What Have We Learned About Cardiac Arrhythmias?
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No subspecialty in cardiology has undergone a more rapid transformation in the last half century than has clinical cardiac electrophysiology. From the creation of the coronary care unit (CCU), with its concept of intensive monitoring of patients who have cardiac arrhythmias, to understanding the genetics of ion channel disturbances responsible for inherited cardiac arrhythmias, clinical cardiac electrophysiology has evolved into an established discipline credited with improving and saving hundreds of thousands of lives. In this review, we will highlight the top 10 significant advances responsible for this remarkable transformation.

Clinical Concepts

Ambulatory ECG
Recording the ECG in the ambulatory individual provided the ability for the first time to obtain online information in an active individual. Begun by Holter and Gengerelli1 in 1949, the initial device weighed 85 pounds and was strapped to the back. The most modern version is implanted subcutaneously and can monitor the cardiac rhythm for long time periods.2 Ambulatory ECG has led to many new insights, including an understanding of the mechanisms of sudden cardiac death, causes of syncope, and the concept of painless ischemia. All implantable pacemakers and cardioverter/defibrillators (ICDs) have the ability to record the cardiac rhythm, which is a useful adjunct to decision making.

The CCU
A major step forward in reducing death from myocardial infarction was the introduction of the CCU,3 where continuous monitoring of cardiac rhythm and hemodynamic status allowed early recognition and correction of life-threatening complications.4 Closed-chest cardiac massage and defibrillation became important life-saving measures, and the value of the well-trained nurse in this milieu became clear. The CCU also taught us to develop short- and long-term risk profiles of the patient, based on ECG, hemodynamic, and enzymatic findings. The concept of warning arrhythmias emerged along with the use of prophylactic lidocaine administration.5 Neither stood the test of time.5,7 The CCU was also the testing site for appraising the value of pharmacological and nonpharmacological interventions in reducing infarct size with β-blocking agents, thrombolytic agents, or primary angioplasty. Reducing infarct size has also helped to lower the incidence of postinfarction ventricular arrhythmias. The CCU became the center of modern cardiology, the place where rapid, informed decision making for diagnosis and treatment determined the future of the cardiac patient.

Sudden Cardiac Death and Out-of-Hospital Resuscitation
As recently reviewed,8 sudden, unexpected cardiac death continues to be a very common mode of death. In fact, 20% of all deaths are sudden and unexpected.9 The growing number of patients with heart failure; the aging population in industrialized countries; and the increasing number of patients in the Third World with coronary heart disease due to smoking, altered dietary habits, and a move from rural to urban areas make it likely that the number of victims from sudden cardiac death will continue to increase in the coming years. Unfortunately, our efforts in using noninvasive and invasive tests, such as evaluation of ischemia, hemodynamic status, neurohumoral responses, and so forth, to identify people at high risk who die suddenly have resulted in the recognition of only a small segment of those patients. They are primarily the people with syncope or hemodynamically poorly tolerated ventricular tachyarrhythmias, patients with nonsustained ventricular tachycardia in the presence of poor left ventricular function in whom a sustained ventricular tachycardia can be induced, and patients resuscitated from cardiac arrest. Those patients, once identified, can be helped by implanting an ICD (Hallstrom et al, unpublished observations, 2000). The number of defibrillator shocks can often be reduced by prescribing antiarrhythmic drugs like sotalol and amiodarone.

About 40% of sudden death victims have cardiac arrest as the first manifestation of coronary artery disease. In patients with known coronary heart disease, sudden death is frequently caused by the sudden rupture of an unstable plaque, leading to occlusion of the coronary artery in a vessel previously having only a slight narrowing. Our current tests do not allow us to recognize those patients before plaque rupture. Even if we were able to do so, we do not know what measures to take to prevent plaque rupture. Although molecular genetics has helped unravel the location of genes responsible for the long-QT syndrome (LQTS),11,12 a genetically determined primary electrical disease of the heart

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Mechanisms of Cardiac Arrhythmias

Basic
The quest to understand basic mechanisms of cardiac arrhythmias derives in part from the electrophysiologist’s desire to pair an antiarrhythmic drug that has a specific mechanism of action with a cardiac arrhythmia initiated or maintained by a specific electrophysiological event. The hope was that drugs so tailored could be applied much as we use antibiotics. Despite >50 years of effort, our failure to attain this goal is due more to the complexity and heterogeneity of cardiac arrhythmias and the focused action of antiarrhythmic drugs, mostly “sons of quinidine,” than the lack of effort by investigators. Well-defined arrhythmias caused by specific ion channel abnormalities such as the LQTS or Brugada syndrome may yet yield to such a targeted approach, but the vast number of clinical ventricular tachyarrhythmias in patients with coronary heart disease and cardiomyopathies will probably not. Nevertheless, lessons learned about clinical arrhythmias, albeit not at an ion channel level, have permitted the application of radiofrequency catheter ablation techniques based on understanding their site of origin and/or pathways used, as noted below.

Research at the basic level over the past 50 years has shown that the mechanisms responsible for cardiac arrhythmias can be divided into 2 broad groups: those due to abnormalities of either impulse formation or impulse conduction. Inappropriate discharge rate of the sinus node or automatic discharge from subsidiary pacemakers in ectopic sites can cause arrhythmias in the first category. Probably most important, however, is the concept of triggered activity, i.e., pacemaker activity consequent to a preceding impulse(s). The preceding impulse triggers an afterdepolarization, which is a membrane oscillation that can reach threshold and initiate 1 or more cardiac responses. When the oscillation occurs before repolarization is completed, it is called an early afterdepolarization (EAD), which appears to be responsible for prolonging the QT interval in the acquired and inherited LQTSs and initiating torsades de pointes. Increased heart rate and magnesium suppress EADs, which explains the therapeutic efficacy of those treatments in the acquired LQTS. Late or delayed afterdepolarizations may be responsible for some arrhythmias as well and can be initiated by digitalis and other causes of intracellular calcium loading. Perhaps afterdepolarizations initiate some specific types of ventricular tachycardias, such as those arising in the right ventricular outflow area or the left ventricular septum in people with structurally normal hearts, which can be suppressed by adenosine or verapamil, respectively. The most rigorous testing of the concept of pairing a drug with a specific arrhythmia mechanism is in the congenital LQTS, in which the exact ion channel abnormality is known and can be affected by a specific drug. These studies are in their infancy, however.

It would appear that most clinical arrhythmias are due to reentry, a form of abnormal impulse conduction caused by reexcitation of an area of the heart previously activated. The resulting “cat-chasing-its-tail” tachycardia can occur over anatomically established pathways, such as the atrioventricular (AV) node and an accessory pathway to produce AV reentrant tachycardia, or it can be functional in nature, as in acute ventricular ischemia. Drugs affecting conduction or refactoriness in the reentry pathways can interrupt the reentry tachycardia. When the electrophysiological characteristics of 1 of the pathways are known, for example, the AV node, drugs such as digoxin, calcium channel blockers, and β-adrenoceptor blockers can be targeted to that tissue, which is often the “weak link” of the tachycardia. Many times, as with reentrant ventricular tachycardias after myocardial infarction, drugs cannot be applied with such precision because the electrophysiology of the pathways is unknown. Furthermore, arrhythmia-initiating mechanisms interacting with the abnormal myocardial substrate can become very complex and lead to unpredictable drug effects, resulting in inadequate arrhythmia control or even a proarrhythmic response. Although understanding the basic electrophysiological mechanisms is unquestionably important, further progress is needed for it to be of help in treating ventricular tachyarrhythmias occurring in damaged ventricles. The paradigm of the LQTS, and perhaps Brugada syndrome, may advance that objective.

Clinical
In the late 1960s, the use of intracardiac catheters for cardiac activation mapping and programmed electrical stimulation of the heart opened a new chapter in the diagnosis and management of clinical arrhythmias. Recording the His bundle electrogram made it possible to investigate normal and abnormal conduction over the AV node–His bundle branch system. The reproducible initiation and termination of supraventricular tachycardias and ventricular tachycardias by critically timed premature complexes allowed localization of the site of origin or pathway of an arrhythmia. Those investigations resulted in our understanding of the mechanisms, such as reentry and origin of an arrhythmia, which
allowed a much better interpretation of tachycardias and conduction disturbances with the 12-lead ECG.

This knowledge also led to the development of new therapies. Cardiac surgeons began to remove or isolate tissue that was the site of origin of abnormal impulse formation or dissected and interrupted critical parts of the tachycardia pathway. They made incisions in areas where multiple reentrant circuits were responsible for the arrhythmia, such as in atrial fibrillation. Close cooperation between clinical electrophysiologists, anatomists, and surgeons played a crucial role in the development of these curative interventions. The ability to obtain information about tachycardia mechanisms and pathways by programmed stimulation and catheter mapping made it possible to study the effect of pharmacological interventions in patients suffering from tachycardias. In the 1980s, drug selection by programmed electrical stimulation of the heart became increasingly popular. Later, it was realized that in a complex arrhythmia substrate, such as a scar after a myocardial infarction, long-term prediction of drug effect is difficult to obtain. Based on findings from programmed stimulation of the heart, devices were developed to interrupt tachycardias. Starting with “underdrive” pacing followed by “overdrive” pacing, growing sophistication resulted in implantable antitachycardia devices that used pacing algorithms able to cope with rate changes during tachycardia.

Therapy

Transthoracic Electrical Cardioversion and Defibrillation

Electrical cardiac resuscitation had its beginning >200 years ago in very crude attempts. In modern times, Beck et al in 1947 first applied Wigger’s concepts of defibrillation developed in animals to a patient and terminated ventricular fibrillation with an AC current shock to the heart exposed by a thoracotomy. Evolving from AC current shocks to DC current to creation of more optimal waveforms, transthoracic electrical cardioversion/defibrillation was quickly applied to patients with sustained supraventricular and ventricular tachyarrhythmias. Now quite routine, this advance for the first time provided a safe, effective, and immediate method of terminating tachyarrhythmias that could be applied to resuscitative needs as well as elective cardioversion. Indeed, its initial development paralleled the initial advances in cardiopulmonary resuscitation. And for that purpose, more recently the AED has been created. This device, operating through paddles placed on the victim’s chest, interprets the cardiac rhythm and automatically determines whether a shock should be issued. The AED is gaining wide-spread popularity for lay public application and has the potential of reducing the mortality from sudden cardiac death. Efforts to lower defibrillation thresholds continue, with the advent of biphasic waveforms. While the electrophysiological basis of shock-induced defibrillation still is debated, there is little doubt that this technique laid the foundation for many subsequent advances in clinical cardiac electrophysiology. In addition to serving as the forerunner of the ICD, transthoracic cardioversion/defibrillation has allowed many interventions, such as invasive electrophysiological studies, to be applied without fear of being unable to terminate an induced tachyarrhythmia.

Pacing

Hyman, credited with inventing the cardiac pacemaker in 1932, probably introduced the clinical era of cardiac pacing. Twenty years later, Zoll reported that the heart could be stimulated transcutaneously by using line-operated equipment. In 1957, Bakken built a battery-operated external pacemaker in an electronics repair shop in just a few days at the request of Lillehei, who was caring for a postoperative child with complete heart block. The need for a battery-based stimulator became evident when a power outage rendered line-operated equipment useless. The pacemaker incorporated an electronic circuit created for the intermittent pulsation of a metronome, taken from the magazine Popular Electronics. The next step occurred when Furman and Schwede recognized the drawbacks of transcutaneous pacing and developed the endocardial pacing approach in 1958. Shortly thereafter, Elmqvist and Senning implanted the first rechargeable pacemaker to treat a patient with Adam-Stokes syncope. That first device lasted just several hours, and its replacement, 8 days. The patient survived and was still alive 40 years later after numerous pacemaker replacements. Two years after the pacemaker implant by Elmqvist and Senning, Chardack et al implanted the first fully transistorized pacemaker. The application of simple asynchronous pacing, so-called VOO mode, in those early units restored the patient with complete heart block from a mortality approaching 50% in 1 year to a normal life span. Although subsequent advances in cardiac pacing for bradyarrhythmias have unquestionably further reduced mortality and improved morbidity, none have matched the mortality reduction gained by the initial VOO pacemaker. Today’s pacemakers are extremely sophisticated devices, capable of treating tachyarrhythmias as well as bradyarrhythmias, and incorporate extensive recording capabilities and a variety of physiological sensors to match the pacing rate and mode with physiological needs. Many of these pacing features are standard in ICDs. Recent applications include biventricular pacing to treat heart failure and biatrial pacing to prevent atrial fibrillation.

Implantable Cardioverter Defibrillator

Amazing vision mixed in equal parts with tenacity and zeal enabled Mirowski et al to conceive and develop the ICD. The details of his saga have been reported many times and will not be elaborated here. Suffice it to say that 2 treatments, the invention of the ICD and the application of radiofrequency catheter ablation, have revolutionized the therapy of patients with cardiac arrhythmias in ways unparalleled by any other modality. At least 5 studies have now documented the superiority of the ICD over antiarrhythmic agents in patients with serious ventricular arrhythmias, both as primary and secondary prevention, permitting the conclusion that if the patient’s risk of dying is from a ventricular tachyarrhythmia, the ICD should be the initial treatment of choice (Hallstrom et al, unpublished observations, 2000). Future advances for the ICD include smaller devices with increased longevity, improved leads, waveforms with lower defibrillation thresh-
olds, and the ability to prevent certain arrhythmias. Improved sensors may allow monitoring for ischemia or the development of heart failure by changes in intracardiac pressures or PO₂. Improved “connectivity” between patient, hospital, and physician may permit transmission of device parameters and patient information over the Internet. This “ambulatory CCU” concept could also establish automatic, closed-loop treatment of a variety of illnesses. For example, if the device sensed the development of acute ischemia, it might trigger the infusion of intravenous nitroglycerin from an implanted drug dispenser or at the minimum, alert the patient of a change in clinical status and to seek physician assistance. If the device sensed the development of heart failure, it might automatically alter its pacing rate, AV interval, or V-V interval (for dual-ventricular pacing devices) or warn the patient to seek medical help. As with the impact of VOO pacing on mortality, however, the ICD in its present configuration has probably realized its major effect. Nevertheless, further advances will continue to incrementally reduce mortality while improving morbidity. Several studies are testing whether the ICD will increase survival in heart failure patients who have not yet had an arrhythmic event. If this proves to be the case and if large numbers of patients will require ICD implantation, then we must call for the manufacture of a “shock box,” an inexpensive ICD with limited function and the ability to deliver perhaps 6 or 8 shocks, which would be implanted prophylactically in these patients.

Antiarrhythmic Drugs
Antiarrhythmic drugs have had a checkered history. Beginning 50 years ago, drugs such as quinidine were used routinely in patients, without monitoring, to treat virtually all symptom-producing arrhythmias, with the assumption that because the drugs had demonstrable electrophysiological actions and were called antiarrhythmic, they naturally functioned in that fashion. Despite an early study reporting “quinidine syncope” due to torsades de pointes, quinidine, procainamide, and disopyramide were used to suppress simple premature ventricular complexes or tachycardias, sometimes in ascending doses to cardiovert atrial fibrillation (quinidine), and were commonly given prophylactically to patients after myocardial infarction. With the development of the CCU, lidocaine was added to that list and was administered prophylactically to patients with acute myocardial infarction to suppress premature ventricular complexes that exceeded 4 or 5 per minute, were multifocal, or occurred in the T-wave vulnerable period. Drugs such as bretylium, still part of some resuscitative strategies, achieved approval with the T-wave vulnerable period. Drugs such as bretylium, still exceeded 4 or 5 per minute, were multiform, or occurred in infarction to suppress premature ventricular complexes that patients after myocardial infarction. With the development of (quinidine), and were commonly given prophylactically to times in ascending doses to cardiovert atrial fibrillation of premature ventricular complexes or tachycardias, some- procainamide, and disopyramide were used to suppress sim- (infarction) could alter drug-substrate interac- tion to create a lethal arrhythmia, and that some surrogates for death, such as premature ventricular complex suppression, were invalid. To date, of the class I and III antiarrhythmic drugs, only amiodarone has been shown to reduce arrhythmic deaths in patients after myocardial infarction and to be the most effective antiarrhythmic drug in maintaining sinus rhythm in patients with atrial fibrillation. More recently, angiotensin-converting enzyme (ACE) inhibitors and spironolactone have also been shown to lower cardiac death in patients with heart failure. While explanations ultimately involving reduced sympathetic effects are hypothesized to explain the action of these drugs, the mechanism(s) by which they alter the arrhythmogenic substrate is not known. However, given the success of amiodarone, a “dirty” drug that affects all of the Vaughn Williams drug categories, β-adrenoceptor blockers, and now ACE inhibitors and aldosterone blockers, coupled with the inefficacy or actual harm produced by most other antiarrhythmic agents, it may be time to rethink the concept that blocking a single, specific ion channel in the heart, I, for example, with a distinctive molecule that has no other actions can ever be antiarrhythmic for large groups of patients who have complex ventricular arrhythmias.

Acute termination of sustained supraventricular tachycardias was achieved 50 years ago with intravenous phenyleph- rine, titrated to elicit a reflex vagal response by acutely elevating the systolic blood pressure to approach or exceed 200 mm Hg, or administration of digitalis preparations. β-Adre receptor blockers, calcium channel blockers, and then adenosine eliminated the need for such an approach by modulating AV nodal conduction and refractoriness for safe and effective treatment of supraventricular tachycardias.

Catheter Ablation
In the early 1980s, Scheinman (Gonzalez et al) and Gallagher et al demonstrated that a high-energy shock delivered over a catheter placed against the bundle of His could interrupt AV conduction to create chronic, complete AV block. Although this treatment had a relatively restricted application for patients with atrial arrhythmias, such as atrial fibrillation with an uncontrolled rapid ventricular rate, it introduced the concept of being able to alter the electrophysiology of the heart with a catheter. What followed was an amazing new therapeutic development that offered cures for patients with a variety of supraventricular and ventricular tachycardias. Radiofrequency energy rapidly replaced the high-energy shocks as the technique was applied to patients with AV nodal reentry tachycardias. Catheter ablation therapy continues to evolve, with investigation of new electrodes, catheters, and energy sources. Presently, radiofrequency catheter ablation can eliminate virtually all tachyarrhythmias with success rates between 70% and 100% and complication rates of <1% to 2%, depending on the nature of the tachycardia and the skill of the electrophysiologist. Tachyarrhythmias that still offer a challenge include atrial fibrillation, although new observations showing a focal origin have facilitated ablation, and ventricular tachyarrhythmias in patients with structural heart disease.
Genetics

Several types of inherited defects in genes encoding cardiac ion channel proteins have been identified to cause cardiac arrhythmias. These abnormalities have been explored in greatest depth in the LQTS. Presently, there are at least 6 variants of the LQTS first described by Jervell and Lange-Nielsen (with sensorineural deafness) in 1957 and then by Romano et al and Ward (with normal hearing) several years later. The Romano-Ward syndrome is autosomal dominant, whereas homozygous mutations of LQT1 appear to be responsible for the Jervell-Lange-Nielsen syndrome. The ionic abnormalities found so far involve a reduction in the repolarizing currents provided by K⁺ channels or an increase in the inward plateau Na⁺ current. These ionic alterations serve to increase intracellular positivity, which results in a prolongation of atrial and ventricular repolarization and creation of the milieu for development of EAD-induced ventricular and possibly atrial tachyarrhythmias. Families with no linkage to any known locus have been described, and therefore, it is likely that additional genetic abnormalities will be described in the future. Interesting phenotypes have been noted, with patients who have LQT1 at risk for sudden death during emotional or physical stress, particularly during swimming. Individuals with LQT2 are at risk both at rest and during exercise and especially during acoustical stimulation. LQT3 patients appear to be at greater risk during sleep. Interestingly, the abnormal gene responsible for LQT3 has also been found to cause the Brugada syndrome. Although genotype-directed therapy is being tested, the fact that patients with identical mutations can have different phenotypes and some may manifest no phenotype at all challenges this approach. These latter patients may be at risk for developing drug-induced ventricular arrhythmias. Thus, identical genetic abnormalities can have different clinical expressions, and therefore, the type of gene mutation may not necessarily predict the clinical phenotype. Nevertheless, the LQTS is once again serving as a “Rosetta stone,” this time by providing new insights into the paradigm of genetically based molecular causes of cardiac arrhythmia.

Conclusions

These 10 major advances over the past 50 years have radically changed the treatment of patients with arrhythmias. Although the next 50 years will undoubtedly explore genetics-based diagnosis and treatment, most of these top 10 advances will remain as fundamental clinical concepts, part of the everyday practice of cardiology. No better testimony of their importance to patient well-being could exist.

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