope. The goal of this section is to provide a concise summary about the types and effects of the most commonly used drugs. For patients affected by neuromediated syncope, drugs are used for both diagnosis and therapy.

In terms of diagnostics, drugs like isoproterenol, edrophonium, nitroglycerine, and adenosine have proven to be useful during the HUTT, permitting the so-called "pharmacological provocation technique" during HUTT. ATP and adenosine have also demonstrated their capability to uncover neuromediated paroxysmal AV block, which is an important indicator of cardioinhibitory VVS. Concerning therapy, drugs can be used for emergency resuscitation of victims of severe hypotensive or bradycardic VVS (e.g., dopamine, norepinephrine, anticholinergic drugs), and for the long-term prevention of syncopal spells. Though drug administration in resuscitation procedures is quite uncommon (e.g., during acute myocardial infarction of the inferior wall complicated by the trigger of the Bezold-Jarisch reflex), administering drugs for long-term prophylaxis is very common. The effectiveness of drugs in the latter case remains controversial for various reasons:

- There is currently no evidence that supports the usefulness of drug therapy for VVS, because no randomized and controlled studies have be conducted with a sufficiently wide population (virtually all studies published up to now are of the non-controlled type).
- For the majority of the proposed treatments, almost all published results refer to retrospective studies conducted with small groups of patients.
- The study end points are often unrealistic (e.g., total suppression of recurrence with a tolerable drug dose).
- Because symptoms may not reappear for several months, it is always difficult to establish the effectiveness of an intervention.

In general terms, the drugs used to prevent VVS recurrence are grouped into two main categories:

- Drugs used to improve the basic pathophysiologic status that triggers the syncopal event in a specific patient, and
- Drugs used to attempt to directly modify the problem in the neural reflex and thus to decrease syncopal recurrence.

The first category is very large and of negligible interest for the malignant VVS. The second category is important, however; it includes β-adrenergic blockers, disopyramide, certain vasoconstrictors, serotonine reuptake inhibitors, and volume retention drugs. Following is a short overview of the specific effects of the main drugs belonging to the second category.

β-blockers: Drugs with a β-adrenergic receptor blocking action (β-blockers) were the first drugs proposed for preventing VVS, and are still widely used for this purpose today. They are a logical choice, because high levels of epinephrine in the blood almost always precipitate VVS. Epinephrine, a β-adrenergic drug, increases the sensitivity of several mechanoreceptors and chemoreceptors, which are the believed source of the signals of the afferent neural reflex, and may potentiate the level of response to the efferent parasymphatetic activity associated to this syndrome. Finally, the β-adrenergic effect of epinephrine may facilitate peripheral vasodilatation.

Disopyramide: Disopyramide has been used successfully in the treatment of neurally mediated syncope. This Type 1 antiarrhythmic has profound negative inotropic effects and anticholinergic properties. The negative inotropic effects may decrease afferent mechanoreceptor activity, while the anticholinergic effects may decrease vagal (efferent) output. The vagal effect of disopyramide helps maintain an elevated cardiac rate and possibly decrease the symptoms related to the vasovagal spell. The negative side effects of this drug include: torsade de pointes in patients in whom the drug induces a prolongation of the QT interval, urinary tract obstruction in elderly patients, and glaucoma.

Serotonin reuptake inhibitors: Serotonin (5-hydroxytryptamine) is an important neurotransmitter for the regulation of blood pressure. Activation of the cerebral serotonin receptors inhibits the activity of the symphatetic nervous system and facilitates the vasodepressive response. Although very little is known about serotonin levels during VVS, two indirect factors indicate its potential negative side effects. First, intracerebroventricular administration of serotonin has been reported to inhibit the sympathetic neural outflow in general, with a simultaneous increase of adrenergic sympathetic stimulation. This phenomenon may explain the link between diminished peripheral vasoconstriction (decreased release of norepinephrine by synapses) and the concomitant excessive release of

epinephrine that is known to happen during VVS. Second, clinical studies suggest that serotonin reuptake inhibitors may reduce the incidence of certain neuromediated syncopal events. Selective inhibitors of serotonin reuptake may block its reuptake in the synaptic clefts, reducing the effects on sympathetic neural activity, and probably moderating the vasodepressive tendency in VVS.

Midodrine and other vasoconstrictors: Drugs that promote vasoconstriction (or that at least impede vasodilatation associated with the vasodepressive component in VVS) are natural candidates for the prophylactic treatment of this syndrome. In the past, ephedrine, dihydroergotamine, and etilephrine were administered, but their scant effectiveness, combined with negative hypotensive side effects, caused them to be quickly abandoned. Recently, midodrine, a β-adrenergic agonist, has been successfully administered. Midodrine, i.e., 1(2',5'-dimethoxyphenyl)-2-glycinamido-ethanol-HCl, induces arteriolar constriction and decreases venous pooling. It is absorbed from the gastrointestinal tract and is transformed into active metabolite desglymidodrine through metabolization at the hepatic level. Active metabolite desglymidodrine reaches peak levels in 40 min and induces arteriolar and venous capacitance constriction. Because neither midodrine nor desglymidodrine crosses the blood-brain barrier, they have minimal cerebral and cardiac effects. The only known and common side effect of this drug is an annoying tingling of the scalp.

Blood volume maintenance: The maintenance of central blood volume is an important aspect in the prevention of VVS, especially in cases where dehydration (e.g., in athletes) or long stays in the orthostatic position (e.g., in soldiers) play a significant role. When consumption of liquids and salts is not sufficient, the administration of fludrocortisone may prove useful. Fludrocortisone increases sodium and fluid retention and it is known to have the capability of sensitizing the adrenergic receptors (possible synergy with midodrine). In general, it is well tolerated and often used in young patients without cardiovascular diseases.

In conclusion, a great amount of pharmacological agents is used in the treatment of VVS. However, none of them have been proven completely effective in the long term, as shown by several randomized clinical investigations. Many of these drugs have proven beneficial, with few side effects, but their use always needs careful and accurate evaluation of the general pathophysiologic status of each individual patient.

Discussion

For some time now, malignant VVS 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 a proper diet and psychological training, while moderate cases may be treated with psycho-physical training or drug therapy. However, these treatments are often unable to prevent the most serious cases of VVS, associated with protracted asystolic periods and requiring emergency medical intervention for resuscitation procedures or to repair physical traumas caused by the syncopal spell. In the last decade, cardiac pacing has been increasingly used to treat serious forms of VVS, refractory to conventional therapy. The mechanisms and clinical efficacy of pacing for the prevention of VVS will be analyzed in the second installment of this review.

Comments on HUTT

In all the studies discussed in this review, HUTT has played a dominant role in patient selection and in the assessment of therapy effectiveness. Nevertheless, there is presently some controversy about this methodology's diagnostic and prognostic power. From the diagnostic point of view, the HUTT tell us that a specific patient with a suspected or real propensity for developing a neuromediated syncope of the vasovagal type has a good probability, when subjected to conditions capable of triggering the Bezold-Jarisch reflex, of developing some type of syncope. Thus, whether or not this specific patient develops a syncopal spell at some point during his or her life, and whether or not this spell is of the same type as that diagnosed by the HUTT is a pure statistical coincidence. The probability will be more favorable if the HUTT was conducted under basal conditions and if the patient's orthostatic intolerance, or at least the venous pooling, are the dominant reasons for the spontaneous occurrence of the syncopal spell. The probability will be less favorable if the HUTT was conducted under potentiated conditions (borderline conditions) and if other neurohumoral factors or psychological influences (during

clinical tests the patient is always more psychologically vulnerable than when at home) were the main conditions triggering the spontaneous syncopal event.
The prognostic capability of HUTT, i.e., the capability to foresee the adverse event, was substantially refuted by all clinical studies discussed in this review. The "false positive" (positive test but no spontaneous recurrence of VVS) is the most frequent result. In all studies, over 50% of treated patients exhibited a positive HUTT even though they did not experience any episodes of VVS during the entire follow-up. A similar percentage was observed in the control group patients. From this we can infer that the HUTT produces extreme conditions that almost never happen during a patient's normal daily life. A "false negative" (negative test followed by spontaneous recurrence of VVS) is highly improbable. None of the patients included in the discussed clinical studies exhibited this type of response to the HUTT (an exception should be made for the study with the Loop Recorder; however, the syncopal etiology of this study was heterogeneous). However, a false negative cannot be excluded a priori.

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