JACC Vol. 28, No. 3
September 1996:798–801

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-

0735-1097/96/$15.00
PII S0735-1097(96)00210-0

tant "extreme" left ventricular dilation, surgical replacement of the valve is not necessarily contraindicated because the increased diastolic dimension is not in itself a marker of irreversible ventricular dysfunction. In multivariate analysis, preoperative left ventricular ejection fraction was the only significant predictor of postoperative ventricular function, and diastolic chamber dimension, as measured by M-mode echocardiography, was not predictive.

Although it has been suggested by others (2) that surgical treatment for aortic insufficiency may be recommended on the basis of preoperative chamber size without adjustment for body surface area, can the present investigators truly support the use of two-dimensional chamber diameter to predict outcome from a study of only 31 patients without acknowledging the subjects' size? It is possible that the subjects were of large enough body habitus to make the two-dimensional diameter measurement relatively less significant. The reason that the study group included only men was quite likely also related to body size. Because women in general have smaller ventricles than men, they would be unlikely to develop an end-diastolic chamber size ≥80 mm. In women (or for that matter, any person of small stature) "extreme" left ventricular dilation might occur at a diastolic dimension of 70 mm, for example. Ejection phase indexes are predictive of outcome and postoperative ventricular function because they are independent of body size.

It would be very interesting to look at the end-diastolic volume index as a variable in this study to see whether it has any predictive value.

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Reply

We appreciate Miller's interest in our recent article (1). He raises important points regarding the management of aortic regurgitation:

1. The rationale for including extreme left ventricular dilation as an indication for operation in patients with severe aortic regurgitation is based on the observation of occurrence of sudden death treated medically with this extreme left ventricular dilation (2,3). However, the postoperative outcome of these patients was poorly defined. As mentioned in our report, the number of patients mentioned in published reports with preoperative extreme left ventricular dilation and followed up postoperatively is very limited, and their outcome was usually described as dismal but was not formally analyzed. Our study (1) fills this gap of knowledge by demonstrating that the postoperative outcome of these patients with extreme left ventricular dilation is acceptable, although mild excess late mortality is observed due to associated left ventricular dysfunction.

Indeed "only" 31 patients had extreme left ventricular dilation based on an end-diastolic diameter ≥80 mm. However, this degree of left ventricular enlargement is unusual, and the present series is, to our knowledge, the largest published. We concur that patients with this degree of left ventricular dilation deserve operation without delay.

2. A very important issue is the problem of the potential bias introduced by using left ventricular diameters unadjusted for body size. We certainly agree that using unadjusted diameters is a problem, particularly for women. We have presented in abstract form (4) a study that is in the process of publication regarding aortic regurgitation in women. Briefly, it shows, as Miller may have suspected, that utilization of unadjusted left ventricular diameters as surgical criteria, either 55 mm at end-systole or 80 mm at end-diastole, is irrelevant in women with aortic regurgitation because they almost never reach this extent of ventricular dilation. This has important consequences for the outcome of women with aortic regurgitation.

3. End-diastolic volume index was not measured, but diameters normalized to body surface area have no better prognostic value than nonnormalized diameters. Therefore, we cannot specifically recommend using the body surface area-adjusted left ventricular diameters for the timing of operation. The ejection phase indexes are predictive of the outcome, not only because they are dimensionless, but mostly because they reflect the reduced myocardial contractility.

4. We think that the good outcome after operation observed in patients operated on early in the course of their disease, as demonstrated in our study (1), should lead to the reassessment of the optimal timing of operation in patients with severe aortic regurgitation. In particular, in light of the poor survival of the patients operated on with New York Heart Association class III or IV symptoms (5), even mild dyspnea or angina should lead to the consideration of operation.

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Measurement of QT Interval

In the January issue of the Journal, Molnar et al. (1) reported exceptionally long QT intervals in their article on the diurnal variation of the correct QT interval (QTc). They measured the QT interval manually from QRS-T wave templates representing 5-min averages obtained from 24-h Holter recordings. However, they do not discuss the reasons why their QT intervals are radically longer than those usually reported. For example, in the Framingham study data (2), which Molnar et al. use in heart rate correction, the measured QT intervals are ~50 ms shorter at respective heart rates. Figure 1 shows the average measured QT intervals at different heart rates in the