PART I
Historical Perspectives
CHAPTER 1

Cardiac Activation Mapping: The Amsterdam Years

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Summary

Starting in the late fifties of the last century professor Durrer and his cardiology group in Amsterdam developed a very strong base to expand our knowledge of electrocardiography and electrophysiology. It resulted in major accomplishments such as the unraveling of the complete excitation of the isolated perfused human heart and the introduction of programmed stimulation of the heart to induce and study clinically occurring cardiac arrhythmias. Deciding factors in these advances were the presence of a brilliant leader, an interested and motivated group of coworkers, and the constant support from the department of medical physics.

Introduction

Essential for our understanding of cardiac function in health and disease is knowledge about the way, and in what sequence, the muscle cells of the different parts of the heart are activated. We require insight into the time course and instantaneous distribution of the excitatory process of the heart, and how this is represented in the electrocardiogram (ECG), which is a global representation of the activation process.

 Already in 1918, Boden and Neukirch understood that in order to obtain data about total excitation of the heart the beating isolated heart should be studied [1]. It would take 50 more years, however, before epicardial and transmural activation of the isolated intact human heart would be accomplished by Dirk Durrer and colleagues in Amsterdam.

In the 1950s, Durrer, a cardiologist, started to study the cardiac activation process in the mammalian heart. He recognized from the beginning the necessity, especially in the ventricle, to study not only the activation process on the epicardium but also intramurally, in order to clearly delineate cardiac excitation and to correlate this excitation with the ECG.

Together with the physicist Henk van der Tweel, head of the department of medical physics at the University of Amsterdam, instrumentation was developed to study the activation in the ventricular wall. Needles were constructed allowing accurate measurements of transmural activation (Figure 1.1). Essential in this process was demonstration of the physico-mechanical basis of the intrinsic deflection of the electrogram indicating the timing of myocardial activation at the recording electrode. The outcomes of these 2D and 3D studies were published in four articles in the American Heart Journal in 1953–1955 [2–4].

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Total Excitation of the Isolated Human Heart

The observations discussed above were made in the dog heart. But Durrer wanted to know how global electrical activation takes place in the intact human heart to help us understand its relation to the ECG. He assembled a group of investigators experienced in keeping the heart beating after being removed from the body, recording from multiple intramural terminals, and careful offline measurements of the recorded signals. Apart from Durrer, the group consisted of Rudolf van Dam, Gerrit Freud, Michiel Janse, Frits Meijler, and an American engineer, Robert Arzbacher.

After control experiments in canine hearts had shown that isolation and perfusion of the heart outside the body did not affect mode and speed of excitation as measured in situ, human hearts were studied. With informed consent of family members, hearts were obtained from individuals who had died from various cerebral conditions without a previous history of heart disease. This was at a time before cardiac transplantation! ECGs taken several hours before death showed no evidence of cardiac disease. The hearts were removed within 30 min after death, the criterion being cessation of cardiac activity. The aorta was cannulated and attached to a Langendorff perfusion apparatus. The hearts were perfused with an oxygenated, heparinized, modified Tyrode solution, with washed bovine erythrocytes. Most hearts resumed beating spontaneously within the first 5 min of perfusion; in a few cases electrical defibrillation was needed because of ventricular fibrillation. The hearts continued beating in a spontaneous sinus rhythm for periods ranging from 4 to 6 hr.

The electrical activity of the heart was recorded from epicardial (hand-held) and intramural (needle) electrodes. Unipolar and bipolar leads were recorded on a 14-channel Ampex tape recorder. Data quality was controlled online using a 14-channel Elema inkwriter. For measuring activation times the tapes were played on the Elema inkwriter at a paper speed of 960 mm/sec, giving a time resolution of better than 1 msec.

All activation times were expressed in milliseconds following the onset of left ventricular depolarization. Measurements were made from as many as 870 intramural terminals. Figures 1.2 and 1.3 are from the publication in Circulation [6] showing both a 2D and 3D isochronic representation of ventricular activation of an isolated human heart using epicardial and intramural activation times. The figures beautifully illustrate early activation at the exits of the bundle branches and the spread of activation thereafter.

The Wolff–Parkinson–White syndrome

Starting in the 1930s, Holzman and Scherf [7] and Wolferth and Wood [8] postulated that in patients with the Wolff–Parkinson–White (WPW) syndrome, two connections between atrium and ventricle were present, and that they could be incorporated in a tachycardia circuit with the impulse going from atrium to ventricle over one connection and from ventricle to atrium over the other.
Figure 1.2: Isochronic representation of ventricular activation of an isolated human heart, using measurements at 870 intramural electrode terminals. Each color represents a 5-msec interval.
The author remembers discussions in Amsterdam in the early 1960s about this possibility, especially during visits from Howard Burchell of the United States. Around that time, a unique opportunity presented itself to obtain more information. In 1966, at Leiden University Hospital, A. G. Brom was scheduled to operate on a 21-year-old woman with an atrial septal defect of the secundum type. But the patient also had ECG changes that met the criteria for a diagnosis of WPW syndrome, and Brom consented to an epicardial map in the patient during sinus rhythm. So, Durrer and Jan Ross travelled to Leiden to map the epicardium of the heart prior to surgery.

Figure 1.4 shows the 12-lead ECG of the patient before the operation. Figure 1.5 shows the ventricular epicardial map during sinus rhythm. It is clear that in this patient, in contrast to epicardial, ventricular activation in a person with a normal ECG did not start in the area pretrabecularis, close to the descending left coronary artery. The earliest epicardial activation was found in the anterolateral part of the right ventricle very close to the tricuspid annulus [9].
That observation clearly demonstrated an abnormal ventricular activation pattern that was very suggestive of a connection between the right atrium and the right ventricle. Then the question arose of how to prove that such a connection could play a role in the tachycardias that are so often present in the WPW patient. Again, an important contribution came from the department of medical physics.

Already in the early 1950s, experiments had been performed to study cardiac excitability in dogs. This required a special stimulator. This stimulator, and several more versatile ones thereafter, was developed in close collaboration with van der Tweel and his group. To study WPW patients, however, a stimulator was required not only able to synchronize to the patient’s rhythm and to give timed premature beats, but also able to perform basic pacing and induce premature stimuli at selected intervals.

Such a device was built by a young engineer, Leo Schoo, after long discussions between the medical physicists van der Tweel and Strackee, and the cardiologists Durrer and Reinier Schuilenburg. With this stimulator, stimuli with a regular rhythm could be produced by two basic pulse generators. The cycle length of these pulses could be varied with an accuracy of 1 msec from 9999 to 100 msec. Instantaneous changes in driving rate could be achieved by switching from one stimulator to the other. Two (in a later version, three) independent test pulses could be delivered during the spontaneous rhythm or during regular driving, with a selected interval accurate to 1 msec. The basic pulses and the two (or three) test pulses could be applied to one pair of stimulating electrodes or to separate pairs in any desired combination (Figure 1.6).

In the fall of 1966, this versatile stimulator was used in a patient with WPW syndrome. With catheters in the right atrium and right ventricle it was shown for the first time that by giving accurately timed stimuli, the properties of the two connections between atrium and ventricle differed, resulting in the initiation of a circus movement tachycardia using one connection for atrioventricular and the other one for ventriculo-atrial conduction. It was also demonstrated that these tachycardias could be terminated from atrium and ventricle by giving appropriately timed stimuli [10]. A registration from such a study is shown in Figure 1.7.

These observations, also the one by Coumel et al. [11], rapidly led on both sides of the Atlantic to the use of programmed electrical stimulation of the heart to study patients suffering from supraventricular tachycardias [12]. By placing catheters at
Figure 1.6 Photo of the sophisticated stimulation and registration equipment used in Amsterdam during the early studies in patients with tachycardias.

Figure 1.7 Example of the initiation and termination of a circus movement tachycardia by high right atrial stimuli. The intracardiac catheter is located in the coronary sinus. RK = retrograde Kent, sa = stimulus artefact.
different sites in the atrium, the ventricle, and the coronary sinus it soon became possible to map the site of origin or pathway of the tachycardia. This opened the door to new therapies for supraventricular tachycardias. The reproducible initiation and termination of ventricular tachycardia by programmed stimulation followed rapidly thereafter [13]. It took a while, however, before Mark Josephson and colleagues showed the importance of cardiac mapping in those patients [14].

In retrospect the advances made in Amsterdam were based on the presence of a brilliant, inspiring leader, a hard-working, motivated, interested group of coworkers, and the constant support from the department of medical physics. The Amsterdam years will always be remembered as an exciting journey into a new discovered land!

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