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EDITORIAL COMMENT

Can We Assess the Efficacy of Therapy in Neurocardiogenic Syncope?*

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Blood pressure and heart rate are controlled by complex interactions between different reflexes, including input from low-pressure cardiopulmonary receptors and high-pressure baroreceptors that are within the aortic arch and carotid sinus. Although the exact mechanisms leading to neurocardiogenic (vasovagal) syncope remain somewhat unclear, during central volume unloading the inactivation of high-pressure baroreceptors and paradoxical activation of low-pressure cardiopulmonary mechanoreceptors leading to efferent sympathetic inhibition and parasympathetic stimulation have been proposed as a model of neurocardiogenic syncope (1–3).

See page 554

It has been shown that head-up tilt-table testing can be used to identify patients with syncope in whom hypotension and bradycardia are likely to develop (4–8). Beta-adrenergic receptor blocking drugs were among the first agents used, and they continue to be widely used for prevention of neurocardiogenic syncope (9–11). This is a logical choice because both spontaneous and tilt-induced syncope are preceded by elevated levels of catecholamines (12). Although beta-blockers have been evaluated during both acute intravenous (IV) and long-term oral use in patients with neurocardiogenic syncope, their efficacy during long-term use remains somewhat controversial because of conflicting data among studies (13,14), and there is an absence of large randomized trials.

As with any other condition, all patients with neurocardiogenic syncope may not respond to any particular intervention. Consequently, the appropriate use of pharmacological therapy in patients with neurocardiogenic syncope has been undermined by a number of factors, including difficulty in demonstrating the efficacy of a therapy under controlled conditions, unrealistic end points (e.g., a goal of entirely eliminating all symptoms) and inadequate understanding of the natural history of this problem.

In the study published in this issue of the *Journal* (15), 50 patients with syncope underwent tilt-table testing (80° tilt angle for 45 min). Twenty (40%) of these patients had an abnormal response, and IV atenolol prevented a positive second test in only 5 (25%) of these 20 patients. All 50 patients were then randomized to receive either atenolol (50 mm/day) or a placebo. Of the 20 patients with a positive tilt-table test, 8 had received atenolol. It is unclear how many of these eight patients had a second positive tilt-table test on atenolol. Forty of the 50 patients completed the study, but it is not clear why the other 10 did not, nor is it reported to what group they had been assigned. During one-year follow-up, 16 patients on atenolol and 11 patients on placebo had recurrent syncope (61% vs. 45%, $p = 0.09$). Again, it is unclear how many of the patients with recurrent syncope while on atenolol belonged to a positive tilt group.

Although treatment of neurocardiogenic syncope may be controversial, there is no evidence in the literature showing any role for elective beta-blocker therapy in patients with presumed neurocardiogenic syncope. It is, therefore, surprising that the investigators elected to assign all patients who had a negative tilt-table test to the trial along with the patients who had a positive tilt-table test, this despite the fact that even a steep angle and long duration of test led to a negative tilt test in the majority of patients included in the study (16). This clearly dilutes the results of the study significantly, making any interpretation of the findings difficult.

This could also explain the discrepancy in results between the current study and the study by Mahanonda et al. (14), where 42 patients with neurocardiogenic syncope (i.e., a history of syncope or presyncope and a positive tilt-table test) were randomly assigned to treatment with either atenolol or placebo. At one-month follow-up, response rates (negative tilt-table test) in the atenolol group were 62% versus 5% in the placebo group ($p = 0.0004$). Moreover, 71% of the patients who received atenolol reported that they felt better, whereas only 29% on placebo did.

Can IV beta-blocker administration be used to determine the proper oral therapy in patients with neurocardiogenic syncope? The question is important, as only five patients in the study reported in this issue of the *Journal* had a negative tilt-table test on atenolol. Intravenous esmolol, metoprolol, and propranolol have all been used in this regard (10,17,18). Some studies have shown a strong concordance between the effects of IV beta-blocker and oral beta-blocker therapies. Use of IV esmolol administration seems to be particularly helpful in this regard, as rapid dose-dependent beta-blockade can be achieved, maintained, and provided consistently from one patient to another. A high concentration of esmolol (4 μg/ml) has been seen when it is given in a loading dose of 500 μg/kg per minute for 4 min followed by a 300 μg/kg per minute maintenance infusion. This concentration can be maintained throughout the infusion. Its effects also dissipate rapidly, as demonstrated by increased levels of its metabolite, ASL-8123 (19). In contrast, with

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some other beta-blockers, there may be significant variation between patients when lipid solubility and a large volume of distribution delay sufficient beta-blockade (20).

It has also been shown that in the electrophysiology laboratory, esmolol challenge during head-up tilt-table testing can help identify patients who will have a long-term favorable or unfavorable response to oral beta-blocker therapy. In the study by Natale et al. (21), 112 patients with syncope and positive tilt-table test underwent a repeat test during infusion of esmolol. Regardless of the test's result, all patients were treated with oral metoprolol (50 to 100 mg b.i.d.). During follow-up of 2.7 ± 1.2 years, 36 patients had recurrent symptoms, 32 of whom had not responded to IV esmolol infusion. Only four patients with a positive tilt-table test on esmolol had a favorable response on metoprolol. Similar results have been reported by Cox et al. (10) using propranolol. In their study, only 12 (10%) of 118 patients with a negative tilt-table test during IV propanolol had recurrent symptoms during 28 ± 11 months of follow-up.

A favorable response during IV beta-blockade seen only in five patients in this current study and elective therapy in 60% of the patients who had a negative tilt-table test could thus explain a high incidence of recurrence in patients irrespective of type of therapy—that is, treatment with atenolol or placebo. Given the complexity of the problem and inadequate information on therapy, it is important that a consensus be reached as to how the efficacy of therapy can be assessed accurately in patients with neurocardiogenic syncope. It should also be agreed that a single recurrence is an inappropriate end point because the physiological aspects of the problem can cause symptoms to occur in clusters, and there can be long symptom-free periods. A large-scale multicenter trial using the appropriate pool of patients, which can be followed up for an extended period of time, will then be needed to address the issue more appropriately.

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