CME CREDIT

# Evaluating unexplained syncope with upright tilt testing

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**SUMMARY** Trials of upright tilt testing for vasovagal syncope are difficult to evaluate, owing to differing methods used and the lack of a gold standard with which to compare this test. This paper reviews the studies to date and offers recommendations for the clinical use of this test.

**KEY POINTS** Upright tilt testing is performed either alone ("passive testing") or with isoproteronol infusion. Few comparative studies have been performed, but the rate of positive responses appears similar with both types of testing using the same angle of tilt, while the specificity is better with passive testing. At present, tilt testing should be performed only in patients with recurrent and disabling syncope in whom standard testing has failed to disclose a cause and in whom a positive result would help in devising a treatment plan. Patients with heart disease and arrhythmias should be carefully evaluated for arrhythmias before considering tilt testing. Controlled trials of therapy for vasovagal syncope have not yet been done. Treatment is reserved for patients with disabling symptoms.

INDEX TERMS: SYNCOPE; POSTURE; HYPOTENSION, ORTHOSTATIC
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IN NEARLY 45% of patients with syncope, a cause cannot be established.[1,2] Many of these patients may have vasovagal syncope that is difficult to diagnose clinically. Upright tilt testing was developed to provoke vasovagal syncope in the laboratory, a finding that would aid in diagnosis and management in this group of patients. This test has been used since 1984, and approximately 40 studies have evaluated its methodology, sensitivity, specificity, reproducibility, and treatment outcome. This article reviews the usefulness of this test in patients with unexplained syncope.

## PATHOPHYSIOLOGY OF VASOVAGAL SYNCOPE

Vasovagal syncope results from a sudden, transient decline in cerebral blood flow due to hypotension or bradycardia or both, initiated by inhibitory reflexes.[3,4] This reflex is widely believed to originate in the cardiac sensory receptors (mechanoreceptors), located primarily in the inferior and posterior wall of the left ventricle. These sensory nerves can be stimulated by stretching, cardiac

distention, forceful and rapid systolic contraction, and a variety of chemicals. Stimulation of these receptors results in an increase in neural discharges through unmyelinated C fibers to the vasomotor center in the medulla, leading to a sudden increase in parasympathetic activity and a decrease in sympathetic activity. These pathophysiologic changes culminate in sudden hypotension or bradycardia or both, resulting in syncope. Hypotension is considered the central element of this response and precedes the bradycardia.

Upright posture causes blood to pool in the lower limbs, resulting in decreased venous return (*Figure*). The normal compensatory response consists of reflex tachycardia, more forceful contraction of the ventricles, and vasoconstriction. However, in people susceptible to vasovagal syncope, forceful ventricular contraction while the ventricle is relatively empty may activate the cardiac mechanoreceptors, triggering reflex hypotension and bradycardia. Catecholamine release (which may occur with anxiety, fear, and panic) may also activate the nerve endings responsible for triggering this reflex by increasing ventricular contraction. For this reason, catecholamines have been used to potentiate the vasovagal response to upright tilt testing.

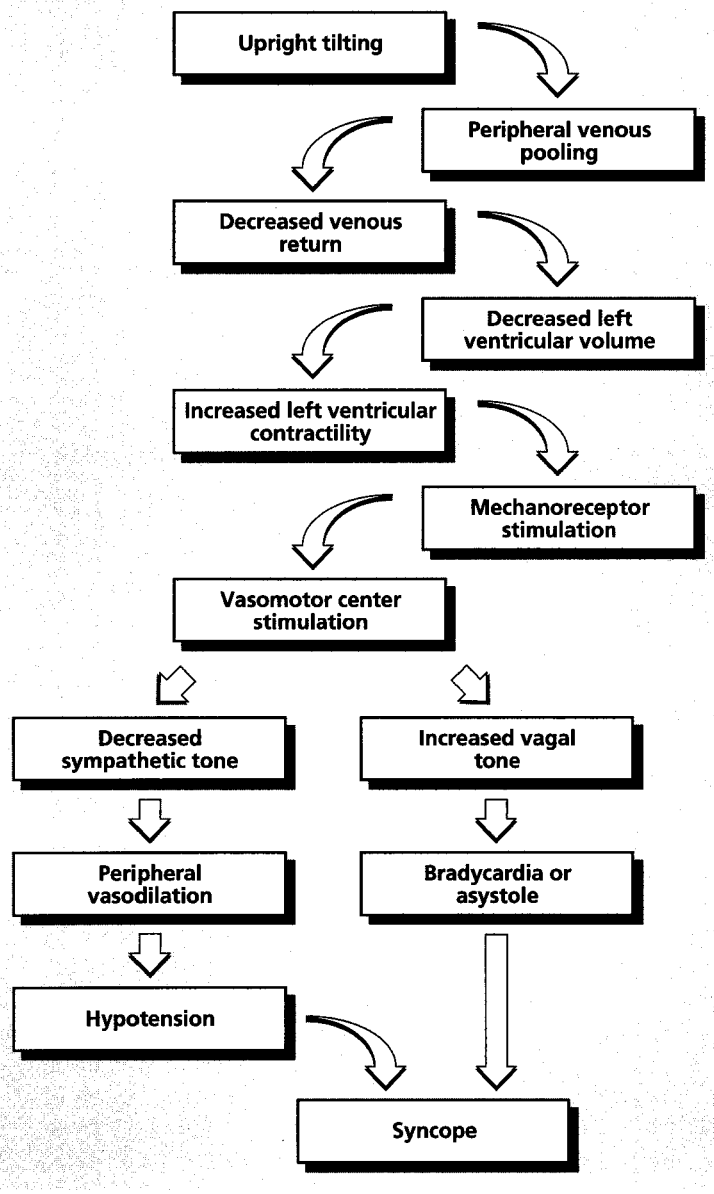


**FIGURE. A pathophysiologic mechanism for induction of vasovagal syncope during upright tilt testing.**

## COMMON TESTING PROTOCOLS

The most widely used protocols use footboard support and tilt testing either alone ("passive testing") or with isoproterenol infusion after a brief period of passive tilt testing. Experiences with other agents such as epinephrine, edrophonium, or nitroglycerine are very limited. Tilt testing with saddle support is not used clinically because of concern about lack of specificity.

### Passive tilt testing

After the baseline supine blood pressure has been measured and continuous monitoring of heart rate

started, patients are suddenly brought to an upright position. Syncope or presyncope (defined as severe lightheadedness or impending loss of consciousness) in association with hypotension or bradycardia constitute a positive response. Most studies of passive tilt testing have used a tilt angle of 60 degrees.[5–8] Although some protocols call for 60 minutes of testing, Fitzpatrick et al[5] advocate 45 minutes total duration, which is two standard deviations more than the mean time at which a positive response occurs (approximately 24 minutes).

### Tilt testing with isoproterenol

All testing protocols incorporating isoproterenol start with a passive phase of testing, usually lasting 10 to 15 minutes.[9–13] If an end point is not reached in this time, the patient is generally brought back to a supine position and an isoproterenol infusion is started. The most common starting infusion rate is 1 μg/minute, continued for 10 to 15 minutes. If the patient does not experience an end point during this phase of testing, he or she is again brought to a supine position and the isoproterenol infusion is increased. The patient is then tilted again for a similar duration as before. This procedure is continued until the patient has a positive response or another end point (eg, a heart rate of more than 150 beats per minute or intolerance to isoproterenol) while upright. The maximum infusion rate of isoproterenol used in reported studies was 3 to 5 μg/minute.

## DIFFERENCES IN METHODS

Tilt testing methods vary, and one must consider several issues in performing upright tilt testing.

First, approximately half the studies explicitly stated that testing was done after an overnight fast. Since fasting is a predisposing factor for vasovagal syncope, it may affect the results. Additionally, vasoactive drugs (eg, calcium-channel blockers, vasodilators, diuretics) should be withdrawn approximately five half-lives before testing.

Second, blood pressure was monitored either noninvasively (eg, by blood pressure cuff) or invasively (eg, intra-arterially). Although concern has been voiced that invasive procedures may provoke vasovagal reactions, the effect of intra-arterial monitoring has not been clearly established. Further, invasive monitoring increases the cost and complexity of testing. In addition, no standard definitions of hypotension or bradycardia have been used in all the studies.

Third, the environment in which the testing was done was frequently not stated. The test should generally be performed in a quiet room, minimizing the surrounding noise such as beepers and traffic. There should be ample lighting, and the temperature should be kept comfortably cool. Noisy conditions and warm room temperatures affect the positive responses to this test.

Fourth, the angle of tilt has varied. Most studies with isoproterenol used 80 degrees, although some studies used 60, 70, or 90 degrees. The duration of the passive phase of testing has also varied, ranging from 5 minutes to up to 60 minutes.[14] Finally, different studies used different dosages of isoproterenol: most used starting infusion rates of 1 μg/minute, but one started with bolus doses of 2 μg and one has varied the infusion rate according to body weight. The maximum dose of isoproterenol has also varied.

The effect of these variations in protocol on response rates has not been well studied, and which protocol has the best sensitivity and specificity has not been determined. Additionally, it is difficult to compare the results of passive tilt testing with the results of isoproterenol tilt testing, as the angles used differed markedly and the isoproterenol tests lasted longer. There have been very few comparative studies in which passive and isoproterenol testing was performed at the same institution.

## RESULTS IN PATIENTS WITH UNEXPLAINED SYNCOPE

In studies of passive upright tilt testing,[5–8,15–19] approximately 50% of patients (range 26% to 90%) had a positive response. Most of the positive responses were considered identical or similar to the patients' spontaneous symptoms in studies that reported symptom correlation. In studies of isoproterenol tilt testing,[9–13,20–28] approximately 66% of patients (range 39% to 87%) had positive responses. Approximately two thirds of the positive responses occurred during the isoproterenol phase. With either type of testing, most responses appear to be cardioinhibitory (defined as bradycardia with or without associated hypotension), and approximately one third are pure vasodepressor reactions (defined as hypotension without significant bradycardia).

As noted above, it is difficult to compare the

proportion of patients who have positive responses in the two types of tests because the tests were done at different angles and for different durations. A similar number of patients have positive responses to tilt testing at 60 degrees with isoproterenol and to passive tilt testing at 60 degrees for 60 minutes, 52% vs 54%, respectively.[5–7,15,16,18,20,27,28]

## PROBLEMS WITH SENSITIVITY AND SPECIFICITY

One of the problems with tilt testing to provoke vasovagal syncope is that specificity and sensitivity may not have their usually accepted meanings when applied to this test.

### Specificity: What is 'normal'?

Specificity is defined as the proportion of normal subjects who have negative test results. Therefore, to determine the specificity of a test, it must be performed in subjects who are free of the disease in question. The specificity of upright tilt testing has been determined by testing subjects who had not had syncope previously[14] and who were free of heart disease or electrocardiographic abnormalities.[13]

However, the pathophysiologic mechanisms of vasovagal syncope suggest that this reflex is part of a normal cardiovascular response. Thus, all normal people have the potential of having vasovagal syncope, and it is not surprising that a large number of normal subjects have positive responses. Since it is not possible to define individuals who are disease-free at this time, the concept of specificity may not apply to vasovagal syncope.

The reported specificity of passive tilt testing has ranged between 0% and 100%, although the overall rate is approximately 90%.[14] The specificity of isoproterenol testing is lower at approximately 75%; the false-positive rate has been low in most studies but has been as high as 65%. The subjects in studies that reported poor specificity of tilt testing with isoproterenol were generally younger than those in studies reporting higher specificity.[13,14]

Several studies have performed upright tilt testing in patients with other putative causes of syncope such as arrhythmias. In one study, 54% of patients with sick sinus syndrome and syncope had positive responses[15]; in another study, 24% of patients with various arrhythmias and 11% of patients with sinus-node abnormalities had positive responses.[5] Thus, the specificity calculated in these groups of patients appears to be low.

### Sensitivity: Gold standard lacking

The concept of sensitivity is also problematic, for two reasons. One, sensitivity is determined by dividing the number of patients who have positive test results by the number of patients who have the disease. Thus, the disease must be diagnosed independently of the test by using a separate gold standard. However, there have been very few studies of tilt testing in patients with vasovagal syncope diagnosed independently of the tilt-test response. Two, if false-positive rates are high in controls, it is possible that a similar proportion of patients with syncope may have false-positive responses. Thus, the calculation of a reliable sensitivity may not be possible.

In small studies of patients who had vasovagal syncope that was diagnosed clinically, 67% to 83% had positive responses to tilt testing, and these figures have been taken as the sensitivity of this test.[28,29] Further studies are needed to better define the sensitivity of tilt testing. These studies could use well-defined groups of patients with clinically diagnosed vasovagal syncope, since this is the only gold standard available.

## REPRODUCIBILITY

There has been concern that the results of tilt testing may not be reproducible, since the vasovagal response may depend on autonomic tone, which can vary from day to day. Most studies have shown this test to have adequate reproducibility, with concordance rates ranging between 67% and 85%.[5,7,22,30] One recent study, however, showed the test to have a remarkable lack of reproducibility.[31] In 109 patients who underwent two consecutive days of passive testing, there was a 63% rate of discordance between the first and second days. Of patients who had vasovagal syncope on the first day, only 31% had it on the second day.[31] This problem needs to be further investigated.

## TREATING VASOVAGAL SYNCOPE

Vasovagal syncope varies in its severity and natural history. Patients may have a cluster of syncopal episodes that may diminish or resolve spontaneously. Thus, the frequency and severity of events need to be considered when starting long-term therapy. Because of potential side effects, treatment should be reserved for patients with frequent or disabling symptoms.

Various drugs and pacemakers (*Table*) have been tried for vasovagal syncope, and uncontrolled studies have reported a decrease or resolution of symptoms with all of them. Most commonly used are the beta blockers (eg, metoprolol and atenolol).[11,24,25,27] How beta blockers prevent syncope is not fully understood, but they may inhibit the activation of cardiac mechanoreceptors by decreasing cardiac contractility. Anticholinergic drugs such as transdermal scopolamine may be useful, particularly in patients with profound bradycardia during upright tilt testing.[7,8,11,25] Disopyramide has anticholinergic and negative inotropic effects that may inhibit activation of cardiac mechanoreceptors. Measures to expand volume have been tried and include increased salt intake, custom-fitted counter-pressure support garments from ankle to waist, and fludrocortisone acetate (0.1 to 1 mg/day).[11,25,27] Potential side effects of volume-expanding measures may include recumbent hypertension, hypokalemia, fluid retention, and congestive heart failure.

Theophylline has been used on rare occasions.[32] Its mechanism of action in the treatment of vasovagal syncope is not known, but a blockade of the effects of adenosine, which has vasodilatory effects, is postulated. Finally, atrioventricular pacing may be considered in patients who have recurrent disabling symptoms for whom medical therapy has failed and who have significant bradycardia in response to upright tilt testing.[7,17,24]

There is concern about the efficacy of any of the treatments for vasovagal syncope, since one recent randomized trial showed no difference in recurrence of syncope between a group of 15 patients treated with variety of drugs such as atenolol, dihydroergotamine, and cafedrine, and 15 untreated patients.[33]

**TABLE**
**COMMONLY USED DRUGS FOR RECURRENT VASOVAGAL SYNCOPE**

| Drug | Dosage |
|---|---|
| Beta blockers | |
| Atenolol | 25–200 mg/day |
| Metoprolol | 50–200 mg/day |
| Propranolol | 40–160 mg/day |
| Disopyramide | 200–600 mg/day |
| Fludrocortisone | 0.1–1 mg/day |
| Fluoxetine | 20–80 mg/day |
| Scopolamine patch | 1 patch every 2–3 days |
| Theophylline | 6–12 mg/kg/day |

## RECOMMENDATIONS

Although upright tilt testing is commonly used for evaluating syncope, there are several problems with the performance characteristics of this test. Furthermore, controlled trials of the therapy of this disorder have not been done. However, the available data allow the following recommendations to be made.

The test should be used only when other workup has been negative and the information will help in devising a treatment plan. In particular, patients with heart disease or abnormal electrocardiographic findings should undergo careful evaluation for arrhythmias (including electrophysiologic testing if needed) before one considers tilt testing. Tilt testing is most likely to be helpful in patients with recurrent and disabling symptoms, since therapy is generally reserved for these patients.

Because of problems with specificity, the only test of potential clinical significance is the one that reproduces the patient's spontaneous symptoms.

If the angle of testing is taken into account, the positive response rates are similar in passive testing and in isoproterenol testing. Since the specificity appears to be better with passive testing, this type of protocol is recommended.

Only patients who have disabling symptoms should undergo treatment, since patients with rare or only one episode of syncope may not have future recurrences and thus may not need any treatment.

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