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QUARTERLY FOCUS ISSUE: HEART RHYTHM DISORDERS

Year in Cardiology Series

The Year in Review of Clinical Cardiac Electrophysiology

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Atrial Fibrillation

Previous randomized controlled clinical trials of atrial fibrillation (AF) patients have failed to demonstrate a benefit of a rhythm control strategy (using cardioversions and/or drugs) over a rate control strategy (with atrioventricular [AV]-nodal blocking drugs and anticoagulation) (1,2). This year brought the first report of a similar trial in AF patients with heart failure (3), a particularly important group given data from observational studies that heart failure patients with AF have an especially poor prognosis compared with similar patients in sinus rhythm (4,5). These investigators enrolled 1,376 patients in a multicenter, randomized unblinded trial comparing a rhythm control strategy with a rate control strategy in AF patients with a left ventricular ejection fraction (LVEF) ≤35% and a history of congestive heart failure or an ejection fraction (EF) ≤25% (3). Rhythm control was achieved with cardioversions and either amiodarone, sotalol, or dofetilide (82% received amiodarone), and rate control was achieved with beta-blockers and, if needed, digitalis. Over a mean 37 ± 19 months of follow-up, there were no significant differences in either the primary end point of death from cardiovascular causes (27% in the rhythm control group vs. 25% in the rate control group, $p = 0.59$ by the log-rank test) or the secondary outcomes of overall survival, risk of stroke, or worsening heart failure (either individually or as a composite). Importantly, although only 27% of the rhythm control group exhibited prevalent AF at 4 years of follow-up, 58% had at least one recurrence of AF during follow-up. Therefore, as with previous similar studies, it is important to emphasize that the hypothesis being tested was whether a rhythm control strategy is superior to a rate control strategy. It remains unknown whether actually achieving sinus rhythm maintenance would result in better outcomes, and we remain limited by the poor efficacy and potential toxicities of current antiarrhythmic drugs.

Important studies were published in 2008 and early 2009 describing the experience with 2 novel antiarrhythmic drugs, vernakalant (Cardiome, Vancouver, British Columbia, Canada) and dronedarone (Sanofi-Aventis, Bridgewater, New Jersey). Vernakalant hydrochloride (RSD1235) is one of several new agents that takes advantage of the fact that some ion channels may be specific to the atria (6). By blocking those more atrial specific ion channels, these new drugs theoretically reduce or may even eliminate the risk of ventricular proarrhythmia. In 2008, the first phase 3 study of one of these agents was described: 356 patients were randomized in a 2:1 fashion to intravenous vernakalant versus placebo for the acute cardioversion of AF (7). Patients were prospectively stratified by duration of AF: 3 h to 7 days (short duration) and 8 to 45 days (long duration). Seventy-five of 145 vernakalant patients (51.7%) in the short duration group converted to sinus rhythm within 90 min (median time to conversion was 11 min in the treatment group) compared with 3 of the 75 placebo patients (4%; $p < 0.001$). Six of the 76 patients in the long duration group converted on vernakalant (7.9%) compared with 0 of the 40 placebo patients ($p = 0.09$). Two of the vernakalant-treated patients suffered hypotension (neither had a systolic blood pressure <80 mm Hg and both responded to intravenous fluids), but no other significant adverse effects were seen more often in the treatment group than placebo group. There were no episodes of torsade de pointes or ventricular arrhythmias during the first 24 h after infusion, an important finding given that the half-life of the drug is 2 to 3 h. Although the efficacy of this new drug is clearly lower than what would be expected with electrical cardioversion, sedation is not necessary. The efficacy appears to be similar to the most potent intravenous agent available for pharmacologic cardioversion of AF in the U.S., ibutilide (8,9). As ibutilide carries a risk of torsades de pointes (8,9) and other potentially efficacious agents, such as flecainide and propafenone may also result in proarrhythmia or negative inotropy (10,11), this new class of agents may provide a relatively efficacious way to pharmacologically convert AF safely. One caveat is that the peri-cardioversion risk of thromboembolism is thought to be the same whether a

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patient undergoes electrical or pharmacologic cardioversion, necessitating consideration of thromboembolic prophylaxis regardless of the method used (12).

Dronedarone is a multichannel blocker similar to amiodarone developed for the treatment of AF. Unlike amiodarone, dronedarone does not contain iodine and therefore does not cause iodine-related adverse reactions. Previously, dronedarone was shown to safely reduce recurrence of AF in 2 randomized placebo-controlled clinical trials, but patients with New York Heart Association (NYHA) functional class III or IV congestive heart failure were excluded (13). The choice of antiarrhythmic drugs in patients with systolic heart failure is essentially limited to dofetilide and amiodarone due to the unacceptable toxicities of other agents (12), and use of dronedarone may avoid the risk of torsades de pointes seen with dofetilide and the noncardiac adverse effects of amiodarone. In 2008, the ANDROMEDA (Antiarrhythmic Trial With Dronedarone in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease) study was published; it was a double-blind, placebo-controlled trial comparing 400 mg of dronedarone twice daily to placebo in patients with NYHA functional class III or IV congestive heart failure and a wall-motion index of no more than 1.2 (approximating an EF of no more than 35%) (14). Although a sample size of 1,000 patients was planned, the trial was terminated after enrolling 627 patients due to an excess number of deaths in the dronedarone group. Although the number of deaths attributed to arrhythmia or sudden death did not differ between treatment and placebo, more participants on dronedarone had worsening heart failure when they died, and the risk of death on the drug was increased among patients with a lower wall motion index. The primary end point of all-cause mortality or hospitalization for worsening heart failure was not significantly different between the 2 groups, nor was there a difference in the prevalence of AF at the 1-month visit. As in previous studies, dronedarone significantly reduced creatinine clearance, but this was believed to represent an effect on the inhibition of specific renal tubular cation transporters rather than a true reduction in the glomerular filtration rate. Some have speculated that the higher creatinine levels may have prohibited providers from prescribing or optimally dosing cardioprotective agents such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and/or aldosterone in the dronedarone group. For now, the implication of this study is that dronedarone should not be used in patients with heart failure and left ventricular systolic dysfunction.

Published in early 2009, the ATHENA (A placebo-controlled, double-blind, parallel arm Trial to assess efficacy of dronedarone 400 mg bid for the prevention of Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter) study was a randomized, double-blind, placebo-controlled trial comparing 400 mg of dronedarone twice daily with placebo in patients with paroxysmal or persistent AF or atrial flutter, who met at least 1 of the following criteria: age ≥70 years, diabetes, history of stroke, transient ischemic attack, systemic embolism, left atrial diameter ≥50 mm, and an EF ≤40% (due to lower mortality than expected during the study, inclusion criteria changed during enrollment to include age ≥75 years or age ≥70 years and 1 of these additional risk factors) (15). NYHA functional class IV heart failure was an exclusion criterion. A total of 4,628 patients were enrolled: 25% were in AF or atrial flutter at presentation, 60% had evidence of structural heart disease, 4% had an EF <35%, and 4% had NYHA functional class III heart failure. Over a mean follow-up of 21 ± 5 months, the primary outcome of first hospitalization or death occurred in 734 (32%) patients in the dronedarone group and 917 (39%) in the placebo group ($p < 0.001$). The dronedarone group exhibited significantly fewer hospitalizations (29% vs. 37% in the placebo group, $p < 0.001$), a difference driven primarily by a reduction in the number of hospitalizations for AF. There was also a small, but statistically significant, reduction in acute coronary syndromes in the dronedarone group. Although there was no significant difference in overall mortality, 63 (3%) of the dronedarone patients compared with 90 (4%) of the placebo patients died of cardiovascular causes ($p = 0.03$), a difference driven primarily by fewer deaths due to cardiac arrhythmia in the dronedarone group (1% vs. 2% in the placebo group, $p = 0.01$). Although patients on dronedarone more often developed bradycardia, QT prolongation, diarrhea, nausea, rash, and an increase in serum creatinine levels compared with patients on placebo, pulmonary symptoms, interstitial lung disease, and abnormalities of thyroid function were not significantly more common. An important caveat is that the follow-up period may have been too short to preclude development of some of these amiodarone-like toxicities in the long term. There was no evidence of harm in those with NYHA functional class II or III symptoms or those with a low EF, and differences compared with the ANDROMEDA study were attributed to exclusion of class IV patients and the fact that the ANDROMEDA study included patients with a recent heart failure exacerbation. Despite the safety found in the ATHENA study, the authors warned against use of dronedarone in patients with severe heart failure and left ventricular dysfunction. The reason for a reduction in cardiovascular death remains unknown; a reduction in acute coronary syndromes and arrhythmic death suggests that the reduction may be due to effects independent of AF prevention, a notion that fits well with the fact that amiodarone was originally developed as an antianginal agent.

In order to answer the question regarding the optimal nonpharmacologic therapy for AF in heart failure, the PABA-CHF (Comparison of Pulmonary Vein Isolation Versus AV Nodal Ablation with Biventricular Pacing for Patients with Atrial Fibrillation with Congestive Heart Failure) study randomized 81 patients with symptomatic AF, NYHA functional class II or III heart failure, an EF ≤40% to AV node ablation, and biventricular pacing versus

pulmonary vein isolation (PVI) using catheter ablation (16). At 6 months, 88% of the 41 patients in the PVI arm were free of AF, although 8 required a second ablation procedure and 10 remained on antiarrhythmic drugs. PVI was associated with groin bleeding in 3 patients, pulmonary vein stenosis in 2 patients, pericardial effusion in 1 patient, and pulmonary edema in 1 patient; AV node ablation and biventricular pacing was associated with lead dislodgement in 2 patients, pocket hematoma in 2 patients, and pneumothorax in 1 patient. End points were measured at 6 months, and all patients returned for follow-up. Although AV node ablation and biventricular pacing resulted in mild improvements in the 6-min walk test and the Minnesota Living with Heart Failure questionnaire, PVI proved to be the superior strategy: PVI resulted in greater improvements in EF, 6-min walk test, and the Minnesota Living with Heart Failure scores. One caveat to this study is that the mean heart rate in the AV nodal ablation group was 82 ± 11 beats/min, and this procedure has typically been reserved for those who cannot achieve adequate ventricular rate control. In addition, PVI was performed by experienced ablationists, and it is unclear if the success rates of PVI in this population can be reproduced in usual clinical practice.

Ventricular Arrhythmias

Although early repolarization or J-point elevation is commonly seen on the 12-lead electrocardiograms (ECGs) and is generally believed to be benign, 2 case control studies in 2008 described an association between early repolarization and idiopathic ventricular fibrillation (VF). Haïssaguerre et al. (17) compared ECGs of 206 patients with resuscitated idiopathic VF with those of 412 healthy controls. VF subjects were rigorously screened to exclude any underlying cardiac structural abnormality, ischemia, or evidence of known ion channel disorders. Early repolarization was defined as an elevation of the QRS-ST junction (J-point) of at least 1 mm (0.1 mV) in at least 2 leads, either as QRS slurring or notching in inferior or lateral leads; leads V_1 to V_3 were excluded to avoid inclusion of patients with right ventricular dysplasia or the Brugada syndrome. Although early repolarization occurred in 64 (31%) of the VF patients, it was found in only 5% of controls ($p < 0.001$), a finding that remained highly significant after adjusting for potential confounders. There are several important caveats to this study. First, the cases included only survivors of VF, hence the possibility that the ECG findings represent a protective effect cannot be excluded. Second, although attempts were made to adjust for potential confounders, the controls, selected from a group of health care professionals, did not necessarily rise from the same population as the patients, leaving open the possibility that ECG differences reflected some other unmeasured difference (a problem inherent to most case control studies). However, in favor of the hypothesis that early repolarization reflects the underlying pathophysiology was the finding that J-point elevation frequently increased compared with baseline before arrhythmic events. Finally, because this was a case control study, this report could not comment on the natural question a clinician might take away from this study: when confronted with a patient with early repolarization, what is the risk of VF?

A second study attempted to answer this question. Rosso et al. (18) found that 45 VF patients with structurally normal hearts (43 ultimately diagnosed with idiopathic VF and 2 with the Brugada syndrome) more often exhibited J-point elevation than a control group ($n = 124$) matched for age and gender (42% vs. 13%, $p = 0.001$). In a second control group of 132 19-year-old noncompetitive athletes, the proportion with J-point elevation lay in between the prevalence found in patients and controls. As with the Haïssaguerre et al. (17) study, the majority of the J-point elevation observed in VF patients was in the inferior leads. In contrast, the finding in the young athletes was most common in leads V_4 to V_6. Based on an estimated risk of idiopathic VF in the general population of those ages 35 to 45 years of 3.4 per 100,000 individuals, the investigators derived a clinically relevant measure of the positive predictive value using Bayes' formula of conditional probabilities (19): they estimated that the presence of a J-wave in the ECG of an individual age 35 to 45 years increases the chances of having idiopathic VF from 3.4 in 100,000 to only 11 in 100,000.

A study published early in 2009 revealed important data related to the treatment of idiopathic VF in the setting of inferolateral early repolarization: of 122 patients with the syndrome, 33 patients with at least 3 VF episodes before the onset of antiarrhythmic therapy over a mean follow-up period of 69 ± 58 months were identified for study (20). In the 16 of these 33 patients with an episode of VF storm (defined as ≥3 episodes in 24 h), none of the following were effective: verapamil in 3 patients, lidocaine or mexiletine in 9 patients, and beta-blockers in 11 patients. Amiodarone was effective in 3 of 10 patients receiving the drug. Importantly, 7 of 7 VF storm patients responded to isoproterenol: all arrhythmias were eliminated when the sinus rate was increased above 120 beats/min. During long-term follow-up for the entire 33 patients, verapamil, mexilitene, beta-blockers, 1C agents (including flecainide, propafenone, and pilsicainide), and amiodarone were generally not effective. In contrast, quinidine (in 3 patients) or hydroquinidine (in 6 patients) was totally successful in 9 of 9 patients over a mean follow-up of 25 ± 18 months. Of interest, these effective therapies are consistent with the theory that an overactive transient outward potassium current (Ito) may be responsible for the early repolarization pattern and proarrhythmia in these patients; Ito is active in early repolarization, its activity is accentuated with bradycardia (and will therefore be reduced with isoproterenol), and it is blocked by quinidine (21).

The search has begun for genetic variants that might explain this recently described phenomenon of idiopathic VF with inferolateral early repolarization dubbed "Le Syn-

drome d'Haïssaguerre" (22). The first report of a rare genetic variant in a 14-year-old girl with the disease was reported in early 2009: in this young woman with idiopathic VF and striking J point elevation that varied and was accentuated with bradycardia, several genes involved in the transcription and regulation of potassium channels, sodium channels, calcium channels, calcium binding proteins, and cytoskeletal proteins interacting with ion channels were sequenced (23). Sequencing of the KCNJ8 gene encoding the Kir6.1 subunit of the K_{ATP} channel identified a missense variant in exon 3. The variant was absent in 764 alleles from healthy controls. Although the current understanding of this gene suggests that there may be a causal link, functional experiments have not yet been performed to more definitively demonstrate a cause-effect relationship or details regarding the mechanism. Given the absence of the variant in 156 additional patients with idiopathic VF and early repolarization, the culprit gene variants affecting the majority of these patients remain unknown.

Building on data that a witnessed cardiac arrest treated with an immediately available automatic external defibrillator (AED) could be effective (24,25) and that most cardiac arrests occur in the home (26), investigators performed the HAT (Home External Defibrillator Trial) (27). There were 7,001 participants with a history of an anterior wall myocardial infarction but not meeting current indications for an implantable cardioverter-defibrillator (ICD), who were randomized in equal proportions to receive an AED for home use or no AED. All participants had to have a spouse or companion willing to call emergency medical services, perform cardiopulmonary resuscitation (CPR), and use an AED. Both study groups received video-based CPR training; those randomized to the AED were instructed to place a call for assistance and perform CPR after application of the AED (if more than 1 rescuer was present, these tasks were to occur simultaneously). Of the 450 patients who died over a median follow-up of 37.3 months, 228 (6.5%) were in the control group and 222 (6.4%) were in the AED group ($p = 0.77$). The primary outcome did not differ among any of the multiple pre-specified subgroups. Only 169 of 450 deaths (37.6%) were deemed to be caused by a tachyarrhythmia consistent with ventricular tachycardia (VT) or VF, and only 160 were from sudden cardiac arrest (defined as a sudden loss of consciousness requiring cardiopulmonary resuscitation or transthoracic defibrillation). Of those 160, initial collapse occurred in the home in 117; of those 117, only 58 (50%) were witnessed. Of the 38 patients resuscitated from sudden cardiac arrest and surviving for at least 48 h, 19 were in the control group and 19 were in the AED group. Correlative documentation of AED rhythms was available for 21 of 29 unresponsive patients in the AED group; a shock was advised for 13 of these and delivered in 12 (in 1 case, the device was inadvertently turned off). Of the 12 patients, 4 were long-term survivors. There were no documented inappropriate shocks. There are several potential explanations for the overall negative result: first, the overall mortality and incidence of sudden cardiac arrest were substantially lower than anticipated, resulting in less power than initially projected to detect a difference between the groups; all participants in the control group received CPR training, including frequent reminders, which likely improved outcomes in those not receiving AEDs; and only one-half of the sudden arrest events that occurred at home were witnessed.

Late 2008 and early 2009 brought 3 important studies examining the predictive value of microvolt T-wave alternans (MTWA) in the 3 main populations typically considered for primary prevention ICDs. MTWA is a noninvasive test of arrhythmia vulnerability that has shown some promise in predicting which patients may benefit from an ICD (28–30). Of note, previous studies have been largely observational, and the value of the test has generally been in its negative predictive value (if it is normal, the risk is low) (28,31). Gold et al. (32) published a prospective substudy of the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial), in which 490 of the 2,521 patients with an EF ≤35% and NYHA functional class II or III heart failure, randomized in equal proportions to ICD therapy, amiodarone, or placebo, underwent MTWA testing. In short, MTWA did not predict the composite primary end point of the first occurrence of any of the following: sudden cardiac death (SCD), sustained VT or VF, or appropriate ICD discharge. Although the authors acknowledged that insufficient power could not be excluded as an explanation for their negative findings, the study was quite large relative to previous studies, the duration of follow-up was likely adequate, and the 10% primary event rate in MTWA-negative patients suggests that this test is unlikely to be useful in risk stratifying patients meeting SCD-HeFT criteria. Similarly, negative results were found in the MASTER (Microvolt T Wave Alternans Testing for Risk Stratification of Post MI Patients) trial, a study in which 575 patients meeting MADIT-II criteria (an earlier myocardial infarction and EF ≤30%) underwent MTWA testing and ICD implantation (33). Over a mean 2.1 ± 0.9 years, MTWA testing failed to discriminate between those who did and did not ultimately experience SCD or an appropriate ICD discharge. Of interest, total mortality was significant greater in MTWA non-negative (either positive or indeterminate results) patients than in those with a normal result (hazard ratio: 2.04, $p = 0.02$). Finally, the ABCD (Alternans Before Cardioverter Defibrillator) trial addressed the MUSTT (Multicenter Unsustained Tachycardia Trial) population: 566 patients with an EF ≤40% attributable to ischemic heart disease and nonsustained VT underwent MTWA and invasive electrophysiological testing (EPS) with programmed ventricular stimulation (34). ICD insertion was mandated in all patients with either positive MTWA or EPS. The primary end point was first appropriate ICD discharge or SCD. The positive predictive value was poor for both tests. The study fulfilled the main objective in demonstrating that the negative predictive value of

MTWA, found to be 95% for predicting events at 1 year, was not inferior to the negative predictive value of EPS. However, because 55% of patients had discordant results, it does not appear that MTWA should serve as a substitute for EPS. The authors suggested the 2 tests may be complementary in this patient population: the event rate in patients with 2 normal tests (MTWA and EPS both normal) was approximately 3-fold lower than in patients with 1 abnormal test and approximately 6-fold lower in patients with 2 abnormal tests. The 1-year event rate was 3% for those with 2 normal tests. Despite the publication of these important studies, the role of MTWA in clinical practice remains uncertain; although the positive predictive value is clearly not useful, the utility of the test used in conjunction with others to aid in risk stratification likely requires further study.

Genetic Arrhythmia Syndromes

Important basic as well as clinical advances continue to be reported for patients with genetic arrhythmia syndromes. Interest in this area has greatly expanded; for example, PubMed lists 96 citations in 2008 for just the long-QT syndrome (LQTS) alone. It will be obviously not possible to discuss all the important new studies.

LQTS

LQTS is due to abnormalities in ion channel function. Most abnormalities involve the delayed rectifier k+ channels, less commonly the Na+ channel and very rarely the L-type calcium channel. It is will known that abnormalities in the IKs (slow k+ delayed rectifier current) channel (LQT1) are enhanced by catecholamines. Novel insights into the mechanism of impaired channel function by stressors were reported by Seebohm et al. (35). Reaction to stress involves production of cortisol, which in turn regulates expression of the gene serum- and glucocorticoid-inducible kinase (SGK1), which in turn enhances the IKs current. This is normally done by enhanced insertion of KCNQ1 (alpha subunit) and KCNE1 (beta subunit) into the channel membranes (36). Seebohm et al. (35) showed altered SGK1 regulation of some IKs mutant channels. Some mutant channels showed paradoxically reduced IKs current by SGK1. This effect was induced by downregulation of recycling of the IKs channels. The authors' findings provide key insights relative to the proarrhythmia effects of stressor hormones on IKs channel function and help explain the adverse clinical response to stressors (i.e., exercise, swimming, emotional upsets).

Another important paper (37) related to a rather rare form of the LQTS called the Timothy syndrome or LQT8. This rare disease is manifest by QT prolongation, SCD, autism, webbed fingers and toes, and immune deficiencies. Three genetic mutations have been identified that result in slowed inactivation of the L type Ca++ current. (38) Increased cytosolic Ca++ results in prolongation of the QT interval and predisposes to triggered arrhythmia. Thiel et al. (37) infected rat cardiomyocytes with mutant L-type Ca++ (Cav1.2) channels. These myocytes showed decreased inactivation, prolongation of the action potential duration, and after-depolarizations. They found that this mutation resulted in increased calcium/calmodulin-dependent protein kinase II (CaMKII), which results in enhanced Ca++ release from the SR, enhanced Ca++ influx, and slowed inactivation. Inhibition of CaMKII with an inhibitory peptide completely reversed the above abnormalities. These studies clearly showed the critical role of CaMKII in the genesis of this syndrome. A very thoughtful accompanying editorial (39) expanded on the potential implications of these findings relative to other disorders that involve abnormalities in Ca++ metabolism.

Clinical Studies

An excellent "state-of-the-art" paper by Goldenberg and Moss (40) is recommended. In addition, an interim report from the international LQTS registry provided long-term follow-up information for patients older than 40 years of age (41). The study involved 2,759 subjects with mean follow-up time (after age 40 years) of 19 ± 13.5 years. Clinical data were obtained prospectively and included detailed symptoms, annual ECGs, treatment, and genetic testing. The authors defined the risk factors for death or aborted sudden death. For example, females with a corrected QT interval ≥470 ms had a cumulative risk rate of 26%. Other risk factors included a history of syncope within 2 years, and the most powerful predictor was for those with LQT3 genotype. Before this study it was felt that patients with the LQTS who survived to age 40 years were at relatively low risk for fatal events. This important study documented the substantial risk for those with the above-enumerated risk factors.

There is continued interest in finding more effective treatment modalities for those with the LQTS. Experimental studies showed that the antianginal agent ranolazine both blocks IKr as well as the late Na+ current. Wu et al. (42), using an in vitro guinea pig model, showed this drug reduced action potential duration and ventricular arrhythmia by agents that mimic the LQT3 syndrome. In a recent study, Moss et al. (43) showed that in patients with LQT3 due to the ΔKPQ deletion mutation, ranolazine infusions significantly shortened the corrected QT interval and suppressed myocardial relaxation in these patients.

Catecholaminergic Polymorphous VT

A very important observation was reported by Cerrone et al. (44) involving a mutant mouse model of catecholaminergic polymorphic ventricular tachycardia (CPVT). This syndrome is associated with exercise-induced premature ventricular complexes, bidirectional VT, polymorphic VT, and VF. The authors used an elegant epicardial and endocardial optical mapping system in mice with a knockin mutation of

the RyR2 receptor channel. They also used Lugol's solution for chemical subendocardial ablation. They found that this model replicated the cardiac arrhythmias observed clinically and could be repeated in single cell Purkinje preparation (after-depolarizations and triggered activity). This important seminal observation found that the His-Purkinje system was a source of arrhythmias in a CPVT mouse model.

Molecular Biology and Genetics of AF

Familial AF has been long recognized. A large survey from Mayo Clinic, Rochester, Minnesota showed that 36% of 994 patients had lone AF and among those, 15% had a familial history (45). A great deal of recent work has identified the link between a number of genes and AF. This information has led to development of a number of possible pathogenetic mechanisms of AF. An excellent review by Tsai et al. (46) is recommended. The genesis of AF appears to be dependent on triggers (often from the pulmonary veins) as well as a suitable atrial substrate. Modification of atrial structure and function appears after prolonged rapid atrial rate, which results in abnormalities in cycle length-dependent shortening of the atrial effective refractory period. Maintenance of AF appears to be dependent on factors that encourage generation of wavelets in the atrium. The wave length is the distance traveled by an electrical impulse during 1 refractory period (conduction velocity × refractory period). The safety margin for conduction in a re-entrant circuit is determined by the difference between the path length of the circuit and the wave length. Therefore, factors that result in decreases in action potential duration or conduction velocity will favor atrial wavelets and hence will serve to stabilize AF. Other important factors involve changes in the atrial substrate (i.e., fibroses) that tend to stabilize atrial wavelets (in conduction slowing or block).

Role of the k+ Channel

The first genetic abnormality causing AF was described in a 4-generation Chinese family and a mutation of the KCNQ1 gene (responsible for the IKs current), resulting in a gain of function of the k+ channel (47). The same group (48) described a familial form of AF involving KCNE2, the beta subunit for the k+ channels. Again this mutation produces a gain of function of the k+ channel.

Of note were the discovery of 2 additional familial genes associated with mutations that produced overexpression of the Kir2.1 channel with enhanced IK1 current (49) and overexpression of the KCNH2 gene, which resulted in a gain of function of IKr.

All of the above-described k+ genes associated with familial AF showed properties of enhanced k+ currents and decreased action potential duration. As discussed above, decreased atrial refractoriness would serve to promote multiple wave re-entry and AF. Recently, Ellinor et al. (50) found no mutations in KCNJ2 or KCNE genes in 96 probands of a Caucasian population with AF. The k+ channel abnormalities may, therefore, be more prevalent in Chinese people.

Another interesting paradox relating to atrial k+ channel function was reported by Olson et al. (51). They found a familial form of AF associated with early onset of symptoms refractory to drugs and ablation, associated with a nonsense mutation in KCNA5, which encodes Kv1.5 responsible for the atrial selective Ikur current. Expression studies showed failure to generate the Ikur current and action potential prolongation with after-depolarizations in human atrial myocytes.

These authors further demonstrated enhanced susceptibility to AF in a mouse model. This interesting study introduced a novel mechanism for genetic induction of AF involving loss of function of an atrial selective k+ channel with lengthening of the action potential duration and producing an atrial variant of "torsades."

Role of the Na+ Channel

Several sparse reports documented a familial association between "loss of function" caused by SCN5A mutation with AF, cardiac conduction system disease, and sick sinus syndrome or with AF and cardiomyopathy (52,53). A recent very interesting observation described the association of a novel mutation of the SCN5A gene (M1875T), which was associated with "gain of function of the Na+ channel" (54). Gain of function of the Na+ channel has been well documented as a cause of one of the long-QT syndromes (LQT3), but in these patients the QT interval was normal. The mutant channel by expression studies was found to show a gain of function in relation to steady-state inactivation kinetics but there was no persistent Na+ channel current. The authors speculated that the prolonged atrial action potential leads to atrial-triggered activity. Benito et al. (55) described a mutation in the SCN5A gene associated with both AF and the LQT variant. Of clinical interest was the positive response of these patients with respect to AF control with use of flecainide, a drug that is a potent Na+ channel blocker.

The largest genetic study examining the relationship between AF and SCN5A mutations was provided by Darbar et al. (56). They sequenced the entire coding region in 375 patients with either lone (n = 118) or cardiac-associated AF (n = 257). They found that 5.9% showed an association between AF and rare SCN5A variants. In 10 patients, 8 novel variants were identified; in 12, SCN5A variants previously associated with other syndromes (i.e., LQTS, Brugada) were found. Ellinor et al. (57) also reported a link between SCN5A mutations and AF. In addition, Chen et al. (58) studied 157 patients with early-onset AF and 314 matched controls. They found an association between common SCN5A polymorphisms (with loss of function) and nonfamilial lone AF. They speculated that loss of Na+ channel current results in

decreased upstroke velocity, a shorter wave length, and hence, promotion of AF.

Clinical Implications

The early finding of an association between familial AF and gain of function of only k+ channels has to be modified. More recent observations have documented an association between AF and genetic mutations that result in loss of function of the k+ channel (increased action potential duration and delayed after depolarization) (59), as well as those associated with both loss and gain of function of the Na+ channels. These findings open up exciting new therapeutic avenues to help correct for the genetic deficiency. This was, for example, fruitfully applied in use of flecainide for familial AF associated with gain of function of the Na+ channels (55). There is continued interest in the association of AF with upstream genetic mutations. Candidate genes involved in the renin-angiotensin system genes (60) (angiotensin II is known to be profibrotic) have been studied. In addition, there is continued interest in genes controlling the expression of connexin 40. Genetic variations producing decreased expression of connexin 40 can lead to impaired conduction and block, which may facilitate AF (61). Previous studies by Gollob et al. (62) emphasized the importance of somatic mutations of the connexin 40 gene and the genesis of AF. These exciting advances in our understanding of the links between genetic mutations and AF open up a variety of novel clinical strategies (i.e., use of anti-inflammatory agents or blockers of the renin-angiotensin system) in selected individuals.

Implantable Devices

In the past year, there were no pivotal clinical trials that would redefine or expand the use of devices in clinical practice. Two proof-of-concept clinical trials failed to show cardiac resynchronization therapy (CRT) benefit in patients with heart failure and narrow QRS complexes and in patients with mild heart failure (63,64). Subgroup analysis of data from previous published seminal trials (65,66), however, revealed an alarming negative association of ICD shocks with patient mortality that may affect our practice approach (67,68). The search for better patient selection for ICD and CRT continued (69–73). There were no new device recalls and safety alerts, although the Sprint Fidelis high-voltage leads from Medtronic (Minneapolis, Minnesota), which were placed on Food and Drug Administration recall in October, 2007 continue to be an active problem (74,75). The American College of Cardiology/American Heart Association/Heart Rhythm Society published the new 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities (76). In this part of the review, we will examine how some of the published works may affect our approach to device implantation and clinical practice.

ICD. Post-hoc analyses were performed on the MADIT II (Multicenter Automatic Defibrillator Implantation Trial II) and the SCD-HeFT to examine the prognostic significance of appropriate and inappropriate ICD shocks. Daubert et al. (65) reported that the all-cause mortality of patients in MADIT II who received appropriate and inappropriate shocks (but not antitachycardia pacing [ATP]) was 4 times higher than for those without shock therapy. In particular, inappropriate shocks (occurring in 11.5% of the patients) increased all-cause mortality 2-fold. Atrial fibrillation (44%) and supraventricular tachycardia (36%) were the major triggers for inappropriate shocks. In the SCD-HeFT, patients who received shocks for any arrhythmia had a significantly higher risk of death (progressive heart failure being the most common cause) than those who did not receive shocks (64). Even 1 single appropriate ICD shock, as compared with no appropriate shock, increased the mortality rate nearly 6-fold. Inappropriate shocks occurred in 17.4% of the patients and, similar to MADIT II results, an inappropriate shock increased the mortality rate nearly 2-fold. The risk of death increased as much as 16-fold in patients who had more than 2 appropriate and 1 inappropriate shock. The patients who received appropriate shocks had a lower EF, a higher NYHA functional class, and were more likely to have AF. Available data demonstrated an association between shocks and increased mortality only and did not suggest any mechanism or a causal relationship. Besides adverse psychological consequences, direct damage to the myocardium is the most apparent explanation for the observed association between shocks and increased mortality. However, in the case of appropriate shocks, it is conceivable that, as a patient's medical status approaches the end stage, serious ventricular tachyarrhythmias (especially occurring near the time of death) are expected to increase. These arrhythmias, presumably less likely to be successfully treated by ATP, will require more appropriate shock therapy, thereby creating an association, but not a causal relationship, between increased mortality and appropriate shocks.

Although a causal relationship has yet to be determined, the association of shocks with increased mortality in primary prevention is potentially alarming and must be recognized by physicians who care for these patients (77). Clinicians must familiarize themselves with all the available device detection and therapy algorithms to formulate programming strategies to minimize inappropriate shocks while delivering shocks for life-threatening situations only. For example, a higher detection rate would decrease the number of shocks delivered; a longer detection-to-shock duration would allow some VT/VF that would otherwise result in shock delivery to terminate spontaneously. Use of morphology discrimination should be a part of the regular detection criteria, especially in patients with AF and single chamber ICD. Extending ATP to a faster rate may reduce shock therapy. Remote monitoring will help to identify inappropriately detected tachyarrhythmias that can be treated medically or with ablation before inappropriate shocks are delivered. Optimizing therapy for AF, especially in rate

control, and congestive heart failure that are often linked to ventricular tachyarrhythmias or shocks may have a potentially added beneficial effect on the prognosis of these patients by reducing shock instances.

The safety and possibly favorable outcomes of the above programming strategies were evaluated by the PREPARE (Primary Prevention Parameters Evaluation) study (67). Comparing them with a historical control cohort, the investigators showed that a standard detection and treatment protocol with the above key programming elements reduced the morbidity index. In particular, shocks for any cause and inappropriate shocks were reduced and the incidence of untreated VT and arrhythmia syncope were similar between the study patients and the control cohort. Although the study patients had a lower mortality rate compared with the control cohort (4.9% vs. 8.7%), the difference was not statistically significant once the differences in patient baseline characteristics (more PREPARE patients were taking beta-blockers, had shorter QRS duration and higher LVEF and nonbiventricular ICD) were included in the analysis. Prospective randomized trials are surely needed to confirm if there is a causal relationship between shocks (and magnitude of energy delivered) and increased mortality, and whether strategic programming aimed to reduce shocks will result in a mortality benefit.

In view of the negative impact of even 1 single shock on mortality, one has to ask if shocks delivered during defibrillation threshold testing (DFT) at the time of implant are detrimental to patients who receive ICD for primary prevention. The necessity for DFT has been questioned (78,79). A recent subgroup analysis of the SCD-HeFT data indicated that successful defibrillation was achieved with ≤10 J and ≤30 J in 86.8% and 100%, respectively, of the patients tested during device implantation (67). Furthermore, low defibrillation energy at implant did not predict long-term mortality or shock efficacy. Based on these results, a strong argument could be made to eliminate DFT at implant in this group of patients (80). However, until data show that successful treatment outcomes can be achieved even when implant DFT is greater than the maximal ICD output, the prudent approach is to continue to perform DFT but limit it to 1 test shock when possible. On the other hand, in view of the above studies, one may ask if DFT should be performed during generator replacement in the primary prevention patients who have had a satisfactory safety margin at the initial implant.

In order to further identify patients with low LVEF who would benefit most with ICD implantation, the MADIT II investigators used subset regression analysis to create a simple risk scores for risk stratification (68). After separating a group of very high-risk patients (blood urea nitrogen ≥50 mg/dl and/or serum creatinine ≥2.5 mg/dl), a clinical risk scoring system made up of 5 clinical factors (NYHA functional class >II, age >70 years, blood urea nitrogen >26 mg/dl, QRS >012 s, and AF) was developed. Low-risk (score = 0) and very high-risk patients received no mortality benefit from ICD implantation. The former had very low mortality (8% over 2 years), even without ICD despite a low LVEF; the latter had such high mortality (50% over 2 years) from multiple comorbidities that ICD failed to affect outcomes. However, ICD benefit was most pronounced in patients with risk scores of 1 or 2 (2-year mortality was reduced from 22% to 27% to 10% to 15%).

ICD therapy was reappraised in 2 state-of-the-art reviews (81,82). Focusing primarily on the negative data, Tung et al. (81) opined that the clinical benefit of ICD therapy was overestimated in the clinical trials. The authors argued that: 1) The ICD treatment arm benefited from the underperformance (oftentimes, detrimental) of antiarrhythmic drugs comprising the control arms; 2) in most primary and secondary prevention trials, when compared with subjects in the control arm, more ICD patients were treated with beta-blockers, whose beneficial effects on arrhythmic and all-cause mortality had been well documented; 3) the adverse effects on morbidity and mortality, quality of life, potential proarrhythmia from ICD therapy, and device malfunction have been underestimated; 4) the published cost-effective analyses represented hypothetical "best-case scenario" estimates and did not accurately reflect real-world figures; and 5) some of the published implant guidelines were based on statistically insignificant results and often failed to take into account changes in standard practice since the publication of the clinical trials. However, despite these assertions, the authors concluded that ICD therapy has been clearly shown to be effective in aborting sudden arrhythmic death. In an accompanying editorial, Epstein (83) addressed the authors' concerns by redirecting the readers' attention to the many undisputable ICD benefits established by multiple clinical trials. In his review on the use of ICD after myocardial infarction, Myerburg (82) discussed some of the factors that should be considered in selection of patients for ICD therapy. The use of LVEF of 35% in the published practice guidelines was questioned. Although clinical trials set a maximum upper limit on LVEF (mostly 35%) for the enrollment criterion, the median values of patients in the trials were substantially lower. Subgroup analyses of MADIT, MADIT II, and SCD-HeFT data indicated that patients with LVEF >30% did not benefit from ICD therapy. The authors suggested that heart failure, ambient nonsustained and induced VT, QRS interval ≥120 ms, and deteriorating LVEF over time may improve patient selection within a given range of LVEF.

CRT

Since last year's review, there were 2 proof-of-concept clinical trials on CRT indications. The RethinQ (Cardiac Resynchronization THerapy IN patients with heart failure and narrow QRS) study investigated if symptomatic heart failure patients (NYHA functional class III) with echocardiographic evidence of left ventricular mechanical dyssynchrony and systolic dysfunction (LVEF <35%) but narrow

QRS complexes (<130 ms) would benefit from CRT (63). At 6 months, there were no differences between the CRT group and the non-CRT group in the primary end point of an increase in peak oxygen consumption. Quality of life score, 6-minute walk distance, and LVEF were not different. The REVERSE (Resynchronization reverses Remodeling in Systolic left vEntricular dysfunction) study asked if mildly symptomatic (NYHA functional class I and II) heart failure patients with reduced LVEF (≤40%), increase LV end-diastolic diameter ≥55 mm, and prolonged QRS duration (120 ms) would benefit from CRT (64). Not surprisingly, during a 12-month period, CRT did not improve heart failure symptoms or mortality despite echocardiographic evidence of reversed remodeling by CRT. Although CRT significantly delayed the time-to-first heart failure hospitalization, the absolute reduction was small (at 12 months, about 7% of the control group was hospitalized vs. 4% of the CRT group). This small benefit was more than offset by the high peri-operative (4%) and post-operative (16%) system-related complications. One should also consider that this group of patients will live with an implanted device for a longer period of time, which exposes them to more device replacement, potentially more generator and lead malfunctions, and shocks. Until more convincing outcomes data are available, benefits from CRT are most evident in moderate-to-severe heart failure patients with LV systolic dysfunction and prolonged QRS duration only.

It is well recognized that even among this group of "best" candidates, more than one-third of patients did not respond to CRT (84,85). A number of small observational reports have suggested that echocardiographic measurements may predict response to CRT. A multicenter prospective trial (PROSPECT [Predictors of Response to CRT]) clearly established that an elaborate set of echocardiographic parameters of dyssynchrony failed to improve patient selection (70). Thirty-one percent of the patients failed to show improvement of clinical composite score and 44% showed a <15% decrease in LV end-systolic volume. The role of echocardiography in either patient selection or adjustment of pacing parameters is questionable; the search for other deterministic factors continues (86).

Device Recall

In October 2007, the Food and Drug Administration placed the Medtronic Sprint Fidelis high-voltage leads on class I recall because of a high incidence of fracture involving the pace-sense conductor (90%) or the high-voltage coil conductor (10%). Fractures can occur suddenly, resulting in oversensing and clusters of inappropriate shocks, which can be proarrhythmic and may have long-term negative effects on mortality in view of the connection between shocks and mortality. Kallinen et al. (74) reported that oversensing and inappropriate shocks often occurred very shortly after or even before impedance changes were detected. A downloadable self-programming Lead Integrity Alert (LIA) algorithm was introduced by Medtronic to address this problem (75). When the device detects an abnormal change in lead impedance or nonphysiological noise (ultra-short VV intervals), self-reprogramming will be initiated to minimize shock delivery before the patient can obtain medical help. The programming changes include: 1) an increase of the detection duration (the number of intervals to detect, VF is changed to 30 of 40); 2) emission of an audible alert every 4 h (instead of once daily); and 3) transmission of an alert message to the Medtronic Carelink Network Website, where it can be read by the patient's physician, if the generator is capable of wireless transmission.

Whether this approach will reduce the number of inappropriate shocks and ensure patient safety in clinical practice remains to be documented. The weakest link is in prompt notification. For nonwireless devices, the alert process is entirely dependent on the ability of the patients (many of whom are old and hearing impaired) to hear the audible alert. Furthermore, as pointed out in the accompanying editorial, the algorithm has only been simulated with historical data (87). Nevertheless, this self-programmable functionality may be a first step in need-based or condition-based approaches in dynamic device and disease management.

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Key Words: sudden cardiac death ■ atrial fibrillation ■ ventricular tachycardia ■ cardiac resynchronization ■ genetic arrhythmia syndromes.