



Twenty-eight years of research permit reinterpretation of tilt-testing: hypotensive susceptibility rather than diagnosis

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In 1986, the first report of tilt-testing used for the diagnosis of reflex syncope was published.¹ There followed wide dissemination of its use in worldwide clinical practice with vast numbers of publications (>2000 from the Internet).² As these publications accumulated, there followed growing scepticism over the test's utility. The limitations of the test, perceived today, are summarized by these statements:

- 'Too often negative in patients who have likely reflex syncope implying low diagnostic sensitivity';
- 'Too often positive in patients without history of reflex syncope implying low diagnostic specificity';
- 'Of no value in assessing efficacy of treatment with drug or pacemaker due to the low reproducibility of the test'.³

Review of 28 years' research involving tilt-testing now permits re-interpretation of its clinical meaning. Sensitivity and specificity require a gold standard for their calculation. Universal agreement may be expected on the diagnosis of vasovagal syncope in patients with typical emotionally (e.g. fear, pain, instrumentation, venipuncture) triggered syncope, who show signs of autonomic activation (abdominal discomfort, nausea, sweating, etc.) and have no competing diagnoses.⁴ There are published data from patients with true vasovagal syncope allowing calculation of sensitivity ranging from 78 to 92%.⁵ Furthermore, in those who have no history of syncope specificity ranged from 87 to 92%^{6–8} (Figure 1). The problem with tilt-testing is, therefore, not sensitivity and specificity, which are at acceptable levels for these populations. In a recent meta-analysis,² the test showed to be able to differentiate between patients with syncope and control subjects with an odds ratio of 12. There is, however, an inability to apply the test to populations with syncope of uncertain cause, where it is hoped tilt-testing might prove decisive. In these clinical settings, tilt-testing fails to deliver. Indeed, tilt-testing was positive in 51–56% of patients with atypical clinical features, suggesting a reflex mechanism,^{9,10} in 30–36% in patients with unexplained syncope after full investigation^{5,11} and in 45–47% of those with true cardiac arrhythmic syncope.^{10,12} In other words, tilt-testing

offers no diagnostic value in those for whom it is most needed providing the basis for its critical appraisal by NICE¹³ and others.

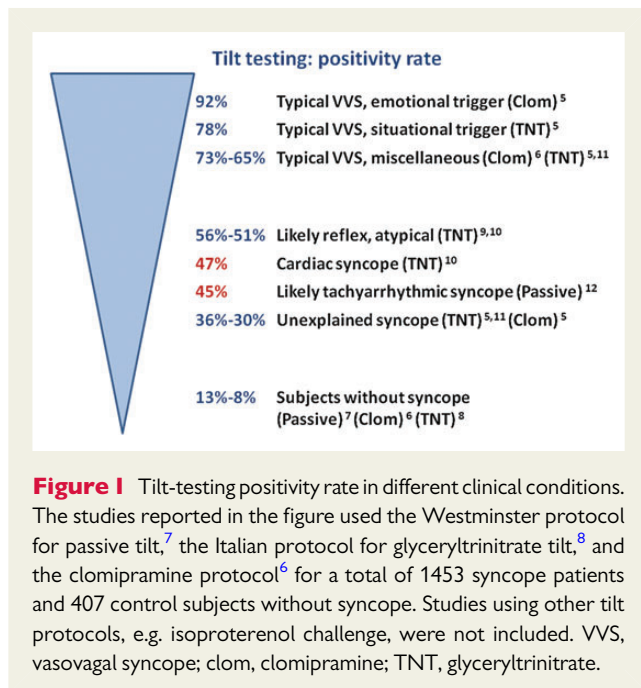
The discrepancy can be explained by a new different interpretation of tilt-testing. Our interpretation is that tilt-testing reveals a susceptibility to vertical posture stress, which is initially due to fluid shift, vertically induced, and in the majority involves the hypotensive (vasodepressor) aspect of reflex syncope. This hypotensive susceptibility is present in many, possibly all, humans but most obvious in those who have a history of syncope and a positive tilt-test. Thus, a positive tilt-test suggests the presence of a hypotensive susceptibility, which plays a role in causing syncope irrespective of the aetiology and mechanism of syncope. For example, in arrhythmic syncope caused by paroxysmal atrial tachyarrhythmias, the mechanism is a combination of the onset of the arrhythmia itself and hypotensive susceptibility, corroborated by positive tilt-testing.^{12,14} Similarly, multifactorial mechanisms are likely in other types of cardiac syncope, for example, aortic stenosis,¹⁵ hypertrophic cardiomyopathy,¹⁶ and sick sinus syndrome.¹⁷ The presence or absence of susceptibility explains the occurrence of syncope in some and not in others affected by the same severity of arrhythmia or structural defect.

This re-interpretation of tilt-testing has recently raised important practical utility because the presence or absence of hypotensive susceptibility plays a major role in guiding pacemaker therapy in patients affected by reflex syncope. The ISSUE 3 randomized controlled trial¹⁸ demonstrated for the first time that some older patients with ECG documentation of spontaneous asystolic reflex syncope can benefit from pacing. However, the benefit shown was less than perfect with a 2-year recurrence rate of 25%. The patient group that most greatly benefited from pacing was that where tilt-testing was negative (showing 5% 2-year recurrence) in contrast to those who were tilt-positive but had similar ECG findings who did not differ from untreated patients (55% 2-year recurrence).¹⁹ We explain this by the hypothesis that tilt positivity is indicating an associated hypotensive susceptibility, involving both reduced pre-load and after-load, to reflex syncope rendering cardiac pacing less effective. In these patients tilt-testing can now be regarded as a risk stratification tool rather than being diagnostic. This re-interpretation will drastically change indications for pacing in patients

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with reflex syncope. Indeed, before ISSUE-3 trial, cardiac pacing has only been evaluated in positive tilt-test patients; no indication for patients with negative tilt-testing existed. Now, permanent pacing can be offered to 'tilt-negative, spontaneous asystolic' patients with a fairly good probability of effective therapy. Similarly, in carotid sinus syndrome patients who also had positive tilt-tests there was 2.7-fold greater syncope recurrence probability after dual chamber pacing than in those with negative tilt-tests.²⁰ In these two types of reflex syncope when tilt-testing is positive caution must be recommended over pacemaker implantation.

There is also strong rationale for discontinuation or dose reduction of hypotensive medication and use of measures to increase systemic blood pressure in patients with syncope of any aetiology and hypotensive susceptibility to tilt-testing, but larger controlled studies are necessary to confirm this initial observation. Some small studies^{21,22} have shown that tilt-positive hypertensive patients with syncope benefit from a withdrawal of medication. This is a logical extension of the hypothesis enunciated above.

In addition to this reinterpretation, it should be stated that tilt-testing remains valuable in assessing some conditions, such as delayed orthostatic hypotension, postural orthostatic tachycardia syndrome, and psychogenic pseudosyncope, which remain undiagnosed after the initial evaluation.⁴

In conclusion, evidence from the last 28 years suggests that tilt-testing reveals a hypotensive/vasodepressor susceptibility, which may exist not only in reflex syncope, but also in coincidence with other causes of syncope. Its identification is important in management including selection of effective therapy.

Conflict of interest: none declared.

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