The Year in Electrophysiology

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The advances in cardiac electrophysiology during 2003 will be divided into three basic categories: mechanisms, genetics, and therapy, the latter including ablation, devices, drugs, and a unique pacing application in heart failure. This brief summary is not a comprehensive review article, and cannot do justice to all the efforts and many publications by outstanding clinical and basic investigators. To those whose work is not mentioned, I apologize in advance. I have limited most references to 2003, with occasional exceptions.

MECHANISMS

Probably the major recent advance in our understanding of clinical cardiac arrhythmias is the recognition that the pulmonary veins play a role in the initiation of atrial tachyarrhythmias, particularly atrial fibrillation (AF). Although interest in the electrophysiology of the thoracic veins dates back many years (1), Haïssaguerre et al. (2) opened a new chapter on mechanisms of atrial arrhythmias. Since then, multiple groups have demonstrated initiation of AF from pulmonary veins (3), which may have larger diameters (4) and be associated with larger left atria (5), than in patients without AF. Most of the foci responsible for AF appear to come from the upper pulmonary veins and are ostial in location (6).

The mechanisms responsible for pulmonary vein depolarization are still being investigated, but may include early afterdepolarizations (7) and re-entry (8). Even the vein of Marshall and the venae cavae may be sources of ectopic discharge provoking AF (9). In the latter study, of 240 patients with 358 ectopic foci initiating paroxysmal AF, 68 had AF initiated by foci discharging in the left atrium, superior vena cava, crista terminalis, ligament of Marshall, interatrial septum, and coronary sinus ostium.

Once initiated, the maintenance of AF may depend on the periodic activity of a small number of rotors located in the posterior left atrial wall near the pulmonary veins. Experimental data suggest that these rotors activate the atria rapidly to produce fibrillatory conduction that propagates from the left to the right atrium and may help explain the success of ablation in and around the pulmonary veins (see the following text) (10).

Animal studies often presage subsequent clinical observations. Ausma et al. (11) demonstrated in the goat that AF caused remodeling of electrophysiologic, contractile, and structural atrial properties, subsequently replicated by many investigators in humans. Elvan et al. (12) showed that chronic AF impaired sinus node function in dogs with reversal after cessation of AF. Recently, Hocini et al. (13) demonstrated reverse remodeling of sinus node function after radiofrequency ablation of AF in patients who had symptomatic sinus pauses exceeding 3 s on termination of paroxysmal AF. Satoh and Zipes (14) in dogs found that cesium induced early afterdepolarizations triggering a polymorphic atrial tachycardia and suggested the possibility of atrial torsade de pointes occurring in patients with long QT syndrome. Subsequently, Kirchhof et al. (15), using monophasic action potential recordings, demonstrated a similar phenomenon in patients with the long QT syndrome.

Finally, although not an electrophysiologic mechanism, it is important to consider recent data suggesting that thrombogenesis in AF may not result solely from left atrial hemostasis. Recent data suggest that AF can alter the extrinsic coagulation pathway. Tissue factor expression is overexpressed in the endothelia of atrial tissue in patients with non-valvular AF, particularly those containing inflammatory cells and denuded matrix. These changes may be involved in the pathogenesis of thrombosis in patients with non-valvular AF (16).

Ventricular tachyarrhythmias. Understanding mechanisms of ventricular tachyarrhythmias has also progressed. Significant research has centered on the restitution properties of the heart. These represent the dynamic dependence of action potential duration (APD) or conduction velocity on the previous diastolic interval (17). The restitution hypothesis (18) is based on the concept of a steep APD restitution slope as a primary dynamic factor predisposing propagating cardiac waves to break up and cause ventricular fibrillation (VF). Flattening this curve might suppress the ability to develop VF. Adrenergic agonists can steepen the APD restitution curve and may be related to the known effects of adrenergic stimulation in facilitating VF (19). Two types of VF have been demonstrated in isolated perfused rabbit hearts. The first type of VF is associated with steep APD restitution and normal excitability but, because of acute global ischemia, the APD restitution curve can flatten and decrease excitability, converting it to the second type of VF. The latter might occur when acute or chronic regional ischemia precedes the onset of VF. Chen et al. (17)
postulate that type 1 VF may be present in a non-ischemic area with type 2 VF in the ischemic zone, a combination unlikely to self-defibrillate and possibly more difficult to defibrillate by electrical shocks. Conversely, spontaneous termination of VF might be facilitated by acute global ischemia that flattens the APD restitution while providing a brief window of opportunity for self-defibrillation before progressive ischemia converts type 1 to lethal type 2 VF owing to reduced excitability. However, other studies have demonstrated that a single, rapidly firing re-entrant scroll wave or rotor may underlie VF (20).

Understanding mechanisms responsible for VF will be critical for the development of future drug interventions. But, at the present time, no antiarrhythmic drug, except possibly amiodarone, based on a meta-analysis (21), impacts favorably on VF and sudden cardiac death. In fact, it is the drugs that affect “upstream” cardiac events provoking the electrical instability (e.g., ischemia, fibrosis) leading to VF (22), including aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, spironolactone, fish oil, and statins, which have had a major impact on mortality. Hypercholesterolemia in rabbits produces proarrhythmic neural and electrical remodeling (23), while lipid-lowering drugs reduced the hazard for ventricular tachycardia (VT)/VF recurrence in implantable cardioverter-defibrillator (ICD) patients who were part of the Antiarrhythmics Versus Implantable De-fibrillators (AVID) trial. Perhaps statins have a direct anti-arrhythmic effect (24).

**Brugada syndrome.** We now know that there are multiple types of VT, some of which have very distinct mechanisms of origin. For example, the Brugada syndrome is thought to be due to early repolarization of right ventricular epicardium, with loss of action potential dome at some epicardial sites but not others. The resulting transmural dispersion of repolarization can lead to conduction of the action potential dome from sites at which it is maintained to sites where it is lost, inducing phase 2 re-entry and a closely coupled extrasystole that triggers a ventricular tachyarrhythmia due to re-entry (25). Prolongation of the QT interval in the right precordial leads may be consistent with that hypothesis (26). In these patients, sodium channel blockade can induce typical electrocardiographic (ECG) changes and VT (27). A variety of provocations, including temperature and other drugs, have been demonstrated to provoke the typical ECG changes.

**Long QT syndrome.** The long QT syndrome is thought to result from an increase in transmural dispersion of repolarization and the development of early afterdepolarization-induced triggered activity that provokes a ventricular extrasystole. The latter, interacting with the dispersed repolarization, can then cause a VT sustained by re-entry. Preferential prolongation of M-cell APD can contribute to an increase in the QT interval as well as the dispersion (25).

**Catecholaminergic polymorphic VT.** Catecholaminergic polymorphic VT appears to result from abnormalities in ryanodine receptors, which are responsible for release of calcium from the sarcoplasmic reticulum in response to calcium entry. The exact electrophysiologic mechanism responsible for the VT, which often takes the form of bidirectional VT, is still under investigation, but probably relates in some fashion to increased calcium release (28).

**Arrhythmogenic right ventricular cardiomyopathy.** Arrhythmogenic right ventricular cardiomyopathy is characterized by fibrofatty replacement of cardiomyocytes, beginning primarily in the right ventricle, but in more advanced stages involving the left ventricle and intraventricular septum (29). Electroanatomic mapping in some patients demonstrate VTs consistent with a re-entrant mechanism.

**Commotio cordis.** Link et al. (30) have performed a series of studies in juvenile swine demonstrating the mechanism by which chest wall impact during the ventricular vulnerable period can provoke VF. This can help explain sudden death suffered by young athletes when struck with hockey pucks, baseballs, and other objects.

**GENETICS**

The concept that cardiac arrhythmias might have a genetic basis, although not new, accelerated rapidly with the mapping of the first long QT gene to the short arm of chromosome 11 (31). However, it is important to stress that a single clinical phenotype may be caused by different genetic substrates, while a single gene can cause very different phenotypes by acting through different pathways (32).

In the past several years we have gained insight into a group of electrophysiologic diseases previously included under the heading of primary electrical disease. When VF occurred, it was often called “idiopathic.” However, we now realize that molecular abnormalities in ion channels or their supporting elements cause many (and most probably, ultimately, most) of these diseases. Ion channels consist of proteins and glycoproteins that form pores across the membrane permitting ions to flow, causing a voltage change across the membrane responsible for the propagated action potential. Multiple currents produced by sodium, potassium, calcium, chloride, and other ions can become abnormal and create the substrate for the development of cardiac arrhythmias. The following will only briefly elucidate major ionopathies, highlighting advances in the past year.

**Long QT syndrome.** The long QT syndrome represents the first of these ionopathies to have a genetic basis established. Presently, seven genotypes caused by mutations in six genes affecting the cardiac potassium currents, \( I_{\text{Ku}} \) and \( I_{\text{Kr}} \), and sodium inactivation, as well as an anchoring protein called ankyrin-B, can be responsible for the long QT syndrome. Mutations in ankyrin-B, an abnormality that interrupts normal sodium and calcium function, appears as a possible cause for LQT4 (33). Because these ionopathies account for perhaps 50% to 60% of the patients with long QT syndrome, it is clear that additional abnormalities have yet to be determined. It is known that patients with
mutations in the pore region of the HERG (LQT2) gene have a significantly higher risk of cardiac events than subjects with mutations in the non-pore region. However, this does not appear to hold true for patients with LQT1 (34). An epinephrine challenge can help establish the ECG diagnosis in patients with LQT1 mutation carriers with QTc < 460 ms (35). This may be important because “silent carriers” of the congenital long QT syndrome may develop significant QT prolongation when exposed to drugs that in ordinary circumstances produce only minimal QT prolongation.

An approach to risk stratification based on the locus of the causative mutation affects the clinical course of long QT patients and modulates the effects of the QTc and gender on clinical manifestations. For example, the incidence of a first cardiac event before the age of 40 years and before the initiation of therapy was lower among patients with a mutation at the LQT1 locus (30%) than among those with a mutation at the LQT2 locus (46%) or those with a mutation at the LQT3 locus (42%). Genetic locus and QTc, but not gender, were independent predictors of risk. QTc was an independent predictor of risk among patients with a mutation at LQT1 locus and those with a mutation at LQT2 locus but not among those with a mutation at LQT3 locus, whereas gender was an independent predictor of events only among those with LQT3 location (36).

Sinus bradycardia in LQT3 patients may result from sodium channel mutations displaying a persistent inward current or a negative shift in inactivation, leading to sinus pauses or arrest (37).

Autoantibodies may also play a role in some long QT patients, as demonstrated in rabbits (38) and in patients (39). The latter patient had autoantibodies against the HERG channel, which reduced IKr and prolonged APD.

In the future, it may be possible to genetically treat patients with the long QT syndrome. A transgenic mouse with a long QT phenotype (Kv1DN) created by overexpression of a truncated potassium channel in the heart was tested to determine whether direct injection of adenoviral vectors expressing wild-type Kv1.5 (AV–Kv1.5) into the myocardium would correct the QT. Overexpression of the Kv1.5 reconstituted a 4-aminopyridine-sensitive outward potassium current associated with shortening of ventricular APD, elimination of early afterdepolarizations, a shortened QT interval, decreased dispersion of repolarization, and increased heart rate (40).

**Short QT syndrome.** Another abnormality, short QT syndrome (corrected QT <300 ms), contrasts with the long QT syndrome in that these individuals have a short QT interval, and ventricular refractory period, and at least some of them have abnormalities of cardiac IKr (KCNH2). The mutations increase IKr, leading to heterogeneous abbreviation of APD and refractoriness. This gain of function mutation can cause death in infants and may be linked to the sudden infant death syndrome (41). There is a high risk of sudden death in young, otherwise healthy, individuals (42).

**Andersen’s syndrome.** Mutations in KCNJ2 encoding Kir2.1 or IK1 channels recently have been linked to long QT 7, which is known as Andersen's syndrome (43). This rare autosomal-dominant inherited disorder is characterized by physical abnormalities including short stature, scoliosis, lateral or medial deviation of one or more fingers, hypertelorism, low-set or slanted ears, micrognaphia, and broad forehead, as well as periodic paralysis, cardiac arrhythmias, and long QT.

**Brugada syndrome.** Brugada syndrome (44), characterized by an accentuated J-wave primarily in V1 to V3, with ST-segment elevation, often followed by a negative T-wave and an R prime, may be the cause of sudden unexplained death syndrome, especially in those from many southeast Asian countries. It is an autosomal-dominant mutation in the SCN5A gene encoding for the alpha subunit of the cardiac sodium channel, with almost 60 different mutations demonstrated (25). Individuals with Brugada syndrome and no previous cardiac arrests may have a high risk of sudden death if they have inducibility of ventricular arrhythmias and a previous history of syncope (45). Hyperthermia can unmask the Brugada ECG pattern in the SCN5A-H681P mutation (46). The mutation in SCN5A results in loss of function due to failure of the sodium channel to express a shift in voltage and time dependence of sodium activation, inactivation, or reactivation; entry of the sodium channel into an intermediate state of inactivation from which it recovers more slowly, or accelerated inactivation of the sodium channel (25). Brugada patients can display fever-induced polymorphic VT, and a host of agents can unmask the Brugada syndrome or lead to accentuation of ST-segment elevation (25).

**Catecholaminergic polymorphic VT.** Defects in the ryanodine receptor (RyR2) on the sarcoplasmic reticulum, responsible for the release of calcium required for muscle contraction, may cause this syndrome. “Leaky” ryanodine channels can trigger fatal cardiac arrhythmias and provide a possible explanation for catecholaminergic polymorphic VT (47). The mutant RyR2, found in patients with catecholaminergic polymorphic VT, has decreased calstabin2 binding affinity, which can trigger ventricular arrhythmias and sudden cardiac death after stress and exercise (48). Mutations of calsequiterine2 may also cause catecholaminergic polymorphic VT and appear to be less common (49). Symptomatic patients have a poor prognosis unless treated with an ICD (50).

**Familial AF.** Familial AF due to abnormalities in KCNQ1, also responsible for the LQT1 syndrome. This is the first gene to be linked to familial AF (51). This gain of function mutation appears to be responsible for AF by an unknown mechanism. It is likely that more genes may be responsible for, or contribute to, the development of AF (52). Chen et al. (51) identified a four-generation family with autosomal-dominant hereditary AF without structural
heart disease. The QT interval was prolonged but there was no sudden death. Thus, in contrast to the long QT-associated mutations in KCNQ1, which all have a dominant negative effect, the AF-associated KCNQ1 mutation leads to a gain of potassium channel function and may produce AF by reducing APD and effective refractory period in atrial myocytes.

**Bradyarrhythmias.** Progressive familial heart block has been described in association with mutations in SCN5A. It appears to be an autosomal-dominant disease of the cardiac conduction system, one form occurring early and progressing rapidly while affecting primarily the bundle branches and a second form occurring later in life and affecting primarily the atrioventricular node. In a French family with 65 potentially affected members, 25 individuals were carriers of the SCN5A mutation and exhibited various types of conduction defects involving the P-wave, PR interval, and QRS duration, all progressing with age. These findings demonstrate that the hereditary disease described by Le-negre is caused by a haploinsufficiency mechanism, which in combination with age, leads to progressive alternation in conduction velocity (53).

Atrial standstill has been associated with the SCN5A gene (54) as well as changes consistent with dilated cardiomyopathy and severe degenerative abnormalities of the conduction system (55). The sodium channel mutations may also produce sinus node dysfunction in LQT3 families (37). A novel mutation in SCN5A and rare polymorphisms in the atrial specific connexin40 gene may be responsible for atrial standstill (54).

**Arrhythogenic right ventricular cardiomyopathy.** Linkage analysis previously mapped the involved gene to chromosome 14Q24.3, whereas the present study confirms that locus and failed to detect causative mutations in exonic sequences of four genes (56). First- and second-degree relatives of patients with arrhythogenic right ventricular cardiomyopathy have a high percentage of people who are similarly affected (57), further supporting a genetic origin.

Naxos disease is a recessively inherited form of arrhythmo-genic right ventricular cardiomyopathy in which the cardiac phenotype is associated with palmoplantar keratoderma and woolly hair. Thus, this form of the disease is a heart muscle disorder with distinctive physical characteristics (58). It may be caused by a deletion in plakoglobin (59).

**Wolff-Parkinson-White (WPW) syndrome.** This well-known and well-characterized electrophysiologic disorder has been created in transgenic mice by overexpressing an Asn488Ile mutant [(TG) N488I] human PRKAG2 complementary deoxyribonucleic acid. The transgenic mice recapitulate an electrophysiologic phenotype similar to human WPW syndrome (60). They exhibit a procainamide-sensitive, adenosine-resistant, accessory pathway. Mutations in this gene produce an unusual human cardiomyopathy characterized by ventricular hypertrophy and electrophysiologic abnormalities consistent with WPW syndrome, along with progressive degenerative conduction system disease. PRKAG2 mutations create a glycogen storage cardiomyopathy, which provides an anatomic explanation for the electrophysiologic findings, and implicate disruption of the annulus fibrosis by glycogen-engorged myocytes, as the cause of pre-excitation in Pompe, Danon, and other glycogen storage diseases. These findings are consistent with the original identification of a genetic defect as a missense mutation in the gene that encodes the gamma 2 regulatory subunit of PRKAG2. The mutation results in the substitution of glutamine for arginine at residue 302 in the protein (61). It has not been established that these molecular abnormalities are responsible for sporadic WPW syndrome (62).

**THERAPY**

**Ablation.** One of the most exciting applications of radiofrequency catheterization ablation has been in patients with AF. After the Haissaguerre et al. (2) observation, a number of investigators have pursued various techniques in ablating focal discharge originating in pulmonary veins (63). Pappone et al. (64) developed a technique for anatomic pulmonary vein isolation and demonstrated the superiority of this approach over medical therapy for recurrence of AF and all-cause mortality and morbidity resulting from heart failure and ischemic cerebrovascular events. Quality-of-life assessment reached normal values in contrast to medically treated patients. The success rate using circumferential left atrial ablation was approximately 85% in patients who had paroxysmal or chronic AF at a mean of 900 days after ablation.

Circumferential left atrial ablation strategy is significantly more effective than segmental ostial ablation, with success rates at 6 months of 87% and 67%, respectively. The average procedure duration with both approaches was approximately 2.5 h (65). Major potential side effects include pulmonary vein stenosis and pericardial tamponade. Pulmonary vein stenosis can occur in 15% to 20% of pulmonary veins, depending on the particular technique used (66) and how stenosis is diagnosed.

The pulmonary veins appear to be more important in paroxysmal or possibly persistent AF rather than a chronic, sustained AF, where ablation may be successful in only a one-quarter of patients (63).

Radiofrequency catheterization ablation of virtually all other supraventricular tachycardias is now relatively routine, though challenges remain in some patients, such as those with hard to locate accessory pathways, congenital heart disease, and after cardiac surgery (63). It is of interest that a recent trial of 224 eligible patients with asymptomatic WPW syndrome randomly assigned 37 patients to radiofrequency catheter ablation of the accessory pathways and 35 patients to no treatment. Two patients in the ablation group (5%) and 21 in the control group (60%) had arrhythmic events, with 1 control patient presenting with VF. The incidence of arrhythmic events was 7% among patients who
underwent ablation and 77% among control patients, with a risk reduction with ablation of 92%. The study challenges the notion that risks of ablation in the asymptomatic WPW patient may be comparable to the risk of a life-threatening arrhythmia (67). Risk stratification in WPW patients by electrophysio logic testing may be useful as well (68).

New catheter approaches, including a magnetic guidance system in which a magnetic field can be used to guide the catheter, are being explored (69). In addition, new catheter designs, as well as alternative energies, including cryoablation and high-intensity focused ultrasound, are being tested (63). Newer mapping systems are capable of improving success rates and reducing fluoroscopy time (70). One approach includes an electromagnetic catheter positioning system that can be superimposed on other images such as those obtained with magnetic resonance, computer tomography, or fluoroscopy that have been previously acquired (71). Ablation procedures can also be performed intraoperatively (72).

Advances in the application of ablation to patients with ventricular tachyarrhythmias include elimination of premature ventricular complexes that may trigger ventricular tachy arrhythmias, including VF (73,74). Ventricular tachycardia can be ablated from either ventricular outflow tract, including the valve cusps and in the epicardium (75) in patients without or with coronary artery disease. The epicardial origin of VTs may be responsible for some failures of endocardial ablation (76).

DEVICES

We have all become used to, and even perhaps complacent with, the fundamental reliability of implantable pacemakers and ICDs. Recent advances have been the development of pacemakers and ICDs to monitor comorbidities, such as heart failure, and their increasing application to include broader groups of patients (see section entitled “Heart Failure” in the following text). It is now clear that the ICD decreases the risk of arrhythmic deaths and all-cause mortality, the extent related to the underlying risk of arrhythmia-related death relative to competing causes (77).

The study perhaps raising the most interest and discussion was the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) (78), which demonstrated the improved survival with an ICD compared with conventional therapy in patients with previous myocardial infarction and ejection fraction of 30% or less. The mortality rates were 19.8% in the conventional therapy group and 14.2% in the defibrillator group with a hazard ratio for risk of death from any cause in the defibrillator group compared with conventional therapy of 0.69. The application of ICD implantation in this large group of patients has major medical and economic implications.

The Dual Chamber and VVI Implantable Defibrillator (DAVID) trial determined the efficacy of dual-chamber pacing compared with backup ventricular pacing in patients with standard indications for ICD implantation but without an indication for bradycardia pacing. Five hundred six patients were randomly assigned to have ICDs programmed to backup ventricular pacing at 40 beats/min (VVI) or dual-chamber rate-responsive pacing at 70 beats/min (DDDR). The authors found that one-year survival free of the composite end point of death or hospitalization for heart failure was 84% for patients treated with VVI pacing at a rate of 40 compared with 73% for patients treated with DDDR pacing at a rate of 70, yielding a relative hazard of 1.61. It was concluded that dual-chamber pacing offered no clinical advantage over ventricular back-up pacing and may be detrimental. Some have interpreted the results of this study to indicate that right ventricular apical pacing is potentially harmful, which may be true. However, an often overlooked fact is that the patients receiving DDDR pacing had a minimum rate of 70 beats/min 24 h per day and, therefore, in this population it is possible that the continued rate of 70 beats/min was detrimental, over and above the site of right ventricular apical pacing (79).

The Defibrillator Versus Beta Blockers for Unexplained Death in Thailand (DEBUT) trial randomized patients with sudden unexplained death syndrome to beta-blockers or an ICD. During a three-year follow-up, there were four deaths in the beta-blocker group, whereas seven subjects in the ICD arm had recurrent VF effectively treated by the ICD. When the main and pilot study data were combined, there were 7 deaths in the beta-blocker group and none in the ICD group, with 12 ICD patients receiving ICD discharges owing to recurrent VF (80). Implantable cardioverter-defibrillators have been shown beneficial in high-risk long QT patients (81), patients with right ventricular cardiomyopathy (82), and those with hypertrophic cardiomyopathy (83). The latter may be stratified by a history of cardiac arrest, spontaneous sustained VT, family history of sudden hypertrophic cardiomyopathy-related death, syncope, non-sustained VT, abnormal blood pressure response with exercise, or extreme left ventricular hypertrophy.

T-wave alternans may help define the patient who will benefit from ICD implantation. Among patients with previous myocardial infarction and left ventricular ejection fraction of 30% or less, those without microvolt T-wave alternans had no sudden death or cardiac arrest, compared with an event rate of 15.6% among the remaining patients (84). Similarly, patients with dilated ischemic cardiomyopathy can be stratified by the presence of microvolt T-wave alternans as well as baroreflex sensitivity to identify those at risk of life-threatening ventricular arrhythmia for whom an ICD might be beneficial (85).

A remaining issue with the ICD is its usefulness as primary prevention of sudden cardiac death in patients with non-ischemic dilated myopathy. Published data have produced conflicting results. In a recent trial of 103 patients with non-ischemic dilated cardiomyopathy, left ventricular ejection fraction ≤35%, non-sustained VT, mortality and
quality of life in patients treated with amiodarone or an ICD were not statistically different (86). However, the Sudden Cardiac Death–Heart Failure Trial (SCD-HeFT) results will be known shortly and hopefully will provide definitive information.

The Public Access Defibrillation (PAD) trial was a prospective trial, multicenter, randomized clinical study testing whether volunteer non-medical responders could improve survival from out-of-hospital cardiac arrest by using automated external defibrillators. As presented at the last American Heart Association meeting, survival almost doubled with the use of PAD (87). Importantly, patients resuscitated from out-of-hospital cardiac arrest with early defibrillation have long-term survival similar to that among age-, gender-, and diseased-matched patients who did not have out-of-hospital cardiac arrests. The quality of life among the majority of survivors is similar to that of the general population (88).

DRUGS

One of the potential reasons for the lack of difference between rate and rhythm control in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AF-FIRM) may be the inadequacy of presently available drugs to maintain sinus rhythm. One new approach for atrial arrhythmias is to target an ion channel found in the atrium and not in the ventricle. A novel potassium channel blocker, AVEO118, has been demonstrated in pigs to prolong atrial effective refractory period and prevent atrial arrhythmias with no apparent action on ventricular repolarization. This drug blocks the molecular basis for the human cardiac ultrarapid delayed rectifier potassium current (IKur) and the transient outward current (89). Potassium channel gene, KCNA5, whose expression underlies the ultra IKur, is also expressed in extra-cardiac tissues so that extra-cardiac adverse effects might arise (90).

At the recent American Heart Association meeting (April 2, 2003), Halperin (91) reported the results of the third Stroke Prevention Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF-III) trial, which demonstrated that ximelagatran treatment compared with warfarin was associated with a lower incidence of stroke and of major complications other than a transient elevation of liver enzymes.

HEART FAILURE

The Multicenter InSync Randomized Clinical Evaluation Implantable Cardioverter Defibrillator (MIRACLE ICD) trial examined the efficacy and safety of combined cardiac resynchronization therapy (CRT) and ICD therapy in 369 patients with ventricular ejection fraction of 35% or less and QRS duration of 130 ms, who were at high risk for life-threatening ventricular arrhythmias and in New York Heart Association functional class III or IV. A total of 182 patients were randomized to receiving ICD activated but CRT off, and 187 receiving ICD activated and CRT on. At six months, patients assigned to CRT had greater improvement in median quality-of-life score and New York Heart Association functional class compared with control subjects. Peak oxygen consumption increased, as did treadmill exercise duration, but 6-min walk did not. The authors concluded that CRT improved quality of life, functional status, and exercise capacity in these patients (92).

Bristow presented the results of the Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial on March 31, 2003, which randomized 1,520 patients with moderate to severe heart failure to receive standard medical therapy, CRT, or CRT plus an ICD. Over a median follow-up of 14 months, the CRT groups had fewer hospitalizations and improved symptoms. In addition, the CRT plus ICD group showed more than a 40% reduction in mortality (93).

Cardiac resynchronization therapy not only improves functional status but also can result in improved systolic and diastolic function, and decreased mitral regurgitation possibly by reverse left ventricular remodeling (94). However, caution is needed because left ventricular epicardial pacing can at times cause a ventricular arrhythmia (95,96).

A new approach in heart failure patients to increase ventricular contractility is to apply electric currents during the refractory period. Very early data suggest an improvement in cardiac contractility (97).

CONCLUSIONS

It is clear, from the synopsis presented in this review, that the past year has witnessed striking advances in both our understanding and treatment of cardiac arrhythmias. Major challenges remain, particularly in patients with atrial fibrillation and ventricular tachyarrhythmias. No doubt, this following year will bring further progress in our attempts to help these patients.

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