In 2007, we marked the 40th anniversary of the birth of
invasive clinical electrophysiology. Of course, before
1967, cardiac arrhythmias were documented electrocardiographically, and their possible mechanisms were analyzed
ingeniously and explained beautifully by giants such as Katz
and Pick,1 Scherf and Schott,2 and Bellet.3
In the 1940s and 1950s, Hecht,4 Latour and Puech,5 and
Giraud et al6 used catheters to measure intracardiac electric
activity and to record the sequence of cardiac activation. In
1958, Furman and Robinson7 showed that in patients with
atrioventricular block, the heart could be stimulated by
connecting an intracatheter to a stimulator.

The Early Years
In 1967, the analysis of the site of origin and mechanism of
cardiac arrhythmias became possible in the intact human
heart through the use of programmed electric stimulation
combined with intracardiac activation mapping. Independently,
Durrer et al8 in Amsterdam (in patients with the
Wolff-Parkinson-White syndrome) and Coumel and coworkers9
in Paris (in a patient with an atrioventricular junctional
tachycardia) showed that by connecting intracardiac catheters
to a versatile stimulator, it was possible to reproducibly
initiate and terminate clinically occurring tachycardias and to
identify the site of origin of the tachycardia and, in the case of
a reentrant mechanism, the pathway of the arrhythmia by
placing catheters at different sites in the heart.8,9 Soon after,
on both sides of the Atlantic, this technique was used to
unravel the place of origin of different types of supraventricular
tachycardias.10–14 The first book on the use of pro-
grammed stimulation of the heart in the analysis of supraventric-
ular tachycardias was published in 1971.15

In the late 1960s, Scherlag et al16 made another important
breakthrough in the analysis of cardiac arrhythmias with the
reproducible registration of the His bundle electrogram. Not
only did this advance allow accurate localization and risk
stratification of atrioventricular conduction disturbances, but,
as shown by groups led by Ken Rosen, Onkar Narula, and
Paul Puech, much better identification of the path for impulse
propagation during a tachycardia was now possible.17

A very exciting aspect of the use of programmed electric
stimulation of the heart, when combined with recording the
His bundle electrogram, was the progress made in the
interpretation of the 12-lead ECG during cardiac arrhythmias.
Careful reexamination of the ECG after an intracardiac study
brought new insights, ultimately leading to a clinically useful
classification of tachycardias and allowing correct recogni-
tion of different types of arrhythmias from the 12-lead ECG.18

Although initially considered dangerous, the reproducible
initiation and termination of wide QRS tachycardias by
programmed electric stimulation of the heart19 introduced
new ways to study ventricular arrhythmias in the intact
human heart. Those invasive studies made it possible to
validate and expand earlier observations by Sandler and
Marriott20 of the ECG patterns of the different kinds of wide
QRS tachycardias. Better identification of the ECG character-
istics of ventricular tachycardias was now possible, an
advance of obvious importance for making the correct diag-
nosis and managing the patient.21

New Therapies
As shown in the Table, the possibility of localizing the site of
origin or the pathway of a tachycardia and being informed
about the tachycardia mechanism was followed by the de-
velopment of new therapies. One of the first was arrhythmia
surgery, started, not surprisingly, in patients with the Wolff-
Parkinson-White syndrome by a group at Duke University.
Both Gallagher (cardiology) and Sealy and Cox (surgery)
played major roles in advancing our understanding of the
Wolff-Parkinson-White syndrome and in the development of
surgical therapy.22,23 The contributions of cardiac surgeons,
including Sealy, Guiraudon, Cox and Harken, have been of
great importance not only for treating cardiac arrhythmias but
also in advancing the understanding of arrhythmia
mechanisms.24

Better knowledge of cardiac anatomy became a must for
the invasive electrophysiologist. The pathologists Becker and
Anderson25 made us aware that insights into cardiac anatomy
are essential to “cure” cardiac arrhythmias and to avoid
cardiac damage.

Thanks to Guiraudon and Fontaine and the work of
Josephson and coworkers,26,27 surgical therapy became pos-
sible in patients with ventricular tachycardia. Accurate local-
ization of the area of abnormal impulse formation followed by
excision of that area cured the arrhythmia. Cox et al28
showed that atrial fibrillation (AF) could be controlled

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Forty Years of Invasive Clinical Electrophysiology
1967–2007
Hein J. Wellens, MD

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surgically by making several incisions in the atria, thereby inhibiting the development of multiple reentry circuits responsible for AF.

Another logical consequence of the ability to reproducibly initiate and terminate tachycardias in the human heart was the use of these methods to evaluate the effect of pharmacological interventions on tachycardia mechanisms, obviously with the hope that such information would be helpful in the selection of the best pharmacological approach to terminate and prevent cardiac arrhythmias. It was shown that prevention of tachycardia induction by programmed stimulation was useful in patients with a single reentrant pathway with well-defined electrophysiological properties but not in patients with a complex arrhythmia substrate such as a scar after myocardial infarction. The extent of cardiac damage and the degree of functional impairment had an inverse relationship with the ability to prevent arrhythmia recurrences. In fact, as shown by the Cardiac Arrhythmia Suppression Trial (CAST) investigators, in damaged hearts, antiarrhythmic drugs administered preventively could kill more people than they save.

Shortly after the demonstration that reentrant arrhythmias could be terminated by critically timed stimuli, that principle was applied to therapy. Initially, it was implemented in implanted pacemakers with continuous pacing at a rate below the tachycardia rate until an appropriately timed pacing stimulus created refractoriness for the circulating impulse in the tachycardia circuit, so-called underdrive pacing. Thereafter, increasingly sophisticated devices were developed with algorithms for terminating and preventing tachycardia.

A very important advance in rescuing patients with life-threatening arrhythmias was the implantable automatic defibrillator pioneered by Mirowski et al. Major advances in technology resulting in increasing effectiveness have led to widespread acceptance of the device.

The wish to interrupt conduction pathways and to destroy sites of abnormal impulse formation nonsurgically led to the application of ablative energy with intracardiac catheters. Originally, high-energy shocks were given to interrupt conduction in the His bundle, in the accessory atroventricular pathway, in the circuit of atrial flutter, and at the site of origin or pathway of ventricular tachycardias. The first to interrupt conduction in an accessory atroventricular pathway using radiofrequency current.

Use of that energy source to cure arrhythmias was achieved by Borggreve et al. They were the first to interrupt conduction in an accessory atroventricular pathway using radiofrequency current. In addition, on the basis of information from intracardiac activation mapping and response to pacing, it became possible to use radiofrequency catheter ablation successfully in patients with ventricular tachycardia.

### Table. Development of New Therapies

<table>
<thead>
<tr>
<th>Therapies</th>
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<tbody>
<tr>
<td>Arrhythmia surgery</td>
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<td>Antiarrhythmic drug therapies</td>
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<td>Antitachycardia pacing</td>
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<td>Catheter ablation</td>
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<td>Resynchronization of cardiac activation</td>
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**Recent Years**

During the past decade, invasive electrophysiology brought important advances in areas such as the management of life-threatening ventricular arrhythmias, AF, and heart failure.

Despite extensive efforts to better identify people dying an arrhythmic death out of hospital, we are able to recognize only ≈10% of those victims as being at high risk before the event. Identification is not difficult in patients who have been resuscitated from circulatory arrest or who suffer from a poorly tolerated ventricular arrhythmia. These patients in the so-called “secondary prevention” category benefit from an implantable defibrillator, although the price per life-year saved may be high.

Despite a wide array of tests, correct assessment of the level of risk remains difficult in patients with poor left ventricular function, with or without nonsustained ventricular arrhythmias, and with coronary or noncoronary heart disease. Although general guidelines have been published concerning cardioverter-defibrillator (ICD) implantation for primary prevention in coronary and noncoronary high-risk patients, we still need to fine tune the risk stratification process to limit costs and to spare people from inappropriate ICD discharges. The suggestion that ICD shocks may accelerate the progression of heart failure led to an increasing use of antitachycardia pacing to terminate ventricular tachycardia.

The use of ablative procedures incorporating intracardiac catheters has grown considerably in recent years. Indications for (curative) radiofrequency catheter ablation have expanded from the classic patients with accessory pathways, atroventricular nodal reentrant tachycardia, atrial tachycardia, atrial flutter, and ventricular tachycardia to those with arrhythmias in complex congenital heart disease and AF. Recognition of the role of impulse formation in and around the pulmonary veins in the genesis of paroxysmal AF led to ablative approaches in that area. Short-term results are satisfactory in patients with paroxysmal AF. Outcomes are less clear in persistent and permanent AF. Long-term results (>4 years) are not yet available. Complex changes (structural, functional, electric, metabolic, and neurohumoral remodeling) occur after the onset of AF related to the duration of the arrhythmia. More information is needed about the severity and reversibility of these changes in the individual patient to allow the correct selection of AF patients who benefit in the long term from an ablative procedure.

In the catheterization laboratory, we also learned that cardiac arrhythmias may have their origin outside the heart, being connected by a muscle bridge to the atrium or ventricle. Those sites of ectopic impulse formation can be found not only in pulmonary veins but also in the superior and inferior caval veins, around the coronary sinus, around the ligament of Marshall, and in the root of the aorta and pulmonary artery. The ECG recognition of an epicardial origin of ventricular tachycardia became possible, leading to successful epicardial
by guest on August 29, 2017

Catheter ablation. In addition, it became possible to ablate unmanageable and hemodynamically unstable ventricular tachycardia and to ablate triggers of ventricular fibrillation.

Another important development has been the use of pacing in heart failure patients with intraventricular and/or interventricular conduction disturbances. Resynchronization of ventricular activation by permanent pacing with transvenous leads inserted into the coronary veins resulted in improvement in exercise tolerance, well-being, and ventricular performance and decreases in hospitalizations, neurohumoral activity, and death for 70% of selected patients.

The Future
Cardiac arrhythmias will continue to be present in the coming years. Nevertheless, new developments will allow us to control them better and possibly cure them in an increasing number of patients. Use of device therapy will increase. We hope that we will be able to better select the ICD and resynchronization candidate. Methods will be developed to reduce the number of appropriate and inappropriate ICD shocks by measures such as prophylactic substrate-based catheter ablation for secondary prevention in patients with myocardial infarction. In addition, new antiarrhythmic drugs will be introduced to diminish the number of shocks and to facilitate termination of ventricular tachycardia by pacing. A better understanding of the arrhythmia mechanisms in the different types of AF and long-term follow-up in these patients will lead to better selection of AF patients who can be treated successfully by catheter ablation. Improvements in catheter design, hybrid imaging, and use of energy sources other than radiofrequency should improve results and diminish complications. The electrophysiological effects of new atrium-specific antiarrhythmics will be tested in the intact human heart.

Cell transplantation to replace damaged or lost myocardial cells will be an area of increasing activity. So far, stem cell therapy has not been reported to induce cardiac arrhythmias, but insufficient information is available about the ability of transplanted cells to couple electromechanically among themselves and with host cardiomyocytes. The invasive electrophysiologist should play an important role in answering questions about impulse formation, conductivity, and possible arrhythmogenicity after cell transplantation.

Our knowledge of genetic arrhythmogenic syndromes will grow. Further studies on the value of the ECG phenotypes for diagnosis and risk stratification are needed. Because we are far from implementing gene therapy, we need better information from basic electrophysiology, about arrhythmia mechanisms. Better knowledge of arrhythmia mechanisms will lead to appropriate pharmacological interventions and possibly to catheter intervention at the site of the initiating ectopic arrhythmic event or tachycardia pathway, which seems even more promising than pharmacological therapy.

Conclusions
During the past 40 years, important progress has been made in the diagnosis and treatment of cardiac arrhythmias. The present review has looked at the role of the invasive clinical electrophysiologist in the past and present. We still have a long way to go. Despite many advances, we can offer a cure or adequate protection in the event of a cardiac arrhythmia for only a minority of our patients. This concern especially holds for the prevention of sudden arrhythmic death. New developments are needed to bring us better results in the future.

Disclosures
None.

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**Key Words:** arrhythmia ■ tachycardia ■ electrophysiology
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