EDITORIAL COMMENT

Implantable Defibrillators in the Third Millennium: Increasingly Relegated to a Standby Role.*

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In the last five years, evidence has accumulated confirming the superiority of implantable cardioverter-defibrillator (ICD) therapy compared to antiarrhythmic drug therapy for prevention of sudden death (1,2). Clinical trials, with rare exception, have established mortality benefits of ICD therapy in a variety of patients at risk for sudden arrhythmic death. Just as clinicians have begun to incorporate this new device therapy into everyday medical practice, recent reports and analyses of existing databases have complicated this relatively straightforward perception. These concepts have taken future development of ICD therapy in several new directions.

Implantable defibrillators and quality-of-life. In contrast to mortality end points, the benefits of ICD therapy with respect to patient morbidity and quality-of-life vis-a-vis drug therapy have always been less convincing. In these trials, device-related complications requiring treatment have ranged from 6% to 16% (1,3). While quality-of-life measures show some areas of patient benefit, this is not apparent in other areas of daily life. Despite patient education and in-hospital experience, the delivery of programmed shock therapy is rarely welcomed by its recipient. Psychologic profiles of ICD recipients regularly identify a fear of ICD shocks, and an association between multiple or “cluster” shock experiences and mood disorders (4,5). Limitations in physical activity, and even temporary suspension of driving privileges, for arrhythmia recurrences after device implantation are generally resented, particularly by active patients. It is therefore not surprising that a variety of technologic and research initiatives have been designed to alleviate these concerns.

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In this issue of the Journal, Higgins and coworkers (6) report the initial results of a randomized comparison of atrial synchronous biventricular pacing with support biventricular pacing on the need for antitachycardia therapy in patients with recently implanted cardioverter-defibrillators using a crossover study design. They report a decline in the number of patients receiving antitachycardia interventions (pacing or shocks) with atrial synchronous biventricular pacing during three-month observation periods in each mode. These findings are intriguing, clinically novel and merit careful consideration. The potential clinical contribution of their findings is to extend the capability of pacing techniques in reducing undesirable effects of antitachycardia interventions, particularly shock therapy delivery in ICD recipients.

Nearly a decade ago, the ability of antitachycardia pacing to diminish the need for shock delivery for ventricular tachycardia (VT) events by 89% was documented by prospective study (3). However, a proportion of VT events, particularly faster episodes and ventricular fibrillation (VF), remained amenable only to shock delivery. The VT episodes, particularly those with rates >180 to 200 beats/min, have been tested with low-energy transvenous shocks (7,8). Even biphasic waveforms have required initial shock voltages >300 V or energies of 5 J with current transvenous lead systems to achieve acceptable efficacy (≥80% initial shock success). While these data have produced rational two- or three-zone VT/VF detection and programming algorithms (9), shock delivery with its attendant patient discomfort has remained the initial therapy in at least two of the three potential arrhythmia detection zones (9). Most shocks are now delivered in the nonsyncopal state, without impairment of consciousness and often occurring during the course of important daily activities of life (10).

Can electrical therapies reduce arrhythmic events? Alternative strategies are being sought to reduce shock exposure. The “holy grail” of electrical therapy for tachyarrhythmia prevention has been prevention of arrhythmia onset by electrical techniques. Strategies to this end have included dual-site stimulation to prevent reentrant ventricular rhythms (11). Stimulation performed at two disparate sites in experimental studies can alter the nature and extent of the arc of conduction block or advance activation in other regions. This can prevent initiation or maintenance of a reentrant tachycardia (11). Widespread clinical use of this technique has actually been performed in patients with atrial fibrillation (12). Contact and noncontact mapping studies have demonstrated that dual-site atrial stimulation can advance biatrial activation and prevent initiation of atrial fibrillation in patients with refractory atrial fibrillation (13–15). The technique has been clinically validated in large observational trials for prevention of drug-refractory atrial fibrillation in a “hybrid” therapy approach. Monotherapy with conventional single-site pacing has been less successful in arrhythmia prevention, particularly in patients with refractory conditions (16). For dual-site ventricular pacing,
the relative location of the stimulation sites to the regions critical to triggers or reentry, as well as the timing of the two stimuli relative to each other, critically influences the extent of electrophysiologic effects (11).

Clinical application of dual-site ventricular stimulation for arrhythmia prevention has hitherto been lacking. In this report, Higgins and coworkers (6) have performed a retrospective analysis of event rates with biventricular stimulation, performed largely for hemodynamic benefit in an ICD population at high risk for recurrent VT or VF. Angiotensin-converting enzyme inhibitor therapy, with its favorable effects on ventricular hemodynamics and remodeling, has been associated with reduced risk of sudden arrhythmic death (17). Biventricular pacing clearly alters atrioventricular filling relationships, especially on the left side with potential hemodynamic advantage, although no data to this effect are presented in this analysis. Thus, the role of improved ventricular function, reduced left ventricular volumes and secondary electrophysiologic effects on triggers or ventricular arrhythmia substrate cannot be judged from their report.

The extent of electrophysiologic impact also cannot be evaluated from the end points presented. The effects of dual-site pacing on ventricular activation patterns and duration can vary in populations with and without intraventricular conduction defects. In atrial fibrillation populations, global P-wave duration decreases by 10% to 25%, as does regional activation times (13). While it has been demonstrated that QRS durations do decrease with effective biventricular stimulation in patients with intraventricular conduction defects, these data are not presented (18). Furthermore, the magnitude and location of these effects are also not available from this study.

The site of ventricular stimulation is an important variable. Over two decades ago, the relationship between the site of origin of a ventricular contraction and its mechanical efficacy in stroke output was reported (19). More recently, Blanc and coworkers (20) showed superiority of left ventricular pacing and biventricular pacing over right ventricular apical or outflow tract pacing with respect to hemodynamic variables such as wedge pressure, cardiac index and systemic blood pressure during short-term studies. Left ventricular pacing was similar to biventricular pacing. Apical ventricular stimulation, particularly if performed simultaneously from the right and left ventricle, produces more effective hemodynamic results than basal ventricular stimulation (21). The difference between epicardial left ventricular pacing in this report and endocardial stimulation has not been well studied. A recent report on the feasibility of chronic endocardial left ventricular stimulation may well stimulate this discussion (22). It is also worthy of note that there may not be concordance between optimal ventricular electrical resynchronization and hemodynamic results. Thus, an activation sequence that may suppress VT/VF onset may not necessarily have the preferred hemodynamic impact.

There are significant methodologic issues in any retrospective analysis, and this clinical trial is no exception. In atrial fibrillation populations, the degree of pacing achieved influences suppression of triggers and atrial fibrillation recurrences (23). No quantitative data are available as to the extent of biventricular pacing achieved in the two groups. The observation periods for arrhythmia prevention were relatively brief (three months) in each mode. While the first six months clearly are associated with the highest event rates, there is an exponential decline over the first year (24). While randomization clearly addresses some of the short-term results, the long-term benefits of biventricular pacing, especially during the period of reduced VT/VF event rates on follow-up, cannot be judged from these data. The timing of individual shocked events, as well as the actuarial presentation of the same over a longer observation period, would be needed. Another important issue is the management of concomitant antiarrhythmic therapy and dosing. Information on this pivotal issue would assist interpretation of these findings.

There are data analysis issues. There was significant attrition from the overall study group with nearly 41% of patients being unsuitable for paired analysis. The impact of censored deceased patients in whom event rates may be quite unequal as well as incomplete data resulting in elimination of nearly 25% of patients is a significant concern. In another randomized trial design without crossover periods, an intention-to-treat analysis would clearly have dealt with these patients quite differently. The number of patients likely to receive ICD therapy is relatively small due to the modest study cohort and observation period. Despite this, there was trend toward fewer VT/VF recurrences with biventricular pacing. The episode data are skewed by the large number of events in two patients, both of which favor the active treatment group. A larger study population would be important to assess these trends. It is also unclear if the benefits could be due to the pacing rate or the dual-site stimulation mode. The absence of a single-site stimulation cohort or period in the design, as the authors wisely acknowledge, does not allow assessment of the benefits of biventricular stimulation mode per se versus rate support with ventricular pacing at any site. Finally, reduction in programmed ICD interventions should not be equated with aborted sudden death.

Alternative approaches to VT/VF prevention. PREVENTATION WITH ANTIARRHYTHMIC DRUG THERAPY. With an increasing availability of large ICD trial databases, statistically valid analyses of subpopulations are now more feasible. A recent subgroup analysis indicated that the mortality benefits of ICD therapy were largely confined to patients with left ventricular ejection fractions of \( \leq 35\% \) (25). Mortality benefits conferred by the device may thus be most prevalent in the patients with a more limited life expectancy based on cardiac co-morbidity due to markedly impaired left ventricular function with a possibly lesser likelihood of
quantitative prolongation of life. Patients with marginally impaired left ventricular function could obtain comparable survival benefit with empiric amiodarone therapy with effective VT/VF prevention. Thus, in certain VT/VF subpopulations, amiodarone monotherapy may be an acceptable preventive intervention.

‘HYBRID’ THERAPY. Recently, combining ICDs and other antiarrhythmic therapies has been formally examined (26). Combination or ‘hybrid’ therapy involving different electrical or antiarrhythmic therapies was initiated in the hope that the drawbacks of ICD shocks can be alleviated. The introduction of antitachycardia pacing prior to shock delivery in these devices greatly advanced the cause of reducing shocks delivered for arrhythmia termination (6). A prospective controlled trial recently confirmed the benefits of addition of an antiarrhythmic drug to reduce ICD shocks received by patients (26). In a controlled crossover trial, sotalol therapy reduced shock delivery by 63%. Similar trends are being noted with some newer type 3 agents such as azimilide (Procter & Gamble, data on file). Observational studies have also shown the benefit of map-guided transcatheter ventricular ablation in reducing shocks in highly selected patients experiencing cluster shocks for VT storms (27). Innovations in these individual approaches to widen their applicability are under active investigation. For example, a recent report of linear ventricular ablation lesions in sinus rhythm could simplify the use of ablation in a “hybrid” antiarrhythmic therapy algorithm (28).

Conclusions. There are many issues raised by the current report in the Journal. The major strength of this report from Higgins et al (6) is its provocative inference that suggests some merit to clinical evaluation of dual-site stimulation in a highly symptomatic ventricular tachyarrhythmia population. This could extend the potential of the clinical technique beyond atrial arrhythmias and test fundamental concepts of preventative pacing in different ventricular arrhythmic substrates. However, the report can only be considered hypothesis-generating. It should prompt meaningful discussion of an appropriate study design, populations and end points for dual-site ventricular pacing in the patients with high risk heart failure and sudden death.

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