Editorial Comment

Cardiac Pacing for Prevention of Vasovagal Syncope*

DAVID G. BENDITT, MD, FACC
Minneapolis, Minnesota

This issue of the Journal provides the eagerly anticipated formal report of the North American Vasovagal Pacemaker Study. The communication is notable for several reasons. First, although prior reports had suggested a possible benefit of pacing in patients with vasovagal syncope (1–4), none were randomized or controlled studies. Consequently, the observation in the North American Study that cardiac pacing was so effective in diminishing risk of syncope recurrences in highly symptomatic vasovagal fainters remained a surprise. If substantiated, such a finding could markedly alter treatment strategy in these patients. Second, the end points examined in this report were more sophisticated than have typically been used in syncope studies heretofore. Specifically, both syncope recurrence and the duration of the asymptomatic interval to first recurrence (a methodology that has become widely accepted in the evaluation of antiarrhythmic drugs [5–7]) were reported. Third, this is the first multicenter randomized study examining a treatment strategy in patients with vasovagal syncope to be reported in its entirety; as such, it is a refreshing departure from the many nonrandomized uncontrolled studies that comprise the bulk of the literature on this topic.

The North American Vasovagal Pacemaker Study was an ambitious project given the considerable uncertainty at the time of its initiation that pacemakers had any role to play in treating vasovagal syncope patients. The goal of the study as stated in the Introduction was to examine the hypothesis that “a decision to implant a pacemaker” would reduce the risk of syncope in a group of patients at high risk of vasovagal syncope recurrences. However, it seems clear that all enrolled patients had to have wrestled with and had to be ready to accept the notion of pacemaker implantation before randomization (only one patient who was randomized to a pacemaker subsequently refused to proceed). Thus, the “decision” process was a prerequisite for all candidates. The treatment effect being tested was, as is more accurately stated in the Abstract, the pacemaker implantation itself. The control group did not undergo a surgical procedure with all its attendant real and psychologic impact, in addition to the additional care and follow-up that a pacemaker requires. Further, although the findings indicate reduced syncope risk in pacemaker-implanted patients, the study design did not permit obtaining direct evidence that it was the pacing (in this case with a “rate-drop response feature”) that did the trick. To be fair, the investigators acknowledge these limitations. In regard to controlling for the implantation itself, investigators provide an eminently reasonable defense that the knowledge base at the time was too shaky to justify device placement in all candidates. In addition, they argue that the absence of any reduction of presyncope frequency in paced patients essentially obviated concerns regarding the “pacemaker placebo” effect. Nevertheless, the principal result cannot yet be considered cast in stone, and for now the clinician must live with doubts that future studies will need to address.

Apart from global issues raised by the study design, a number of other features of the study warrant attention. The inclusion criteria required multiple faints (at least six) as well as a positive tilt-table test in which bradycardia (meeting a predetermined standard) was documented. The duration of time over which the faints had occurred is not expressly stated, but given a median lifetime history of 35 events, it seems reasonable to conclude that the symptomatic period was long, and as such the enrolled patients comprise a relatively high-risk group (4). Clearly, stringent symptom criteria helped justify the offer of pacemaker implantation despite considerable uncertainty as to its value, and also accelerated determination of any treatment effect. However, as the investigators point out, these were not the average vasovagal fainter. The reader needs to be alert to the very symptomatic nature of the study population when considering clinical application of the results. In addition, the study does not permit making any statement regarding the relative merits of pacing versus “conventional” pharmacologic approaches in these patients. Little is stated regarding the aggressiveness with which prior medical therapy had been pursued, or the criteria for failure of prior medical treatment. It appears that only 32 of the 54 patients had received drug treatment (principally beta-adrenergic blockers or disopyramide). Other possibly more effective agents, such as midodrine, may not have been available at the time of the study. Nevertheless, such therapies need to at least be considered by the clinician before pursuing a pacemaker for vasovagal faints. Furthermore, the treatment of the nonpaced control group appears to have been at best haphazard. The investigators may argue that it was immaterial vis-à-vis the study goal. In contrast, absent such a comparison, the reader is left in limbo. It would have been of interest to have selected a single (albeit arbitrary) drug regimen for comparison. Finally, the report does not indicate clearly the distribution of patient enrollment across the multiple participating centers. Pre-

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From the Cardiac Arrhythmia Center at the University of Minnesota, Minneapolis, Minnesota.

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Address for correspondence: Dr. David G. Benditt, Cardiac Arrhythmia Center, Box 508 UMH, Minneapolis, Minnesota 55455.
publication of the data suggests that the vast majority of enrollees came from two sites, and many centers made little or no contribution to the patient population. Consequently, the impact of local treatment biases on study outcome cannot be excluded.

The ultimate impact of the North American Vasovagal Pacemaker Study on pacing practice remains to be seen. Guidelines from several major professional societies (American College of Cardiology/American Heart Association [9], British Pacing and Electrophysiology Working Group [10]) already provide a class II indication for pacing in vasovagal syncope, and the North American Study may substantially increase the frequency with which this indication is cited. Nevertheless, a number of factors may, at least for the time being, limit physician enthusiasm for the pacemaker option. Most importantly, the average vasovagal syncope patient is relatively young, and consequently would be exposed to pacing and its hassles (follow-up, device problems and replacements) for a long time. Second, there is reasonable concern regarding our ability to discern the relative contributions of cardioinhibitory and vasodepressor features of the faint in individual patients. Currently, tilt-table testing is the only widely available approach to this issue, and was relied upon in the North American Study. However, the relationship between observations during tilt-table induced faints, and the pathophysiology of spontaneous syncopal events in the same patient (i.e., the relative magnitudes of cardioinhibitory and vasodepressor contribution), has yet to be studied adequately. This limitation is crucial, because a detectable cardioinhibitory component is needed to even trigger the pacing operation (at least for current generation devices). Furthermore, substantial bradycardia would seem to be an important aspect of spontaneous clinical events for pacing to be useful. It seems unlikely that even relatively rapid pacing could ameliorate a marked vasodepressor element to any important extent. Conversely, not all bradyarrhythmic events (including some relatively abrupt drops in heart rate) equate to vasovagal faints even in highly susceptible patients. Comparable rate changes may occur, for instance, during sleep or even with marked sinus arrhythmia. Finally, it remains uncertain whether spontaneous vasovagal events always exhibit the same pathophysiological features in a given individual. Findings during repeated tilt-table-induced faints have been at odds on this issue. For instance, Chen et al. (11) reported a strong correlation between heart rate and hemodynamic findings in each of two sequential head-up tilt tests undertaken on the same day. These investigators suggested that the characteristics of the induced episodes were generally reproducible within a given patient. In contrast, Fish et al. (12) found that, although syncope or presyncope was reproduced by tilt-table testing in the majority of cases (67%), the pattern of physiologic response (i.e., cardioinhibitory, vasodepressor, mixed) varied. Thus, they raised the concern that the physiologic pattern may be variable in the same patient. Further clarification of this issue by even more careful evaluation of moment-to-moment heart rate and blood pressure changes is needed.

What then should be the role for pacemaker therapy in treatment of vasovagal syncope in the year ahead? Clearly, for most vasovagal syncope patients, education to facilitate recognition and avoidance of provoking events, along with supportive reassurance, remain essential first steps in the treatment strategy. In fact, usually these steps are all that are needed. However, when more than these basic measures are necessary, pharmacologic approaches (perhaps someday supported by randomized trials comparable in quality to the North American Vasovagal Pacemaker Study) are likely to remain more appealing than cardiac pacing for most patients. In this regard, various drugs have been thought to be helpful for prevention of recurrent vasovagal faints (13–24). Beta-adrenergic blockers, disopyramide, certain vasoconstrictor agents (e.g., etilephrine, midodrine), and serotonin reuptake inhibitors have been of greatest interest. However, for any of these agents, current experience is largely limited to small nonrandomized and uncontrolled studies in which syncope recurrence is the only recorded end point. Other end points, such as time to first recurrence, asymptomatic interval and total syncope “burden” (i.e., the number of events per unit time) have yet to be assessed. In any event, if at this stage pharmacologic treatment is deemed to have failed (based on end points for which a consensus needs to be developed) or not to be tolerable, one might reasonably consider the addition of cardiac pacing with some form of rate-drop response and high-rate pacing feature.

Currently, it seems prudent to place a conservative spin on the present status of cardiac pacing in vasovagal syncope. However, it would not be appropriate to cast an excessively negative shadow on what may be a very promising treatment avenue: physicians should not be so reluctant to use pacing that important treatment opportunities are missed. They must be cognizant of the fact that, while vasovagal faints are most often “benign,” recurrent vasovagal symptoms may cause unwanted lifestyle changes in some individuals (e.g., loss of independence, excessive health insurance premiums, restriction of driving privilege) and predispose them to injury or accidents. Additionally, prevention of even infrequent faints may be essential for certain occupations (e.g., airline pilots, commercial vehicle operators, critical-care medical personnel) or vocations (e.g., mountaineers, skiers).

In conclusion, the North American Vasovagal Pacemaker Study has contributed importantly to the concept that implantation of a cardiac pacemaker may benefit certain patients with recurrent troublesome vasovagal syncope. For now, however, the take-home message is one of careful patient selection with cautious optimism regarding treatment benefit. Ultimately, if a number of important barriers can be overcome, pacing for treatment of recurrent troublesome vasovagal syncope may become more common. These barriers include 1) confirmation that symptomatic benefit is clearly attributable to the pacing intervention, 2) development of pacing algorithms that permit specific and sensitive recognition of vasovagal syncope at a relatively early stage in an evolving episode, 3) documentation that the benefits of pacing (i.e., prolonging asymptomatic intervals, reducing symptom severity) are maintained over the
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References