Cardiac Arrhythmias: The Quest for a Cure
A Historical Perspective
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During the last 40 years, much progress has been made in our understanding and management of cardiac arrhythmias. A major step in the late 1960s was to combine programmed electrical stimulation of the heart with intracardiac activation recording. This allowed: 1) localization of the site of the block in the atrioventricular conduction system in patients with bradycardia; and 2) identification of the site of origin and the mechanism of supraventricular and ventricular tachycardia. Combining information from intracardiac studies with findings on the 12-lead electrocardiogram (ECG) resulted in much better localization of conduction abnormalities and arrhythmias using the ECG. This new knowledge led to the development of new therapies, such as bradycardia and antitachycardia pacing, and surgery for supraventricular and ventricular tachycardia. A very important development in the treatment of life-threatening arrhythmias was the implantable defibrillator. Growing concern about failure to protect patients at risk for dying suddenly with antiarrhythmic drugs led to a rapid increase in their number. Cure by catheter ablation became possible for patients with different types of arrhythmias. Genetic analysis allowed the identification of different monogenic arrhythmic diseases. Several challenges remain: the epidemic of atrial fibrillation, arrhythmias in heart failure, and sudden death out-of-hospital. One-fifth of all deaths are sudden and unexpected. The important issue is how we are going to prevent these unnecessary deaths from occurring.

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looking at the 12-lead electrocardiogram (ECG) (16). This was especially important in the presence of a widened QRS complex during tachycardia. In the early 1970s, it was shown that, also in patients with a ventricular tachycardia, the arrhythmia could reproducibly be initiated and terminated by programmed electrical stimulation of the heart (17) (Figs. 1 and 2). That allowed the identification of the ECG characteristics diagnostic for a ventricular tachycardia, a finding of obvious importance not only for a correct diagnosis but also because of therapeutic and prognostic consequences. Together with earlier observations by Sandler and Marriott (18), those findings allowed the correct diagnosis of a ventricular tachycardia based on presence or absence of a relation between atrial and ventricular events and the width, the frontal plane axis, and configurational characteristics of the QRS complex during tachycardia (19). By correlating the information from programmed electrical stimulation of the heart with the findings on the 12-lead ECG, it now became possible to correctly classify all the different types of clinically occurring tachycardias as to their site of origin or pathway, their clinical presentation (paroxysmal, incessant), and their mechanism (re-entry or a focal origin) (20).

The development of new therapies. ARRHYTHMIA SURGERY. The demonstration that in WPW syndrome an extra connection between the atrium and the ventricle plays a pivotal role in the tachycardia mechanism made Cobb et al. (21) decide to cure such a patient by interrupting the extra connection surgically. Since then, the Duke group (22), both cardiologically (Dr. Gallagher) and surgically (Drs. Sealy and Cox), played an important role in our understanding of WPW syndrome and the development of surgical therapy. Arrhythmia surgeons such as Drs. Sealy, Guiraudon (23), Cox, and Harken played an important role in our

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**Figure 1.** A programmed ventricular stimulation study done during the early 1970s. The selected extra and intracardiac electrograms in the four panels show the reproducible initiation of a ventricular tachycardia by single ventricular premature beats during right ventricular pacing with a basic cycle length of 700 ms. As shown, ventricular premature beats given in the interval range 500 to 410 ms result in the initiation of the ventricular tachycardia. Premature beats given later than 500 ms or earlier than 410 ms do not create the conditions required for initiation and maintenance of a reentrant ventricular tachycardia.
understanding of cardiac arrhythmias and their treatment. This was again demonstrated when Josephson et al. (24,25) showed in patients with ventricular tachycardias that accurate localization of the area of abnormal impulse formation could be followed by cure from the arrhythmia when the abnormal area was excised surgically. Cox et al. (26) showed that atrial fibrillation (AF) could be controlled by making several incisions in the atria, thereby preventing the mechanism responsible for the arrhythmia.

**ANTITACHYCARDIA PACING.** Originally, the pacemaker was a device that provided a fixed rate ventricular rhythm in patients with (intermittent) bradycardia. However, immediately after the demonstration that re-entrant tachycardias could be terminated reproducibly by critically timed stimuli, this principle was applied by (implantable) pacing techniques in patients with tachycardias. Already in 1968, Ryan et al. (27) used “underdrive” pacing for that purpose. In the years that followed, growing sophistication occurred using tachycardia terminating and preventing algorithms (28).

**THE IMPLANTABLE DEFIBRILLATOR.** Mirowski and Mower (29) deserve credit for their pioneering role in the development of an implantable automatic defibrillator to rescue patients from life-threatening ventricular arrhythmias. Major advances in technology resulted in increasing effectiveness and widespread acceptance of the device (30), to such an extent, as will be discussed later, that the implantable defibrillator now threatens the limits of our medical financial budget!

**CATHETER ABLATION.** The possibility of localizing the site of origin or the pathway of a tachycardia using catheter techniques led to the application of ablative energy at that site. Originally, high-energy shocks were given to interrupt conduction in the His bundle (Gallagher et al. [31] Scheinman et al. [32], the accessory pathway (Weber and Schmitz [33], the circuit of atrial flutter (Saoudi et al. [34], and the site of origin or circuit of ventricular tachycardias (Hartzler [35], Puech et al. [36], and Fontaine et al. [37]. This was followed by the use of radiofrequency current, pioneered by Budde, Breithardt, and Borggreve (38). Successful outcome in a large series of patients with supraventricular tachycardias was thereafter reported by Lee et al. (39), Jackman et al. (40), and Kuck and Schulter (41), making catheter ablation one of the few curative treatments in cardiology.

**The rise and fall of antiarrhythmic drugs.** Continuous monitoring of cardiac rhythm in the coronary care unit provided us with information about arrhythmias during cardiac ischemia and their role in life-threatening complications (42). This also resulted in the concept of so-called “warning arrhythmias” (43) and the use of prophylactic lidocaine (44). Both warning arrhythmias and prophylactic lidocaine did not stand the test of time (45) but influenced our thinking about the ventricular premature beat as a target for pharmacologic prevention of serious ventricular arrhythmias and sudden death.

Before the Cardiac Arrhythmia Suppression Trial (CAST) (46), the treatment of ventricular arrhythmias was mostly empiric without large controlled studies. Premature ventricular beats were considered to be markers of risk, and sodium channel blockers (quinidine, disopyramide, and flecainide) were the antiarrhythmic drugs used most commonly. The CAST study opened our eyes to possible proarrhythmic effects of antiarrhythmic drugs. It became clear that antiarrhythmic drugs may kill more people than they save. That knowledge came at a time when many of us still believed that programmed electrical stimulation of the
heart could be helpful in selecting the best antiarrhythmic drug in a patient suffering from an arrhythmia. The wake-up call from the CAST study made us more critical about serial drug testing. It became clear that the assumption that prevention of tachycardia induction by programmed stimulation might predict long-term efficacy was correct in patients with a single re-entry circuit with fixed electrophysiologic properties but not in a complex arrhythmia substrate such as a scar after myocardial infarction (Fig. 3). The extent of cardiac damage and the degree of functional impairment were found to have an inverse relationship with the ability to find an antiarrhythmic drug able to prevent arrhythmia recurrences. Only beta-blocking agents and amiodarone were able to reduce arrhythmia mortality in patients with severely diminished left ventricular (LV) function after a myocardial infarction or in non-ischemic dilated cardiomyopathy (47,48).

**THE PRESENT**

**Risk stratification for sudden death.** One of our greatest problems is sudden arrhythmic death outside the hospital. Although we are putting a lot of effort and money into trying to identify the person at risk of dying suddenly, only 10% of sudden cardiac arrest victims have a high-risk profile (49,50).

Unfortunately, most of the tests shown in Figure 4 alone or in combination, have a low positive predictive accuracy, especially when decisions have to be made about expensive preventive treatment such as a defibrillator implant. That decision is easy in patients resuscitated from circulatory arrest or suffering from a hemodynamically poorly tolerated ventricular arrhythmia (51–53), although the price per year life saved may be expensive (54). More recently, patients have been identified that will profit from a defibrillator implant to protect them from sudden arrhythmic death. They are characterized by having a poor LV function with or without non-sustained ventricular arrhythmias and with coronary or noncoronary heart disease (55–59).

Cost-effectiveness analysis of these studies suggested a cost of $16,000 to $22,000 per year of life saved for Multicenter Automatic Defibrillator Implantation Trial (MADIT) I (55) and Multicenter UnSustained Tachycardia Trial (MUSTT) (56), an extremely cost-effective result (54). Earlier termination of the MADIT II (57) made the cost-effectiveness in that study much less (around $150,000 per year of life saved). That finding from MADIT II, which will probably also be the case in the Sudden Cardiac Death in Heart Failure Trial (SCDHfT) (58) population makes it mandatory to look for better ways to select patients that should receive an implantable defibrillator for the primary prevention of an arrhythmic death. This requires that several aspects should be studied, such as the QRS width, presence of T-wave alternans, value of ventricular tachycardia induction during electrophysiologic study, size and location of a postmyocardial infarction scar, New York Heart Association functional class, and heart rate turbulence to fine tune the selection of the implantable cardioverter defibrillator recipient to make this financially affordable.

**AF.** As pointed out a decade ago (59), AF is the last big hurdle in treating supraventricular tachycardias. Currently, in the U.S. 2.5 million suffer from AF, and that number is predicted to double in the next 35 years. Atrial fibrillation increases mortality two-fold and is found in one-third of the patients above the age of 65 years who suffered a stroke.

**ATRIAL REMODELING.** During the last decade, new information has become available about the effect of AF on electrical, structural, and functional properties of atrial tissue (60–62). It was shown that, during AF, the refractory period shortens and looses its rate-related behavior. This occurred in a non-uniform way, increasing disparity in refractory period duration. Also, conduction velocity in the
atrium slowed. All of these changes promote the recurrence and persistence of AF. Reversibility of these changes was found to depend upon the duration of AF and presence of cardiac disease resulting in factors such as stretch of atrial fibers and increased fibrosis formation in the atrial wall.

**Catheter Ablation.** It was found that ectopic impulse formation in or around the pulmonary veins plays an important role in the initiation and maintenance of paroxysmal AF (63). That observation resulted in catheter ablative approaches originally inside (64,65), and later around, the pulmonary veins, with or without additional atrial ablation lines. Short-term efficacy of catheter approaches has been demonstrated, more so in paroxysmal than in persistent AF. There are still questions about the end point of catheter ablation, both at the end of the catheterization (complete isolation of pulmonary veins (66), termination of AF during ablation, prevention of re-initiation of AF) and long term (no AF or less AF during follow-up, symptomatic or nonsymptomatic AF, no recurrences without or with antiarrhythmic drugs, and effect of ablation on cardiac function).

It is also not clear what ablative approach (radiofrequency, cryo, laser, ultrasound, or microwave) is best and which one is giving the least number of complications. Randomized studies comparing catheter ablation with antiarrhythmic drug therapy with a sufficiently long follow are needed. At present, cost and duration of the procedure make it likely that only a minority of AF patients can be helped by catheter ablation.

**Rate Versus Rhythm Control.** In the 1980s and 1990s, cardiologists tried in most of their AF patients to convert the arrhythmia by pharmacologic or electrical cardioversion, and then to keep them in sinus rhythm by antiarrhythmic drug therapy. However, the relative inefficacy of antiarrhythmic drug therapy to prevent recurrences of AF, their side effects, the efficacy of anticoagulant therapy to prevent strokes, and the adequate control of the ventricular rate during AF with drug therapy gave rise to the question whether sinus rhythm should be preferred and repeatedly attempted to be restored. Recently, five studies were completed in which rate versus rhythm control of AF was evaluated in regard to mortality, strokes, hospitalizations, quality-of-life, and costs (67–71). In total, 5,239 patients were included. Persistent AF was present in four studies, and both persistent and paroxysmal AF in one study (68). All-cause mortality in the rate control group was 339 of 2,609 = 13%, and in the rhythm control group 383 of 2,630 = 14.6% (p = 0.08). There were also no significant differences in stroke incidence between rate or rhythm control. The incidence of sinus rhythm at the end of the study varied from 38.0% to 73.3% in the rhythm control group and from 9.0% to 34.6% in the rate control group (not surprisingly with the highest number in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AF-FIRM) study (68) because they also included patients with paroxysmal AF). These studies suggest that, in general, there seems to be no advantage of rhythm control when the patient with AF is 65 years and older. However, no definite data are available as to subgroups such as the young patient or the patient with heart failure (HF). It did become clear that, in patients with a history of AF and risk factors for stroke, anticoagulant therapy should be continued (and well-controlled!) also in sinus rhythm.

**HF.** Currently, we are not only witnessing an epidemic of AF but also of HF. Arrhythmic death is a common mode of death in HF occurring in approximately half of the cases. In recent years, two things have become clear: 1) in patients with HF, symptomatic ventricular arrhythmias and syncope predict an increased risk of sudden death, but that is not the case when asymptomatic ventricular arrhythmias are present (72); and 2) in HF patients drugs that were not developed as antiarrhythmic drugs such as beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, statins, aldosterone receptor antagonists, polyunsaturated fatty acids, and aspirin are more effective in reducing arrhythmic death in HF than antiarrhythmic drugs (73). The SCD-HeFT study (74) suggests that, in patients with HF, the presence of New York Heart Association functional class II or III and a LV ejection fraction of <35% are markers for selecting HF patients who may profit from an ICD implant. But as discussed earlier, to make this financially affordable, further fine-tuning in selecting implantable cardioverter defibrillator candidates is required.

**Cardiac resynchronization therapy.** Almost 25 years ago, epidemiologic studies indicated that the presence of left bundle branch block (LBBB) predicted a shorter life span (75,76). Grines et al. (77) showed that isolated LBBB resulted in interventricular asynchrony. Endocardial mapping studies in patients with LBBB (78) indicated that the activation sequence of the left ventricle may vary consider-
ably resulting, as shown in Figures 5 and 6, in different patterns of LV contraction and degree of mitral incompetence. In LBBB, the degree of QRS widening is a predictor of life expectancy (79). When it was shown that permanent pacing was possible with transvenous leads inserted into the coronary veins (80), studies were started to evaluate the effect of biventricular pacing to restore resynchronization of ventricular contraction in patients with intraventricular and interventricular conduction disturbances and HF (81). It was found that resynchronization of ventricular activation by LV pacing with or without synchronized right ventricular pacing in patients with LV electromechanical dyssynchrony (usually caused by LBBB) resulted in improvement in exercise tolerance, well-being, ventricular performance, a decrease in hospitalizations, a decrease in neurohumoral activity, and a decrease in death (82). Unfortunately, about 30% of HF patients with ventricular electromechanical dyssynchrony do not respond to pacing-regulated resynchronization of ventricular activation. As shown in Table 1, there are still many questions that need to be answered to optimize the selection of patients profiting from cardiac resynchronization therapy.

### Genetic arrhythmology
During the last decade, it became possible to make a genetic diagnosis in patients who have certain ECG features. That has been of help in risk-stratification and management of carriers of monogenic diseases prone to cardiac arrhythmias and sudden death (Table 2). The current impression is that the ECG has high specificity but low sensitivity because of marked differences in phenotypic expression (83). The experience in the long QT syndrome and the Brugada syndrome indicates that the ECG can be helpful in making decisions about management (84,85).

### THE FUTURE
Cardiac arrhythmias will continue to be present in the coming years. But new developments will allow us to control them better and possibly cure them in an increasing number of patients. Device therapy will increase. It is expected that in 2006 the number of implanted cardioverter defibrillators will double those in 2003, raising the question of how to control this rapidly growing implantable cardioverter defibrillator population. Will wireless home monitoring and reprogramming be the solution?

The MADIT II (86) and the Defibrillator in Acute

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### Table 1. Questions in CRT

<table>
<thead>
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<th>Question</th>
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| 1. How to select the responder? | a. By measuring LV electromechanical dyssynchrony?  
  b. RV size and function?  
  c. Ventricular arrhythmias (+ ICD)?  
  d. BNP value?  
| 2. How to select the appropriate pacing site(s) and pacing (AV and LV–RV) intervals? | |
| 3. Role of CRT in atrial fibrillation and conventionally paced patients? | |
| 4. Impact on mortality? | |
| 5. Cost-effectiveness? | |
| 6. Preventive application in patients with electromechanical dyssynchrony but in NYHA functional class I or II heart failure? | |

AV = atrioventricular; BNP = brain natriuretic peptide; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter defibrillator; LV = left ventricular; NYHA = New York Heart Association; RV = right ventricular.

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### Table 2. Familial Diseases With a Monogenetic Basis for Cardiac Arrhythmias and Sudden Death

<table>
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<td>Hyperthrophic cardiomyopathy</td>
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<td>Dilated cardiomyopathy</td>
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<td>Long-QT syndrome</td>
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<td>Short-QT syndrome</td>
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<td>Brugada syndrome</td>
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<td>Catecholaminergic polymorphic ventricular tachycardia</td>
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<td>Arrhythmogenic right ventricular dysplasia</td>
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<td>Wolff-Parkinson-White syndrome</td>
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<tr>
<td>Atrial fibrillation</td>
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<td>Sick sinus syndrome</td>
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<tr>
<td>Atrioventricular block</td>
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<tr>
<td>Myotonic dystrophy</td>
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Myocardial Infarction Trial (DINAMIT) (87) study suggest that implantable cardioverter defibrillator shocks may accelerate the progression of HF. This may lead to an increased use of antiarrhythmic drugs to diminish the number of shocks and to facilitate termination of ventricular tachycardia by antitachycardia pacing (88). Cell transplantation to replace damaged or lost myocardial cells will be an area of increasing activity. The initial experience with autologous skeletal myoblasts indicated that arrhythmic complication may occur (89,90). That finding is not surprising because the myoblast is not able to make electromechanical contact with neighboring host cells. So far, stem cell therapy has not been reported to induce cardiac arrhythmias, but insufficient information is available about the ability of transplanted stem cells to couple electromechanically among themselves and with host cardiomyocytes (91). Studies are needed to answer these questions and to establish when implantable cardioverter defibrillators need to be implanted to protect the patient.

In AF, we will see growing interest in the development and evaluation of antiarrhythmic drugs specifically binding to atrial tissue. Another area of research to combat the AF epidemic is to develop measures that interfere with age-related fibrosis formation in the heart, which is an important factor in promoting AF, conduction disturbances, and diastolic dysfunction.

Genetic analysis will continue to improve our diagnostic abilities and will become increasingly helpful in advising preventive measures. It is also likely that, in the near future, information about our genetic background will facilitate selection of medication and their correct dose (pharmacogenomics).

However, it seems that we still have a long way to go before gene therapy will be a curative option in patients with serious arrhythmias. Sudden cardiac arrest out-of-hospital will continue to haunt us. In the Western world, one-fifth of all deaths occur suddenly and unexpectedly with about half of the cases having cardiac arrest as the first manifestation of heart disease. With our current efforts including wide distribution of automatic external defibrillators, the number of victims successfully resuscitated remains small.

As indicated earlier (92), a crucial step in the management of this problem could be the development of wearable devices reliably able to recognize cardiac arrest, making an audible alarm, and transmitting the location of the victim to the site of the nearest automatic external defibrillator and advanced life support team.

**Conclusions.** As in other subspecialties in cardiology, important progress has been made in the diagnosis and treatment of cardiac arrhythmias during the last four decades. In this review we looked at the past and discussed the present. The conclusion is that, in spite of many advances, we are at present only able to really cure cardiac arrhythmias and to prevent sudden arrhythmic death in a minority of our patients. New developments are needed to bring us better results in the future.
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