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LETTERS TO THE EDITOR

Acute and Long-Term Beta-Adrenergic Blockade for Patients With Neurocardiogenic Syncope

We enjoyed the study by Cox et al. (1) on beta-adrenergic blockade therapy for neurocardiogenic syncope. This study attempted to show that patients who presented with syncope and near syncope had significantly fewer episodes of recurrent syncope and near syncope in 12 months of follow-up if the baseline abnormal tilt table study result normalized on a repeat study using beta-blocker therapy. We had several concerns with the study:

The first concern was the tilt table protocol used. More specifically, we wondered whether the investigators had assessed what their false positive rate of tilt studies was in normal subjects, given the relatively short (10 min) baseline study followed by an aggressive isoproterenol infusion protocol. This is important because isoproterenol has been associated with an increased false positive rate (2). Second was the absence of a placebo arm, which we think was ethical in view of the benign prognosis that these patients have. This issue has obvious clinical implications regarding the need for long-term therapy. Third, the inclusion of patients with near syncope was questionable because it was never defined and may represent a "soft" end point that would be difficult to measure. It would be interesting to see whether therapy still appeared to offer some clinical benefit if only patients with recurrent syncope were analyzed and only recurrences of syncope were acceptable end points. The stated benefit of therapy for this scenario would be unlikely because 39.8% of patients had either near syncope or one episode of syncope. Finally, the duration of follow-up relative to the frequency of reported episodes appeared truncated. More specifically, a 12-month follow-up period would be inadequate in many of these patients because their event rate was not stated to be at least two episodes/year without therapy. If most of the patients had episodes of syncope years apart, a longer follow-up period would be needed, and the ability to prove drug efficacy would be problematic.

In summary, although we think that Cox et al. (1) had a clinically relevant hypothesis to test, the study design flaws noted here make the study results and conclusions difficult to accept.

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Reply

In response to the comments and questions of Vigh and DeAntonio, we did not estimate the false positive rate in normal subjects with our protocol. However, we followed the protocol of Almquist et al. (1), which revealed an 11% false positive rate. The mean age of their control group was 37 ± 17 years, which is significantly younger than our patients (53 ± 20 years for tilt-positive and 59 ± 20 years for tilt negative patients). Brignole et al. (2) studied 25 control patients with an age distribution similar to ours (60 ± 17 years) and observed a 4% false positive rate. The study by Kapoor and Brant (3), using a protocol similar to ours, had 20 control subjects with a mean age of 25 years (range 18 to 37), which, again, is significantly younger than our patients and therefore cannot be considered an appropriate comparison because younger age has been associated with a higher false positive rate in tilt testing (4).

We did not have a placebo arm in the study. Because most of the patients had undergone an extensive workup for recurrent symptoms without a definitive diagnosis or treatment, and given the severity of the patients' symptoms, we did not consider it ethical to withhold treatment. We included patients with near syncope but did not consider this a "soft end point" because all patients referred had symptoms so severe that their activities of daily living were significantly altered. Those patients who had one episode of syncope also had multiple episodes of near syncope, and the one episode of syncope was associated with trauma (broken limb, fall requiring stitches) or an adverse event, such as a car accident.

The event rate was not stated in the article, but recurrent symptoms were present in patients for a mean of 6 months before the initial evaluation. The duration of follow-up relative to the frequency of reported episodes was truncated at 1 year because recurrences, when they did occur, occurred within the first 12 months. The follow-up period extended up to 48 months, but in the absence of events after 12 months there was no need to extend the period.

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Aortic Regurgitation With Extreme Left Ventricular Dilation

The article by Klodas et al. (1) in a recent issue of the Journal concluded that in patients with severe aortic regurgitation and resul-

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