



From *Galvani's* Frog and *Norman Jefferis Holter* (1914–1983) to the “Implantable Holter Monitors” of Today

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Luigi Galvani (1737–1798) studied the contractions of the leg muscle of a decapitated frog, becoming the founder of electrophysiology. His work even inspired artists such as *Paul Peel* (1860–1892), who painted his famous painting “The Young Biologist” in 1891. *Galvani's* work was the foundation for the revolutionary inventions of many other scientists, such as *Willem Einthoven* (1860–1927), the inventor of the electrocardiogram (ECG). The scientist whose name is pronounced daily by almost every cardiologist in the world is *Norman Jefferis Holter* (1914–1983), who brought together all previous research and merged them with the ideas of *Nikola Tesla* on the wireless transfer of energy and information. As his most famous invention, the holter ECG monitor is only one derivate of what can be termed *Holter's* technology and can be considered the biomedical part of the discipline called telemetry. Today, we use a number of devices that are fundamentally based on *Holter's* technology, e.g. implantable loop recorders or pacemaker interrogations. The technique called continuous arterial pressure monitoring is also based on *Holter's* technology, and it is an open question whether we can call this method holter blood pressure monitoring. Regardless, the implantable pulmonary artery pressure monitoring device is the result of the fundamental ideas of *Holter* and *Tesla*, and, like many other great scientists, *Jeff Holter* deserves to have his eponym – holter – used in biomedical literature and in the general history of science.

Keywords: electrocardiography, 24-hour electrocardiographic monitoring, holter monitor, 24-hour ambulatory blood pressure monitoring.

As children, the first time we saw a frog left few of us indifferent. Looking at these amphibians, some of us thought them to be beautiful creatures, while others saw them as hideous. Many of you, the current readers of this journal, were among the children that were fascinated by these amphibians. However, you were not the children elated by the perfect swimming motions of frogs, which were studied even by the ancient Egyptians, who depicted them on the walls of the Cave of Swimmers, and neither did you become film directors showing that cave in films such as *The English Patient*. Nor were you the children overjoyed at the singing of the frog choir,

which was for example better heard than seen by *Ray Charles* when composing the song *It Ain't Easy Being Green*. Instead, I believe, most of you were multit talented geniuses, but I have noticed that over time you began to increasingly deny your inherent inclination towards natural sciences and instead brag about your knowledge of French wines, Catalanian architecture, the history of Florence, or New Orleans music. Nevertheless, at heart, you were surely the kind of children that inspired the Canadian *Paul Peel* (1860–1892) to paint his famous painting “The Young Biologist” in 1891 (1), shown in *Figure 1*.

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FIGURE 1. Illustration of the painting "The Young Biologist" by Paul Peel (1860–1892) at the Art Gallery of Ontario and Luigi Galvani's experiment with the frog (1737–1798) (illustrated by Lucia Lukenda)

How was *Peel*, at the turn of the 19th century, inspired to connect frogs with biology? The answer lies in the 18th century, when the famous Italian physician, biologist, physicist, and philosopher *Luigi Galvani* (1737–1798) conducted a spectacular experiment showing that an electrical impulse can cause the contraction of the leg muscle of a decapitated frog, laying the foundations of electrophysiology (*Figure 1*) (2).

In 1860, a century after *Galvani* and the same year in which *Paul Peel* was born, *Willem Einthoven* (1860–1927) was also born in Semarang on the island of Java in what was then called the Dutch East Indies, now Indonesia. As a child, *Willem* probably also resembled the boy from *Peel's* painting, and he did indeed become a physician when he grew up. After graduating, *Willem* began research at Leiden University in the Netherlands, studying – the frog gastrocnemius muscle. He used electrodes connected to a galvanometer; a measuring instrument also based on the work of *Luigi Galvani*. However, *Einthoven* quickly transferred his focus from the frog gastrocnemius muscle to another muscle – the heart (3). The rest is history, which tells us that *Willem Einthoven* won the Nobel prize in physiology and medicine in 1924 for his discovery of the electrocardiogram.

The mid-19th century was the time when geniuses were

born, and in addition to *Peel* and *Einthoven* it also saw the birth of *Nikola Tesla* (1856–1943). While *Einthoven* worked on his electrocardiogram (ECG), the great *Tesla* was working on the wireless transfer of energy, demonstrating it to doubters in Madison Square Garden by remotely and wirelessly controlling his wooden boat, the "devil automata".

Some fifteen years after *Tesla's* achievement, in 1914, the main hero of this story, who would bring together the works of all these great scientists, was born in the city of Helena in the US state of Montana. His name was *Norman Jefferis Holter*, nicknamed "Jeff" (1914–1983). We can also imagine young *Jeff* as resembling the boy in *Peel's* painting. During his studies, the first contact *Jeff* had with science took place at the University of California, Los Angeles, as the assistant of *Dr. Lawrence Detrick*, studying – frog muscles. *Jeff* did not become a physician, but instead pursued his interest in science by graduating in physics (University of California, Los Angeles) and chemistry (University of Southern California). As a young scientist at the start of his career, *Jeff* began working in the laboratory of *Joseph A. Gengerelli* in 1939, working on the idea of stimulating the nerves and muscles of frogs without direct mechanical contact or direct electrical stimulation.

As in *Tesla's* wireless technology, *Gengerelli* wanted to

stimulate the muscles and nerves of a frog "remotely". Soon, as early as 1940, the work of *Gengerelli* and *Jeff Holter* resulted in the creation of a "devil automata" in the biological sense. They managed to cause contractions in the muscles of a frog by stimulating the nerves with changes in an electric field, without direct contact via electrodes (4). In further research on this biophysical technology, they implanted electrodes into the brain of a rat that were connected to a miniature radio receiver, studying the behavior of the rat during the emission of radio signals of different frequencies and amplitudes – remotely.

This research conducted by *Gengerelli* and *Holter* resulted in their fundamental theory and the basis of what we consider *Holter* technology today: if we can use remote stimulation to stimulate nerves and muscles, we can probably obtain some information from these structures in the same way (5). *Gengerelli* and *Jeff Holter* were then joined by another scientist, *Wilford R. Glasscock*, called "*Bill*", and they started a project that resulted in a completely new biophysical field – biomagnetics (6).

The late 1930s saw the beginning of the dark times brought about by World War Two. *Jeff* had to suspend his postgraduate studies and joined the American navy as a physicist. He became the leader of a group of 33 oceanographic engineers stationed on the Bikini atoll, where the first extensive atomic bomb tests were performed. Using newly-designed instruments weighing almost 40 tons, his group measured underwater waves and other phenomena caused by the explosion (7). While serving his country, his genius and his soul that were so inclined to natural science, biology, and medicine did not remain idle, and his work on radiation resulted in *Jeff* becoming the founder of the Society of Nuclear Medicine (8). This field, as we all know, proceeded along its own grand path, but after returning from the army in 1947 *Holter* went back to his pre-war research and continued working with his old teacher and friend, *Joseph A. Gengerelli*.

After the war, *Holter* and *Gengerelli* started working in their own laboratory, situated at the back of the family ironworks plant owned by *Jeff's* father. They subsequently moved to an abandoned old passenger terminal of the Great Northern Railway, where *Jeff* founded the *Holter* Research Foundation. The foundation initially relied on personal funds, but when his work began garnering attention in early 1952 he started receiving support from the National Institutes of Health, and later also from private donations (4). *Holter's* laboratory continued to focus on recoding the electrophysiological phenomena emitted via radio waves, mostly working with the brains of rats. We can assume that *Gengerelli* was familiar with the work of *Nikola Tesla*, but I am not sure whether *Jeff*, who was not a physician, was well-acquainted with the work of *Willem Einthoven* at the time. Ideas are often born of informal communica-

tion with educated colleagues, and *Holter's* laboratory was at one point visited by the famous cardiologist *Dr. Paul Dudley White*, who described *Einthoven's* work to *Jeff* and informed him about the burden of cardiovascular diseases and the fact that the voltage in the heart is at least ten times higher than in the brain, and thus more suitable for research (9). After *White's* visit, *Holter* and *Gengerelli* reoriented from studying the brain to re-searching the heart. After a number of experiments, the two of them once again succeed in remotely obtaining information from nerves or muscles. They thus recorded the first ECG of a man who was exercising while carrying a backpack full of electronic gear with an in-built transmitter, all of which weighed approximately 35 kilograms (*Figure 2*) (10).

The first transistor had just been developed during this period (in 1947), and at the time electronics were built on the basis of electronic vacuum tubes, so *Holter's* heavy backpack contained a number of vacuum tubes in addition to a heavy battery. As the use of transistors in practice increased, these much smaller electronic components changed the shape of *Holter's* large backpack to a small portable transmitter with an antenna, which sent signals generated from electrodes placed on the surface of the body. The next innovation was similar to what we today call a *holter* ECG monitor, with electrical signals being sent from electrodes on the surface of the body to a small portable recorder with its own power source and additional magnetic tape. The device could be carried easily and could store extensive ECG data. The first clinical application of this technology was described in 1954 (11), and *Holter* published his discovery in a review article in 1957 (12). In addition to this small recorder, *Holter* and *Glasscock* subsequently developed a device for analysis of the results which was similar to a tape recorder. Audio-Visual Superimposed ECG Presentation Methodology was the name they gave to the methodology used for reproducing and analyzing the recorded information. The discovery was published in the journal *Science* in 1961 (13). The new method could thus begin moving down the path of clinical trials and clinical application. The cooperation between *Jeff Holter* and *Dr. Eliot Corday* from the Cedars of Lebanon (now Cedars-Sinai, Los Angeles) hospital was crucial in this period. In the 1960s, *Corday* had studied heart rhythm and ECGs in heart failure and myocardial infarction (14). At the time, *Jeff Holter* was spurred to conduct further research on continuous ECG monitoring by the death of a close friend who was a surgeon by profession. His surgeon friend had suffered from attacks of weakness and occasional unclear dyspeptic and epigastric symptoms, specifically while anxiously awaiting his turn to perform surgery during morning's shift. *Holter* suggested setting up his small new monitor, a *holter* ECG, which his friend accepted. Unfortunately, immediately after the completion of the operation, wearing the device, the sur-

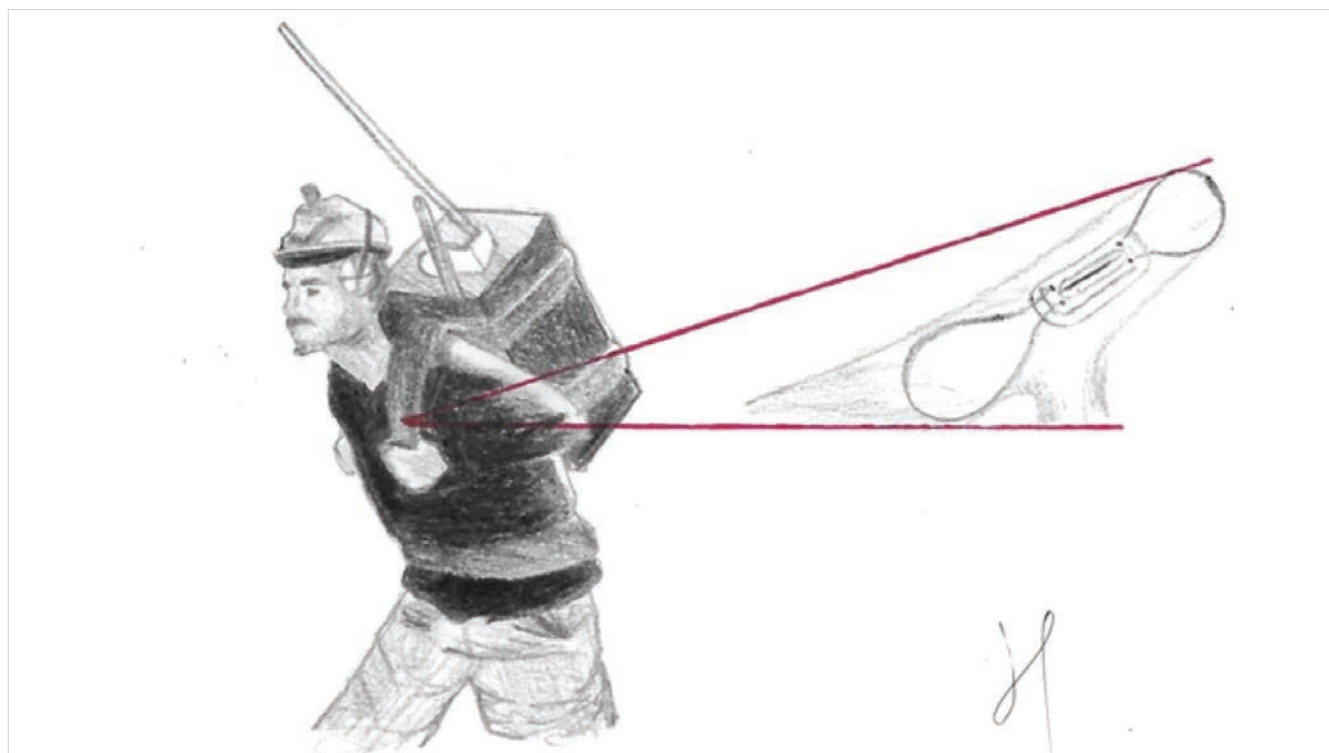


FIGURE 2. Illustration of the first human holter monitor that recorded and emitted an ECG during exercise and an implantable (remote) pulmonary arterial pressure monitor that we could perhaps call an implantable pulmonary arterial pressure holter monitor (illustrated by Lucia Lukenda)

geon suddenly passed away. When *Jeff* subsequently took the ECG results to *Corday*, it turned out that his friend had asymptomatic elevations and depressions of the ST segment, tall peaked T-waves, paroxysmal ventricular tachycardias, and finally ventricular fibrillation. After confirming the clinical significance of the device, further development of continuous ECG monitoring was taken over by the Bruce Del Mar company and the Avionics Research Products Corporation, from where this technology reached its current widespread use that was hard to imagine at the time. *Jeff Holter* and *Willem Einthoven*, the researchers who started out as the young biologists from *Peel's* painting, achieved their childhood dreams and gifted us, the readers of this journal, with the basis of our profession and prosperity, with neither of them obtaining any financial benefit, neither *Einthoven* from the ECG (except as a Nobel prize received three years before his death), nor *Holter* from the holter ECG.

After the research and development of holter ECG monitors in the USA in the 1960s, these devices arrived to Croatia in the second half of the 1970s. The first publication from this field that is known to me was a conference abstract written by *Dubravko Petrač*, *Josip Gjurović*, *Krešimir Birtić*, and *Ljubo Barić* in Split in 1983 at the "IX Joint Meeting of the Cardiological Sections of the Croatian Medical Association and the Serbian Association of Physicians" titled "Holter ECG in the Monitoring of Patients with Pacemakers". This was a time when al-

most all of the science conducted in former Yugoslavia was almost exclusively presented at national, i.e. joint conferences. Over the course of the whole of the last decade of the existence of Yugoslavia, holter ECG monitors were mentioned in Croatia only in one paper written by a group of authors from the Sisters of Mercy Clinical Hospital Centre, in a clinical observation published in the *Liječnički Vjesnik* journal in 1985, which described a series of patients with arrhythmogenic right ventricular cardiomyopathy. The authors correctly call this methods "24-hour dynamic ECG according to *Holter*" (15). After the Republic of Croatia achieved independence, the first papers were published that list their research method as holter ECG monitoring, one in a conference abstract written by our colleagues at the Zadar General Hospital, registered in the *Liječnički Vjesnik* journal in 1991 (16), and the second in 1992 in the same journal, which was a case report published by our colleagues from the Zagreb Clinical Hospital Centre (17). The first systematic study, performed on 41 patients, was published in 1993 in the Croatian medical journal *Acta Medica Croatica* (18), and the first paper reviewed in a non-Croatian journal, the *Texas Heart Institute Journal*, was published in the same year. That paper, tragically, was titled "Penetrating heart wounds repaired without cardiopulmonary bypass. Evaluation and follow-up of recent war injuries" by the authors *Čatipović-Veselica K*, *Sinčić V*, *Đurijaček J*, *Kozmar D*, *Burić D*, *Juranić B*, *Kristek J*, and *Amidžić V* (19). These painful days for Croatia, filled with inju-

ries caused by war, have been well-documented by our nation in the international scientific community (20), in particular through the founding of the Croatian Medical Journal, starting with War Supplements 1 and 2 (21), which showed the bestiality of the aggression aimed at our country. To date, authors from Croatia have published 29 articles in Medline that contain the keyword "*Holter*". Given our recent inclusion in the international scientific community as an independent country, these are results that we can be satisfied with. Of course, we have not matched achievements of Austria, but our rating is quite good in relation to other comparable countries (*Table 1*).

Today, *Holter* technology uses many computer algorithms (*al-Khwarizmi*, Iranian mathematician, astronomer, and geographer; 780–850), and we occasional write down our holter ECG results using a simple pen (*Eduard Slavoljub Penkala*; 1871–1922). These two eponyms, the algorithm and the pen, are words that stem from the generalization of the names of their inventors. *Miroslav Krleža*, the famous Croatian writer, would say of *al-Khwarizmi* and *Penkala* that they are "title-holders", while *Vjekoslav Klaić*, another famous Croatian writer, would call them "name-givers". Eponyms are thus nouns and adjectives formed from names of persons, collective nouns, names of peoples, mythological or real persons, or mythological creatures (22). Eponyms are generally written in lowercase, showing that the greatest individuals in human history become indelible parts of it when they are "humbled", losing the capitalization of their name, such as in the case of the Croatian inventor *Penkala* or of *Tesla*, whose name became the tesla, the measurement unit for magnetic induction, or like *Charles Stent*, who was the title-holder or name-giver for the stent as a medical device (23). Examining the story of *Jeff Holter* and *Joseph Gengerelli* and their ideas of registering and wirelessly transmitting biophysical signals, the technology used in cardiology today which is based on their work is what we call telemetry in Croatia, using it for monitoring patients in clinical departments. However, the word "telemetry" actually denotes a whole discipline that focuses on measuring different physical variables remotely and transmitting the measured signals by wire, radio waves, light, or mechanically. If we look back at the fundamental theory of the two scientists, which is: if we can use remote stimulation to stimulate nerves and muscles, we can probably obtain some information from these structures in the same way, we can observe a fundamental correspondence to the field of interest of the discipline called telemetry and the technology we call *Holter's* technology. Finally, we can perhaps say that telemetry is a scientific and technological discipline which in the field of biomedicine is based on *Holter's* technology, and that the technological systems which measure, transmit, and record biophysical variables can be called – holter devices.

TABLE 1. Papers published in the Medline database with the keyword "*Holter*" by authors from Croatia, Austria, and authors from some comparable countries (January 2024)

Country	Number of papers	Papers per million inhabitants
Austria	185	20.8
Slovenia	18	8.6
Croatia	29	7.6
The Czech Republic	79	7.2
Serbia	41	5.7
Hungary	37	3.7
Slovakia	21	3.6

Today, when spaceships collect samples from Mars, working according to the principles used in *Tesla's* wooden boat, different monitoring devices also record and remotely transmit information from the human body according to the principles of *Holter's* technology. For example, based on *Holter's* ideas, we now use implantable heart monitors, and the question remains whether these devices, usually called implantable loop recorders, can be called – implantable holter ECGs. Similarly, recorded heart rhythms in the memory of a cardiac pacemakers or implantable cardioverter-defibrillators (ICDs), and its subsequent analysis, interrogation, we might also call holter of electrostimulators or ICDs. Finally, the fundamental theory established by *Holter* at the start of his research defined not only the transmission and analysis of electrical impulses, but of other physical variables as well. One of the most important variables in everyday cardiological practice is blood pressure (BP), which has historically been measured since the discovery by *Stephen Hales* in 1733 (24). However, some two hundred years later, *Ayman* and *Goldshine* expressed doubts about the (prognostic) value of individual clinical BP measurements in 1940 (25). Their doubts resulted in the development of devices which measure BP continually, at multiple points during the day and night. In English, this technology is called noninvasive ambulatory blood pressure measurement (ABPM). The first of such devices was developed in San Francisco due to the efforts of *Maurice Sokolow*, whose colleagues published this discovery in 1962 (26). For some reason, *Sokolow* was not among the authors of this first article, but *Sokolow* introduced this technique to science and practice through a number of subsequent publications. It should be noted that the word "ambulatory" in the name of this technology refers not to ambulances, but denotes being adapted to walking, i.e. ambulation. Therefore, this is fundamentally *Holter's* idea of recording and transmitting biophysical variables, in this case measuring a different variable – BP. Since holter ECG monitors were historically developed much earlier, many clinicians worldwide and in Croatia called, and sometimes still call these BP measurement devices – holter blood pressure monitors. For

some reason, societies for hypertension, which are often subordinated to nephrological societies, have always resisted the name "holter blood pressure monitor". This practice was also adopted by cardiological societies, and thus the Task Force for the management of arterial hypertension of the European Society of Cardiology and European Society of Hypertension never mention the term holter blood pressure monitor in their 2018 guidelines, not even in a historical context, insisting on the term "ambulatory blood pressure monitoring" (27). This is also the case in the newest guidelines on hypertension from 2023, published by the Task Force for the management of arterial hypertension of the European Society of Hypertension, the International Society of Hypertension, and the European Renal Association (28). On the other hand, in Croatia there is an insistence on "our" syntagm "continuous arterial pressure monitoring". However, this measurement is not continuous, it is actually closer to being discontinuous, or, more precisely, intermittent, with results being shown as the mean of multiple measurements along with a number of statistical calculations. BP measurement that is truly continuous is invasive measurement of blood vessel pressures during invasive interventions or during monitoring in intensive care units, which is usually called pressure monitoring in Croatian practice. This raises the question whether ambulatory blood pressure monitoring devices could still be called holter blood pressure monitors, and in case of invasive monitoring – invasive holter blood pressure monitors. Similarly, for example, remote pulmonary artery pressure monitors could be called implantable pulmonary artery pressure holter monitors.

Ultimately, medical literature in English most commonly uses the term 24-h Holter monitor(ing), where is the term capitalized. We can ask ourselves, how is it that unlike *Charles Stent*, the name-giver of the stent, *Jefferys Holter*, has still not fully won the right to the humble uncapitalized first letter of his – holter device? It is clear that this terminology and spelling in English have not yet been fully settled, and we would also require a lexicographic study and a clear consensus to resolve these questions in Croatian language.

Finally, even this is not the end of the story of *Jeff Holter's* fundamental ideas. Let us look back on the story described at the start of this text on the electrodes implanted in the brain of rats and the subsequent remote influence exerted on animals in the laboratory. Is this not the start of the idea that has today been reified by *Elon Musk* and his *Neuralink*?

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