EDITORIAL COMMENT

Tilt Methodology in Reflex Syncope: Emerging Evidence

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Tilt-table testing for patients with unexplained syncope was first described in 1986 by Kenny et al. (1) and later by Almquist et al in the U.S. (2). The tilt protocols proposed differed, with the Westminster Protocol favoring prolonged passive tilt alone (1,3) and the Minneapolis Protocol routinely using isoproterenol provocation (2). Although there is now widespread acceptance of tilt testing, many patients with unexplained syncope still remain undiagnosed (4,5), and a drug challenge during tilt has been part of efforts to raise the sensitivity of the test. Unfortunately, such efforts inevitably reduce specificity, which all tilt protocols lack to a degree (2,3,5,6). During development of the test over the last decade, there is still no universally accepted protocol. Also, many published series have included very different patients, and these two factors together have resulted in uncertainty about the true value of the test. There is controversy over the angle of tilt, the duration of tilt, and the role of drug provocation. Further, it is still unclear what triggers a spontaneous or tilt-induced reflex syncope, why the hemodynamic responses are so variable, why the test is often not reproducible, and what the treatment of the condition should be, if needed at all!

One of the most puzzling of all findings is the wide variation in the yield of tilting in unexplained syncope, ranging from 26% to 87% (3,7–9), and the pretest likelihood of a positive response may explain this. One study reported 145 consecutive unselected patients with syncope referred for tilting (10). Subgroup analysis showed that in young patients with structural heart disease and a single episode there were no positive tests, whereas at the other extreme, in patients over age 50 with recurrent syncope and no structural heart disease, 73% had tilt-induced syncope. A range of yields was noted in other subgroups between these extremes. Also in that study (10) two different drug provocations (isoproterenol or edrophonium) were randomly applied after prolonged tilting, with a maximum added yield of positive responses of 17%. Clearly, if patients included in different series were different, then the yield of a particular protocol would also be expected to be different in different centers.

Another variable is tilt-angle, with 60° the minimum used, but many groups deploy a variety of angles up to 90° (2,11,12). Some investigators have suggested that a steeper tilt angle increases yield (6,13), but steeper angles are more difficult for patients because they limit support. One study examined the hemodynamic consequences of randomly tilting at 45°, 60°, 75° and 90° on control subjects, and investigators found no evidence of an increased hemodynamic stress above 60° (14).

A major controversy has centered around the value of passive tilt alone versus drug-provoked tilting. The benefits claimed for drug-provoked tilt are that it shortens the time needed for tilt testing and increases yield. The first drug promoted was isoproterenol. It was chosen for tilt-testing because it was widely believed that reflex syncope resulted from inappropriate triggering of left ventricular stretch receptors with the high inotropic state achieved during orthostatic stress (15,16). This mechanism is no longer thought likely, partly because of syncope induced in orthotopic heart transplant recipients (17). However, very high false positive rates have been demonstrated in control subjects (5,6), and the dose of the drug used is clearly critical. More recently, Morillo and co-workers (18) evolved a low-dose regime that shortens tilt-testing while allowing acceptable specificity. One of the remaining concerns of isoproterenol regimes is the need for intravenous (IV) cannulation. This has been shown to increase the chance of tilt-induced syncope fivefold in controls (19).

Another drug in common use for tilt provocation is glyceryl trinitrin (GTN) (20–22). Initial regimes used IV drug challenge (20), raising similar concerns about false positive tests due to vascular instrumentation, as above. However, recent work has demonstrated that the drug can be administered as a sublingual tablet, can be effective, and is even more effective when given as 400 μg in an aerosol spray (the “Italian Protocol”) (21,22). A large body of evidence has now been accumulated to show that sublingual GTN substantially increases the yield of tilt-testing in unexplained syncope and that false positive rates are similar to those achieved with prolonged passive tilting (23). However, the mechanism of action is still uncertain. Clearly, venodilatation and some arteriolar vasodilation must occur, but we do not know whether the vascular response is specifically abnormal in patients who have spontaneous reflex syncope. Echocardiography during tilt-induced syncope has shown ventricular “collapse” and cavity obliteration (24,25), and this was thought to be due to a great increase in inotropy. However, it is far more likely to be secondary and due to an abrupt fall in venous return, which GTN might help to trigger. Difficulty in measuring venous return directly makes it the confounding hemodynamic variable in understanding the pathogenesis of reflex syncope.

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In this issue of the Journal, Theodorakis et al. (26) describe the use of drug provocation with clomipramine during tilting in unexplained syncope; they have achieved a high yield in patients with low false-positivity. Use of this drug is interesting, as it acts by stimulating central serotonergic activity by inhibition of serotonin re-uptake in the synaptic space. There is growing evidence that serotonin plays an important role in normal blood pressure regulation through modulation of sympathetic tone (27), and other work has indicated a possible role for a disturbance of the serotonergic system in reflex syncope (28). Further work is needed to confirm the results.

As we enter a new millennium, tilt-testing has achieved respectable ability in helping to manage patients with troublesome recurrent unexplained syncope, with 60% to 70% of such patients responding to orthostatic stress by reproduction of their presenting symptom. We know that a period of passive tilt is needed, with 60° seeming to be the optimum angle of tilt. Drug provocation with certain isoproterenol or GTN regimes is acceptable and may increase yield but not cause too many false-positive tests. The continuing challenges include understanding what happens during reflex syncope, explaining why patients have episodes so sporadically, and finding more effective treatment for them. It is likely that the latter will be available only when we have come to understand the former.

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