Impact of Willem Einthoven (1860-1927) and his contemporary Nobel prize laureates on present day medical technology

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Summary

The discovery of animal electricity by the Italian physician-scientist Luigi Galvani (1737-1798) was the starting point for the broad discipline of electrophysiology, with important implications in cardiology and neurosciences. Later, following the recording by Waller of the electrical activity originating from the canine heart, Einthoven succeeded in obtaining sensitive measurements allowing for detailed interpretation of cardiac abnormalities observed in humans. Nowadays, the field embraces integrated advanced medical imaging modalities, as well as enrichment based on artificial intelligence. This survey briefly covers three centuries of bioelectricity, reaching a summit with reliable measurements and clinical interpretation of the electrocardiogram (ECG) by Willem Einthoven at Leyden University, for which efforts he was awarded the 1924 Nobel Prize for Physiology or Medicine.

Historical introduction

Galvani, and later his nephew Giovanni (Jean) Aldini (1762-1834), recorded the electrical activity in various animals using an invasive method, culminating in primitive forms of electrotherapy and attempts of reanimating decapitated criminals. [Parent] The French physiologist Étienne-Jules Marey (1830-1904) added the option of photographic registration when recording the electrical activity of the exposed heart of frog and tortoise, using the mercury filled capillary electrometer. [Snellen] It then was a matter of time for someone to come up with a noninvasive technique to derive directly from the skin the electrical signal as generated during the heart beat. This major step forward was accomplished by Augustus Desiré Waller (1856–1922), a British physiologist born in France, employing the device developed by Marey. He recorded the ECG from electrodes attached to the limbs of his dog Jimmy, and later also in man, employing electrodes positioned on the chest (1887). [Waller]

Career of W. Einthoven

Willem Einthoven was born in 1860 (Semarang, Java, Dutch Indies). After becoming an MD at Utrecht University, he earned his PhD degree in 1885 on a study regarding stereoscopy by color difference, under the supervision of the famous ophthalmologist F.C. Donders. In that same year he was appointed successor to A. Heynsius, Professor of Physiology at the University of Leyden. His inaugural address was about the theory of specific energies. His first important research in

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Leyden was published in 1892: *Über die Wirkung der Bronchialmuskeln nach einer neuen Methode untersucht, und über Asthma nervosum* (On the function of the bronchial muscles investigated by a new method, and on nervous asthma). While still continuing his research on optics, his attention was attracted to the accomplishments of Waller on electricity generated by the heart. Importantly, having developed a more reliable measurement method, namely the string galvanometer, Einthoven successfully improved the technique of recording the ECG.

As we will see next, Einthoven had the pleasure of working in a stimulating environment, surrounded by prestigious physicists and skillful professionals in the adjacent mechanical workshop. Soon this laboratory in Leyden became a place of pilgrimage, visited by scientists from all over the world. These visitors often added further refinements once they applied the technique. For example, Frank Norman Wilson (1890-1952) developed the concept of the central terminal, used for deriving precordial and augmented leads. [Snellen] [Bacharova] Later, reference values were established for the various leads, [Kerkhof 2018b] and gradually such recordings were being analyzed with the aid of early generations of computers. [Macfarlane]

The Kamerlingh Onnes Laboratory

Leyden University (in the Netherlands) was established February 8, 1575. The institution (Figure 1) where Einthoven carried out his experiments was founded in 1859, and located not far from the old main academy building, situated along the famous Rapenburg canal. The laboratory offered excellent research facilities for anatomy, chemistry, physiology and physics. Later, the experimental physics division of the building was named after professor Heike Kamerlingh Onnes, who together with his colleagues became worldwide known as the low temperature experts in the building. The theoretical physics part was built later as an attached but separate unit, and named after professor Lorentz.

As a physiologist, Einthoven had his laboratory in the same institution. The interaction between the various professors active in neighboring disciplines was not only scientific, but also involved serious conflicts at the one-way "vibrational interference" level. In 1895 Kamerlingh Onnes installed in his cryogenic laboratory a 25 horsepower steam engine, operating 24 hours a day in order to run his experiments, as the city of Leyden did not have access to an electrical power network around that time. As expected, the resulting engine vibrations distorted the delicate ECG recordings. Therefore, the two experimenters had to agree on a schedule for sequentially carrying out their individual research activities.

Figure 1. Kamerlingh Onnes Laboratory in Leyden, the Netherlands. The construction was completed around 1860, and Einthoven worked there from 1886 through 1927.

Apart from these tensions, the institution was (and still is) also known for its prestigious mechanical workshop, developing precision instruments for advanced studies and building devices never constructed before, such as coolers for liquefaction of helium, reaching temperatures as low as a few degrees above absolute zero (i.e. minus 273.15 degrees Celsius). During his stay in Leyden the present author, while completing his PhD in the department of Pediatrics, enjoyed the privilege to count on several exponents of a later generation of these craftsmen. They created for him a flow- and pressure controllable artificial afterload system for pumping hearts (Figure 2), as well as a simple tool to apply a ligature around a remote vessel using only one port of entry, as well as electronics to monitor premature born babies.

A remarkable fact about the research institution shown in Figure 1 concerns the observation that, within slightly more than 2 decades, this early excellent “island of science” produced five Noble Prize winners.

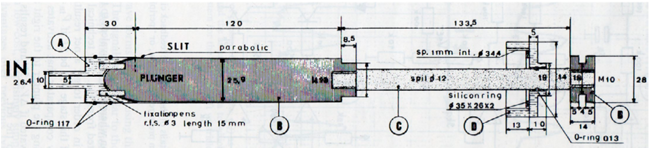

Figure 2. The Hofkessel, a fully controllable artificial afterload system for the left ventricle, as designed in 1980 by a later generation of craftsmen working in the famous mechanical workshop connected with the laboratory where Einthoven and Kamerlingh Onnes carried out their research. [Kerkhof 1986]

Nobel prize winners from Leyden (period 1902 through 1924)

Around the beginning of the 20th century, Leyden University was an attractive place for both experimental and theoretical physicists. Many famous scientists, including Albert Einstein, spent some time in this flourishing center. The following five Nobel prize awarded scientists were affiliated with the institution, which was later named after Kamerlingh Onnes:

- Pieter Zeeman (1902 [shared], the influence of magnetism upon radiation phenomena);
- Hendrik Antoon Lorentz (1902 [shared], the influence of magnetism upon radiation phenomena);
- Johannes Diderik van der Waals (1910, on the continuity of the gas and liquid state);
- Heike Kamerlingh Onnes (1913, liquefaction of helium) + superconductivity;
- Willem Einthoven (1924, discovery of the mechanism of the electrocardiogram).

Two of these laureates are shown on stamps, issued to celebrate their discoveries (Figure 3). Four of them are physicists, while Einthoven represented physiology. In fact, the work of Kamerlingh Onnes later also found application in the field of medicine, as superconductivity refers to a property required for magnetic resonance imaging (MRI), nowadays worldwide applied in hospitals.

Figure 3. Postal stamps referring to Van der Waals and Einthoven, showing the continuity equation as used in physics, and the QRS-complex of the electrocardiogram, respectively. To the right the plaque of April 2022, referring to an IEEE milestone. [van Etten]

The Leyden University Hospital in 1905

Figure 4. View of the Leyden Academic Hospital at the time when Einthoven remotely recorded the ECG of cardiac patients who were admitted to this famous medical center.

The refined string galvanometer, as developed by Einthoven and his craftsmen in the mechanical workshop, was not a portable piece of equipment. Unfortunately, the university hospital was not next door. The solution to this problem was a 1.5 kilometer long cable, connecting the patient to the galvanometer in the Kamerlingh Onnes laboratory. In 1905 Einthoven succeeded in measuring this so-called telecardiogram of heart disease patients admitted to the Academic Hospital (Figure 4), located elsewhere in the city.

Sex-specific Findings, also for the ECG

Until recently, most investigation in the field of cardiology focused on the disease patterns observed in male patients. [Kerkhof 2018a] Until then, for the most part physicians thought of gender-related illnesses as pertaining to obstetrics, gynecology and genitourinary diseases. However, cardiologists have long had similar concerns, albeit to a limited degree. [Altschule] For example, since 1950 it is known that false-positive ECGs during exercise tests are common in women, including young women. [Scherlis] [Cuming] Nowadays, full details on various intervals, durations and electrical axes referring to the "normal" ECG have been described, with attention to sex, age, and ethnicity. [Kerkhof 2018b]

ECG, Imaging and Artificial Intelligence

The ECG as displayed by the combination of various leads is an ideal challenge for interpretation by computers, although cardiology expert consultation is always advised. Major progress has been made since the early pioneering explorations, more than half a century ago. [Macfarlane] In particular, current artificial intelligence approaches can contribute to further advancements in ECG analysis, as it also enhances comprehensive studies regarding medical imaging.

Electrocardiographic imaging (ECGI) represents an inverse technique to determine noninvasively and with high resolution the electrical activity of the heart from electrical data recorded on the body surface, when combined with cardiac computed tomography images (based on projecting X-rays through a section of the body, which are then processed by computer to reconstruct the cross-sectional image). [Intini]. A more sophisticated imaging technique is based on superconductivity, and for heart studies known as cardiomagnetic resonance (CMR) imaging, allowing excellent soft-tissue contrast.

The remarkable combination referring to an integrated interpretation of electrical signals and three-dimensional shape changes of the heart carries a bright future. The zenith where nowadays the spin-offs of two separate and competing worlds meet, once centered around galvanometer and superconductivity. New developments are born, based on inventions realized by two Noble prize winners, working independently within the same institution, but fighting for a time schedule to perform their individual and (at that time totally) unrelated experiments.

Conclusions

Some 125 years ago, a special blend of medicine and physics found its origin in the city of Leyden. The promising future started with the development of a device to accurately measure the electrical activity of the heart, still today being of eminent importance for early noninvasive diagnostics in cardiology. Independently, and even despite conflicting experimental interests between Einthoven and Kamerlingh Onnes, the foundations were laid for what many years later resulted in a revolutionary medical imaging modality, known as magnetic resonance imaging (MRI), with far-reaching capabilities, notably also in the field of cardiology.

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