The Year in Clinical Electrophysiology

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DEVICE RECALLS

The paper with the most far-reaching ramifications in the field of device therapy in 2005 was not published in any scientific journal but by an investigative reporter in the New York Times on May 24, 2005 (1). The article reported that a 21-year-old patient with hypertrophic cardiomyopathy and an implantable cardioverter-defibrillator (ICD) had died suddenly. Analysis of the explanted ICD (a Guidant 1861 Ventak Prizm 2, Guidant, Indianapolis, Indiana) showed that a catastrophic device failure had occurred. When the device attempted to deliver a shock in the presence of ventricular tachyarrhythmia, electrical arcing occurred in the device header, resulting in a short-circuit with extensive damage to the generator integrated circuit, and no shock therapy was delivered to treat the fatal arrhythmia. Two months later, the physicians involved published their account in the journal Heart Rhythm (2). This was then followed by commentaries in the New England Journal of Medicine (3) and Circulation (4) and more articles on related issues in the New York Times (5–8).

One of the many issues and questions raised in these articles is whether it was appropriate for Guidant officials not to inform the physicians of a potentially fatal flaw in its 1861 Ventak Prizm 2 ICD, of which they had known since February 2002 and for which changes in the manufacturing process had been made twice, in 2002. By not reporting the problem to the physicians, as pointed out by Hauser and Maron, Guidant had in effect assumed an unprecedented role in managing the patients (4). The authors also questioned the effectiveness of the Food and Drug Administration (FDA) in monitoring the safety of market release medical devices, especially low-frequency, device failures. Since February 2005, several major ICD and pacemaker recalls, safety alerts, and advisories have been issued by Medtronic (Minneapolis, Minnesota) (9), Guidant (10–15), and St. Jude Medical (St. Paul, Minnesota) (16). In response to the Guidant controversies, the Heart Rhythm Society and the FDA co-sponsored a one-day Policy Conference on device performance to discuss the current state of device technology, surveillance, and communications on product performance among industry, the FDA, and health care providers (17). Several areas requiring improvement have been identified. The FDA seeks to increase the ability of its Center for Devices and Radiological Health (CDRH) to develop active surveillance and identification of medical device failure and to improve communication between the FDA, manufacturers, physicians, and the public. Changes being considered include creation of an electronic database system for adverse event reporting that would allow faster, more critical evaluation of data by CDRH, allocation of more resources to target quality assurance, and development and improvement of guidelines for adverse-events reporting by manufacturers and for the FDA review of post-marketing changes to devices.

At the same conference, Maisel (18) presented some disquieting data on the reliability of ICDs. The author reviewed device malfunctioning reports filed with the FDA from 1990 to 2002 by manufacturers of pacemakers and ICDs. Eighty percent of malfunctions were due to hardware problems (electrical, battery/capacitor, connector/header, charge circuit, and hermetic seal). The malfunction replacement rate for ICDs was much higher than that of pacemakers (the overall replacement rates for pacemaker and ICD were 5 and 21 per 1,000 devices, respectively). During the study period, the rate of ICD malfunctions followed a bimodal pattern. The replacement rate for malfunction first peaked at about 39 per 1,000 devices in 1993, which was followed by a sharp drop to about 11 in 1994. From 1994 to 1998, the malfunction rate remained stable at about 8 to 9 per 1,000. It then increased rapidly to a peak of about 36 per 1,000 in 2001. The report found that 50% of the defibrillator malfunctions had occurred in the last 3 years of the study (2000 to 2002). It has been speculated that the drive to miniaturize defibrillators might be a factor in the growing rate of malfunctions; however, because the time from implant to failure was not reported, the higher failure rate in 2001 could have occurred in larger devices implanted in the late 1990s. More aggressive reporting of malfunction and replacement of devices might have contributed to the upward trend, as suggested by the author. After reaching a peak in 2001, the malfunction replacement rate dropped from 39 to 22 per 1,000 in 2002. Inclusion of data from 2002 to 2004 would provide a better picture of recent trending. Many malfunctions have lesser clinical impact than others. Most importantly, the report serves to provide us with a time-line of device performance. We will have a more informative picture only after we achieve better and more standardized reporting protocols and detailed analysis of data.

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One of the repercussions of the recalls is that the number of device alerts, advisories, and recalls will predictably increase, because the bar for identifying device adverse events will be set very low. The physicians might be burdened with information overload. It is therefore important for the FDA, manufacturers, and professional societies to work together to provide the practicing physicians with more defined practice guidelines to handle the reported device failures.

**ICD THERAPY**

The much-anticipated results of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) were published in January 2005 (19). This trial examined whether amiodarone or ICD reduced all-cause mortality compared with placebo in patients with either left ventricular ejection fraction (LVEF) ≤0.35 or heart failure due to ischemic or non-ischemic dilated cardiomyopathy. When compared with placebo, amiodarone did not improve survival, but ICD reduced mortality by 23%. The reduction was observed in both the ischemic (hazard ratio [HR] = 0.79) and the non-ischemic group (HR = 0.73), regardless of QRS duration. An interesting finding is that patients with New York Heart Association (NYHA) functional class II seemed to benefit more from ICD therapy than patients with more severe heart failure. The defibrillation testing protocol at the time of implantation was intriguing. If a 30-J ICD shock (highest deliverable energy) failed to restore sinus rhythm, no further testing or lead repositioning would be attempted. The device was implanted and the patient enrolled in the study. It is not known how many such patients were included in the study and how successful their ICDs were in treating clinical tachyarrhythmias during the follow-up period. If the number of patients was high and their outcome was similar to those with lower (20-J or lower) defibrillation testing threshold, one can postulate that defibrillation testing might not be necessary at the time of implant. This would greatly simplify the implantation protocol. The results of DEFibrillators In Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) and SCD-HeFT argue strongly for implantation of an ICD in patients with non-ischemic dilated cardiomyopathy with reduced LVEF and moderate heart failure (NYHA functional class II and III) for mortality benefits. As a result of these studies, the Centers for Medicare & Medicaid Services (CMS) broadened the coverage for ICD implantation (20).

In 2004, 135,000 ICDs were implanted in the U.S., accounting for $3.5 billion in sales. With expanding indications for ICD implantation, the numbers of implantations are expected to increase to as high as 500,000 (21). The cost-effectiveness of ICDs becomes an increasingly significant health economic issue. This was analyzed by using a decision model to estimate costs and survival among patients who received either an ICD for the primary prevention of sudden death or control therapy (22). The health and economic outcomes of the prophylactic implantation of an ICD as compared with control therapy were computed for the eight published ICD primary prevention trials (MADIT-I, CABG Patch, MUSTT, MADIT-II, DEFINITE, DINAMIT, COMPANION, SCD-HeFT). The authors found that the cost-effectiveness of the ICD in the six patient cohorts where survival benefit was demonstrated ranged from $34,000 (MUSTT) to $70,200 (SCD-HeFT) per quality-adjusted life-year gained (CABG Patch and DINAMIT were excluded in this analysis because these two studies showed no survival benefit). The authors reported that in appropriately selected patients, the incremental cost-effectiveness of ICDs is similar to that of other interventions often accepted as cost-effective. It is apparent from the modeling that by using a lower-cost ICD with a longer battery life in high-risk patients, we can reduce the cost per quality-adjusted life-year gain. It is obvious that better risk stratification of patients will allow us to better target our therapy and lower expenditures. As a very first step in an attempt to improve device use, CMS now mandates registering of ICDs and clinical data of patients under Medicare coverage with the ICD Registry of the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR) (23). Furthermore, remote full-disclosure device monitoring will also provide reliable active surveillance. The data will allow us to perform longitudinal analysis to measure device performance, clinical outcomes, and to refine risk stratification for better use of our health dollars.

**CARDIAC RESYNCHRONIZATION THERAPY (CRT)**

The benefits of CRT in heart failure were further demonstrated by the results of the Cardiac Resynchronization-Heart Failure (CARE-HF) trial (24). Patients with NYHA functional class III and IV heart failure from non-ischemic and ischemic cardiomyopathy, LVEF ≤0.35, left ventricular end-diastolic dimension ≥30 mm, and QRS duration ≥120 ms were randomized to receive medical therapy alone or with cardiac resynchronization (biventricular pacing therapy). The primary end point was the time to death from any cause or an unplanned hospital stay for a major cardiovascular event. The secondary end point was overall mortality. During the mean follow-up period of 29.4 months, there were significantly more patients in the medical-therapy group reaching the primary end point than in the CRT group (39% vs. 55%; HR, 0.64). Overall mortality was significantly lower in the CRT group (20% vs. 30%; HR, 0.64). The beneficial effects of CRT in this group of patients were impressive, considering that these patients were receiving optimal medical therapy with diuretics, beta-blockers, spironolactone, angiotensin-converting enzyme inhibitor, or angiotensin-receptor blocker at the time of the enrollment. Strikingly, the results showed that for every nine devices implanted, one death and three hospital
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stays were prevented (for comparison, it was 18 for 1 life saved in MADIT-II). These very favorable results for CRT raise the question of whether inclusion of defibrillation therapy will add any significant mortality benefit. It has been recently shown that in MADIT-II patients, among other events, worsening heart failure, increasing blood urea nitrogen, and NYHA class >II were associated with an increased risk for ICD therapy for ventricular tachycardia/ventricular fibrillation (VT/VF) and death (25). By reversing ventricular remodeling, CRT provides an added theoretical benefit over ICD by favorably modifying the substrate for arrhythmogenesis to prevent VT/VF (26). We have no knowledge, however, of the time line for achieving such theoretical benefit; 7% of the CRT group died suddenly, which could have been prevented by defibrillation. Further investigation on the relationship between reverse remodeling by CRT and arrhythmias will be very rewarding in our understanding of mechanisms of arrhythmogenesis and allocation of resources in treatment of heart failure.

PACEMAKERS

Even as we are well into the fifth decade of pacing for bradycardia, the controversy over single-chamber versus dual-chamber pacing has yet to be settled. This controversy was re-examined in patients with high-grade atrioventricular block in the United Kingdom Pacing and Cardiovascular events Trial (UKPACE). In this trial patients were randomized to receive a single-chamber fixed rate ventricular pacemaker, single-chamber rate-adaptive pacemaker, or a dual-chamber pacemaker. The average age was 80 years. The primary end point was all-cause mortality with a median follow-up period of 4.6 years. Secondary end points included atrial fibrillation (AF), heart failure, and thromboembolic events with a median follow-up period of 3 years. There were no significance differences in survival benefit and in the secondary end points between the single-chamber groups and the dual-chamber group. With the exception of AF, the findings are similar to the Canadian Trial Of Physiologic Pacing (CTOPP), which included patients with sick sinus syndrome and atrioventricular block (27). Subgroup analysis showed that NYHA functional class and history of chronic heart failure did not affect the primary end point. This study provides a very strong argument for implantation of a single-chamber pacemaker in elderly patients whose perception of quality of life is probably different from the younger population. Despite recent publications supporting implantation of single-chamber pacemakers and similar professional fee reimbursement for single-chamber and dual-chamber pacemaker implantation, the percentage of dual chamber implants remains at 80% (28,29). One can argue that if the adjusted costs for a dual-chamber pacemaker over the lifetime of the patient are comparable to those for a single-chamber pacemaker, then the biggest reason for implanting the simpler single-chamber pacemaker no long exits. This is the conclusion of a recent report on the analysis of the cost-effectiveness of these two pacing modes (30).

BIOLOGY OF CARDIAC FIBRILLATION

Over the past 12 months, information related to the biology of fibrillation—once almost always in the exclusive province of the basic physiologist—has now shown signs of invading the clinical domain. We have decided to briefly review this information and describe the possible clinical links. Because the mechanism of both AF and VF seem to be similar, a more generic term “cardiac fibrillation” will be used.

It is now accepted that fibrillation is initiated by wavebreak, the latter occurring when an emerging wave front encounters refractory tissue and splits into daughter waves (31). A number of important factors have been found to influence the dynamics of wavebreak. These factors have been separated into “functional factors,” action potential duration (APD), and internal calcium (Ca++) cycling or to differences in tissue heterogeneity. Weiss et al. (32) have popularized the designation of wavefront as phase O of the APD and waveback as its termination (Fig. 1). Wavebreak occurs when the wave front collides with the waveback, and if the break is spatially localized re-entry might result. This might occur around a fixed anatomic site or might produce a rotor (33). A rotor represents the three-dimensional expression of functional factors, its physiology is best explained by examination of the spiral wave that is the two-dimensional expression of the rotor or scroll wave (Fig. 2). The scroll wave differs from anatomic re-entry because it is perpetuated by a core of excitatory but unexcited cells. The region adjacent to the core is exposed to large electrostatic gradients that serve to significantly shorten the APD. The increased curvature of the leading edge of the spiral wave leads to a decreased safety margin for conduction, causing the wave to rotate around an anchor. Wavebreaks can occur in relationship to focal prolongation of refractoriness and/or altered conduction. These factors might be affected by tissue heterogeneity (infarction/scar) or by drugs or ischemia (34,35).

Once a rotor is established it might become anchored to a specific site and produce a monomorphic arrhythmia or might prove to be unstable and break into numerous daughter wavelets. Rotors might be thus characterized as being due to a dominant mother rotor with fibrillatory conduction from a localized area, or rotors might meander in time and space (36).

A powerful predictor of wave front instability is gleaned from analyses of the APD restitution relationship. The APD or cardiac refractoriness will shorten in response to an increase in the paced cardiac rate. Actually, the interval between the end of one action potential and beginning of the next or diastolic interval (DI) determines the length of APD. PACING at short lengths produces a short DI (and APD), and the restitution curve is characterized by the
DI:APD relationship. When the DI to APD slope is very steep (i.e., $1 > 1$), then small perturbations in DI will produce large changes in APD and will promote APD alternans (37,38). The alternans might be either concordant or discordant (opposite long-short dynamic between cells) alternans. These states are highly arrhythmogenic as pre-

Figure 1. The cardiac impulse as an electrical wave, with a wave front (black) corresponding to the upstroke of the AP, and a waveback (gray to white), corresponding to repolarization. Wavelength ($\lambda$) is the product of action potential duration (APD) and conduction velocity (CV). (A) Uniform wave. (B) Wave with waveback instability due to APD local prolongation. (C) Wave with wave front instability due to local CV slowing. Reprinted from Weiss et al. (32).

Figure 2. Action potential duration (APD) restitution slope and rotor stability. (A) APD shortening and APD alternans as pacing cycle length (PCL) decreases (computer simulation). (B) APD restitution curves, with slope $> 1$ (solid line) or $< 1$ (dashed line, obtained with 50% block of the calcium current). (C, D) Spiral wave behavior several seconds after initiating a rotor in homogeneous 2D tissue. All cells are identical, with either a steep (C) or shallow (D) APD restitution slope. (E, F) Optically measured surface voltage maps in an intact Langendorff rabbit heart before (E) and after (F) partially blocking the L-type calcium current with D600 (0.5 mg/ml) to flatten the APD restitution slope to $< 1$. In E, multiple wave fronts move in a complex VF pattern. In F, VF has converted to VT, manifested as a stable double-armed rotor. Reprinted from Weiss et al. (32).
mature impulses emerging from cells with the short APD meet refractory tissue in cells showing a long APD, thus leading to wavebreak and fibrillation (39).

The important roles of changes in channel function (short-term memory) as well as with internal Ca++ flux are beyond the scope of this review but are well described in a recent review article (40).

The preceding consideration explains the two dominant theories related to the pathogenesis of fibrillation. One posits the random collision of multiple co-existing wavelets (41), whereas the other suggests that fibrillation is driven by a focal source (rotor) (42). Others have shown, both in animal models as well as in dense atrial mapping studies of patients in AF, evidence that suggest a dominant frequency (DF) detected by Fast-Fourier signal analyses of the fibrillatory wave (42).

Use of DF mapping of humans during invasive clinical studies has recently been reported (43). These studies are based on the findings that rotor activity identified by optical mapping correlated with the DF found by signal analyses (36). Sanders et al. (44) studied 32 patients with either permanent or persistent AF with a system that allows for determination of Fast-Fourier signal analyses for patients with AF. They mapped 58 electrogram sequences from 126 ± 13 sites from both the right and left atrium. Three-dimensional maps were constructed on the bases of highest amplitude frequency analyses. The operators were unaware of the findings and used standard techniques for left atrial ablation. The sites of ablation were correlated with regions of highest DF and change in AF cycle length and arrhythmia termination. They found that 13 of the 15 (87%) who had AF termination did so at DF sites. In addition, patients with paroxysmal AF had more DF located within the pulmonary veins whereas those with persistent AF more likely had other atrial sites. In summary, the technique described involves a totally new approach for potential ablation of patients with AF.

Lin et al. (45) nicely characterized the mechanism of AF in a subgroup of patients with paroxysmal AF localized to the right atrium. These authors used a non-contact mapping system during sinus rhythm, atrial pacing, or induced AF. They found channels through lines of block that acted as mother rotors, which gave rise to daughter waves and fibrillatory conduction. In addition, Fast-Fourier transform analyses allowed for identification of the sites of these channels. They found, as opposed to the usual findings, a DF gradient from right to left atrium (coronary sinus septum). Ablation lines directed at putative channel sites resulted in acute success for 11 of 13 patients. This study nicely characterizes the pathogenesis of a unique form of paroxysmal AF.

Everett et al. (46) used a non-contact mapping system to explore the mechanism of VF in canine models of heart failure. During VF, the DF was obtained with Fast-Fourier transform of signals derived from the ESI non-contact mapping system (Endocardial Solutions Inc., St. Paul, Minnesota). Of interest was the finding that the mechanism of VF (i.e., meandering, focal, or rotor activity) varied depending on the etiology of the congestive heart failure. In control dogs subjected to VF, meandering rotors were found, whereas those with heart failure showed a stable rotor or focal source. Those with ischemia initially showed a focal source that became reentrant. These studies highlight the idea that fibrillation is not a totally random, chaotic event, and better understanding of underlying mechanism(s) promises to allow for better treatment of fibrillation.

Another study that was directed toward application of these basic physiologic concepts was an innovative approach to assess APD restitution curves in patients with heart disease. Koller et al. (47) recorded monophasic action potentials from a catheter in the right ventricular septum both in patients with normal hearts and in those with structural cardiac disease. The authors analyzed ventricular APD restitution curves in response to overdrive pacing. They found that patients with structural cardiac disease had a wider DI, at which APD alternans was found. Even though the recordings were obtained from the right ventricle (in a group with predominant left ventricular dysfunction) the authors described a novel approach for assessment of electrical stability and raise the idea that this approach might prove to be one alternative target for drug therapy.

**ANTIARRHYTHMIC DRUG THERAPY**

There has been continued interest in the development and study of new antiarrhythmic agents. Perhaps the closest agent nearing FDA approval is Dronedarone (48). This is a drug that is structurally similar to amiodarone (benzofuran derivative) but without iodine. Amiodarone is the most effective drug available for treatment of patients with either VT or AF but its use is limited because of the frequency of side effects. Recent studies have corroborated the initial results of the DAFNE trials (48), which showed that Dronedarone was more effective than placebo for maintenance of sinus rhythm after cardioversion. In addition, the major toxicity proved to be gastrointestinal intolerance and there were no reports of cardiac, hepatic, thyroid, or pulmonary toxicity.

Another drug with interesting potential for acute cardioversion of patients with AF is known as RSD1235. This agent is both an atrio-selective potassium (K+) channel blocker as well as a sodium (Na+) channel blocker. Two studies have been published that explored the efficacy and safety of this drug. Roy et al. (49) showed that AF terminated in 61% of patients treated with this drug without significant adverse effects. Similar results are reported at the late-breaking trials of the Heart Rhythm Society (May 2005) (50). In this larger trial including 221 patients treated with drugs, conversion to sinus rhythm occurred in 52%, again with minimal side effects (transient alteration in taste). The initial reports using RSD1235 seem to compare well with other agents (ibutilide, flecainide) used for acute conver-
sion to sinus rhythm. The favorable side effects are especially noteworthy.

Singh et al. (51) reported the results of a large-scale, randomized, double-blinded Veteran’s Administration hospital study comparing the efficacy of amiodarone, sotalol, and placebo for both conversion and maintenance of sinus rhythm in patients with AF. They found that both amiodarone (27.1%) and sotalol (24.2%) had similar conversion rates but that amiodarone was statistically superior to sotalol in maintenance of sinus rhythm after external cardioversion. Atrial fibrillation recurred over a mean of 487, 209, and 13 days (amiodarone, sotalol, and placebo, respectively).

In a follow-up substudy from the same group (52), the patients who maintained sinus rhythm had better quality of life scores compared with those who reverted to AF. The latter finding seems to contradict the initial findings of the AFFIRM trial but is probably closer to our clinical experience.

GENETIC DISORDERS

Several notable advances have been made in the realm of the inherited channelopathies. Probably the most important is discovery of the genetic mutation causing Timothy’s syndrome (53). This syndrome was initially reported in children with multisystem disorders and sudden death due to cardiac arrhythmia. The disorder results from a missense mutation (G406R) of the gene encoding the calcium channel Cav1.2, owing to loss of inward Ca++ inactivation. The cardiac arrhythmias are attributed to Ca++ overload state. The authors recently reported an expanded series including 21 phenotyped patients (54). The median age at death was 33 months and the electrocardiogram showed a mean corrected QT interval of 600 ms with a pattern similar to that described for the Long QT3 syndrome (prolonged JT-segment with normal T-wave). Timothy’s syndrome has been designated as the LQT8 syndrome.

There continues to be great interest in the genetic analysis of patients with arrhythmogenic right ventricular dysplasia (ARVD). This is a fascinating cardiomyopathy that affects the right ventricle (and left ventricle with time) and is associated with sudden death due to ventricular arrhythmia. In the past, only a small number of patients were found to have abnormalities in genes encoding the adherens or desmosome proteins. These proteins are responsible for maintenance of the cytoskeletal structure of the heart. Abnormalities of the genes encoding plakoglobin (Naxos disease) and desmoplakin (Caravajal syndrome) were reported earlier. More recently, mutations in plakophilin have been found responsible for approximately 30% of the genetic mutations for patients with ARVD (55). An excellent summary of the genetics of this disorder was recently published (56).

CATHETER ABLATION

There is continued interest in the growing field of catheter ablation for cure of AF. Over the past year interest has been focused both on the traditional methods of pulmonary vein isolation and wide area left atrial ablation. The newer approaches involve better understanding of the relationship of fractionated electrograms (57) with left atrial ganglionic plexes (58). Vagal denervation was found by Lemery et al. (59) to be associated with excellent short-term success in patients with AF.

A most interesting study by Haissaguerre et al. (60) involved use of ablative procedures for 60 patients with chronic AF. Successful ablation in patients with chronic AF has proved particularly difficult to achieve. The French group used both pulmonary vein isolation, together with lesion across the left atrial roof and mitral isthmus (from the left inferior pulmonary vein to the mitral annulus), as well as ablation of fractionated electrograms and reported an 82% short-term success. The report offers new hope for expansion of ablative procedures to the chronic group. This procedure is, however, lengthy and involves numerous ablative lesions; hence, caution must be used in wider application of this approach.

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