Od Galvanijeve žabe preko Normana Jefferisa Holtera (1914. – 1983.) do današnjega „ugradbenog holter EKG-a“

From Galvani's Frog and Norman Jefferis Holter (1914-1983) to the "Implantable Holter Monitors" of Today

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SAŽETAK: Luigi Galvani (1737. – 1798.) istraživanjem kontrakcije mišića noge dekapitirane žabe postao je utemeljitelj elektofiziologije. Njegov je rad inspirirao čak i umjetnike poput Paula Peela (1860. – 1892.), koji je 1891. godine naslikao znamenitu sliku „Mladi biolog." Na Galvanijev rad poslije se naslanjaju mnogi znanstvenici sa svojim revolucionarnim izumima, poput Willema Einthovena (1860. – 1927.) izumitelja elektrokardiograma (EKG). Znanstvenik čije ime svakodnevno izgovara gotovo svaki kardiolog na svijetu Norman Jefferis Holter (1914. – 1983.) povezao je sva prethodna istraživanja i spojio ih sa zamislima Nikole Tesle o bežičnom prijenosu energije i informacija. Holter EKG-a kao njegov najpoznatiji izum samo je jedan derivat tehnologije koju možemo nazvati Holterovom tehnologijom i smatrati je biomedicinskim dijelom discipline zvane telemetrija. Danas se koristimo nizom uređaja koji su u biti zasnovani na Holterovoj tehnologiji, primjerice ugradbeni srčani monitor ili analizu memorije srčanog elektrostimulatora ili defibrilatora. Takozvano kontinuirano mjerenje arterijskoga tlaka također je zasnovano na Holterovoj tehnologiji i ostaje pitanje možemo li tu metodu nazivati holterom tlaka. No, svakako, ugradbeni monitor plućnoga arterijskog tlaka iznjedren je iz osnova Holterova i Teslina razmišljanja tako da je poput mnogih velikana i Jeff Holter zaslužio svoj eponim – holter u biomedicinskoj literaturi i sveukupnoj povijesti znanosti.

SUMMARY: 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.

KLJUČNE RIJEČI: elektrokardiografija, 24-satno snimanje elektrokardiograma, Holter, 24-satno kontinuirano mjerenje arterijskoga tlaka.

KEYWORDS: electrocardiography, 24-hour electrocardiographic monitoring, Holter monitor, 24-hour ambulatory blood pressure monitoring.

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Kad smo se kao djeca prvi put susreli sa žabom, malotko od nas ostao je ravnodušan. Promatrajući toga vodozemca, za neke od nas bile su to prekrasne, a za druge od-

As children, the first time we saw a frog left few of us indifferent. Looking at these amphibians, some of us though them to be beautiful creatures, while others saw them as

vratne životinje. Među djecom koju je opčinio taj vodozemac bilo je i mnogo vas, sadašnjih čitatelja ovog časopisa. Međutim, niste vi bili djeca oduševljena savršenim plivačkim pokretima žaba, koje su primjerice istraživali još stari Egipćani, prikazujući to na zidovima „Špilje plivača", a niste postali ni filmski redatelji prikazujući tu špilju u filmovima poput „Engleskog pacijenta". Niste bili ni djeca primarno oduševljena pjevom barskoga žabljeg kora, koji je primjerice bolje čuo nego vidio Ray Charles, skladajući pjesmu *It Ain't Easy Being Green*. Doista vjerujem da ste većina od vas multitalentirani genijalci, ali primijetio sam da s vremenom sve više negirate svoje urođene prirodoslovne sklonosti i hvalite se poznavanjem francuskih vina, katalonske arhitekture, povijesti Firenze i glazbom New Orleansa. Ipak, u srži, vi ste, zasigurno, bili djeca kakva su inspirirala Kanađanina Paula Peela (1860. – 1892.) naslikati znamenitu sliku „Mladi biolog", 1891. godine,[1] prikazanu na **slici 1**.

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 multitalented 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, Catalonian 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**.

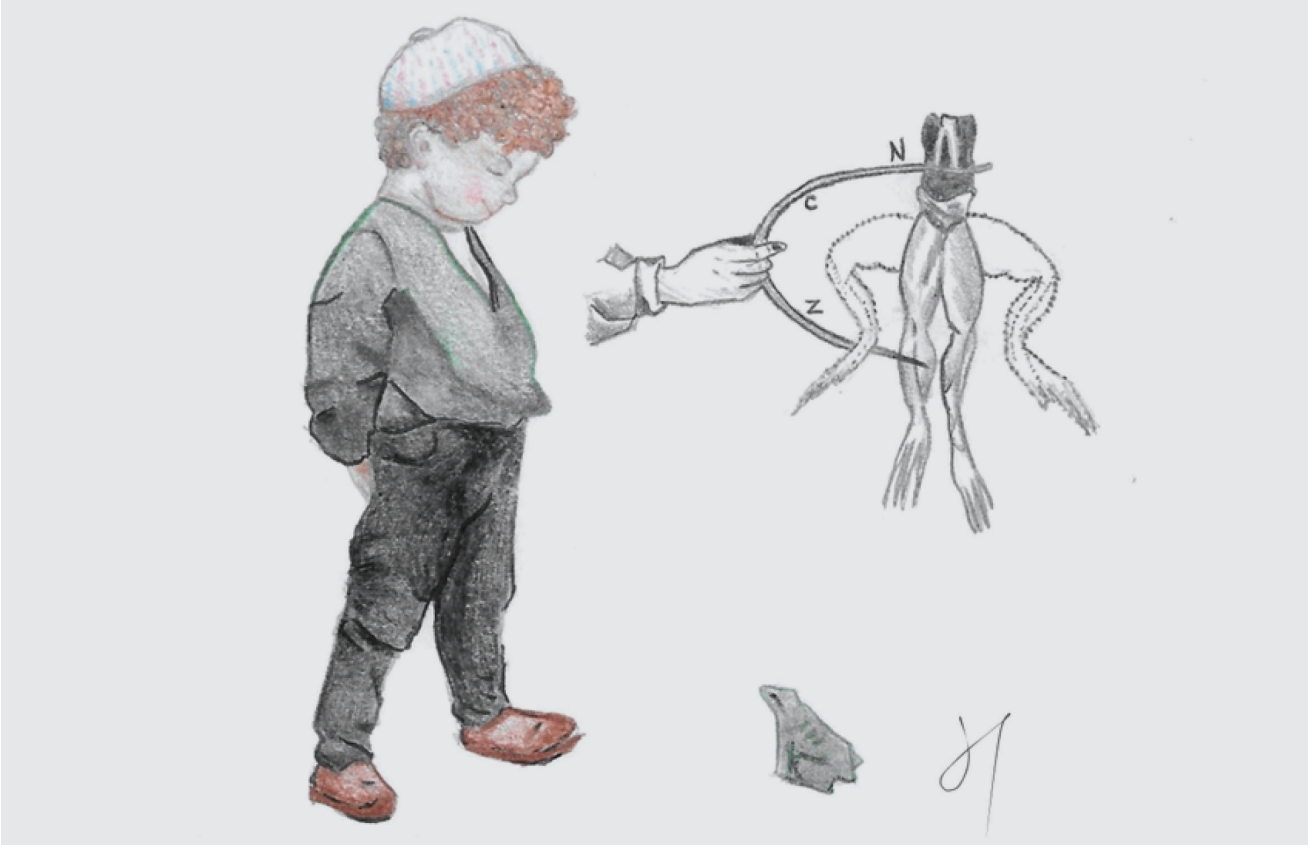

FIGURE 1. Illustration of the painting "The Young Biologist" by Paul Peel (1860-1892) at the Art Gallery of Ontario and Luigi Galvani's experiment with the frog (1737-1798) (illustrated by Lucia Lukenda).

Kako je to Peel, potkraj 19. stoljeća, bio inspiriran povezati žabu s biologijom? Tajna je skrivena u 18. stoljeću, kada je slavni talijanski liječnik, biolog, fizičar i filozof Luigi Galvani (1737. – 1798.) spektakularno pokazao kako električni impuls može izazivati kontrakciju mišića noge dekapitirane žabe, utemeljujući korijene elektrofiziologije (**slika 1**).[2]

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]

Stoljeće nakon Galvanija, iste godine kada se rodio Paul Peel, rodio se 1860. u Semarangu, na otoku Javi, tadašnjoj „Nizozemskoj Istočnoj Indiji," današnjoj Indoneziji, Willem Einthoven (1860. –1927.). Willem je u djetinjstvu vjerojatno također sličio dječačiću s Peelove slike, a, kada je odrastao, postao je liječnik. Nakon diplome započeo je Willem istraživački rad na Sveučilištu u Leidenu u Nizozemskoj, istražujući – gastroknemijus žabe. Koristio se elektrodama povezanima s galvanometrom, mjernim instrumentom ponovno zasnovanom na radu Luigija Galvanija. Međutim, Einthoven se ubrzo s gastroknemijusa žabe preusmjerio na jedan drugi mišićni organ – na srce.[3] Sve ostalo je povijest, koja kaže da je za otkriće elektrokardiograma Willem Einthoven 1924. godine dobio Nobelovu nagradu za fiziologiju i medicinu.

Sredina 19. stoljeća bilo je vrijeme rođenja genijalaca, te se tako, uz Peela i Einthovena, rodio i Nikola Tesla (1856. – 1943.). Dok se Einthoven bavio elektrokardiogramom (EKG), veliki se Tesla bavio bežičnim prijenosom energije pokazujući 1898. godine pred „nevjernim Tomama" na *Madison Square Gardenu* bežično upravljanje na daljinu svojega drvenog brodića, *devil automata*.

Petnaestak godina nakon Teslina pothvata, u mjestu Helena, u američkoj državi Montana, rodio se 1914. godine glavni junak ove priče, čovjek koji je povezao rad svih ovih velikih ljudi. Bio je to Norman Jefferis Holter, zvani Jeff (1914. – 1983.). Mladoga Jeffa također možemo zamisliti dječačićem sličnog onomu s Peelove slike. Tijekom studija prvi dodir sa znanošću imao je Jeff na *University of California*, Los Angeles, kao pomoćnik dr. Lawrencea Detricka, proučavajući – mišiće žabe. Jeff nije postao liječnik, no svoj interes za znanost realizirao je diplomirajući fiziku (*University of California*, Los Angeles) i kemiju (*University of Southern California*). Kao mladi znanstvenik, početnik, Jeff je 1939. godine započeo rad u laboratoriju Josepha A. Gengerellija na ideji stimuliranja živaca i mišića žabe bez izravnoga mehaničkog dodirivanja ili izravne električne stimulacije.

Poput Tesline bežične tehnologije, Gengerelli je želio na sličan način stimulirati mišiće i živce žabe „na daljinu." Ubrzo, već 1940. godine, Gengerelli i Jeff Holter svojim su radom opredmetili *devil automat* u biološkom smislu. Uspjeli su izazvati kontrakciju mišića žabe stimulirajući živce mijenjanjem električnog polja, bez izravna povezivanja elektrodama.[4] U daljnjim istraživanjima bežične biofizikalne tehnologije ugradili su u mozak štakora elektrode povezane s minijaturnim radioprijamnikom i proučavali ponašanje štakora tijekom emitiranja radiosignala različitih frekvencija i amplituda – na daljinu. Gengerellijeva i Holterova istraživanja rezultirala su njihovom temeljnom teorijom i osnovom onoga što danas smatramo Holterovom tehnologijom: **ako možemo stimulacijom na daljinu stimulirati živce i mišiće, tada vjerojatno možemo na isti način iz tih struktura dobiti neke informacije.**[5] Gengerelliju i Jeffu Holteru pridružio se tada još jedan znanstvenik, Wilford R. Glasscock, zvani Bill, te su započeli projekt koji je rezultirao potpuno novim biofizikalnim područjem – biomagnetizmom.[6]

Potkraj 30-ih godina 20. stoljeća započelo je mračno vrijeme 2. svjetskog rata. Jeff je morao prekinuti doktorski studij i pridružuje se američkoj mornarici, kao fizičar. Postaje voditelj grupe od 33 oceanografska inženjera na atolu Bikini, gdje su provedena prva opsežna testiranja atomske bombe. Koristeći se novodizajniranim instrumentima, koji su težili gotovo 40 tona, njegova je grupa mjerila podvodne valove i druge pojavnosti uzrokovane eksplozijom.[7] Tijekom služenja domovini njegov genij i prirodoslovno-biološka i medicinska duša nije

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,

mirovala te je njegovo bavljenje radijacijom rezultiralo činjenicom da Jeff postaje utemeljitelj *Society of Nuclear Medicine*.[8] Ta je struka, kako svi znamo, otišla svojim grandioznim putem, no Holter se povratkom iz vojske 1947. godine vratio svojim prijeratnim temama i nastavio rad sa svojim starim učiteljem i prijateljem Josephom A. Gengerellijem.

Holter i Gengerelli nakon rata započinju rad u vlastitu laboratoriju, u stražnjem dijelu obiteljske željezarije Jeffova oca. Nakon toga preseljavaju se u napuštenu staru putničku zgradu željezničke stanice *Great Northern Railway*, gdje u veljači 1947. godine Jeff osniva zakladu *Holter Research Foundation*. Zaklada se najprije oslanjala na osobna sredstva, no, kada je uočen njegov rad, početkom 1952. godine, počeo je dobivati potporu *National Institutes of Health*, a poslije i privatne donacije.[4] Holterov se laboratorij nastavio baviti zabilježbom emitiranih elektrofizioloških pojavnosti preko radijskih valova, radeći većinom na mozgu štakora. Možemo pretpostaviti da je Gengerelli poznavao rad Nikole Tesle, no nisam siguran da je Jeff, koji nije bio liječnik, u to vrijeme bio dobro upoznat s radom Willema Einthovena. Budući da se ideje često rađaju u neformalnoj komunikaciji s obaviještenim kolegama, tako je Holterov laboratorij u jednom navratu posjetio poznati kardiolog dr. Paul Dudley White i opisao Jeffu Einthovenov rad, uputio ga u raširenu prevalenciju srčanih bolesti i činjenicu da je napon struje u srcu barem deset puta veći i pogodniji za istraživanje od napona koji se bilježi u mozgu.[9] Nakon Whiteova posjeta Holter i Gengerelli preorijentirali su se s istraživanja mozga na istraživanje srce. Nakon niza pokusa njih su dvojica ponovno uspjela **iz živaca ili mišića dobiti informacije na daljinu**. Snimili su tako prvi EKG čovjeka koji je vježbao opremljen naprtnjačom punom elektroničke opreme s ugrađenim odašiljačem što je sve težilo oko 35 kilograma (**slika 2**).[10]

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 communication 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 researching 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

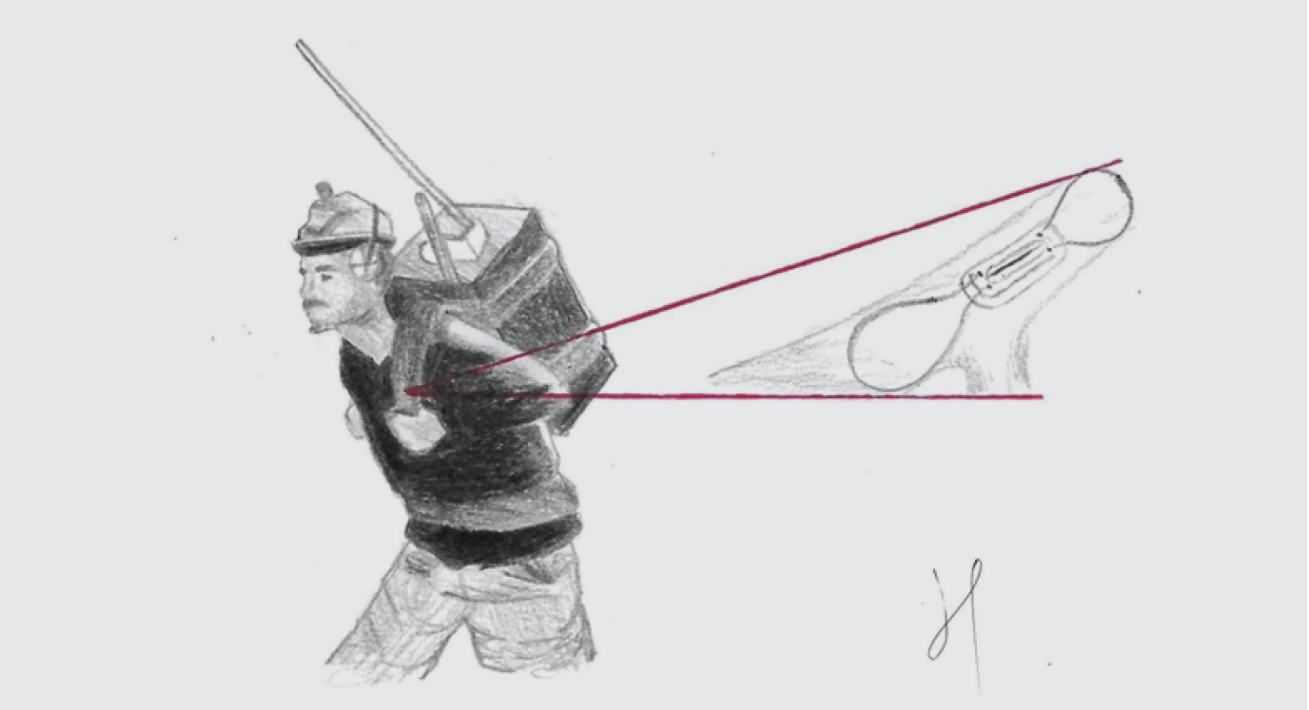

FIGURE 2. Illustration of the first human holter monitor that recorded and emitted an ECG during exercise and an implantable (remote) pulmonary arterial pressure monitor that we could perhaps call an implantable pulmonary arterial pressure holter monitor (illustrated by Lucia Lukenda).

U to vrijeme tek je izumljen prvi tranzistor (1947. god.), a elektronika se razvijala na osnovi elektroničkih cijevi pa je teška Holterova naprtnjača, uz akumulator, sadržavala niz elektroničkih vakuumskih cijevi. Kako se tranzistori počinju ubrzano primjenjivati u praksi, te mnogo manje elektroničke komponente mijenjaju oblik velike Holterove naprtnjače u mali prijenosni odašiljač s antenom, koji šalje signale generirane s elektroda smještenih na površini tijela. Sljedeća je inovacija bila slična onomu što danas nazivamo holter EKG-om, pri čemu se s elektroda na površini tijela električni signali šalju u mali prijenosni snimač s vlastitim napajanjem i dodatnom magnetnom vrpcom. Uređaj se mogao lagano nositi i snimati dugotrajne elektrokardiografske zapise. Prva klinička primjena te tehnologije opisana je 1954. godine,[11] a Holter otkriće objavljuje u preglednom članku iz 1957. godine.[12] Uz mali snimač, Holter i Glasscock razvili su nakon toga i uređaj za očitavanje nalaza koji je bio sličan magnetofonu. Metodologiju reprodukcije i analize zapisa nazvali su *Audio-Visual Superimposed ECG Presentation Methodology*. Otkriće je objavljeno u časopisu *Science* 1961. godine.[13] Nova je metoda mogla tako krenuti put kliničkih istraživanja i kliničke primjene. Ključna suradnja u tom razdoblju bila je ona Jeffa Holtera s dr. Eliotom Cordayem iz bolnice *Cedars of Lebanon* (sada *Cedars-Sinai*, Los Angeles). Corday je tijekom 60-ih godina prošloga stoljeća uz ritam srca istraživao i EKG zapise pri insuficijenciji srca i ishemiji miokarda.[14] U to vrijeme Jeff Holter snažno je na daljnja istraživanja u kontinuiranom praćenju EKG-a potaknut smrću jednoga bliskog prijatelja, po zanimanju kirurga. Naime, kolega kirurg patio je od napadaja slabosti i povremenih nejasnih dispeptičkih i epigastričnih tegoba, navlastito dok se u jutarnjim satima nervirao čekajući svoj red za operaciju. Holter mu je predložio postaviti svoj novi mali monitor, holter EKG-a, što je prijatelj i prihvatio. Nažalost, neposredno nakon dovršetka operacije, noseći uređaj, kirurg je iznenada preminuo. Kada je Jeff naknadno odnio zapis Cordayu, ispostavilo se da mu je prijatelj imao asimptomatske elevacije i depresije ST-segmenta, pojavu visokih šiljatih T-valova, paroksizme ventrikulske tahikardije i konačno fibrilaciju ventrikula. Nakon potvrde kliničke važnosti, daljnji razvoj dugotrajnog snimanja EKG-a preuzele su od Jeffa Holtera tvrtke *Bruce Del Mar* i *Avionics Research Products Corporation* preko kojih se ta tehnologija raširila do današnjih dana u neslućenim brojkama. Jeff Holter i Willi Einthoven, istraživači koji su počeli kao mladi biolozi s Peelove slike, ostvarili su svoje dječačke snove i darovali nama, čitateljima ovog časopisa, osnovu našeg posla i prosperiteta a da pri tome nijedan od njih nije imao financijske koristi, ni Einthoven od EKG-a (osim Nobelove nagrade, tri godine prije smrti) ni Holter od holtera.

Nakon istraživanja i razvoja holter EKG-a u SAD-u 60-ih godina 20. stoljeća stigli su ti uređaji u drugoj polovici 70-ih godina i u Hrvatsku. Prvi meni poznati rad iz tog područja prikazali su kao kongresni sažetak Dubravko Petrač, Josip Gjurović, Krešimir Birtić i Ljubo Barić u Splitu 1983. godine na „IX. zajedničkom sastanku kardioloških sekcija Zbora liječnika Hrvatske i Srpskog lekarskog društva" pod naslovom: „Holter EKG u praćenju bolesnika s elektrostimulatorom srca". Bilo je to vrijeme kada se gotovo sva jugoslavenska znanost prikazivala gotovo isključivo na domaćim, tzv. zajedničkim sastancima. Tijekom cijeloga zadnjeg desetljeća postojanja Jugoslavije, u Hrvatskoj se samo u jednom publiciranom radu grupe autora iz Kliničkog bolničkog centra Sestre milosrdnice spominje holter EKG-a, u kliničkom zapažanju objavljenom ECG of a man who was exercising while carrying a backpack full of electronic gear with an inbuilt 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 surgeon 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 As-

u „Liječničkom Vjesniku“ 1985. godine, opisujući niz bolesnika s aritmogenom kardiopatijom desnog ventrikula. Autori metodu ispravno nazivaju: „24-satni dinamički EKG po Holteru“.[15] Nakon osamostaljenja Republike Hrvatske objavljuju se prvi radovi koji kao metodu istraživanja navode snimanje holter EKG-a, jedan u kongresnom sažetku kolega iz Opće bolnice Zadar, registriranog u „Liječničkom Vjesniku“ 1991. godine,[16] te drugi 1992. godine u istom časopisu u prikazu slučaja kolega iz Kliničkog bolničkog centra Zagreb.[17] Prvo objavljeno sustavno istraživanje na 41 bolesniku nalazimo 1993. godine u domaćem časopisu *Acta Medica Croatica*,[18] a iste godine i prvi rad recenziran u inozemnom časopisu, u *Texas Heart Institute Journalu*. Taj rad, nažalost, nosio je naslov: *Penetrating heart wounds repaired without cardiopulmonary bypass. Evaluation and follow-up of recent war injuries*, autora: Čatipović-Veselica K, Sinčić V, Đurijaček J, Kozmar D, Burić D, Juranić B, Kristek J i Amidžić V.[19] Te bolne dane, pune ratnih ozljeda, kao država dobro smo dokumentirali u svjetskoj znanosti,[20] navlastito pokrenuvši *Croatian Medical Journal*, počevši s War supplementima 1 i 2,[21] pokazujući svu bestijalnost agresije na našu zemlju. Do sada su autori iz Hrvatske objavili u Medlineu 29 članaka s ključnom riječi „holter“. Nakon samostalnog uključivanja u međunarodnu zajednicu možemo biti zadovoljni rezultatima. Naravno, nismo dosegnuli postignuća Austrije, ali stojimo sasvim dobro gledajući druge usporedive zemlje (**tablica 1**).

sociation of Physicians” titled “Holter ECG in the Monitoring of Patients with Pacemakers”. This was a time when almost 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 injuries 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 in relation to other comparable countries (**Table 1**).

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

Holterova tehnologija danas puna je kompjutorskih algoritama (al-Khwarizmi, iranski matematičar, astronom i geograf; 780. – 850. god.), a mi naše nalaze holter EKG-a povremeno napišemo običnom penkalom (Eduard Slavoljub Penkala; 1871. – 1922.). Ova dva eponima, algoritam i penkala, riječi su nastale poopćavanjem vlastitih imena. Miroslav Krleža al-Khwarizmija i Penkalu nazvao bi „naslovnicima“, a Vjekoslav Klaić nazvao bi ih „imenodavcima“, Dakle, eponimi su imenice i pridjevi nastali od vlastitih imena, zajedničkih imenica, naroda, mitoloških i stvarnih osoba ili mitoloških životinja.[22] Eponimi se pišu malim početnim slovom, pokazujući da najveći ljudi iz povijesti ljudskog roda postaju trajno upamćeni kada „postanu ponizni“ i izgube veliko početno slovo svoga imena, poput našeg Penkale ili Tesle koji je prešao u teslu, jedinicu magnetske indukcije ili poput Charlesa Stenta koji je

bio naslovnik ili imenodavac za stent, hrvatski rečeno, žilnu proširnicu.[23]

Kada razmatramo priču o Jeffu Holteru i Josephu Gengerelliju i njihovim idejama registriranja i bežičnog prijenosa biofizikalnih signala, današnja tehnologija u kardiologiji koja je zasnovana na njihovu radu jest ona koju u Hrvatskoj nazivamo telemetrijom i koristimo se njome za praćenje bolesnika na kliničkim odjelima. Međutim, riječ telemetrija zapravo označuje cijelu jednu disciplinu koja se bavi mjerenjem različitih fizikalnih veličina na udaljenosti te prijenosom izmjerenih signala žičanim, radijskim, svjetlosnim ili mehaničkim putem. Ako se vratimo na temeljnu teoriju dvojice znanstvenika koja glasi: **ako možemo stimulacijom na daljinu stimulirati živce i mišiće, tada vjerojatno možemo iz tih struktura dobiti neke informacije na isti način,** uočava se temeljno suglasje u djelokrugu zanimanja discipline zvane telemetrija i tehnologije koju nazivamo Holterovom tehnologijom. Konačno, možda možemo reći da je telemetrija znanstveno-tehnološka disciplina koja se u području biomedicine zasniva na Holterovoj tehnologiji, a tehnološki sustavi koji mjere, prenose i bilježe biofizikalne veličine mogu se nazvati – holterima.

Danas, kada svemirski brodovi skupljaju uzorke s Marsa, radeći pri tome po principima Teslina drvenog brodića, iz ljudskog organizma različiti monitori bilježe i na daljinu prenose informacije po principima Holterove tehnologije. Primjerice, temeljeno na Holterovoj zamisli danas se koristimo ugradbenim srčanim monitorom, te ostaje pitanje možemo li ovu napravu nazvati – ugradbenim holterom EKG-a. Slično tomu, zabilježeni ritam u memoriji srčanog elektrostimulatora ili defibrilatora, čiju kasniju analizu ili raščlambu ružno nazivamo „interrogacijom", možda možemo nazvati holterom elektrostimulatora.

Konačno, osnovna Holterova teorija na početku njegova rada nije definirala prijenos i analizu samo električnih impulsa nego i drugih fizikalnih veličina. Jedna od važnih veličina u našoj svakodnevnoj praksi jest i arterijski tlak (AT), koji se u povijesti mjeri još od otkrića Stephena Halesa 1733. godine.[24] Međutim, dvjestotinjak godina poslije sumnju u (prognostičku) vrijednost pojedinačnih ambulantnih mjerenja AT-a izrazili su 1940. godine Ayman i Goldshine.[25] Njihova je sumnja rezultirala razvojem uređaja koji mjeri AT u nizu navrata, tijekom dana i noći. Na engleskom jeziku ta je tehnologija nazvana *noninvasive ambulatory blood pressure measurement* (*ABPM*). Prvi takav uređaj pojavljuje se u San Franciscu zaslugom Mauricea Sokolowa, čiji kolege 1962. godine prvi objavljuju to otkriće.[26] Zbog nekog razloga Sokolow nije među autorima prvoga izvornog članka, ali nizom kasnijih radova Sokolow uvodi tu tehniku u znanost i u praksu. Moramo znati da engleska riječ *ambulatory* ovdje ne znači „ambulatni", nego onaj koji je prilagođen hodanju, pokretu – „ambulaciji". Dakle, temeljno riječ je o Holterovoj zamisli prijenosa i bilježenja biofizikalnih veličina, samo se u ovom slučaju radi o drugoj veličini – o AT-u. Budući da se holter EKG-a povijesno razvio ranije, mnogi kliničari u svijetu i u nas mjerenje AT-a na ovaj način nazivali su, a neki ga i danas nazivaju – holterom tlaka. Zbog nekog razloga hipertenziološka društva, koja su uglavnom pod kapom nefroloških društava, uvijek su se opirala nazivu holter tlaka. Tu praksu prihvatila su i kardiološka društva te tako Radna skupina za liječenje arterijske hipertenzije Europskoga kardiološkog društva i Europskoga društva za hipertenziju u svojim smjernicama 2018. godine nijednom riječju ne spominju pojam holter tlaka, čak ni u povijesnom

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", loosing 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.

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 meas-

kontekstu, inzistirajući na pojmu *ambulatory blood pressure monitoring*.[27] Isto nalazimo i u najnovijim smjernicama za hipertenziju iz 2023. godine, ovoga puta od Radne skupine za liječenje arterijske hipertenzije Europskog društva za hipertenziju i Međunarodnog društva za hipertenziju te Europske udruge za bolesti bubrega.[28] Slijedom toga, u Hrvatskoj se inzistira na „našoj" sintagmi kontinuirano mjerenje arterijskoga tlaka (KMAT). No to mjerenje nije kontinuirano, u biti je više diskontinuirano, preciznije rečeno, ono je intermitentno, a rezultati se prikazuju kao srednja vrijednost višestrukih mjerenja uz niz statističkih izračuna. S druge strane, mjerenje AT-a koje je uistinu kontinuirano, invazivno je mjerenje žilnih tlakova tijekom invazivnih intervencija ili praćenja u jedinicama intenzivne skrbi, koje u praksi najčešće nazivamo monitoringom tlaka. Nameće se pitanje možemo li ipak za KMAT rabiti termin holter tlaka, a u slučaju invazivnog mjerenja – invazivni holter tlaka. Slijedom toga, primjerice, ugradbeni (daljinski) mjerač plućnoga arterijskog tlaka mogao bi se nazivati ugradbenim holterom plućnoga arterijskog tlaka.

U konačnici, u engleskoj literaturi za 24-satni holter EKG-a najčešće nalazimo pojam: *24-h Holter monitor(ing)*. Možemo se zapitati kako to da se, za razliku od Charlesa Stenta, imenodavca žilne proširnice – stenta, Norman Jefferis Holter još nije potpuno izborio za ponizno prvo malo slovo svojega – holtera. Vidimo da se niti u anglosaskoj literaturi pojmovi i pravopis još nisu ustalili, a o navedenim dvojbama i nama bi trebalo jedno leksičko istraživanje i konačno suglasje ili konsenzus.

Na kraju, ni ovdje priča o temeljnim idejama Jeffa Holtera ne prestaje. Prisjetimo se priče s početka ovoga teksta o implantiranim elektrodama u mozgu štakora i bežičnom utjecaju na ponašanje laboratorijske životinje. Nije li to bio početak ideje koju ovih dana opredmećuje Elon Musk i njegov Neuralink?

urement (ABPM). The first of such devices was developed in San Franciso 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, Jefferis 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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