Editorial

Head-up tilt testing
The balance of evidence

Head-up tilt testing has emerged as a useful investigation in patients who are thought to have recurrent vasovagal syncope with systemic hypotension, bradycardia, or both (the malignant vasovagal syndrome or neurocardiogenic syncope). This is a new approach to an old problem and it is not surprising that many issues are unresolved.

Mechanism
Syncope is probably caused by activation of the Bezold-Jarisch reflex, provoked by a reduction in cardiac venous return and high concentrations of circulating catecholamines. The afferent limb of the reflex is transmitted to the area of the medulla in the brain stem through vagal A and C fibres and may be activated by stimulation of ventricular mechanoreceptors caused by vigorous contraction of the atria and great veins is an important component of vasovagal syncope. In either case, activation of the reflex causes central vagal stimulation and sympathetic withdrawal resulting in arterial vasodilatation, hypotension, and bradycardia. Patients can be divided into either vasodepressor or cardioinhibitory subgroups if they show a predominantly hypotensive or bradycardic response.

The reasons for the inappropriate and abrupt activation of the Bezold-Jarisch reflex in patients with the malignant vasovagal syndrome are not clear. The cardiac mechanoreceptors may be hypersensitive, but this has never been demonstrated. Other possible explanations include changes in endogenous opiate concentrations within the brain stem, unusually high circulating adrenaline concentrations, high concentrations of brain nitric oxide and increased venous pooling with a lack of responsiveness in venous tone.

Methods
Various different tilt test protocols are in use. For example, the recommended tilt angle ranges from 60° to 80° and some centres use a tilt duration of only 15 minutes whereas others continue tilting for up to 45 minutes. Moreover, if there is no response to passive tilting some investigators try to provoke syncope by using a graded infusion of isoprenaline to enhance sympathetic drive and peripheral vasodilatation. The methods used for blood pressure monitoring also vary; though intra-arterial cannulation provides uninterrupted readings it may reduce the specificity of the test because instrumentation has been shown to increase the incidence of syncope.

There is no reference standard or confirmatory test for the diagnosis of malignant vasovagal syncope, so it is impossible to assess the incidence of false negative tilt tests. There is no doubt, however, that the test can induce syncope in “normal” individuals and the false positive rate seems to increase as the protocol becomes more aggressive. Fitzpatrick et al reported that tilt testing was positive in 7% of control subjects with no history of syncope when they were tilted for 45 minutes at 60°. However, the false positive rate may be as high as 46% if subjects are exposed to repeated tilting at 80° augmented by an isoprenaline infusion. Moreover if a saddle support is used instead of the normal footplate up to 67% of control subjects may be tilt test positive. This loss of specificity may occur because the saddle technique abolishes the calf muscle pump and increases peripheral venous pooling. Finally, a positive test is not always reproducible and 20% of tilt test positive subjects will have a negative response to repeated tilting.

A reproducible and strongly positive tilt test is likely to be clinically significant, but the test is not infallible and the results must be interpreted in conjunction with all the available clinical information. Patients with recurrent syncope and evidence of structural heart disease are likely...
to have other causes of syncope such as an arrhythmia or hypotension secondary to ischaemia and should be thoroughly investigated before tilt testing is considered. Early referral for tilt testing, however, is appropriate if the history is typical of vasovagal syncope and there is no evidence of important structural heart disease.

Management

Although the optimum treatment has not been defined both drug treatment and permanent pacing have been used with some success. All patients should be advised to avoid prolonged standing and to lie down as soon as they suspect any premonitory symptoms; indeed, this may avoid the need for specific treatment in some patients with infrequent syncope and adequate warning symptoms.

Petersen et al reported their experience at the Westminster Hospital in treating the cardioinhibitory form of malignant vasovagal syndrome. Patients who developed a bradycardia in response to a relatively benign tilt protocol were treated by inserting a permanent dual chamber pacemaker programmed to DDI mode with rate hysteresis (this avoids pacemaker mediated tachycardia while preserving atrial synchrony during periods of bradycardia). Further syncope occurred in 38% of patients and only 27% of the subjects remained symptom free during a mean follow up of 50 months. However, 89% of patients reported some improvement after pacing.

There have been reports advocating the use of medical treatment guided by repeated tilt testing. Vagolytic drugs such as scopolamine are logical forms of treatment but seem to be effective in only a minority of patients. In contrast several reports suggest that between 25% and 80% of patients with a positive tilt test will become negative when treated with beta blockers. These drugs are thought to act by reducing the force of ventricular contraction and preventing stimulation of ventricular mechanoreceptors. Alpha adrenoceptor agonists may also be effective in some patients—perhaps by nullifying the effects of central sympathetic withdrawal at the time of syncope.

Miletstein et al have reported that treatment with disopyramide is remarkably effective. During follow up over 20 months nine of 10 patients were symptom free and all patients were negative on repeat tilt testing. Disopyramide is believed to act through a combination of negative inotropic activity, anticholinergic activity, and peripheral effects. Morillo et al, however, found no evidence of a beneficial effect from disopyramide treatment in a placebo controlled study. Intravenous disopyramide did not reduce the incidence of positive tilt tests and long-term oral treatment was no better than placebo—less than a third of patients in either group had syncope over 21 months.

In another controlled trial of medical therapy Brignole et al compared treatments with atenolol, dihydroergotamine, domperidone, cafedrine, or elastic stockings with placebo in 30 patients. None of these treatments reduced the incidence of syncope; however, the follow up period was short (average 10 months) and only 27% of patients in the placebo group experienced recurrent syncope.

One of the most successful reported regimens used either medical treatment or permanent pacing chosen on the basis of repeated tilt testing. Six patients with reproducible asystole induced by tilt testing were treated with a beta blocker or disopyramide whereas four were treated by permanent dual chamber pacing; all remained symptom free during a mean follow up of 20 months.

Sra et al also used repeated tilt testing to assess the efficacy of cardiac pacing and drug treatment in 22 patients with cardioinhibitory vasovagal syncope. Twenty patients remained tilt test positive despite temporary dual chamber pacing whereas 19 patients became tilt test negative on drug treatment alone; moreover, 94% of those treated with long-term medical treatment remained symptom free during 16 months’ follow up.

Conclusion

Tilt table testing is now established as a useful investigation for patients with unexplained recurrent syncope. However, we still need well designed controlled trials to define the optimal treatment and target strategies. In addition the development of a confirmatory test would make patient assessment more definitive.

On present evidence it seems reasonable to start treatment with a beta blocker or disopyramide and assess the response by repeating the tilt test. Permanent pacing should be considered only if these measures fail, in which case the logical choice is a dual chamber system programmed to the DDI mode with search hysteresis.

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