Special Article

Historical Perspectives of Cardiac Electrophysiology

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The diagnosis and treatment of clinical electrophysiology has a long and fascinating history. From earliest times, no clinical symptom impressed the patient (and the physician) more than an irregular heart beat. Although ancient Chinese pulse theory laid the foundation for the study of arrhythmias and clinical electrophysiology in the 5th century BC, the most significant breakthrough in the identification and treatment of cardiac arrhythmias first occurred in this century. In the last decades, our knowledge of electrophysiology and pharmacology has increased exponentially. The enormous clinical significance of cardiac rhythm disturbances has favored these advances. On the one hand, patients live longer and thus are more likely to experience arrhythmias. On the other hand, circulatory problems of the cardiac vessels have increased enormously, and this has been identified as the primary cause of cardiac rhythm disorders. Coronary heart disease has become not just the most significant disease of all, based on the statistics for cause of death. Arrhythmias are the main complication of ischemic heart disease, and they have been directly linked to the frequently arrhythmogenic sudden death syndrome, which is now presumed to be an avoidable "electrical accident" of the heart. A retrospective look –often charming in its own right– may not only make it easier to sort through the copious details of this field and so become oriented in this universe of important and less important facts: it may also provide the observer with a chronological vantage point from which to view the subject. The study of clinical electrophysiology is no dry compendium of facts and figures, but rather a dynamic field of study evolving out of the competition between various ideas, intentions and theories.

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The first physician and legendary founder of modern, scientifically-based medicine was Hippocrates. As the spiritual rector of the Hippocratic manuscript collection (*Corpus hippocraticum*), he gained paramount importance in the medical history of the West for establishing the medical profession's tradition of education. As an "Asclepiad" and head of the School of Cos, he was thought to have been, according to tradition, a 19th generation descendent of Asclepius, the legendary god of medical science in Greek mythology.[1,2]

Hippocrates stated in his Aphorisms (Section II, No. 41): "Those who are subject to frequent and severe fainting attacks without obvious cause die suddenly." (Figure 1). This might be the first description of sudden cardiac death.[3] The Aphorism describes recurrent syncope in otherwise healthy individuals. These observations could be linked to electrical diseases (Table 1) such as long-QT syndrome, arrhythmogenic right ventricular dysplasia and arrhythmogenic right ventricular cardiomyopathy (Naxos disease), Brugada syndrome, hypertrophic cardiomyopathy, etc.

It was Étienne-Jules Marey (1830-1904) who first documented such phenomena as premature ventricular beats. E.J. Marey was born on March 5, 1830, in Beaune, Bourgogne (Côte d'Or), France (Figure 2). Marey invented many scientific instruments. He described and interpreted simultaneous pressures in the right atrium and right

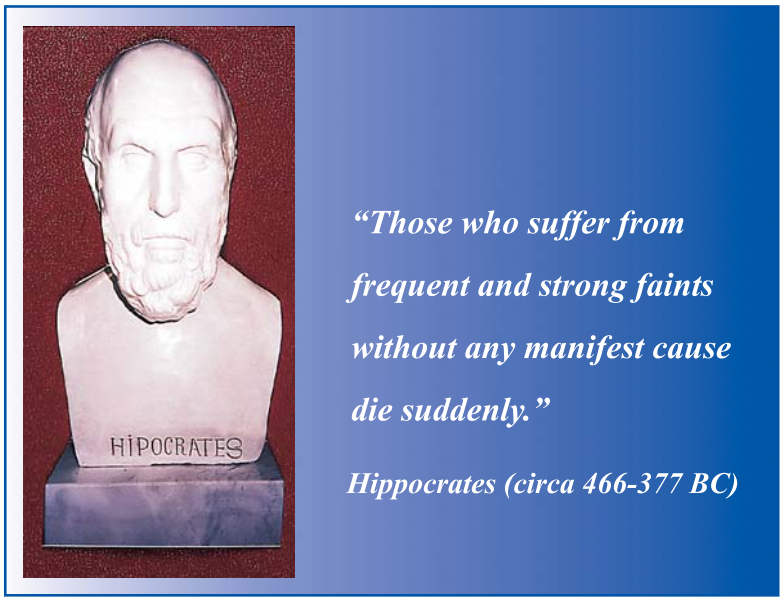

Figure 1. Hippocrates of Cos.

ventricle, the left ventricle and aorta, and the pulmonary artery pressure, the atrial influence on the ventricular pressure curve, the isometric phase of ventricular contraction, the chronology of valve motion, and the synchrony of left and right ventricular contraction (Figure 3). Original work on the heart by E.J. Marey included the discovery of the refractory period of heart muscle in 1875, and the first recording of the electrogram of the heart in animals, using a capillary electrometer, in 1876, preceding the work of Waller who recorded the first human electrogram in 1887.

Graphic recording was replaced after 1881 by the photographic record. Marey contributed considerably to the development of this new tool for the recording and evaluation of movement ("chronophotography"), which finally resulted in the invention of the cinematograph. Furthermore, Marey's studies on the flight of birds led him to research on gliding and aviation. Marey, who was a professor at the Collège de France and a member of the Academy of Science, produced numerous scientific papers, drawings, photographs and films (the first in the history of cinema!). Étienne-Jules Marey, a technical genius, the "engineer of life" and inventor of cinematography, died on May 15, 1904, at his Paris home.[4,5]

Aside from the discovery of the cardiac conduction system (Table 2) and advancements in the electrotherapy of cardiac arrhythmias (Table 3) the development of electrocardiography was the key issue for a more detailed understanding of repolarization as a cause and correlate of cardiac disorders, particularly sudden death (Table 4).

Table 1. Diseases likely to fit Hippocrates' aphorism

Arrhythmogenic disease	Risk of SCD (% per year)	Genetic component?
Hypertrophic cardiomyopathy	1-4	+
Arrhythmogenic right ventricular dysplasia	3	+
Dilated cardiomyopathy	4	+
Long-QT syndrome	1-5	+
Wolff-Parkinson-White syndrome	0.15	+
Idiopathic ventricular tachycardia	High	Unknown
Brugada syndrome	10	+
Naxos disease*	High	+

*Arrhythmogenic right ventricular cardiomyopathy. SCD – sudden cardiac death

Figure 2. Étienne-Jules Marey: "Engineer of Life" (1830-1904).

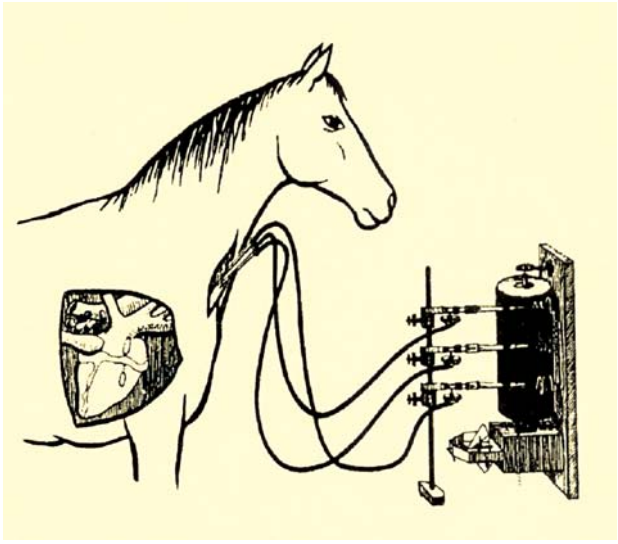

Figure 3. "Intracardiac cardiography." E.J. Marey recorded intracardiac pressure using a catheter with small balloons introduced into the heart chambers of a horse (1861).

In 1865, Carl Friedrich Wilhelm Ludwig (1816-1895) was appointed Professor of Physiology at the University of Leipzig. Ludwig designed a new physiologic institute at Leipzig, which was the most advanced experimental laboratory in the world when it opened in 1869. Ludwig encouraged many of his advanced pupils to investigate the physiology of the heart and circulation: among them were Henry P. Bowditch from the USA; Robert Tigerstedt, Luigi Luciani, Karl Ewald Hering, Adolf Fick, and Otto Frank from the European continent; and also Augustus D. Waller from the UK (Figure 4).

Ludwig's interest in the circulatory system led him to develop an instrument to record hemodynamic and other physiologic events accurately. For example, by simultaneously recording the pulse wave and respiratory pattern, he first described sinus arrhythmia in 1847. The first recording of ventricular fibrillation is depicted in Figure 5. To quote the pioneering Scottish pharmacologist T. Lauder Brunton: "More than to anyone else since the time of Harvey, do we owe our present knowledge of the circulation to Carl Ludwig."[63,64]

Not everybody knows that the first human electrocardiogram was recorded by A.D. Waller in 1897. Augustus Desiré Waller was born in Paris on July 12, 1856. Waller was made a professor in Aberdeen in 1881. He worked first in the physiology laboratory in London, UK, under Professor John Burdon-Sanderson and gave lectures on physiology at the London School of Medicine for Women. Waller held the same position for 16 years at the Medical School of St. Mary's Hospital. He was named Director of the Physiology Laboratory of the University of London in 1902. Waller died in London on March 11, 1922 (Figure 6).

Table 2. Discovery of the sinus node and the cardiac conduction system.

Year	Anatomy	Researcher
1845	Purkinje fibers	J.E. Purkinje[6]
1865/1893	Bundle of Kent	G. Paladino and A.F.S. Kent[7]
1893	Bundle of His	W. His, Jr.[8]
1906	Atrioventricular node	L. Aschoff and S. Tawara[9]
1906/1907	Wenckebach bundle	K.F. Wenckebach[10]
1907	Sinus node	A.B. Keith and M.W. Flack[11]
1916	Bachmann bundle	J.G. Bachmann[12]
1932	Mahaim fibers	I. Mahaim[13]
1961	Bundle of James	T.N. James[14]

Table 3. Historical perspectives of clinical electrophysiology.

Year	Publication
1580	Mercuriale G (1530-1606). Ubi pulsus sit rarus semper expectanda est syncope.[15]
1717	Gerbezius M (1658-1718). Constitutio Anni 1717 a.A.D. Marco Gerbezio Labaco 10. Decem. descripta. Miscellanea Emphemerides Academiae Naturae.[16]
1761	Morgagni GB (1682-1771). De sedibus et causis morborum per anatomen indagatis.[17]
1791	Galvani L, (1737-1798). De viribus electricitatis in motu musculari commentarius.[18]
1800	Bichat MFX (1771-1802). Recherches physiologiques sur la vie et la mort.[19]
1804	Aldini G (1762-1834). Theoretical and experimental essay on galvanism with a series of experiments conducted in the presence of representatives of the national Institute of France at various amphitheatres in London.[20]
1827/1846	Adams R (1791-1875), Stokes W (1804-1878). Cases of diseases of the heart accompanied with pathological observations; Observations of some cases of permanently slow pulse.[21,22]
1872	Duchenne de Bologne GBA (1806-1875). On localized electrical stimulation and its pathological and therapeutic application by induced and galvanized current, both interrupted and continuous.[23]
1882	von Ziemssen H (1829-1902). Studies on the motions of the human heart as well as the mechanical and electrical excitability of the heart and phrenic nerve, observed in the case of the exposed heart of Catharina Serafin.[24]
1890	Huchard H. La maladie de Adams-Stokes (Adams-Stokes Syndrome).
1932	Hyan AS. Resuscitation of the stopped heart by intracardial therapy. II. Experimental use of an artificial pacemaker.[25]
1952	Zoll PB. Resuscitation of heart in ventricular standstill by external electrical stimulation.[26]
1958	Elmquist R, Senning A. An implantable pacemaker for the heart.[27]
1958	Furman S, Robinson G. The use of an intracardiac pacemaker in the correction of total heart block.[28]
1961	Bouvrain Y, Zacouto F. L'entraînement électrosystolique du coeur.[29]
1962	Lown B, et al. Bifocal demand pacing.[30]
1969	Berkovits BV, et al. Bifocal demand pacing.[31]
1972	Wellens HJJ, et al. Electrical stimulation of the heart in patients with ventricular tachycardia.[32]
1975	Zipes DP, et al. Termination of ventricular fibrillation in dogs by depolarizing a critical amount of myocardium.[33]
1978	Josephson ME, et al. Recurrent sustained ventricular tachycardia.[34]
1980	Mirowski M, et al. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings.[35]
1982	Gallagher JJ, et al. Catheter technique for closed-chest ablation of the atrioventricular conduction system.
1982	Scheinman MM, et al. Transvenous catheter technique for induction of damage to the atrioventricular conduction system.[37]
1982	Lüderitz B, et al. Therapeutic pacing in tachyarrhythmias by implanted pacemakers.[38]
1985	Manz M, et al. Antitachycardia pacemaker (Tachylog) and automatic implantable defibrillator (AID).
1987	Borggrefe M, et al. High frequency alternating current ablation of an accessory pathway in humans.[40]
1988	Saksena S, Parsonnet V. Implantation of a cardioverter-defibrillator without thoracotomy using a triple electrode system.[41]
1991	Jackman WM, et al. Catheter ablation of accessory atrioventricular pathways (Wolff-Parkinson-White syndrome) by radiofrequency current.[42]
1991	Kuck KH, et al. Radiofrequency current catheter ablation of accessory pathways.[43]
1994	Daubert C, et al. Permanent atrial resynchronisation by synchronous bi-atrial pacing in the preventive treatment of atrial flutter associated with high degree interatrial block.[44]
1994	Cazeau S, et al. Four chamber pacing in dilated cardiomyopathy.[45]
1994	Wiffels MCEF, et al. Atrial fibrillation begets atrial fibrillation.[46]
1995	Camm AJ, et al. Implantable atrial defibrillator.[47]
1997	Jung W, et al. First worldwide implantation of an arrhythmia management system.[48]
1998	Haissaguerre M, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins.[49]
1999	Josephson M, et al. Hybrid pharmacologic and ablative therapy[50].
2006	Allessie MA. Mechanism of atrial fibrillation - an anatomical 3D labyrinth of multiple narrow wavelets (World Congress of Cardiology, Barcelona, Spain).[51]
2007	Calkins HG, et al. HRS/EHRA/ECAS Consensus statement on AF.[52]
2008	Hohnloser SH. The ATHENA Trial. Heart Rhythm Society 2008 Scientific Sessions; May 15, 2008, San Francisco, CA, USA.

Table 4. Chronology of electrocardiography.

Year	Event	Researcher
1887	First human ECG	A.D. Waller[53]
1902	Surface lead ECG	W. Einthoven[54]
1906	Esophageal ECG	M. Cremer[55]
1933	Unipolar chest wall leads	F.N. Wilson[56]
1936	Vector electrocardiography	F. Schellong[57]
1938	Small triangle "F" (RA, LA, RL)	W. Nehb[58]
1942	Unipolar amplified extremity leads	E. Goldberger[59]
1956	Corrected orthogonal lead systems	E. Frank[60]
1960	Intracardiac leads	G. Giraud and P. Puech[61]
1969	His bundle ECG	B.J. Scherlag[62]

Figure 4. The image of Carl Ludwig—the outstanding pioneer and representative of modern science in the nineteenth century—on the honorary medal named after him. This medal is the highest award of the German Cardiac Society (GCS). His emblem can be found on the program of the annual meetings of the GCS, demonstrating the significance of physiological and pathophysiological topics in the framework of the Society.

Waller primarily studied the electrical phenomena of the heart. As early as 1889, he was able to obtain an electrocardiogram (ECG) from the body surface of a human being with the aid of a Lippmann capillary electrometer. Although the clinical significance of this ECG was not recognized at that time, Waller's work nevertheless laid the foundation for modern electrocardiography.

Waller found that the electrical currents generated by the heart could be recorded with a mercury capillary electrometer when the electrodes were placed on the chest or the limbs. The capillary electrometer was devised in 1873 by Gabriel Lippmann (1845-1921) (Figure 7). It consisted of a glass tube containing mercury, with one end drawn out into a fine capillary (20-30 μm) and immersed vertically in dilute sulfuric acid. Measurement is based on displacement of the mercury meniscus, because mercury contracts and expends according to the potential difference between the mercury and acid, which were connected to electrodes on two points on the body.

Waller's classic demonstration of the human ECG (already called the electrocardiogram at that time) from the intact human heart took place at St. Mary's Hospital, London, in May 1887, with surface electrodes strapped to the front and back of the chest. There were only two distorted deflections: ventricular depolarization and repolarization. The P-wave was not discernible with the 1887 apparatus. This historic event in 1887 was also witnessed by W. Einthoven. The following year, Waller recorded the ECG by using saline jars in which the extremities were immersed. Einthoven himself credited Waller with the first human ECG (Figure 8).[64,66]

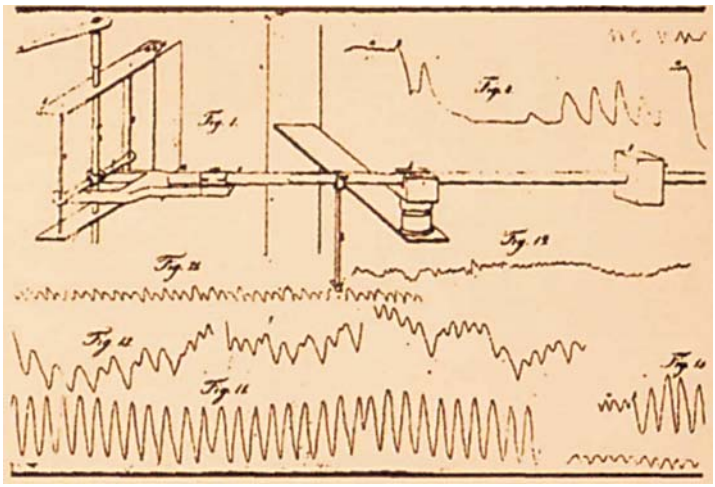

Figure 5. First graphic documentation of ventricular fibrillation. In 1894, while investigating vagal influences on cardiac activity, M. Hoffa, in Carl Ludwig's laboratory, documented bizarre unregulated actions of the ventricles when exposed directly to strong faradic or constant currents. The disorder affected both rhythm and intensity, persisted after termination of electroexcitation, and stopped cardiac output. The atria did not participate in the arrhythmia. (From reference 64.)

Figure 6. A.D. Waller in his laboratory with laboratory dog, "Jimmy".

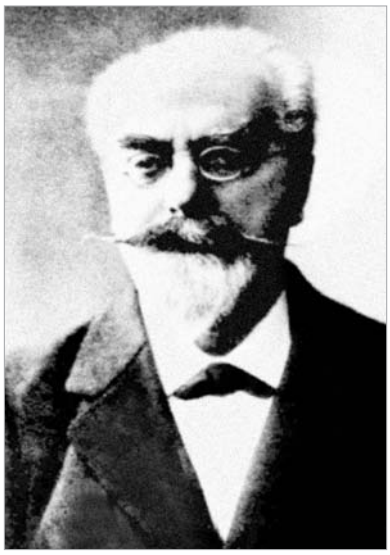

Figure 7. Gabriel Lippmann (1845-1921).

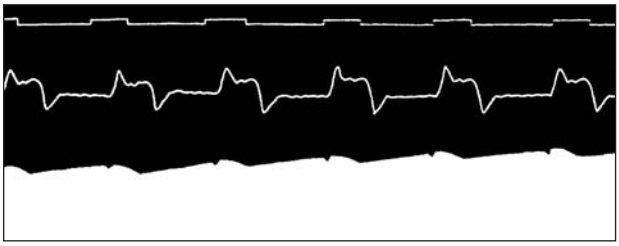

Figure 8. The first human electrocardiogram (ECG), recorded by A.D. Waller in 1897.

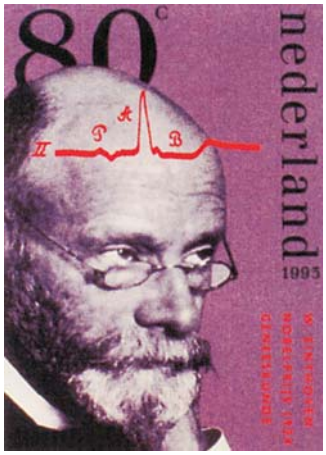

Figure 9. Dutch stamp commemorating the ninetieth anniversary of the first recording of a modern electrocardiogram by Willem Einthoven (1860-1927).

After Waller had succeeded in 1887 in recording the first ECG from the body surface of a human being, Einthoven began his work in 1895 with the Lippmann capillary electrometer (Figure 9). To allow for physical factors, Willem Einthoven corrected the coarsely differentiated capillary image, which led him to refine the string galvanometer invented in 1897 by C. Ader. In his experiments with the capillary electrometer, Einthoven originally identified four waves in each ECG (A, B, C, D). Through mathematical corrections and evaluations of the capillary electrometer curves, Einthoven increased to five the number of distinct points on the electrocardiograph and introduced the designation for them that is still in use today: P, Q, R, S and T (Figure 10). Whereas the qualitative and quantitative measurement of the pulse may be understood as a starting point in arrhythmia diagnoses, true understanding of cardiac rhythm disorders really began with electrocardiography using the string galvanometer refined by Einthoven (Figure 11).[67,68]

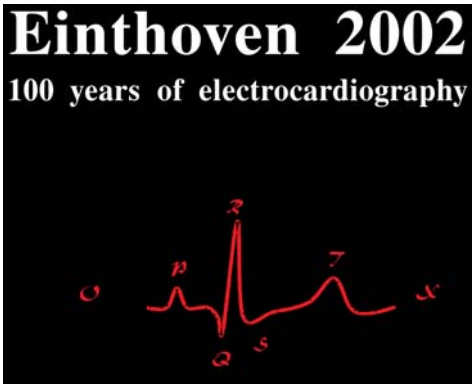

Figure 10. Announcement of the anniversary congress, "Einthoven 2002, 100 years of electrocardiography", on the occasion of the first ECG recording with Einthoven's string galvanometer.

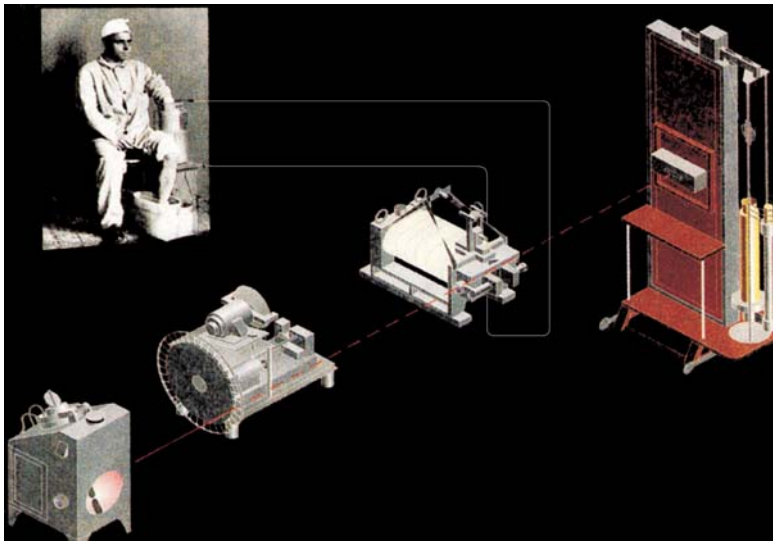

Figure 11. Electrocardiograph installation. Left: Arc lamp, spoked wheel string galvanometer connected to the patient. Right: Camera (top) and the string in the magnetic field of the galvanometer (Museum Boerhaave, Leiden, The Netherlands).

Interventional electrophysiology

The invasive electrophysiologic diagnostic and stimulation procedure is a heart catheter technique based on the historical maneuver performed by Werner Forssmann. Following this pioneer, Scherlag and colleagues described the first intracardiac catheter recordings of the His bundle in 1969, whereas Dirk Durrer and Henrick J.J. Wellens were the first to execute programmed stimulation in man.[69,70]

Dirk Durrer (1918-1984) –a true pioneer of clinical electrophysiology– was appointed Professor of Cardiology and Clinical Physiology at the University of Amsterdam, the Netherlands, from 1957 until his death in 1984. In the early 1960s he introduced the famous multi-terminal intramural needle electrode. This might be considered as the beginning of clinical electrophysiology, setting the stage for programmed electrical stimulation and recording in the human heart. Durrer's experimental and clinical research gave the electrophysiology community important new insights into the reentry (circus movement) concept as an explanation of certain types of tachycardias, particularly in the Wolff-Parkinson-White syndrome. Furthermore, Durrer initiated clinical and scientific approaches to pharmacological treatment of life-threatening tachyarrhythmias (Figure 12).

Henrick Joan Joost Wellens was born on November 13, 1935, in Te's Gravenhaage, the Netherlands. He described the mechanism of reentry tachycardia, including the Wolff-Parkinson-White syndrome. He is a pioneer of interventional electrophysiology and a founder of the modern era of tachycardia management concerning atrial and ventricular arrhythmias (Figure 13). His doctoral thesis (March 18, 1971) was entitled: "Electrical stimulation of the heart in the study and treatment of tachycardias" (Figure 14).[71]

The programmed stimulation technique was initially used to induce ventricular tachycardia and to elucidate the mechanisms of tachycardias in the Wolff-Parkinson-White syndrome. Electrophysiologic testing was then used more and more to guide pharmacological therapy and to delineate the electrophysiologic effects of drugs on the normal and diseased myocardium (Table 5). The recording of the action potential in the experimental laboratory and in the intact human heart via a catheter technique substantially changed our understanding of the mechanisms involved in cellular depolarization and repolarization, antiarrhythmic drug effects and sudden cardiac death and arrhythmogenesis.[72,73]

Figure 12. Dirk Durrer (1918-1984).

Long-QT syndrome

The long-QT syndrome is characterized by QT interval prolongation and syncope or sudden cardiac death due to ventricular tachyarrhythmias. The congenital form can be either familial or idiopathic.[74,75] The familial type consists of two subgroups: 1) the Jervell and Lange-Nielson syndrome, which is associated with deafness; and 2) the Romano-Ward syndrome, which is associated with normal hearing. Two classic descriptions of these functional, hereditary, syncopal cardiac disorders exist (Figure 15).[76-79]

Jervell and Lange-Nielsen syndrome

In 1957, Anton Jervell and Fred Lange-Nielsen described a case of syncopal arrhythmias and QT prolongation combined with profound congenital deafness in a Norwegian family with six children.[75] Four of the children were deaf mutes, suffered from syncopal episodes with loss of consciousness, and demonstrated a clear QT interval prolongation on their surface ECGs. Three of the four children with the disease died suddenly. Interestingly, the parents of those children were healthy: an indication of the recessive genetics in the Jervell and Lange-Nielsen syndrome.

Romano-Ward syndrome

Cesarino Romano was born in Voghera, Italy in 1924. After his study of medicine at the University of Pavia, he worked in pediatrics at the University of Genoa. In 1961 he became a professor of pediatrics and later he served as the director of the First Pediatric Department and the Scientific Institute of the Pediatric Clinics at the University of Genoa. Among numerous publications dealing with hereditary hypothyroidism, cystic fibrosis, and cardiac disorders, he described in 1963 an inherited functional syncopal heart disorder with prolonged QT interval in a 3-month-old female patient ("Aritmie cardiache rare dell'eta'pediatrica").[77] Two brothers of his patient had exhibited the same symptoms and died suddenly at a young age. Independently of Romano, Owen Conor Ward, Professor of Clinical Pediatrics at the University of Dublin, published one year later a work in Ireland entitled: "A New Familial Cardiac Syndrome in Children". He also described syncopal attacks and a prolonged QT interval in both a young female patient and her brother.[78] Ward was born in Monaghan, Ireland on August 27, 1923. After graduating from St. Macarten's College in Monaghan, Ward studied medicine at the University College of

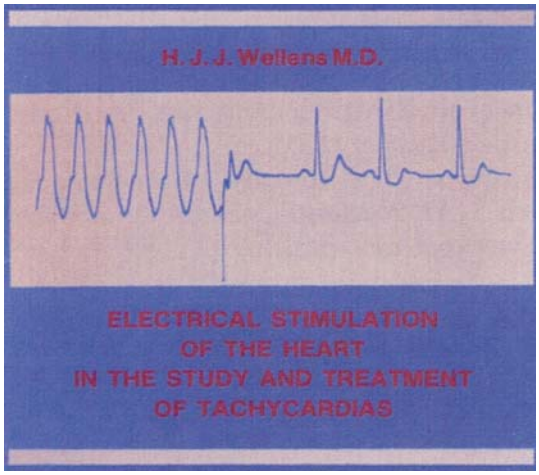

Figure 14. Front page of the thesis of H.J.J. Wellens, 1971.

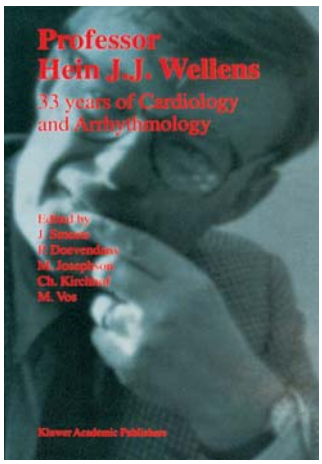

Figure 13. Title page of the book: Prof. Hein J.J. Wellens – 33 Years of Cardiology and Arrhythmology (Kluwer Academic Publishers; 2000).

Table 5. Electrotherapy of atrial fibrillation.

Therapy	Current indication
Atrioventricular nodal ablation and permanent pacing:	Symptomatic patients refractory to other rate- and rhythm-control treatments. Patients who already have an implanted pacemaker or defibrillator.
Catheter ablation:	Symptomatic patients refractory to antiarrhythmic drugs. Younger patients (<60 years) with lone atrial fibrillation. Patients unable or unwilling to take long-term antiarrhythmic drugs.

CONGENITAL DEAF-MUTISM, FUNCTIONAL HEART DISEASE WITH PROLONGATION OF THE Q-T INTERVAL, AND SUDDEN DEATH

ANTON JERVELL, M.D., AND FRED LANGE-NIELSEN, M.D.

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A COMBINATION of deaf-mutism and a peculiar heart disease has been observed in 4 children in a family of 6. The parents were not related, and were, as the other 2 children, quite healthy and had normal hearing.

The deaf-mute children, who otherwise seemed quite healthy, suffered from "fainting attacks" occurring from the age of 3 to 5 years. By clinical and roentgen examination, which was performed in 3 of the children, no signs of heart disease could be discovered. The electrocardiograms, however, revealed a pronounced prolongation of the Q-T interval in all cases.

Three of the deaf-mute children died suddenly at the ages of 4, 5, and 9 years, respectively.

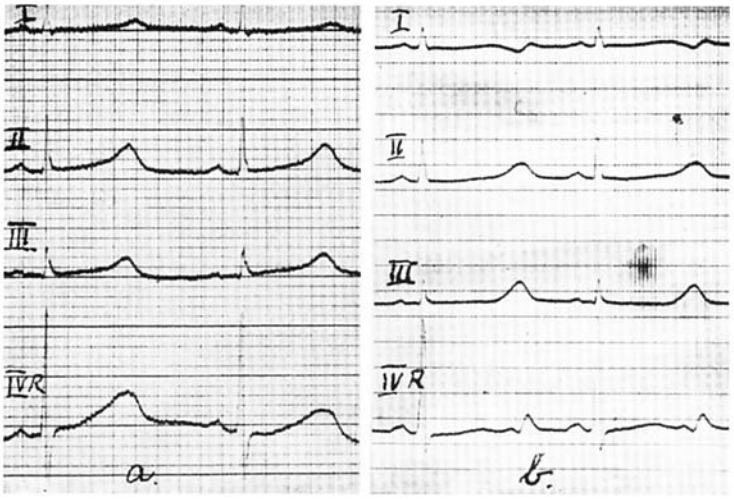

Figure 15. Tormond J. (a) ECG July 20, 1953, during rest. Leads I, II, III, IV R. QT=0.50 s, RR=0.88 s. (b) ECG July 20, 1953, after stair running. Leads I, II, III, IV R. QT=0.60 s, RR=0.86 s. From the American Heart Journal, vol. 54, Anton Jervell and Fred Lange-Nielsen, Congenital deaf-mutism, functional heart disease with prolongation of the Q-T interval, and sudden death, pp. 59-68, copyright Elsevier 1957. Reproduced with permission.

Dublin, where he passed his examinations in 1947. After his internship in various Irish hospitals, Ward specialized in pediatric medicine in 1949 and earned his doctorate in 1951 with a thesis on hypoglycemia in neonates. After that, Ward worked for a few years in a Dublin pediatric clinic. In 1972, he was made Professor of Clinical Pediatrics at the University of Dublin, where he served as the first professor for pediatrics until 1983.

Torsade de pointes tachycardia

The typical arrhythmia of patients with congenital or acquired long-QT syndrome is the *torsade de pointes* tachycardia (TdP). This specific form of dangerous polymorphic ventricular tachyarrhythmia is characterized by a repetitive change of the main QRS vector during tachycardia in the presence of a prolonged repolarization. François Dessertenne[80] first described the TdP morphology in an 80-year-old female patient with intermittent atrioventricular block (Figure 16). The cause of her recurring syncopal episodes was the TdP tachycardia, rather than the bradycardia that had primarily been suspected.

Dessertenne himself suggested in his description that two competing foci were responsible for the typical TdP morphology. This hypothesis was tested in experimental animal studies, one by Christoph Naumann d'Alnoncourt and colleagues[81] using a porcine Langendorff heart technique, and one by Gust H. Bardy and

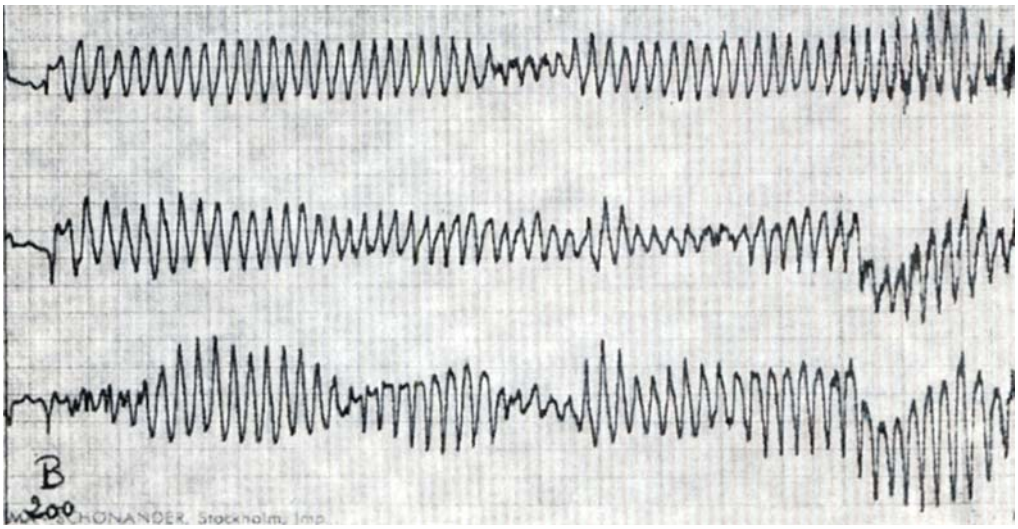

Figure 16. First description of torsade des pointes waves in 1966 by F. Dessertenne. He observed this rhythm disorder in an 80-year-old female patient with complete intermittent atrioventricular block. From Archives des maladies du coeur et des vaisseaux, vol. 59, François Dessertenne, La tachycardie ventriculaire à deux foyers opposés variables, pp. 263-272, copyright Elsevier 1966. Reproduced with permission.

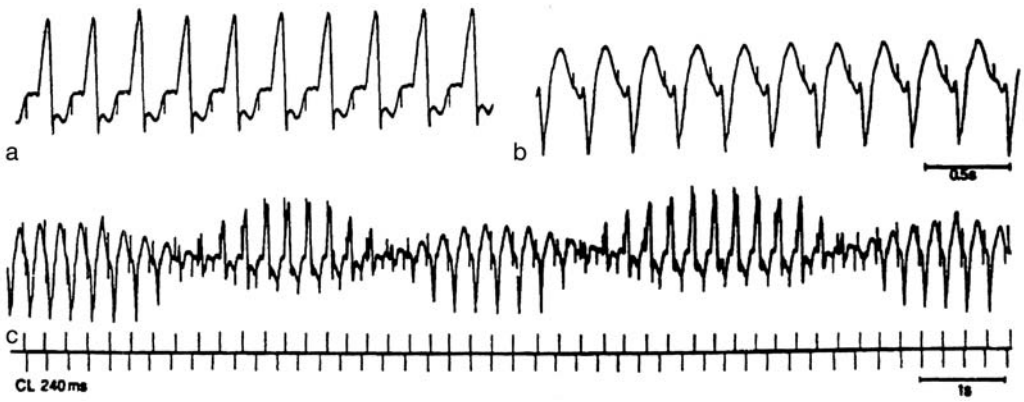

Figure 17. Torsade des pointes morphology in an isolated Langendorff pig heart while bifocal ventricular stimulation is performed. ECGs during stimulation of the right (a) or the left (b) ventricle. If the left ventricle is paced at a constant rate (cycle length 245 ms) and the right ventricle is paced at a similar, but periodically slightly changing rate (cycle length 230 to 260 ms), the electrocardiographic pattern of torsade de pointes occurs (c). Reproduced from: "Torsade de pointes" tachycardia. Re-entry or focal activity?, by D'Alnoncourt CN, et al; Br Heart J vol. 48, pp. 213-216, 1982, with permission from BMJ Publishing Group Ltd.

colleagues[82] in a canine heart *in situ* experiment. In both studies, pacing from the left and right ventricular site at a similar, but periodically changing rate resulted in an ECG with TdP configuration (Figure 17).[81]

Naxos disease

Dr. Nikos Protonotarios and colleagues examined the population of the Greek island of Naxos and described the so-called Naxos disease in 1986:[83] A syndrome of arrhythmogenic right ventricular cardiomyopathy (ARVC), non-epidermolytic palmoplantar keratoderma, and woolly hair (Figure 18). The autosomal recessive ARVC of Naxos disease is similar to autosomal dominant ARVC with respect to age and mode of clinical presentation, distribution of right ventricular and left ventricular involvement, electrocardiographic features, natural history, and morphological

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Cardiac abnormalities in familial palmoplantar keratosis

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SUMMARY Cardiac abnormalities were identified in patients with familial palmoplantar keratosis. All of them were descended from families on the Greek island of Naxos. Four families were studied and nine cases of palmoplantar keratosis were identified; seven of them showed symptoms and signs of heart disease. Cardiomegaly on chest *x* ray and electrocardiographic abnormalities were common findings. Three cases had episodes of ventricular tachycardia and a fourth patient died suddenly. All patients with cardiac signs and symptoms showed echocardiographic enlargement of the right ventricle and a right ventricular band; in three the left ventricle was also affected.

Figure 18. First description of Naxos disease by N. Protonotarios and his wife A. Tsatsopoulou, et al. Reproduced from: Cardiac abnormalities in familial palmoplantar keratosis, by Protonotarios N, et al, Br Heart J vol. 56, pp. 321-326, 1986 with permission from BMJ Publishing Group Ltd.

and histological features. The initial clinical presentation is often with ventricular arrhythmia of left bundle branch block morphology, which suggests a right ventricular origin. All patients originally examined by Nikos Protonotarios and his pediatrician wife Adalena Tsatsopoulou with cardiac abnormalities and familial palmoplantar keratosis were descended from families on the Greek island of Naxos. Cardiomegaly on chest X-ray and electrocardiographic abnormalities were common findings (Figure 19). Three cases had

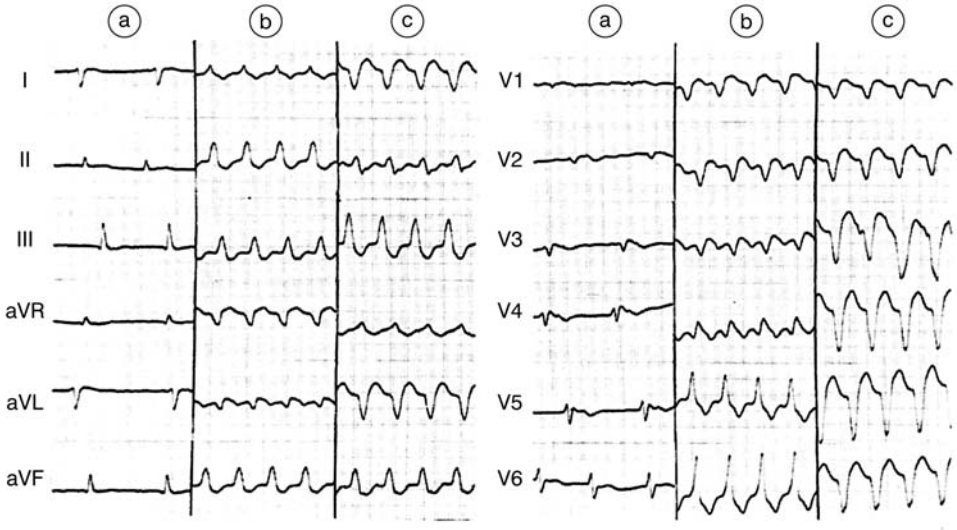

Figure 19. Naxos disease: Normal electrocardiogram (a) and two episodes of ventricular tachycardia (b and c) from a single-channel recorder. In (a) there was a QRS axis of >135 ms, QRS prolongation, low voltage, and T-wave inversion in the precordial leads. In both (b) and (c) the ventricular tachycardia rate is 160 beats per minute and the QRS axes were >75 ms and >135 ms, respectively. Reproduced from "Cardiac abnormalities in familial palmoplantar keratosis", by Protonotarios N. et al, Br Heart J vol. 56, pp. 321-326, 1986, with permission from BMJ Publishing Group Ltd.

Table 6. Molecular-genetic arrhythmic syndromes.

- Caveolin-3-mutations and long-QT syndrome.
- Brugada syndrome.
- Calcium channel abnormalities and the Brugada syndrome.
- Potential drug remedy for the Brugada syndrome.
- New clinical features of the Brugada syndrome.
- Genetic basis for sinus node disease.
- Role of somatic mutations in patients with atrial fibrillation.

episodes of ventricular tachycardia and a fourth patient died suddenly. All patients with cardiac signs and symptoms showed echocardiographic enlargement of the right ventricle and a right ventricular band; in three the left ventricle was also affected.

The term "Naxos disease" was introduced by G. Fontaine, N. Protonotarios, A. Tsatsopoulou and colleagues in an abstract sent to the American Heart Association in 1994.[84] Based on electrocardiography and pathology, the authors suggested that Naxos disease and arrhythmogenic right ventricular dysplasia (ARVD) are two expressions of the same cardiac disorder. It was supposed that in Naxos disease ARVD is genetically transmitted and its morbidity is associated with palmoplantar keratosis.[85] Coonar et al[85] confirmed autosomal recessive inheritance for Naxos disease and mapped the disorder to chromosome 17q21. Recently, McKoy et al[86] have shown a two base-pair homozygous deletion in the plakoglobin gene in individuals with Naxos disease.

Coming back to Hippocrates, we can say that he was the first to describe sudden cardiac death based on electrical diseases of the heart. Hippocrates' observations and intentions inspired experimental and clinical science to detect and to elaborate genetics, mechanisms, treatment and prevention of sudden death, one of the most important causes of mortality today (Table 6).

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