The works of Dirk Durrer (1918–1984)

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Portrait of Dirk Durrer by Marte Röling (1986)

During the 33rd Annual Scientific Sessions of the Heart Rhythm Society in Boston (USA) in May 2012, a special session entitled ‘Dirk Durrer – His laboratory and the enormous impact on cardiac electrophysiology’ was dedicated to the memory of Dirk Durrer. He was praised as the ‘Godfather of Cardiology’ and as a ‘superb

physician, skilful practitioner and exceptional investigator’. During this historical session we each focused on aspects of the person and work of Dirk Durrer. A book published at the occasion of ‘50 Years of Cardiology in Amsterdam’ [1] and three papers [2–4] have already extensively reviewed the works of Dirk Durrer, both as a clinical cardiologist and as a scientist. Therefore, here we will mainly focus on the research underlying his most famous and frequently cited paper [5] on the (total) excitation of the human heart as well as on some bibliographical aspects of that particular paper and of his whole oeuvre.

The early years

Dirk Durrer was born in Schiedam, a small harbour in the Netherlands, on 19 April 1918. He studied in Leiden and Utrecht and graduated in 1943 just before Utrecht University was ordered to close down by the Nazi regime following the earlier closing down of Leiden University. Durrer had been fascinated by the work of pioneers in cardiology as Willem Einthoven, Karl Wenckebach, Thomas Lewis and Frank Wilson. He was stimulated to focus on cardiology by Professor P. Formijne, not only clinically, but also experimentally. A key factor in the career of Durrer was his partnership with the Dutch physicist Henk van der Tweel, who designed and built a 4-channel oscilloscope and a stimulator, enabling them to study the activation patterns in dog and goat hearts. Their first publication stems from 1953 [6]. Soon after that Durrer was appointed professor in cardiology and clinical physiology at the University of Amsterdam (1957). It took until 1969 before an autonomous cardiology clinic was established. A new building, funded in part by revenues from the crossword puzzles in the Dutch newspaper ‘De Telegraaf’, was opened by Her Majesty Queen Juliana on 2 March 1972. The establishment of a revolutionary ‘Eerste Hart Hulp’ (CCU) followed in 1978. In 1972 Durrer founded the Interuniversity Cardiology Institute of the Netherlands (ICIN), a collaboration institute of

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the main cardiology departments in the Netherlands. Its primary objective was to coordinate research and to make it more efficient. In 1993 the ICIN became an Institute of the Royal Dutch Academy of Sciences ('KNAW').

Total excitation of the human heart

In the 1960s, before the era of cardiac transplantation, Durrer started a project to document the activation pattern of the normal human heart [4]. Essential was the cooperation of the neurosurgeons Prof. Dr. W. Noordenbosch and Dr. A.J.M van der Werf, who decided whether patients with 'cerebral conditions' (usually victims of traffic accidents) were 'brain dead', and who also obtained permission from the families to study the hearts after ventilation was stopped. Initially, a period of about 1 h was allowed to pass after cessation of ventilation until no visible palpations were seen, before the chest was opened. However, the anoxic heart did not recover during perfusion in the Langendorff set-up so that it was decided to open the chest immediately after stopping the ventilation. This went against all our instincts; one does not open the chest of a warm body with a vigorously beating heart. Eventually, 7 hearts continued to contract for 4 to 6 h after cannulation of the aorta and perfusing the heart in a Langendorff set-up, and yielded reproducible data on activation. As perfusion fluid we used a modified Tyrode's solution to which washed bovine erythrocytes were added. Twice a week our technician Mr. Schol went to the abattoir to obtain bovine blood. The washed erythrocytes were added to many litres of Tyrode's solution. This solution remained usable for 3 to 4 days. It often took months and months before a heart became available, and the perfusate had to be made over and over again.

In the Langendorff set-up, we initially recorded the epicardial activation pattern and then intramural plunge electrodes, containing 10 to 20 electrode terminals, were inserted into the ventricles. These 'Durrer needles' were the same as those used by Durrer and Van der Tweel in dogs and goats in the 1950s. In the heart that yielded the most complete information, the moment of activation was measured from 870 intramural electrode terminals. Unipolar and bipolar electrograms were recorded by a 14-channel Ampex tape recorder, together with a time code and a reference signal. The tapes were replayed at slow speed and the signals were printed on an Elema ink writer at maximum speed so that a time resolution was obtained of less than 1 ms per mm. Activation moments were measured by hand.

After the experiment, the cavities were filled with molten beeswax, and the heart, with the needle electrodes, was placed in the freezer overnight. The next day the needles were replaced by wooden pins and the hearts were

transected in parallel slices. Despite the fact that data were available from up to 870 intramural sites in the ventricles, isochrones were still partly the result from extrapolation as shown in Fig. 1.

A similar study would be very difficult to perform nowadays, in the era of cardiac transplantation, and it still remains the only study in which the activation pattern of the human heart has been documented in a detailed way. It rightly is a 'citation classic'.

Programmed electrical stimulation

The collaboration of the Department of Medical Physics of Henk van der Tweel resulted in, among other things, the construction by Leo Schoo of a very versatile, safe, and accurate stimulator for use in the catheterisation room. It could deliver driving and testing stimuli, the coupling interval of which could be adjusted with a millisecond accuracy. Initially, initiation and termination of reentrant tachycardias in the Wolff-Parkinson White syndrome were studied [7], later many other supraventricular and also ventricular tachycardias were investigated. Almost simultaneously, the group in Paris of Philippe Coumel and Robert Slama published a similar study and they even treated the patients with an implanted pacemaker [8]. Thus, 1967 marked the beginning of programmed electrical stimulation of the heart by two centres, independently.

Durrer's oeuvre

Between 1953 and 1985, Durrer and his co-workers published 127 original or review papers with a total of 136 different co-authors leading to 404 co-authorships. This number should be appreciated in the correct historical context. Today such a total number would not be impressive. What is special is that Durrer hardly ever published a paper that went unnoticed, in strong contrast to nowadays when some scientists publish the same amount of papers [9] in 1 year as Durrer did in his whole career. Although the initial focus was on activation of the canine heart during the 1950s, this changed to more clinically oriented papers with an emphasis on studies on premature electrical stimulation and an unravelling of the mechanism of tachycardias in the Wolff-Parkinson-White syndrome during the next 15 years (see above). Frequent co-authors of these papers were K.I. Lie (42 papers) and one of us (HJJW; 30 papers). During the 1970s the huge clinical problems of acute ischaemia and myocardial infarction prompted animal research in that direction, leading to 30 papers with one of us as a frequent co-author (MJJ; 30 papers).

papers which in fact can lean on a single or just a couple of experiments [10]. Obviously, a paper on ‘total repolarisation of the human heart’ is a missing link in cardiac electrophysiology [11]. That Durrer and his contemporaries did not analyse repolarisation from their human data is likely attributable to the facts that 1) the T wave could hardly be seen in the -high speed- Elema recordings and 2) the moment of local repolarisation was not as well defined as was the moment of local activation. The latter was recently resolved [12] but, unfortunately, the original data from the human hearts cannot be recovered. The fact that neither we, nor others, have been able to find this missing piece, underscores the strength of Durrer’s work.

Durrer’s new cardiology clinic, only opened in 1972, had to close down again in 1981 because it had been decided that the academic hospitals of the University of Amsterdam should merge into one located at the periphery of the city. Durrer strongly disagreed with this decision. In January 1983, 1 year before his death, Durrer addressed the academia at the occasion of the celebration of the 351st Dies Natalis of the University of Amsterdam [13]. In this remarkable speech he presented his view on the relationship between science, public health, society and politics.

Dirk Durrer left a heritage in clinical and translational cardiology, which can be estimated from the work of his scholars and by comparing his science to what is considered important and original at present. Numerous clinicians from the Netherlands, from Europe and from the USA have worked in his clinic and laboratory. Many of the current studies in translational and clinical cardiology are being carried out by his disciples, the disciples of his disciples and their postdoctoral fellows. As new generations appear, many of them may not even be aware of being part of the huge ‘Durrer family tree’ of cardiac scientists which carries branches spreading across the whole world.

Cardiac science has evolved to a point where electrophysiology and electrocardiology are no longer isolated disciplines. Modern science asks for the combination of methods such as genetics, proteomics, and molecular physiology with cellular and whole heart electrophysiology. We are still often faced with the problem that we need to mechanistically explain associations between genetic changes, pathological

molecular phenotypes and functional electrical changes in the heart. Knowledge about function is pivotal for progress in therapies and for finding common traits among different diseases. When one studies the brilliant work in Dirk Durrer’s laboratory on the electrical excitation of the healthy and diseased heart and the mechanisms of cardiac arrhythmias, it is as if he had, in fact, anticipated these modern needs.

References

1. 50 Jaar Cardiologie Amsterdam (1958–2008). In: Adams R, Arkenbout K, Bouma B, Chamuleau S, De Groot JR, Klomp M, editors. Ridderprint, Ridderkerk, 2008. pp. 1–171 (in Dutch).
2. Wellens HJJ. Durrer and programmed electrical stimulation of the heart. *Int J Cardiol.* 1984;6:759–61.
3. Burchell HB. Dirk Durrer. Thirty-five years of cardiology in Amsterdam. *Int J Cardiol.* 1987;14:239–54.
4. Wellens HJJ, Meijler FL. Dirk Durrer and the Amsterdam School of cardiology. *ACC Curr J Rev.* 2000;9:15–8.
5. Durrer D, van Dam RT, Freud GE, et al. Total excitation of the isolated human heart. *Circulation.* 1970;41:899–912.
6. Durrer D, Van der Tweel LH. Spread of activation in the left ventricular wall of the dog (I). *Am Heart J.* 1953;46:683–91.
7. Durrer D, Schoo L, Schuilenburg RM, et al. The role of premature beats in the initiation and termination of supraventricular tachycardia in the Wolff-Parkinson-White syndrome. *Circulation.* 1967;36:644–62.
8. Coumel P, Cabrol C, Fabiato A, et al. Tachycardie permanente par rythme réciproque. I. Preuve du diagnostic par stimulation auriculaire et ventriculaire. II. Traitement par l’implantation intracorporelle d’un stimulateur cardiaque avec entraînement simultané de l’oreillette et du ventricule. *Arch Mal Coeur.* 1967;60:1830–52 (in French).
9. Opthof T, Wilde AAM. Bibliometrical data in clinical cardiology revisited. The case of 37 Dutch professors. *Neth Heart J.* 2011;19:246–55.
10. Van Dam RT, Durrer D. The T wave and ventricular repolarization. *Am J Cardiol.* 1964;14:294–300.
11. Coronel R. T wave and dispersion of repolarization. *Heart Rhythm.* 2005;2:170–1.
12. Coronel R, De Bakker JMT, Wilms-Schopman FJ, et al. Monophasic action potentials and activation-recovery-intervals as measures of ventricular action potential duration. Experimental evidence to resolve some controversies. *Heart Rhythm.* 2006;3:1043–50.
13. Durrer D. Zondebok, leugenstoffeerder of nietige medicijnmeester. 351st Dies Natalis, University of Amsterdam (in Dutch).