

Feasibility Study on Subcutaneously Implanted Devices in Male Rodents for Cardiovascular Assessment Through Near-Field Communication Interface

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Monitoring of intrabody cardiovascular parameters can benefit from implantation of miniature devices close to anatomical targets, thereby surpassing signal attenuation problems related to the propagation toward body surface while allowing localized sensing at the target site with higher precision. With proper electronic miniaturization, packaging, robustness, and power consumption reduction, such devices can harvest enough energy from the surrounding environment for proper operation. Herein, a near-field communication (NFC)-powered implantable device with acquisition channels for electrocardiogram, arterial pulse, and temperature measurements is introduced. It has been successfully deployed inside rodents for a 72-h trial period to assess external powering and data communication in living animals. Experimental results obtained by this device demonstrate the potential for providing more reliable diagnostic information than that of external wearable devices.

(EMG), or electrooculogram (EOG)), pulse oximetry, or acoustic measurements.^[2,3] In addition, access to body fluids in their natural state inside cavities (cerebral ventricles, heart, urinary bladder, interstitial, and peritoneal spaces)^[4] or circulation (cardiovascular and lymphatic systems) allows to produce more accurate estimates for the concentration of specific biochemical markers relative to the quantities expelled through body sweat, urine, saliva, or blood extravasation.^[5–7] However, in vivo environment by itself imposes a hostile medium to internal device implantation,^[8] namely, in what concerns the biocompatibility of the device, dimensions, mobility within the body, or elution,^[9–11] and energy supply. Successful implantable devices such as pacemakers and neurostimulators rely on

1. Introduction

Implantable devices are natural substitutes for wearable monitoring platforms currently in use today.^[1] Intrabody monitoring offers a direct connection to the body at the cellular and tissue levels that has no precedent in wearable technology. Monitoring at the target anatomical site involves lesser signal attenuation resulting from signal propagation to the exterior of the body, as in conventional biopotential recordings (e.g., electrocardiogram (ECG), electroencephalogram (EEG), electromyogram

batteries as the main source of energy that require scheduled replacement by surgery or lengthy recharging cycles, the latter involving patient immobilization to allow efficient transcutaneous energy transfer. Semi-implantable solutions use either tethered instrumentation^[12,13] or ingestible capsules^[14] inserted through natural or surgically created access points to the interior of the body to provide those power and communication links as required for deep tissue sensing and stimulation.

Over the years, several energy harvesting mechanisms have been developed to power up active implantable devices, that is, devices with continuous acquisition and transmission of biosignals or actuation in the physiological medium, stimulation,^[15,16] and drug delivery.^[17] Without battery supplies, these devices need to rely on the conversion of energy to an equivalent DC level, including on-body pyroelectric,^[18] piezoelectric,^[19] triboelectric,^[20,21] and chemical harvesters^[22] or off-body radiative fields in the form of radiofrequency (RF), magnetic^[23] and ultrasonic waves.^[24,25] Although recent developments in material sciences and new fabrication processes have already produced some efficient harvesters, energy demands posed by active devices still need to be met. In the case of passive devices or sensors,^[26] the intrabody indices to be measured are usually transmitted on the back-scattered signal of the incident radiative wave. However, in addition to the limitation on the number of quantities that can be conveyed through this signal at any given time, the positioning of the passive implant relative to the external receiver influences the detected profile, up to a point where signal characteristics carrying the target indices are effectively masked. Correct tuning and compensation for all path losses during transmission is therefore

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essential to guarantee successful reception, in contrast to active approaches that use the harvested voltage to transmit signals through standard communication protocols in RF, magnetic, or ultrasonic transmissions, while being more resilient to external influence and interference.

The near-field communication (NFC) interface found in many wireless platforms for contactless payments can also be used to power up small implantable devices located at the superficial tissues of the human body. As the body is a harsh environment for propagation of RF waves, external sources need to produce significant power strength to penetrate deep inside the body and within safe exposure standards to radiation.^[27] The maximum output power allowed for the different RF bands is well established and varies from 21 dBm (or, equivalently, 125 mW) for the UMTS/3 G network, 20 dBm (100 mW) for the 2.4 GHz Wi-Fi/ISM band, 4 dBm (2.5 mW) for Bluetooth Classic, and less than 3 dBm (2 mW) for NFC. This makes NFC safer than the other wireless standards when dealing with biological tissues, although the transmission distance is greatly reduced to a few centimeters, enough to reach the subcutaneous and superficial muscular tissues of humans or deeper tissues inside rodents. The subcutaneous tissue contains rich blood and lymphatic supplies, glands, nerves, fat, and other structures that can carry information in the form of biosignals relative to the physiological or pathological states of in vivo structures. In fact, monitoring of physiological signals at the subcutaneous level offers many advantages in comparison with body surface monitoring as previously mentioned, the least of all regarding the protection of the implantable device itself and operation inside a saline medium.^[28] Some studies on implantable devices go even further to plant the device at the subcutaneous level to facilitate external powering and data transfer, from which exploring electrodes or other devices^[23] penetrate deeper inside the body for sensing and stimulation.

New technologies for cardiovascular monitoring are still important for mitigating the effect of cardiac-related diseases, which represent the leading causes of death worldwide. Conventional diagnostic methods involve electrocardiographic monitoring (heart rate and related metrics), cardiovascular imaging, hemodynamic studies (echocardiography and heart sounds), arterial pressure measurements,^[29] and oxygen level estimation at the periphery of the body performed in horizontal bed tests, tilt tests, or exercise.^[30,31] Though some of these tests can capture the pathological condition under investigation, in many cases transient abnormalities remain elusive, therefore the need for continuous monitoring of cardiovascular parameters in the context of normal daily routines. In addition, other complications affecting the nervous, endocrine, immune, or respiratory systems produce alterations to some cardiovascular parameters needing to be monitored closely in the longer term, as well as in situations involving tissue trauma, inflammation, or infection resulting from accidental body injuries, wound healing processes, or medical intervention.

In this article, we study the feasibility of implanting cardiovascular monitoring devices on a rodent model with power and data telemetry links provided by the NFC interface of a mobile phone for a trial period lasting 72 h, as shown in **Figure 1a,b**. Operational parameters such as efficiency of NFC powering and data transmission from within the animals and integrity of such signals are evaluated, as well as mechanical parameters

related to the structural robustness of the device and biocompatibility with the surrounding tissues at the implanted sites. Rodents by themselves constitute the lowest sentient animals supplying relevant physiological data for translation of the implantable technology to humans in future applications.^[32] This work demonstrates the use of Internet-of-Things platforms for intrabody physiological monitoring, therefore facilitating collection and dissemination of medical data for population at large, particularly those elderly with identified chronic diseases. With on-demand and local monitoring of patients at the comfort of home during the recovery period following surgery (or device implantation) allows to alleviate both hospitalization time and postoperative care resources, which is particularly meaningful during periods of lockdown due to pandemics.

2. Results

The proposed implantable device is shown in **Figure 1c**, whose electronic components responsible for the interface with the biological tissues are assembled on a different board layer (bottom) relative to the control and communication (on top). An additional layer of transparent elastomer covers the entire device for mechanical stability and biocompatibility with the animal tissues. More technical details about embedded electronics and device packaging can be found in Section 4.1 and 4.2. Implantation of the devices on the rodents took place inside a controlled trial experiment, with subcutaneous deployment of two equivalent devices on opposite sides of the dorsal region of the animals through surgery. **Figure 1d** shows the location of one such device taken during the explantation surgery performed approximately 72 h after initial implantation, wherein normal tissue formation has occurred after the closure of the surgical site as the image attests. During the 72 h trial period, NFC readings were collected with a mobile phone by a swiping movement performed along the dorsal surface of the rodents while remaining inside the cage, without immobilization medication administered to the animals. Additional NFC readings were collected during the two surgical interventions at the beginning (implantation) and end (explantation) of the trial. More details about the trial protocol followed by this study are provided in Section 4.5, whereas **Figure 1e–g** shows some snippets of the physiological signals captured by the mobile phone's app during a reading process, namely, ECG, arterial pulse, and temperature. Assessment of the signal quality for ECG and arterial pulse reveals a signal-to-noise ratio of 26.4 and 28.7 dB, respectively, enough to discriminate the main events contained within these signals, namely, the QRS complex and dicrotic notch. The requirement for high acquisition rates for ECG and pulse in rodents has led to the recording of these signals within segments that are 1 s long, thus achieving an equivalent update time in terms of app's visualization and data storage inside the phone. For human experimentation, the acquisition rate can be decreased to allow larger temporal windows necessary for more accurate estimation of the heart and pulse rates (HR and PR, respectively), other than relying in the interval separation between main wave peaks (or events) detected in the raw signals as performed in the current study.

Regarding the animal trial, **Figure 2a** shows the evolution on the number of devices remaining functional during the 72 h

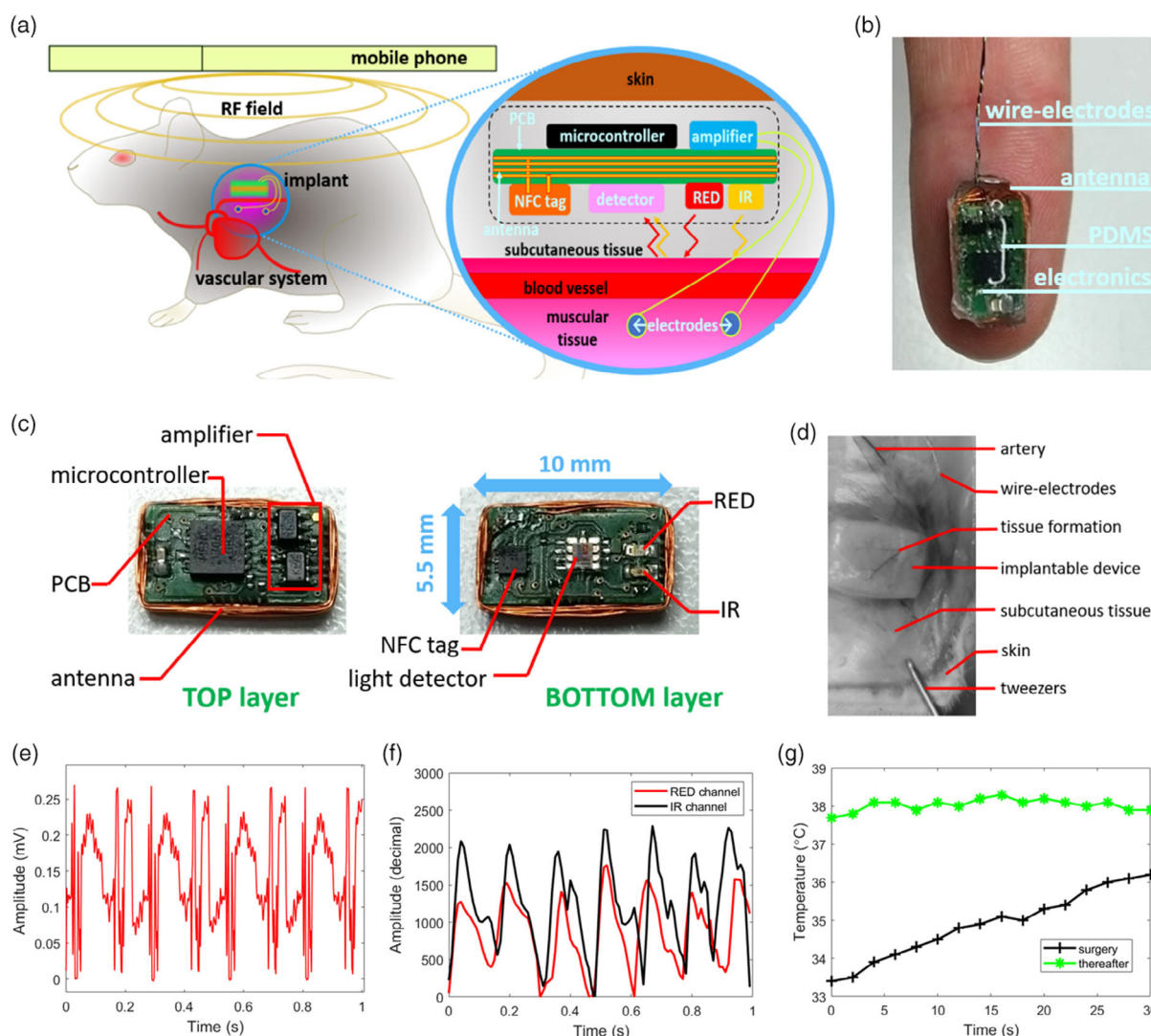


Figure 1. Implantable device developed for cardiovascular assessment inside rodents. a) Contextualization image for device implantation inside a rodent at the subcutaneous level, with wireless transmission of power and data from an external mobile phone, and main device components exhibited inside the image inset: microcontroller unit, amplifier for biopotential detection (wire-electrodes), RED and infrared (IR) light sources, and respective light detector. b) Real dimensions of the implantable device, with protection provided by polydimethylsiloxane (PDMS) material and connection to the wire-electrodes for biopotential detection. c) Top and bottom layers composing the printed circuit board (PCB) of the implantable device with main electronic components highlighted. d) Implantation site located within the subcutaneous tissue of the rodent revealed after the explantation surgery. e) Real-time electrocardiogram signal recorded from the rodent. f) Arterial pulse snippet for the RED and IR channels obtained by the implantable device. g) Temperature signal recorded during the surgical intervention for device implantation and initial period thereafter for the same animal, by stacking together several NFC data readings.

period. A total of 15 NFC data readings were performed after implantation surgery, followed by a final reading taken during device extraction. For each reading maneuver, devices were considered functional if the NFC data packet was successfully received within five swipe attempts performed with the phone. From all the uncorrupted data snippets recorded, posterior calculation of HR variation along the trial allowed to obtain the graph of Figure 2b, in terms of the average rate detected amongst rodents (with functional devices only), together with the estimated average temperature. By its turn, Figure 2c shows the variation of PR (in average) and respective oxygen saturation rate (SpO_2). For this latter parameter, the RED and IR

light signals detected by the implantable device were used to obtain an estimation of the SpO_2 based on the main wave components, as described in Section 4.3. Quantitatively, mean values of 478 ± 32 bpm, 446 ± 43 ppm, $97 \pm 2\%$, and $38 \pm 0.5^\circ\text{C}$ were recorded, respectively, for the heart rate, pulse, oxygen saturation level, and temperature for the trial period between surgeries, whereas during interventions, HR and PR increased to mean values of 652 ± 20 bpm and 603 ± 25 ppm, with temperature and SpO_2 decreasing to $35 \pm 0.5^\circ\text{C}$ and $84 \pm 3\%$, respectively.

The fluctuations between the estimated values for each signal modality (ΔM) originating at the two implant sites (left and right)

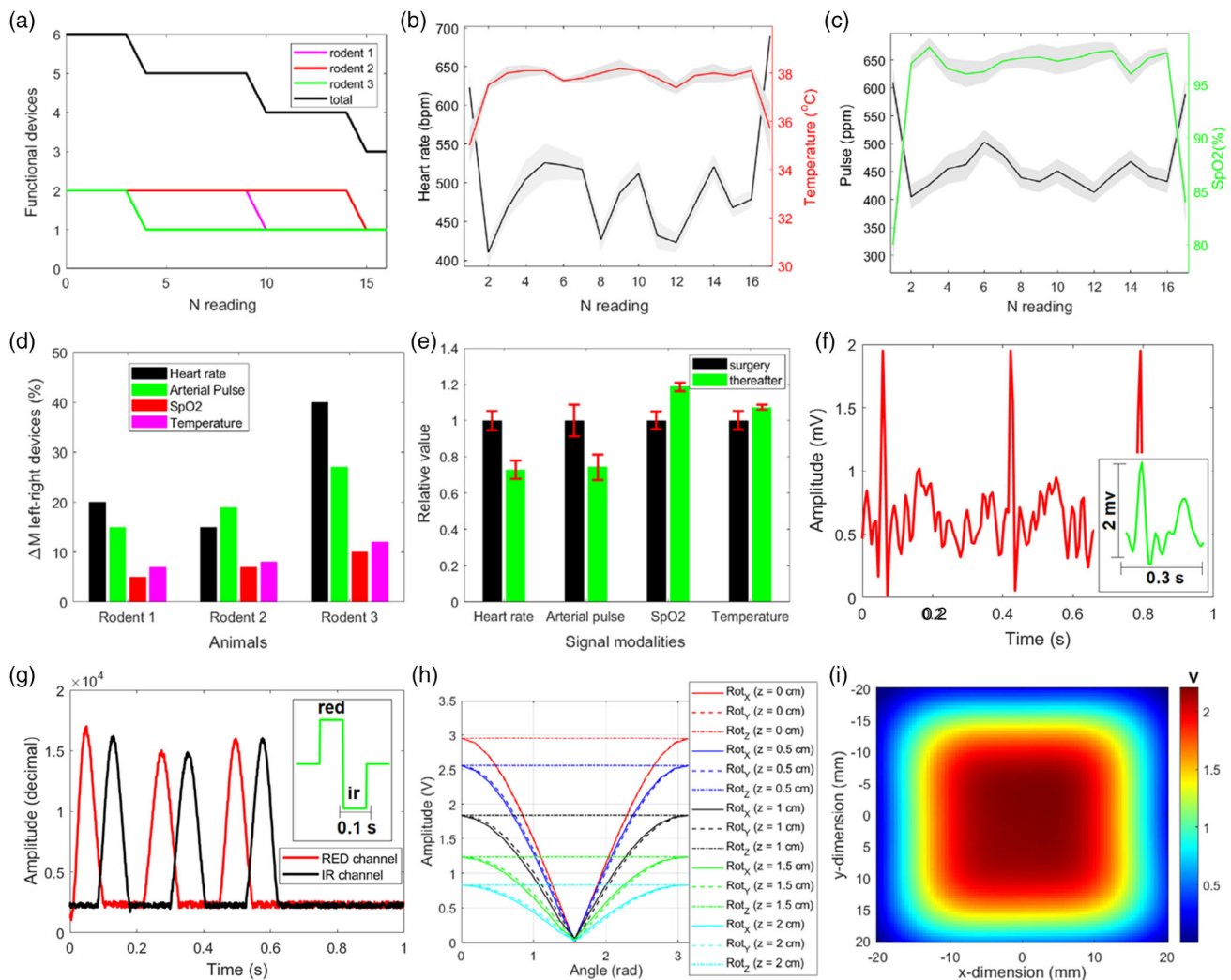


Figure 2. Results obtained during the animal trial period and posterior analysis. a) Evaluation of the functional implantable devices along the trial as detected by NFC readings. b) Average heart rate (left axis) and temperature (right axis) values calculated among the trial rodents, with respective standard deviation (shadow margins). c) Similar graph showing the calculated average pulse rate (left axis) and SpO₂ (right axis). d) Variation of the calculated value for each signal modality tested (ΔM) originating at the two implanted sites (left and right) in each rodent. e) Variation of the average value for the signal modalities during the 72 h trial period (thereafter) in relation to the average values obtained during surgery, and respective error bars. f) Biopotential recording obtained by a functional device retrieved from one rodent at the end of the trial and using as input a synthetic ECG-like signal (in the inset). g) Photodetector signals obtained for the same circumstances when excited by bipolar light pulses (in the inset) driving simultaneously the RED and IR emitters. h) Harvested voltage level calculated as a function of the distance (in z-direction) between the transmission (mobile phone) and reception (implantable device) antennas when both are aligned along the transmission axis, contemplating also possible scenarios for different rotation angles of the transmission antenna in the three Cartesian axes (Rot_x , Rot_y , and Rot_z). i) Harvested voltage profile calculated along a parallel plane to the transmission path with 7.5 mm gap from the implantable device.

in the dorsum region are shown in Figure 2d, which reveals higher variations for the heart and pulse rates, especially in rodent 3 with less functional devices observed during the trial. In other perspective, the variation of the average value calculated for each modality in the recovery period is shown by the bar plot of Figure 2e in relation to the average values calculated during surgeries (rationale of 1), exhibiting a positive shift for SpO₂ and temperature in contrast with HR and PR. Regarding the considerable standard deviations obtained for the latter parameters, they may be related to the incorrect positioning of the

ECG electrodes and photodetector over the target tissues, contributing to wave distortions of the main events carried by these signals and used in the estimation of cardiovascular indices.

From a posteriori visual inspection of the encapsulation protecting the devices (Figure 4f,g from Experimental Section), no significant cracks or notches were detected at the microscopic level, revealing that the proposed encapsulation remained intact at least for a period of 72 h. Further immersion on sterilized solution of the functional devices retrieved from the rodents showed

absence of any liquid leakage toward the embedded electronics, allowing additional tests to be performed to assess the operation of the acquisition channels postexplantation and using as inputs synthetic ECG-like signals for the biopotential acquisition

channel (Figure 2f) and bipolar light pulses for the photodetector channel (Figure 2g), both imposed by a waveform generator (DSOX2024X, Agilent Technologies, USA). In what concerns visual inspection of the implanted site areas at the dorsum of

Table 1. Comparison table in terms of performance metrics and characteristics for implantable devices published in the literature and the current study.

Power source	Ref.	[Year]	Application	Harvested power	Frequency	Data link	Range [mm]	Target site
Electrochemical	[22]	2012	Cochlear implant powered by chemical gradient	1.1–6.3 nW	2.4 GHz	–	–	Guinea pig (ear)
Ultrasounds	[23]	2012	Power delivery to analogue sensors	29 μ W	500 kHz	Ultrasonic pulse (220 bps)	70	Agar solution
Photovoltaic	[35]	2014	Temperature biosensing	27 μ W	–	Optical LED ^{a)} (16 kbps)	4.7	Pig (subcutaneous tissue)
RF ^{b)}	[36]	2014	Neural data collection	513 μ W	2.4 GHz (RX ^{c)} 5.2 GHz (TX ^{d)}	OOK ^{e)}	30	Saline solution
Thermoelectric	[37]	2015	ECG ^{f)} monitoring	60 μ W	–	OOK (38.4 kbps)	0	Human chest
RF	[38]	2015	Near-field data and power transmission	42 mW	13.56 MHz	PDM ^{g)} (13.56 Mbps)	10	Air
Ultrasounds/RF	[39]	2015	Hybrid bidirectional RF and US ^{h)} link	100 μ W	1 MHz (USA) 4 GHz (RF)	Ultrasonic pulse ($\approx$ kbps)	30	Chicken meat
Ultrasounds	[25]	2016	Electromyogram and neurogram recordings (neural dust)	0.12 mW	1.5 MHz	LSK ⁱ⁾ (0.5 Mbps)	8.8	Mice (nervous system)
Inductive	[40]	2017	Bone plate strain monitoring	–	200 Hz	Magnetic resonance	60	Goat (tibia)
RF	[41]	2017	Wireless strain monitoring	–	600 MHz	RF resonance	0.5–3	Air
Inductive	[42]	2018	Temperature sensor for orthopedic implant	–	27 MHz	Magnetic resonance	10	Porcine fore shank
Ultrasounds	[43]	2018	Peripheral nerve stimulation	3 mW	1.3 MHz	PWM ^{j)} ASK ^{k)} (11 kbps)	105	Mice (nervous system)
Ultrasounds	[16]	2019	Photodynamic stimulation to tumors	108–171 μ W	720 kHz	–	30	Mice (interstitial space)
Ultrasounds	[44]	2019	Neural recording	38 μ W	1.78 MHz	Echo modulation (7 kS s ^{−1})	50	Tissue phantom (model)
RF	[45]	2019	Microcracks detection in orthopedic implants	–	915 MHz	UHF ^{l)} RFID ^{m)}	700	Human hip implant
Inductive	[46]	2019	Monitoring of bone growth and strain	–	10–14 MHz	RF resonance	–	Human femur implant
Inductive	[47]	2019	Micromotion detection in orthopedic implants	–	10 MHz	Magnetic resonance	3.15–5.1	Tibial implant (model)
Inductive	[48]	2019	Force monitoring of artificial bone	–	200 Hz	Magnetic resonance	60	Human tibia
Ultrasounds	[49]	2020	Stimulation and physiological recording. In-tissue EIT ⁿ⁾ imaging	110 μ W	400 kHz	OOK (240 bps)	30	Breast phantom (model)
Ultrasounds	[33]	2020	Neural stimulation (stimDust)	89 μ W	1.85 MHz	AM ^{o)} backscatter (bitstream)	70 (in vitro) 18 (in vivo)	Mice (sciatic nerve)
Ultrasounds	[50]	2020	Deep tissue oxygen monitoring	140 μ W	2 MHz	AM backscatter pulses (10-bit/15 μ s)	50	Muscle tissue-like phantom
Ultrasounds	[34]	2021	Soft tissue pH and lactate monitoring	10 μ W	420 kHz	FSK ^{p)} (50–350 Hz)	50	Breast phantom (model)
RF	This work	2021	Cardiovascular monitoring (ECG, pulse, oxygen, and temperature)	0.9 mW	13.56 MHz	NFC ^{q)} (106 kbps)	10	Rodent (subcutaneous tissue)

^{a)}Light-emitting diode ^{b)}Radio frequency ^{c)}Receiver ^{d)}Transmitter ^{e)}On–off keying ^{f)}Electrocardiogram ^{g)}Pulse delay modulation ^{h)}Ultrasounds ⁱ⁾Load shift keying ^{j)}Pulse width modulation ^{k)}Amplitude shift keying ^{l)}Ultrahigh frequency ^{m)}Radio frequency identification ⁿ⁾Electrical impedance tomography ^{o)}Amplitude modulation ^{p)}Frequency shift keying ^{q)}Near-field communication.

the animals (Figure 1d), no abnormal tissue formation or any structural and morphological changes were observed during the explantation surgery suggesting severe foreign body response against the devices, instead new capillaries were formed over the protective encapsulation layer in addition to normal subcutaneous tissue.

Finally and due to the impossibility of testing the full harvesting capability of the implantable device at different tissue depths inside the animals, mathematical simulations for the harvested voltage profile with distance were performed and encompassing the relative small gap distance between device implantation and external mobile phone, thus obtaining the graph in Figure 2h for the scenario of perfect geometrical alignment between antennas (detection and transmission) and possible rotation of the latter antenna along the three Cartesian axes (Rot_x , Rot_y , and Rot_z) at different heights relative to the implantable antenna (in the z -direction). The complete mathematical formulation used for the calculation of the induced voltage levels at the implant can be found in Section 4.4. For the scenario of antenna misalignment, Figure 2i shows the variation of the voltage levels along a parallel plane above the implantable device, which perfectly documents the situation of swiping the mobile phone over a large surface area (e.g., rodent's dorsum) to provide sufficient power and data telemetry links to the implant underneath. From both scenarios, the implantable device remains operational up to on-axis distances of 1 cm (harvested voltage level >1.8 V), with rotation angles for the RF source less than 45° relative to the transmission plane and off-axis displacements within ranges of ± 7.5 mm.

At the end, **Table 1** exhibits comparison metrics between the proposed implantable device and others published in the literature. From the list, our device is the only one using three different sensing modalities (biopotential, light, and temperature), therefore the higher power level required for operation. Though some ultrasound approaches have been also deployed in small rodents or mice, they have targeted the peripheral nervous system instead of the cardiovascular one while relying on a single transduction mechanism (electrical) for sensing and/or stimulation. By its turn, the operational range achieved by NFC communication (≈ 10 mm) is lower relative to other RF and ultrasonic sources. However, many of these latter approaches are typically used either to interrogate passive sensors only or rely on active customized data links, thus more prone to external influence of the backscattered signals as opposed to NFC, which is a standard data communication link running in most modern gadgets today, with error-detection capability that assures reliability of the data streams sent by the implantable device.

3. Conclusion

A miniature implantable device has been presented for cardiovascular parameters assessment inside rodents in a 72 h trial period. To the best knowledge of the authors, this is the first study where multimodal sensing at the implant side was achieved in animal trials through a single miniaturized device. From the total number of devices implanted within the rodent population ($N = 2 \times 3$), half of them remained fully functional

during the extension of the trial, evaluated by the capability of transmitting uncorrupted NFC data packets. Reasons for the absence of valid data packets from nonfunctional devices can be attributed to device dislodging inside the animals because they could move freely inside the cages postsurgery, thus compromising the optimal orientation of the reception antenna toward the external RF signals. The formation of normal tissue layers surrounding the implanted sites may have also contributed to a slight decrease in NFC transmission efficiency, although not enough to prevent complete RF signal blockage due to the millimeter tissue thickness formation only. However, for the case of deep implantation inside the body, millimeter thickness variation along the signal transmission path can compromise the range of operability for the implant, especially in fast growing cell layers located in regions affected by cancer, metastasis, or tissue angiogenesis. Solutions to surpass this problem include the use of stronger RF fields for deeper tissue penetration, which do not rely on standard communication protocol metrics and whenever deem safe for body exposure. Finally, more extensive trial periods and larger animal populations are required to assess thoroughly implant's biocompatibility and degradation over time inside physiological medium, as well as future histological and toxicological examination to reveal evidence of chemical alterations or metal poisoning in the affected tissues. Whenever the characteristics of the acquired signals remain within acceptable medical levels, the short-term monitoring capability of the proposed device can also be extended to continuous monitoring if the NFC source is kept within the operational range of the implant. This strategy avoids the use of battery and memory modules inside the implant itself for continuous data recordings, which also possess potential deleterious effects associated with them, namely, current leakage from battery operation that can lead to tissue electrolysis and metal poisoning of the physiological environment, in addition to tissue trauma or injury due to an overall increase in the physical dimensions for the implant.

4. Experimental Section

Electronic Circuitry for the Implantable Device: **Figure 3a** shows the several functional blocks embedded inside the implantable device. For biopotential acquisition, threaded wire-electrodes with circular silver tips are used to interface the living tissues, followed by amplification of the tiny voltage signals detected using a low-powered instrumentation amplifier with 4 kHz bandwidth and gain set to 500 v v^{-1} . This configuration allows for acquisition of a single ECG bipolar lead. After amplification, the signal is digitized by a central microcontroller (MCU) at a rate of 128 samples per second (SPS) and 8-bit resolution, translated into a signal range of up to 3.6 mV and resolution of 14 μV . By its turn, the light module uses two light-emitting diodes (RED, wavelength of 650 nm; IR, 940 nm) as illumination sources activated in sequence through electric pulses lasting 4 ms each, with detection performed by a single digital proximity/ambient light sensor, whose spectral sensitivity extends from the visible to the IR range. Data samples collected from the light sensor are then sent to the MCU for digital processing through a moving average filter that reduces the number of collected samples while attenuating high-frequency noise interferences. At the end of this process, 128 processed samples per light channel are generated in a single second-long frame, enough to sample arterial pulse signals with temporal resolution of 7.8 ms. For temperature measurements, eight samples are collected every second from the internal chip die of the microcontroller (range $[-40, 80]^\circ\text{C}$, 0.12°C resolution). Once processed, the data samples from the different acquisition channels

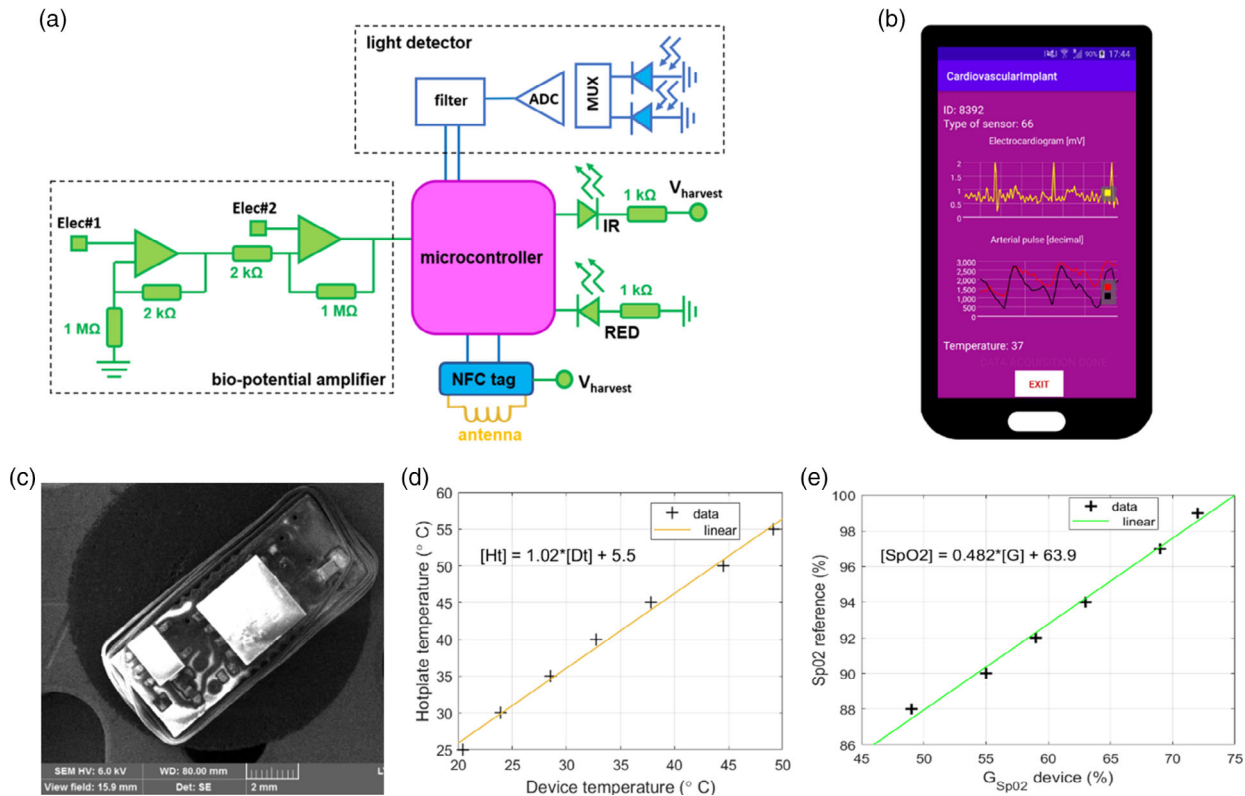


Figure 3. Implantable device design, packaging, and channel characterization. a) Simplified electronic schematic for the developed implantable device with main electronic modules enclosed by boxes. b) Mobile phone's app developed to receive, visualize, and store signals sent by the implantable device through NFC. c) Scanning electron microscopy (SEM) image of device's structure protected by PDMS. d) Calibration curve obtained for the internal temperature channel of the device using a hotplate with controlled-temperature settings. e) Linear fit obtained between the SpO₂ levels calculated by the proposed device and a commercial pulse oximeter (reference).

are transferred to the internal (nonvolatile) memory of an external NFC tag, where they can be accessed almost immediately by the RF field created by the mobile phone and visualized on the app shown in Figure 3b developed with Android Studio (Google, Mountain View, CA, USA).

Finally, the NFC tag is also responsible for harvesting the AC levels generated at 13.56 MHz (transmission frequency) and conversion to a DC equivalent ($V_{\text{harvest}} \geq 1.8 \text{ V}$) that can be used by the embedded electronics, totalizing a current consumption of 0.5 mA or, in terms of electric power, 0.9 mW. Within operational reading distances and angles relative to the external mobile phone (as presented in Section 4.4), a valid NFC data reading always involves transference of 1 kB of data from the implant and reception at the phone inside a transmission interval of 100 ms. Otherwise, whatever data packet is detected by the mobile phone is rejected automatically by the app. Moreover, to increase the reliability of the transmitted data inside the 1 kB-long data packet, a cyclic redundancy check (CRC) is performed along the acquired samples by the implantable device and stored as a final 2 bytes code in the transmission packet for error-detecting at the app, which also rejects any NFC data reading not passing the CRC test.

Circuit Board Design and Device Encapsulation: The PCB for the implantable device was projected as a double-layered rigid board (thickness of 1 mm) with dimensions of 10 mm × 5.5 mm. Copper traces were used as the conductive material for electric signal routing with widths of 100 μm. A surface Ni/Au finishing was used over the exposed electric pads, with protection of the conductive traces provided by liquid photoimageable solder mask. Electronic components were assembled on both layers of PCB with lead-free solder at a temperature of 330 °C. Twenty turns of 0.1 mm-thick copper wire were wrapped around the external perimeter of the PCB, followed by manual soldering of the wire-electrodes involved

in biopotential acquisition. A 2 mm-thick layer of biocompatible PDMS material was then dipped over the structure and cured for 30 min inside a reflow oven at 80 °C, yielding the device shown in Figure 3c. Other materials such as epoxy and parylene have been already proposed in the literature for implant encapsulation,^[33] though we opted for PDMS based on our past experience with wearable and implantable devices.^[27,34] Moreover, the thicker PDMS layer prevents faster degradation of the encapsulation at the expense of reducing the flexure of the implantable device, eventually causing annoyance to the surrounding animal tissues at the implantation site. So, a balance between reduced planar dimensions of the implantable device and loss of flexibility had to be reached to minimize tissue trauma to the implanted animal while mechanically withstanding the harsh saline environment for operation and sterilization process.

At the end, temperature measurements were performed to calibrate this channel by placing the implantable device over a hotplate (model 442-0662, VWR International, Radnor, PA, USA) and varying the temperature values in the interval from 25 to 55 °C (step of 5 °C), thus obtaining the linear fit shown in Figure 3d.

Calculation of the Oxygen Saturation Level: Oxygen saturation level (SpO₂) is calculated in this study as the ratio between oxyhemoglobin (HbO₂) to the total concentration of hemoglobin (Hb) in the blood stream as

$$\text{SpO}_2 = \frac{[\text{HbO}_2]}{[\text{HbO}_2] + [\text{Hb}]} = \frac{\epsilon_{\text{HbO}_2}(\lambda_{650 \text{ nm}}) - G\epsilon_{\text{Hb}}(\lambda_{940 \text{ nm}})}{(\epsilon_{\text{Hb}}(\lambda_{650 \text{ nm}}) - \epsilon_{\text{HbO}_2}(\lambda_{650 \text{ nm}})) - G(\epsilon_{\text{Hb}}(\lambda_{940 \text{ nm}}) - \epsilon_{\text{HbO}_2}(\lambda_{940 \text{ nm}}))} \quad (1)$$

where ε represents the extinction coefficients of the absorbing medium (as defined by the Beer–Lambert's law for light propagation), $\lambda_{650\text{nm}}$ and $\lambda_{940\text{nm}}$ are the optimal wavelengths used for pulse oximetry in the RED and IR regions, and G is the time derivative for the changes in absorption (A) at these wavelengths.

$$G = \frac{dA(\lambda_{650\text{nm}})/dt}{dA(\lambda_{940\text{nm}})/dt} \approx \frac{AC_{\text{RED}}/DC_{\text{RED}}}{AC_{\text{IR}}/DC_{\text{IR}}} \quad (2)$$

The G value can also be calculated experimentally by taking the normalized ratio of the red absorbances to the IR ones as stated by Equation (2). These values are obtained by dividing the AC component of the arterial pulse signal (i.e., frequency of pulse excitation) by the DC component, the latter corresponding to the light attenuation verified along the transmission path connecting the blood vessels to the photodetector. Under normal conditions, arterial blood is 95% saturated with the most common locations for pulse detection being the finger and earlobe, though intrabody location near the main arterial vessels has the advantage of achieving better estimates for SpO_2 because the scattering effects induced by the body surface (skin) are reduced. To prepare the implantable device for real deployment, this G value was also calibrated against a commercial pulse oximeter (model 320, Dolphin Medical, Hawthorne, CA, USA), obtaining the linear fit in Figure 3e.

Magnetic Field Simulation and Equivalent Voltage Level: Matlab (Mathworks Inc., Natick, MA, USA) was used to simulate the magnetic field detected around the implantable device, followed by conversion to a voltage equivalent (emf) at 13.56 MHz. Spatial discretization of the differential line elements ($d\vec{l}$) composing the antennas for the proposed implant (detection) and mobile phone (transmission, dimension:

5 cm $\times$ 3 cm, four turns of copper material) was performed beforehand in order to solve Faraday's law of induction in the harmonic regime of wave propagation as^[27]

$$\text{emf} = \oint_{\text{detection}} \vec{E} \cdot d\vec{l} = \int_S \frac{\partial \vec{B}}{\partial t} \cdot d\vec{S} = -j\omega \oint_{\text{detection}} \vec{A} \cdot d\vec{l} \quad (3)$$

where E and A represent, respectively, the electric field and magnetic potential vector, and ω the radian frequency. In this article, we also assume that the magnetic field B generated by the mobile phone can be written in the terminology of magnetic potential vector, this by satisfying the gauge conditions in Equation (4) in terms of the algebraic curl ($\nabla \times$) and divergence ($\nabla \cdot$) operators.

$$\vec{B} = \nabla \times \vec{A}, \quad \nabla \cdot \vec{A} = 0 \quad (4)$$

Calculation of A for distances device-phone expressed by variable d then follows a variant of Biot–Savart's law in magnetics (Equation (5)), by assuming an approximation to the magnetic permeability of body tissues close to that of air (μ) and knowledge in advance of the circulating current I inside the transmission antenna.

$$\vec{A} = \frac{\mu_0}{4\pi} \oint_{\text{transmission}} \frac{I \cdot d\vec{l}}{d} \quad (5)$$

As different manufacturers may use dissimilar current characteristics inside the mobile phone, this detail led to the use of a mean inductance value ($L = 4 \mu\text{H}$) for the transmission antenna during simulations, in

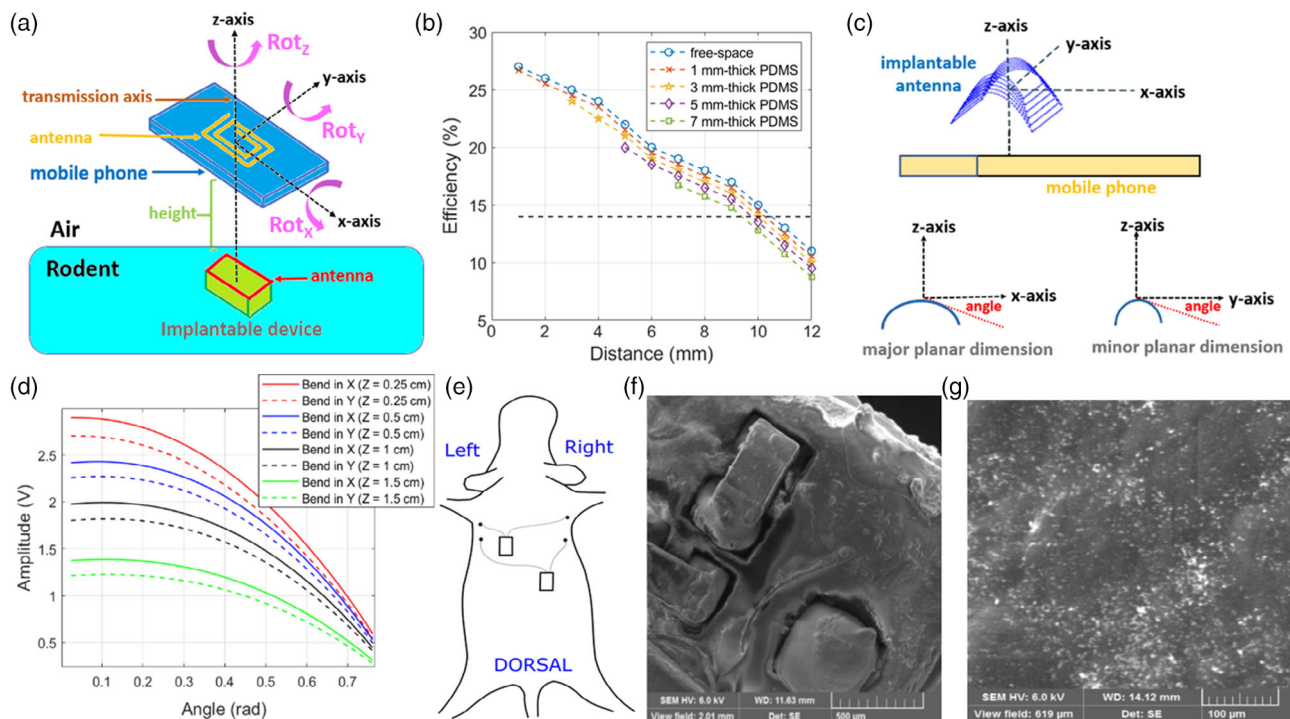


Figure 4. Experimental setups devised for NFC transmission efficiency characterization and the animal trial. a) Diagram and referential axes used for the calculation of the harvested voltage level for the system mobile phone—implantable device by magnetic induction. b) Evaluation of antenna's efficiency (implantable device) with on-axis distance by comparison with a standard-sized loop antenna in the open-air propagation and PDMS blockage scenarios (center alignment). c) Geometry and disposition of the implantable antenna used as references for the estimation of the harvested voltage levels during planar bending. d) Respective harvested levels obtained by planar bending the implantable antenna relative to the x - and y -axes (angle) at different heights from the transmission antenna (in the z -direction). e) Schematization of the two implant sites located subcutaneously at the back of the rodent (with attached wire-electrodes) and used as reference during surgery. f) SEM image revealing details of the outer surface for the encapsulation layer protecting the implantable device after surgical explantation from the rodent. g) Similar SEM image taken at a deeper scale and reduced field-of-view.

conjunction with a 3.3 V level to estimate the amplitude of I , as given by the standard impedance formula for inductors (Equation (6)).

$$I = \frac{V}{j\omega L} = \frac{3.3}{2\pi \cdot 13.56 \times 10^6 \cdot 4 \times 10^{-6}} \approx 10 \text{ mA} \quad (6)$$

Finally, the projection of the different magnetic vector components over the differential line segments composing the detection antenna allowed the calculation of the emf values between these two entities in accordance with the diagram shown in **Figure 4a**, coping also with possible geometrical misalignments or rotations between antennas, thus obtaining the harvested voltage levels exhibited in the Section 2.

However, we went further to estimate the real efficiency of the implantable antenna by means of experimentation. To circumvent the problem of dissimilar power levels produced by different mobile phones, we used a standard-sized loop antenna (ISO10373-7) to measure the emf levels directly connected to an oscilloscope (MSO-X 3054 A, Agilent Technologies, Santa Clara, CA, USA) while comparing these levels with the ones obtained with the implantable antenna in the scenarios of open-air propagation and blockage with several layers of PDMS. This latter scenario contemplated the use of 1 mm-thick slabs of PDMS (planar dimensions of 3 cm × 3 cm) placed in the RF transmission path between the mobile phone and tested antennas to mimic different material thickness. Therefore, the ratio given by Equation (7) corresponds to a relative efficiency calculated for the implantable antenna in comparison with the standard model.

$$\eta = \frac{\text{emf}_{\text{implant}}}{\text{emf}_{\text{standard}}} \times 100 \quad (7)$$

The estimated efficiency is shown in **Figure 4b** as a function of the distance between entities (phone and implantable antenna), both aligned along the central axis of transmission, and the dashed black line in the graph representing the minimum level that could generate a voltage equivalent enough to power up completely the implantable device. From the graph, it can be seen that PDMS blockage produces a slight decrease in antenna's efficiency as compared with free-space propagation, which approaches the operational distance range first obtained by the simulations for on-axis displacements (≈ 1 cm).

The previous harvested levels obtained by simulation or experimentation were based on a concentric layout of the antenna loops around a rigid PCB substrate, which made difficult the bending of the extremities of the antenna relative to the plane of the electronic board. Encapsulation by PDMS further prevents any bending motion of the implantable antenna caused by surrounding tissues, therefore leading to the absence of any previous study of this phenomenon in the proposed device. For future integration of the implantable antenna in thinner or flexible substrates, the bending motion of the antenna must be taken into account, which has prompted us to present a final set of simulation results for the induced voltage levels obtained during planar bending of the antenna and using the same geometry and dimensions of the (rigid) implantable antenna proposed in the current study (**Figure 4c,d**). From the obtained curves, the induced levels start to be severely impaired for bending angles around 22.5° ($\pi/8$ rad), especially relative to the y -axis that affects the minor planar dimension of the antenna.

Animal Trial Intervention and Follow-up: The trial was conducted under the UK Home Office Project License 80/2639 that provides regulatory guidelines for the care and use of laboratory animals. Three male rodents (Sprague Dawley, 9 weeks old, weight of 250 g) were considered as the species of choice due to its applicability as an appropriate model for subcutaneous implantation. The implantable devices were provided on the day of implantation perfectly sterilized in pure ethanol for 24 h, and without specific requirements for special handling or storage. Each rodent received two devices for subcutaneous implantation over the psoas ridge to test the powering efficiency of the NFC interface and detection of the ECG signal through wire-electrodes placed on the termination region of the dorsum close to the upper limbs (**Figure 4e**), in addition to the

detection of the internal body temperature and contact with blood vessels for arterial pulse measurements.

Prior to the insertion surgery, the animals were placed inside an anesthetic induction chamber, with flow of isoflurane plus oxygen gradually increased until the induction of anesthesia. The rodents were then removed from the chamber, the fur of the dorsum was cleared, and the analgesic carprofen administrated subcutaneously. During surgical intervention, the animals remained anaesthetized in the prone position over the operation table, with isoflurane and oxygen supplied through a close-fitting mask. After surgical site closure, immediate NFC readings were taken externally by a phone in close contact with the dorsal body surface of the animal. Additional readings were taken daily at a pace of five times a day, mostly during daytime with minimum gap interval of 2 h. During these readings, animals were immobilized by hand for a period of 5 s to allow correct NFC detection at each time point. The rodents were allowed to recover for a period of 72 h postoperatively inside plastic cages with controlled light cycles of 12 h, and normal diet and water supplies. No known substances were expected in the diet or drinking water that could adversely affect the outcomes of the trial. After 72 h, the animals were terminated using an intraperitoneal injection of a pentobarbitone overdose. A midline dorsal incision was made in each animal to expose the affected tissues, document them, explain the devices, and perform SEM of the surface, as shown in **Figure 4f,g**.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contribution

B.M.G.R. developed the electronics for the implantable device. S.A. developed device packaging and sterilization method. B.M.G.R. and S.A. conducted the animal trial and analyzed the results. G.Z.Y. initiated the project, secured funding for the project, and supervised the work. All authors contributed to the writing of the manuscript.

Data Availability Statement

Research data are not shared.

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