

Vasovagal Syncope

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Background: Vasovagal syncope is the most common type of syncope and is one of the most difficult types to manage.

Purpose: This article reviews the status of mechanisms, diagnosis, and management of vasovagal syncope.

Data Sources: MEDLINE search for English-language and German-language articles on vasovagal syncope published up to June 1999.

Study Selection: Case reports and series, clinical trials, research investigations, and review articles from peer-reviewed journals.

Data Extraction: Findings were summarized and discussed individually. Summaries were made in table format. Statistical analysis of combined data was inappropriate because of differences among studies in patient selection, testing, and follow-up.

Data Synthesis: The population of patients with vasovagal syncope is highly heterogeneous. Triggers of vasovagal syncope are likely to be protean, and many potential central and peripheral triggers have been identified. The specific mechanisms underlying

the interactions among decreased preload, sympathetic and parasympathetic modulation, vasodilation, and cardioinhibition remain unknown. Tilt-table testing is a widely used diagnostic tool. The test results should be interpreted in the context of patients' clinical presentations and with an understanding of the sensitivity and specificity of the test. Assessment of therapeutic outcomes has been difficult, primarily because of patient heterogeneity, the large number of pharmacologic agents available for therapy, and the sporadic nature of the syndrome complex.

Conclusions: Vasovagal syncope is a common clinical syndrome that has complex and variable mechanisms and is difficult to manage. Advancements are being made in laboratory investigations of its triggering mechanisms. Randomized, controlled trials of pharmacologic and nonpharmacologic interventions are needed. Mechanism-targeted therapeutic trials may improve clinical outcomes.

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The common faint is the prototype of vasovagal syncope. The "vasodepressor" component of syncope was first suggested by Hunter in 1773 (1) in reference to a patient undergoing phlebotomy. The "vagally" mediated cardioinhibition as a primary cause of syncope was noted in 1888 by Foster (2), who proposed that profound bradycardia diminished cerebral perfusion to a level inadequate to maintain consciousness. Because of the intriguing, complex interactions between the neurologic and cardiovascular systems, the triggering mechanisms have been thoroughly investigated.

Syncope has an enormous medical, social, and economic impact on the general population. Approximately 1 million patients are evaluated for syncope annually in the United States. It has been estimated that 3% to 5% of emergency department visits and 1% to 6% of hospital admissions are for evaluation of syncope (3–6). Vasovagal syncope is the most common type of syncope and is one of the most difficult types to manage. It has been estimated that up to 40% of syncopal events evaluated in the outpatient setting are vasovagal in nature (3, 7). Calkins and colleagues (8), in a study done at a tertiary care center, estimated that up to \$16 000 of unnecessary diagnostic testing may be performed on patients who ultimately re-

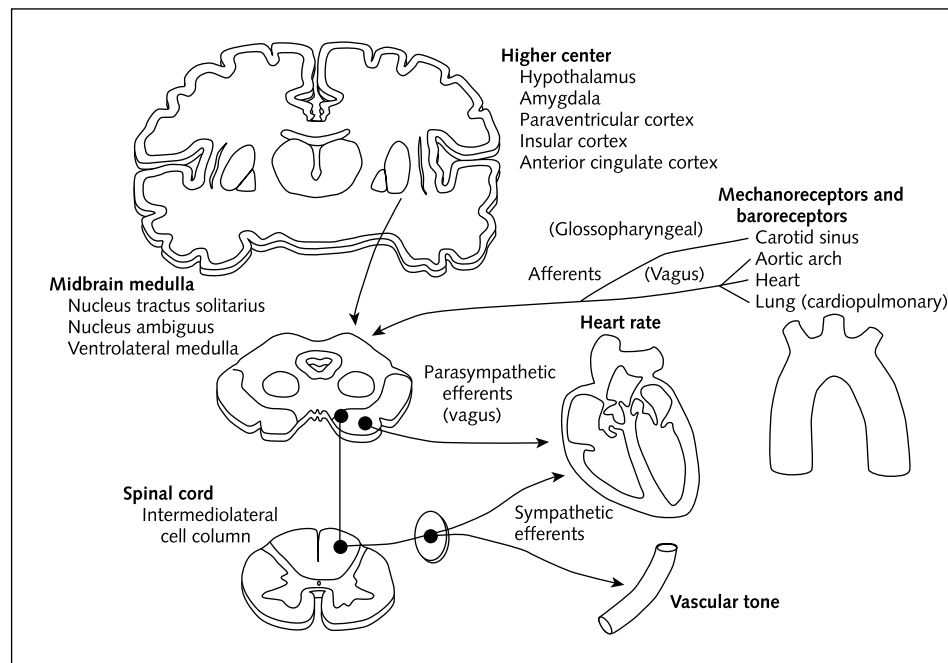
ceive a diagnosis of vasovagal syncope, emphasizing the difficulty of making the diagnosis. Although numerous therapeutic options have been proposed for preventing vasovagal syncope, choice of therapy is usually empirical, and efficacy is suboptimal. This is primarily because of the sporadic and episodic nature of the syndrome complex, the heterogeneous patient population, and difficulties resulting in the lack of large randomized clinical trials.

The primary objective of this paper is to review the current understanding of the triggering mechanisms of vasovagal syncope and to provide a mechanism-based diagnostic and therapeutic approach to this large patient population. The opinions expressed are the results of our interpretation of the available data in the literature in conjunction with our own investigational work and clinical experiences.

METHODS

The data sources were obtained from a MEDLINE search for English-language and German-language articles on vasovagal syncope published up to June 1999. The terms *vasovagal syncope* and *neurocardiogenic syncope* were used in conjunction with the terms *mechanisms*, *diagnosis*,

Figure 1. Autonomic nervous system regulation of cardiovascular hemodynamic responses.



tilt-table testing, or therapy. Case reports and series, clinical trials, research investigations, and review articles in peer-reviewed journals were selected. References were selected on the basis of their relative pertinence. The language used for the search was selected on the basis of accessibility.

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MECHANISMS

Neurocardiovascular Regulation of Blood Pressure

Physiologic control of blood pressure regulation involves complex afferent signal processing by the central nervous system and subsequent efferent modulation of cardiac and vascular targets (Figure 1) (9, 10). Normal moment-to-moment regulation of arterial pressure is controlled predominantly by stretch-activated (high-pressure) baroreceptors located in the aortic arch and carotid sinus. The afferent signals are transmitted from the aortic arch by the vagus nerve and from the carotid sinus by the glossopharyngeal nerve. Phasic distention of these vascular territories after cardiac systole results in phasic discharge of afferent nerves that converge on the nucleus tractus solitarius in the brain stem. At this site, efferent sympathetic

outflow is inhibited and efferent vagal outflow is augmented phasically. This phasic inhibition of sympathetic drive is responsible for the periodic nature of efferent sympathetic nerve traffic seen in recordings from human muscle nerves (11).

With decreases in the tonic level of arterial pressure, the mean level of sympathetic outflow increases and vagal outflow decreases. Conversely, increases in arterial pressure result in sympathetic withdrawal and vagal augmentation. Therefore, the arterial baroreceptor system regulates the beat-to-beat (phasic) firing of efferent sympathetic and vagal nerves as well as the tonic level of nerve traffic.

Mean levels of efferent sympathetic outflow are also regulated by low-pressure baroreceptors located in the heart walls and intrathoracic vessels (so-called cardiopulmonary baroreceptors). Increased cardiac filling pressures activate these receptors, resulting in sympathetic inhibition. Conversely, decreased filling pressures cause sympathetic excitations because these receptors decrease their firing rate. Other inputs to these receptors include the cardiac inotropic state.

The physiologic response to assumption of upright posture involves activation of this autonomic cycle. Approximately 300 to 700 mL of blood pools in the lower

extremities while a person stands (12, 13), decreasing intravascular volume in the ventricle and at the level of the aortic arch and carotid sinus. This in turn results in decreased afferent neural activity from each of these receptors, ultimately producing increased sympathetic tone to the vasculature and the heart, with subsequent vasoconstriction, increased inotropy and heart rate, and maintenance of blood pressure.

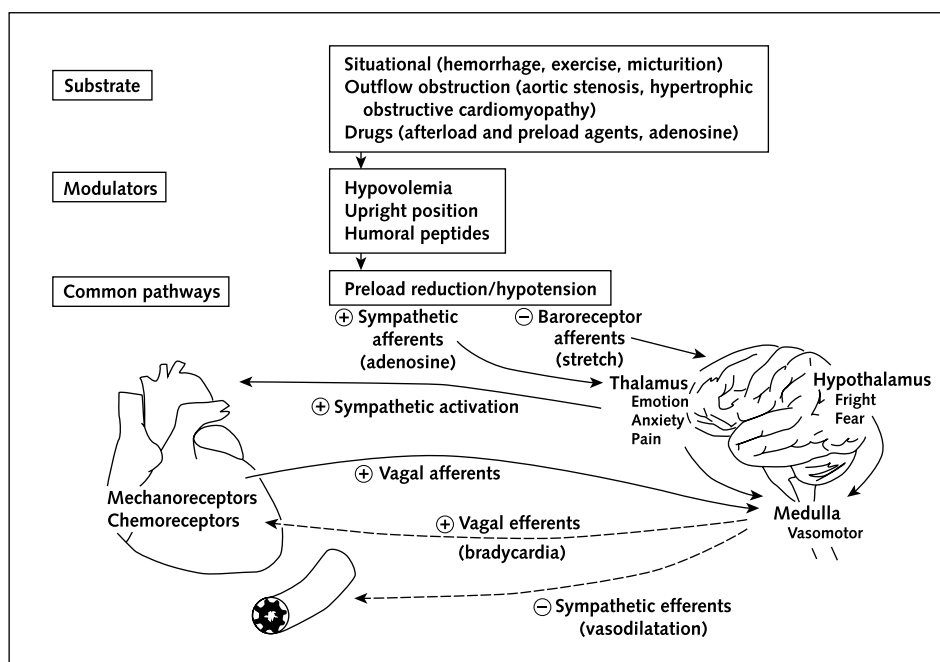
Traditional Concept of Vasovagal Response

The pathophysiology of the vasovagal state is incompletely understood, which makes diagnosis and treatment of vasovagal syncope difficult. The most commonly used model for triggering vasovagal syncope is the Bezold–Jarisch reflex (7, 14–20). In broad terms, the Bezold–Jarisch reflex can be thought of as a perturbation of the negative feedback loop previously described: Excessive venous pooling triggers a chain of events that culminates in vasodilatation and bradycardia (instead of the physiologic compensatory responses of vasoconstriction and tachycardia). This in turn leads to the hypotension and loss of consciousness associated with vasovagal syncope.

The Bezold–Jarisch reflex is thought to be initiated by excessive venous pooling, with resulting decreases in ventricular volume and an increase in ventricular inotropy. This activates sensory receptors that respond to wall tension located in the inferoposterior portions of the left ventricle (21), paradoxically increasing neural traffic to the central nervous system (through the afferents in the vagus nerve). Sympathetic output to the vasculature and the heart decreases, and parasympathetic activity increases. Marked vasodilatation, a key component of the vasovagal response, occurs as a result and is sometimes accompanied by varying degrees of bradycardia. Hypotension, bradycardia, and the loss of consciousness defining vasovagal syncope follow (Figure 2).

Most of our knowledge of these mechanisms is derived from studies of animals subjected to hemorrhage (16) or administration of compounds known to stimulate visceral afferent nerves (15, 17). Similarities in the efferent response (that is, sympathetic withdrawal and relative or absolute bradycardia among different species, including humans) have led to the notion that similar afferent mechanisms are operative. It is likely, however, that multiple

Figure 2. Mechanisms of vasovagal response.



The Bezold–Jarisch reflex indicates that the neurocardiogenic reflex is initiated by the cardiac mechanoreceptor activation. The information is transmitted by the vagal afferents to the cardiovascular regulatory center in the medulla. The negative feedback response is transmitted by an activation of the vagal efferents and an inhibition of the sympathetic efferents. Input to the medulla may originate from extracardiac locations as well as directly from the higher central nervous system.

afferent inputs contribute to the vasovagal response and that therapies directed at a single putative mechanism will have limited success.

In open-chest cats subjected to hemorrhage, an initial sympathetic excitation is followed by sympathetic withdrawal (16). This withdrawal can be prevented by section of cardiac afferent nerves, which suggests that it is caused by some cardiac afferent signal. Similar observations have been made in rats (22). In conscious dogs, however, sequential section of high-pressure baroreceptor afferents and cardiac afferents did not prevent sympathetic inhibition late in hemorrhage (23).

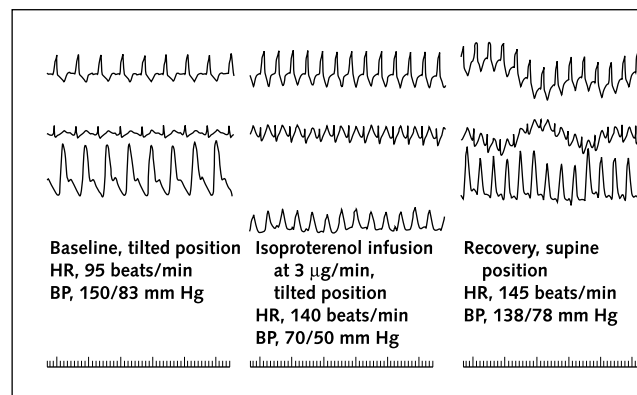
In humans, circumstantial support for a trigger of vasovagal syncope similar to the Bezold–Jarisch reflex has been described. Serum catecholamine levels have been shown to increase before vasovagal syncope during head-up tilt-table testing (24). Use of microelectrodes to directly measure traffic in human peroneal nerve fascicles has revealed increases in sympathetic nerve activity during the period leading up to vasovagal syncope, followed by sudden decreases at the onset of syncope (18). Decreases in end-diastolic volume, presumably reflecting increased venous pooling and decreased preload, have been shown to accompany vasovagal syncope induced by head-up tilt-table testing (25, 26).

Additional Mechanisms of Vasovagal Response

Vasovagal syncope in humans, however, is probably triggered by mechanisms beyond those described by the Bezold–Jarisch paradigm. For example, a vasodepressor response without bradycardia has been observed during vasovagal syncope in some heart transplant recipients (Figure 3). The lack of bradycardia with vasovagal syncope supports the presumption that surgical denervation interrupts cardiac afferent and efferent transmission. Therefore, triggers of vasovagal syncope beyond those described in the Bezold–Jarisch reflex are likely to be active. These findings do not entirely exclude a cardiac contribution to the triggering of vasovagal syncope, however, because complete denervation cannot be proven (some cardiac afferents and efferents may remain in the atrial remnants or the venoatrial junction) and the lack of a bradycardiac response may simply reflect vasovagal syncope of a pure vasodepressor nature (27–29).

It has been suggested that many modulators of central nervous system activity play a role in modulating vasovagal

Figure 3. A vasovagal response induced by tilt-table testing and isoproterenol infusion in a patient who received a cardiac transplant.



Autonomic denervation and absent Bezold–Jarisch reflex are presumed. The top two tracings are from surface electrocardiogram leads 1 and aVL. The bottom tracing is a beat-to-beat arterial blood pressure (BP) tracing recorded from the radial artery. **Left.** Hemodynamic responses at baseline in the tilted position. **Middle.** After isoproterenol infusion at 3 μg/min, the patient became hypotensive and syncopal without significant decrease in heart rate (HR). **Right.** Hemodynamic values during recovery after the patient was returned to the supine position. Reproduced from Shen and Gersh (7) with permission of the Mayo Foundation.

syncope. In addition, the Bezold–Jarisch reflex may describe just one of many possible triggers. These include serotonin (30, 31), adenosine (32), and opioids (33, 34). β -Endorphin levels have been shown to increase in patients during syncope (35), and naloxone (an opiate receptor antagonist) has been shown to enhance cardiopulmonary baroreflex excitation of sympathetic activity (36). Infusion of naloxone has not been shown to affect the vasovagal response (37), however, which suggests that β -endorphins are not uniquely involved in the sole common pathway leading to vasovagal syncope. Input and interaction of afferent responses in the higher central nervous system have also been implicated (38, 39). During emotional stress, modulatory effects from forebrain and hypothalamus could also play a role in patients with denervated ventricles.

Potential peripheral neural triggers of vasovagal syncope, distinct from those described in the Bezold–Jarisch reflexes, have also been identified. For example, our group (40) has shown that sympathetic afferents could be activated directly by intravenous administration of adenosine. These observations suggest that adenosine may be an endogenous mediator of vasovagal response when used in conjunction with head-up tilt-table testing.

In patients with vasovagal syncope, we recently observed that decreases in end-diastolic volume with head-up

tilt-table alone are reversed by addition of isoproterenol infusion (41). This suggests that decreases in ventricular volume may not be necessary for development of vasovagal syncope, further supporting the idea that some triggers are distinct from those described in the Bezold–Jarisch reflex. In addition, in patients with syncope induced by head-up tilt-table testing alone and by head-up tilt-table testing plus isoproterenol, we have observed that hemodynamic responses just before onset of symptoms vary considerably between the two protocols (42). Before onset of syncope, heart rate and cardiac output were significantly higher and total peripheral resistance was significantly lower in patients with isoproterenol-induced vasovagal response than in patients with vasovagal syncope induced by tilt-table testing alone. Because triggering mechanisms of the imminent syncope are expected to be most active just before onset of symptoms, it is likely that these different hemodynamic responses reflect different triggering mechanisms in the same patient.

The mechanisms of profound vasodilatation, the final pathway leading to vasovagal syncope, are the focus of much investigation. Substantial research has been done on the role of alterations in autonomic tone during vasovagal syncope. It is generally accepted that changes in sympathetic tone are integral to the vasodilatory response because alterations in serum levels of norepinephrine and epinephrine during head-up tilt-table testing result in syncope (24, 43). It is not clear, however, whether these changes are active or passive. For example, early research (44) showed vasodilatation of skeletal muscle blood vessels during syncope induced by phlebotomy and high-pressure thigh cuff. This vasodilatation was attenuated by sympathectomy or peripheral nerve block, suggesting that it was active and mediated by increases in anatomically unidentified sympathetic activity in vasodilator nerve fibers. In contrast, recent work showing that vasovagal syncope is associated with withdrawal of sympathetic nerve fiber activity suggests a more passive role (18). Finally, it has been suggested that alterations in sympathetic tone mediated by cholinergic vasodilator nerves (45) play a role in skeletal muscle dilatation.

Nitric oxide has recently been implicated in the vasodilatory response associated with vasovagal syncope. Evidence for the presence of nitroxidergic nerves in skeletal muscle (46, 47) and increased metabolism of nitric oxide in patients with syncope induced by head-up tilt-table testing (48) have been reported. Other studies have shown,

however, that the role of nitric oxide is not unique; infusion of N^G -monomethyl-L-arginine (a nitric oxide blocker) did not prevent vasodilation during syncope (49, 50).

The specific mechanisms underlying the interactions among decreased preload, sympathetic and parasympathetic modulation, and vasodilatation remain unknown. Triggers of vasovagal syncope are likely to be protean, and many potential central and peripheral triggers have been identified (Figure 2). It would be reasonable, therefore, to consider the Bezold–Jarisch paradigm a hypothesis that describes only one of many potential triggering mechanisms.

CLINICAL EVALUATION

History and Physical Examination

A “standard” diagnosis of vasovagal syncope usually involves clinical history and observation of the patient at the time of symptoms, if possible. Onset of vasovagal syncope is usually gradual, but sudden loss of consciousness without warning is not uncommon (7, 51). Information regarding environmental circumstances at the time of syncope may be helpful. Because vasovagal syncope may be precipitated by the sight of blood, loss of blood, sudden stressful or painful experiences, surgical manipulation, or trauma, a history of childhood syncope may provide a clue to the cause of vasovagal syncope in adults. Premonitory signs and symptoms, if present, include pallor, weakness, lightheadedness, yawning, nausea, diaphoresis, hyperventilation, blurred vision, and impaired hearing immediately before the syncopal event. If the patient sits or lies down promptly, frank syncope may be aborted. When consciousness returns, the patient may have a persistent sensation of weakness but is not usually confused. Although orthostatic vital signs should be assessed and cardiovascular and neurologic examination should be performed in every patient, no specific findings from physical examination have been related to vasovagal syncope.

Tilt-Table Testing

Venous pooling provoked by head-up tilt with excessive myocardial contraction has been demonstrated during head-up tilt-table testing (26, 52). It is generally thought that head-up tilt-table testing provokes vasovagal syncope through the Bezold–Jarisch mechanism. The test is performed by using a specially designed tilting table with a footboard. The patient is tilted upright, and vasovagal syncope is precipitated in predisposed patients. Protocols for

Table 1. Passive Upright Tilt-Table Testing in Patients with Syncope of Unknown Cause

Study (Reference)	Total Patients	Patients with Positive Results on Tilt-Table Testing	Total Controls	Controls with Positive Results on Tilt-Table Testing	Tilt Angle	Tilt Duration
	<i>n</i>	<i>n</i> (%)	<i>n</i>	<i>n</i> (%)	°	<i>min</i>
Kenny et al. (61)	15	10 (67)	10	1 (10)	40	60
Fitzpatrick et al. (66)	71	53 (75)	27	2 (7)	60	60
Strasberg et al. (65)	40	15 (38)	10	0 (0)	60	60
Raviele et al. (62)	30	15 (50)	8	0 (0)	60	60
Abi-Samra et al. (60)	151	63 (42)	15	0 (0)	60	20
Almquist et al. (54)	15	4 (27)	18	0 (0)	80	10
Grubb et al. (67)	25	6 (24)	6	0 (0)	80	30
Pongiglione et al. (68)	20	4 (20)	0	–	90	15
Shen et al. (63)	111	35 (32)	23	2 (9)	70	45

head-up tilt-table testing are not standardized, and the duration and angle of tilt used by different investigators vary considerably. Most recent published reports have tended to favor tilts that last 30 to 45 minutes at 60° to 80° (53). Although head-up tilt-table testing is widely used in the diagnosis of vasovagal syncope, questions relating to its specificity, sensitivity, and reproducibility make its interpretation and clinical applicability difficult.

Pharmacologic agents are often used to provoke a positive test result if vasovagal syncope is not induced by head-up tilt-table testing alone. The agents are chosen for their effects on autonomic regulation during head-up tilt-table testing and, by inference, their putative triggering of the Bezold–Jarisch reflex. For example, because serum concentrations of catecholamines are known to increase before spontaneous vasovagal syncope (24), isoproterenol is often infused during head-up tilt-table testing to augment the vasovagal response (54, 55). Similarly, adenosine (with vasodilatory and probable direct activation of sympathetic afferents) (40), nitroglycerin (with direct vasodilatory action) (56, 57), edrophonium (with cholinergic action) (58, 59), and other agents have been used to “provoke” syncope during head-up tilt-table testing. It is expected that diagnostic outcomes will differ according to the agent used because each agent has a specific end target; however, detailed information is not currently available.

Sensitivity—a measure of how often vasovagal syncope is induced by head-up tilt-table testing in patients with a history of vasovagal syncope—is difficult to assess. Many patients with a history of situational syncope undergo head-up tilt-table testing because their physician is not sure whether the clinical event was vasovagal in nature. It is not known whether the syncope induced during head-up tilt-

table testing represents the clinical event; therefore, determination of the denominator used in determining sensitivity (that is, the number of patients with a clinical history of vasovagal syncope) is unclear. Our group prefers to use the longer but less misleading term *positive yield in patients with a syncopal history* or *apparent sensitivity* to describe positive results of head-up tilt-table testing in patients referred for syncope.

The proportion of patients with a clinical history of syncope reported to have a positive result on head-up tilt-table testing varies considerably. Most studies report values that range from 30% to 85% (40, 60–65). This wide range is partially caused by differences in tilt protocols (tilt angle and duration), as shown in Table 1. In addition, differences in patient characteristics at study entry (multiple episodes vs. single episode, rigorous vs. more flexible evaluation, exclusion of other causes of syncope, age of patients, and number and type of comorbid conditions) are likely to have an effect.

Addition of provocative agents to head-up tilt-table testing can increase the positive yield. As many as 75% of younger patients with a negative result on head-up tilt-table testing experienced vasovagal syncope with addition of isoproterenol infusion (68). The method of isoproterenol infusion (dose, duration, and inclusion of a supine period before increasing the dose) differs greatly among investigators, which probably adds to the variation.

Specificity—a measure of how often vasovagal syncope fails to be induced by head-up tilt-table testing in asymptomatic controls—is usually high, ranging from 80% to 90% or greater (56, 63, 66, 67, 69, 70). It is important to note that specificity has a much narrower range than sensitivity.

When provocative agents, such as isoproterenol, are used, specificity can decrease substantially. One study reported values as low as 50% (5), although in most other studies values remained above 80% (71) at lower doses of isoproterenol. In a randomized crossover study of 111 consecutive patients (63), we observed that the positive yields of passive tilt-table testing and tilt-table testing with an intermediate dose of isoproterenol (0.05 $\mu\text{g}/\text{kg}$ of body weight per minute) were 32% and 68%, respectively ($P = 0.002$). Positive yield in response to isoproterenol increased in the patient sample at the expense of a modest reduction of specificity in 23 normal controls (from 91% to 83%). The procedural time was significantly less for the single-stage isoproterenol tilt than for passive tilt-table testing.

Reproducibility of head-up tilt responses between tests varies among published studies (Table 2) (62, 70, 74–76, 78, 79). A positive (syncopal) response is confirmed in 35% to 90% of patients, and a negative response is confirmed in 80% to 100% of patients (73, 80). These differences may reflect different protocols for head-up tilt-table testing (for example, isoproterenol use and the length and angle of tilt), different inclusion criteria (presyncope vs. syncope), or other uncontrolled variables.

Several authors (62, 75, 80) have reported discordant hemodynamic responses (cardioinhibitory, vasodepressor, or mixed) between tests in patients with vasovagal syncope induced by sequential head-up tilt-table testing. This suggests that incomplete concordance with induction of vasovagal syncope may be a function of more than the head-up tilt-table testing itself. The type of hemodynamic response during syncope or even the inducibility of syncope probably reflects the physiologic susceptibility of the patient to vasovagal syncope at that time. A continuum of symptoms in response to provocative situations, ranging from no symptoms to presyncope to full vasovagal syncope, may

reflect the current physiologic susceptibility of the patient. This has important implications for the use of serial head-up tilt-table testing to determine the efficacy of therapeutic interventions.

The American College of Cardiology has published guidelines for head-up tilt-table testing (53). Most studies generally agree that head-up tilt-table testing is warranted in patients whose syncope is presumed, but not conclusively known, to be vasovagal and in patients with one or more of the following: 1) recurrent syncope, including recurrent exercise-induced syncope after exclusion of organic heart disease; 2) a single syncopal event associated with injury or motor vehicle accident; 3) a single syncopal event in a high-risk setting; or 4) syncope of another established cause whose treatment might be affected by vasovagal syncope.

Head-up tilt-table testing is not warranted in patients who have a single syncopal episode without injury in an intermediate- or low-risk setting and have no clinical features that clearly support a diagnosis of vasovagal syncope. Furthermore, head-up tilt-table testing is contraindicated in patients with critical obstructive cardiac disease (for example, critical proximal coronary artery stenosis, critical mitral stenosis, or severe left ventricular outflow obstruction) or critical cerebrovascular stenosis. In several conditions, reasonable differences of opinion exist regarding the usefulness of head-up tilt-table testing. For example, it is not proven to be useful in follow-up evaluation of therapy to prevent recurrence of vasovagal syncope because of the difficulties associated with reproducibility.

NATURAL HISTORY

Vasovagal syncope often presents in clusters. Multiple events occur in a relatively short period and are followed by

Table 2. Reproducibility of Results of Tilt-Table Testing

Study (Reference)	Protocol for Tilt-Table Test	Time between Tests	Positive Reproducibility	Negative Reproducibility
			n/n (%)	
de Buitelir et al. (72)	80° tilt, 10-min duration	5 min	8/14 (57)	16/17 (94)
Brooks et al. (73)	70° tilt, 25-min duration	1 d	11/30 (37)	45/56 (80)
Raviele et al. (62)	60° tilt, 60-min duration	3 d	10/14 (71)	–
Fitzpatrick et al. (66)	60° tilt, 60-min duration	–	24/31 (77)	–
Blanc et al. (74)	60° tilt, 60-min duration	7 d	8/13 (62)	–
Fish et al. (75)	Isoproterenol used	30 min	14–18/21 (67–86)	–
Chen et al. (76)	Isoproterenol used	30 min	12/15 (80)	8/8 (100)
Grubb et al. (70)	Isoproterenol used	5 d	13/14 (93)	6/7 (86)
Sheldon et al. (77)	Isoproterenol used	2 wk	23/26 (88)	17/20 (85)

longer, relatively symptom-free periods. Surprisingly, despite its effect on the choice and evaluation of intervention, there are few published longitudinal data on the natural history of untreated vasovagal syncope. Sheldon and colleagues (81) presented the most comprehensive analysis, in which they followed for up to 3 years 101 patients who were referred for syncope, had vasovagal syncope induced by head-up tilt-table testing (with or without isoproterenol), and received no drug therapy. Several important results were reported. First, the probability of remaining free of recurrent syncope decreased over time (72%, 62%, and 51% at 1, 2, and 3 years, respectively). Second, presence of recurrent syncope could be predicted from the number and duration of pretest syncope episodes. The risk for syncope recurrence always increased with the number of syncope episodes, and the rate of increase was much greater if the symptoms occurred over a shorter time. For example, the probability of remaining syncope-free after 2 years was 26% for a patient with 17 syncope episodes in the 6 months before head-up tilt-table testing but 82% for a patient with only 2 syncope episodes in the same period. Overall, only 28% of untreated patients had recurrent syncope during the study. Intratest variables (for example, inducibility of syncope with head-up tilt-table testing or heart rate during head-up tilt-table testing) did not add to the prognostic value of these pretest variables. Finally, and perhaps of most interest, the frequency of syncopal events decreased substantially after head-up tilt-table testing. The median frequency of syncope was 0.3 per month before testing and decreased to 0.03 per month after testing. In essence, the diagnostic procedure of head-up tilt-table testing and the associated clinical encounter had the effect of a positive therapeutic intervention. Although a causal relationship cannot be inferred, the clinical encounter, which included counseling on avoidance of situational provocation and assumption of postural maneuvers during presyncope to abort syncope, may play a large role in reducing frequency of future events even without medical treatment.

TREATMENT

Because the specific physiologic triggers of vasovagal syncope have not been clearly identified, approaches to treatment are largely empirical and are based on putative (but unproven) causal mechanisms. Rational approaches to treatment are further hampered by the highly variable recurrence rate of vasovagal syncope. Patients have re-

Table 3. Long-Term Therapy for Vasovagal Syncope

Type of Therapy	Specific Therapy
Preload agents	Fluids, salt, compression hose, steroids
Vasoconstrictors	α_1 -Adrenergic agonist (ephedrine, midodrine), adenosine blocker (theophylline), β_2 -Adrenergic blocker (propranolol)
Anticholinergic agents	Scopolamine, propantheline, disopyramide, hyoscyamine
Negative cardiac inotropes	β_1 -Adrenergic blocker, disopyramide
Central agents	Serotonergic reuptake blockers (fluoxetine, sertraline), α_2 -adrenergic agonist (clonidine), central stimulants (phentermine, methylphenidate), brain-stem suppressant (phenobarbital)
Mechanical device	Pacemaker therapy for prevention of bradycardia

sponded favorably to many drugs in short-term uncontrolled treatment trials.

Infrequent episodes of vasovagal syncope that are preceded by a warning prodrome probably do not require any intervention besides counseling and observation. Attention to hydration and salt intake may suffice, especially in warm weather. When treatment is considered necessary, it is often difficult to choose rationally among the widely diverse published options. β -Adrenergic receptor blockers, anticholinergic agents, disopyramide, adenosine receptor blockers, selective serotonin reuptake inhibitors, α -adrenergic agonists, mineralocorticoids, anticonvulsants, compression hose, and permanent pacemakers, among other therapies, have been advocated. The vast majority of the published studies evaluating these therapies, however, are uncontrolled, unblinded, and relatively short-term, which limits their usefulness in guiding treatment. A MEDLINE search from 1969 to the present revealed four controlled and blinded trials (82–85).

Ward and colleagues (85) performed a randomized, double-blind, placebo-controlled trial in 16 patients with recurrent vasovagal syncope. They found substantial improvement in quality-of-life score and symptom-free days after treatment with midodrine (an α -agonist) compared with placebo. In another randomized, double-blind, placebo-controlled multicenter trial of an α -agonist, etilefrine, in 126 patients, Raviele and coworkers (84) reported that the incidence of recurrent syncope and the median time to first recurrence did not differ in the etilefrine and placebo groups (24% vs. 24% and 106 days vs. 112 days, respectively). Follow-up was considered complete at 1 year or when the first episode of syncope occurred.

The effectiveness of a serotonin reuptake blocker,

paroxetine, was recently examined in a double-blind, placebo-controlled study of 68 patients who had not improved with standard therapy. During a mean follow-up of 25 months, syncope recurred in significantly fewer patients in the paroxetine group (18%) than in the placebo group (53%). Morillo and colleagues (82) assessed the incidence of recurrent syncope as a primary end point in a double-blind study of 21 patients. They observed no difference between patients who received disopyramide (which has an anticholinergic effect) and those who received placebo (27% vs. 30%, respectively). The divergent results of these four controlled studies could be explained by 1) heterogeneous patient population and patient selection, 2) differences in the size of the study samples and statistical power, 3) different study end points, 4) differences in duration of follow-up, and 5) a wide range of pharmacologic target (that is, α -receptor [midodrine, etilefrine], serotonin transporter [paroxetine], and cholinergic receptor [disopyramide]).

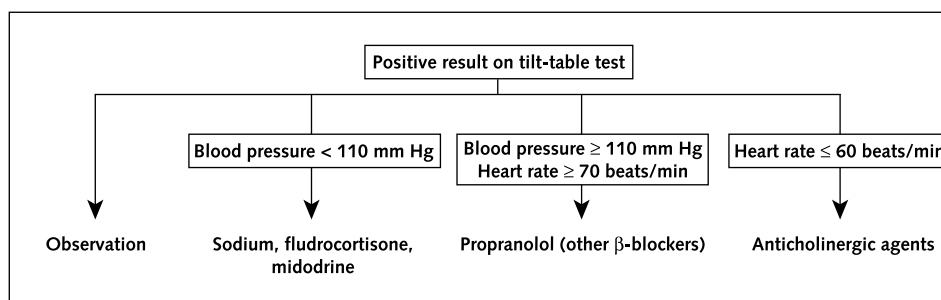
Use of pharmacotherapy for vasovagal syncope is limited by the absence of a large-scale blinded trial of β -adrenergic blockers, probably the most widely prescribed therapy for this condition. An often-cited observational study of β -adrenergic blockers included a sample of 118 patients followed for 28 months in which the recurrence rate was 10% (86). The study had several limitations, including the lack of a control group and the inclusion of patients with “near syncope” and infrequent syncopal events. Of the initial 193 patients with a positive response to tilt-table testing, 20% had no history of frank syncope and 12% had only one episode of syncope.

Some clinicians advocate permanent pacing as treatment for vasovagal syncope, and anecdotal series have supported this approach (61, 87, 88). In the North American Vasovagal Pacemaker Study (89), which attempted to ad-

dress the design errors of the anecdotal series, patients with at least six lifetime episodes of syncope, positive results on tilt-table testing, and relative bradycardia during tilt-table testing were randomly assigned to receive a permanent pacemaker with or without a rate-drop feature. The rate-drop feature of the pacemaker allowed detection of the slope of the decrease in heart rate in addition to the lower rate-limit detection. If the slope of the decrease in heart rate in a given time interval exceeded preset values, pacing was activated at a programmable higher rate. Medical therapy was permitted and was nonstandardized in patients who received pacing and those who did not. The main outcome measure was time to recurrence of syncope. Initially, enrollment of 284 patients was planned. At the first interim analysis of 54 patients, however, an unexpected large and beneficial treatment effect was identified and the study was halted.

The North American Vasovagal Pacemaker Study has been criticized for the extraordinarily small number of patients enrolled, the lack of a true control group (that is, the pacemaker was implanted in all patients but was programmed off in some), and the lack of standardized medical therapy. In the Vasovagal Pacemaker Study II, which is now under way, all patients are randomly assigned to receive pacemakers with effect-pacing mode or no-pacing mode. Guidelines from the American College of Cardiology and the American Heart Association suggest a class IIb indication for pacing in patients who experience vasovagal syncope in the presence of significant bradycardia reproduced by a head-up tilt with or without isoproterenol or other provocative maneuvers (90). For treatments with a class II indication, conflicting evidence or divergent opinions exist about usefulness or efficacy. A class IIb indication denotes less supporting evidence and opinion.

Figure 4. Clinical guidelines for vasovagal syncope therapy.



Blood pressure and heart rate values are typical baseline ambulatory values, not the values documented during tilt-table testing.

As these findings show, the clinician must rely on less than optimally designed studies for guidance in treating vasovagal syncope. In our group, we have broad guidelines for treatment, which are summarized in Table 3. Blockers that may interfere with the Bezold–Jarisch reflex are the first-line choice because of their antagonistic actions to catecholamines; however, although this choice is logical, it is not proven. Blockers remain widely used because of their relatively low-risk pharmacologic profile. In patients with borderline low blood pressure who may be subject to symptomatic orthostasis, fludrocortisone, midodrine, and compression hose are often used initially. Patients with substantial resting bradycardia may benefit from anticholinergic agents, such as propantheline (Figure 4). The duration of pharmacologic therapy should be determined on an individual basis. A conservative, nondrug approach should be considered in patients with infrequent occurrences and recognizable premonitory symptoms. For patients with frequent and clustered occurrences, a 6- to 12-month trial of pharmacologic therapy seems reasonable. The role of pacing is unclear at this time, and the results of Vasovagal Pacemaker Study II are eagerly awaited.

The success of therapy for vasovagal syncope is similar to that for other chronic cardiac diseases, such as atrial fibrillation, because it is often measured by reduced severity and frequency of symptoms rather than by total eradication of symptoms. It is helpful to inform the patient ahead of time that complete resolution of symptoms is often not possible and that a satisfactory end point may be reduced frequency or severity or a longer prodromal period. Finally, the role of counseling for avoidance of prosyncopal behavior cannot be overemphasized. Patients should be given information on orthostatic changes and should be told to avoid situations that may result in volume depletion. In addition, all patients, especially those who are elderly, should be advised of the effects that common drugs (including alcohol, diuretics, β -adrenergic blockers, angiotensin-converting enzyme inhibitors, nitrates, sildenafil, tricyclic antidepressants, and others) may have on syncope.

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