Implantable device for long-term electrical stimulation of denervated muscles in rabbits

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Abstract—*Although denervating injuries produce severe atrophic changes in mammalian skeletal muscle, a degree of functional restoration can be achieved through an intensive regime of electrical stimulation. An implantable stimulator was developed so that the long-term effects of different stimulation protocols could be compared in rabbits. The device, which is powered by two lithium thionyl chloride batteries, is small enough to be implanted in the peritoneal cavity. All stimulation parameters can be specified over a wide range, with a high degree of resolution; in addition, up to 16 periods of training (10–180 min) and rest (1–42 h) can be set in advance. The microcontroller-based device is programmed through a bidirectional radiofrequency link. Settings are entered via a user-friendly computer interface and annotated to create an individual study protocol for each animal. The stimulator has been reliable and stable in use. Proven technology and rigorous quality control has enabled 55 units to be implanted to date, for periods of up to 36 weeks, with only two device failures (at 15 and 29 weeks). Changes in the excitability of denervated skeletal muscles could be followed within individual animals. Chronaxie increased from 3.24 $\pm$ 0.54 ms to 15.57 $\pm$ 0.85 ms ($n = 55$, $p < 0.0001$) per phase in the 2 weeks following denervation.*

Keywords—*Implantable stimulator, Skeletal muscle, Denervation, Rabbit, Excitability, Radiotelemetry*

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1 Introduction

SOME SPINAL cord and peripheral injuries cause irrecoverable lower motor neurone damage. This results in flaccid paraplegia and, over time, extremely severe atrophy of the affected muscles.

For many years, no effective treatment could be offered to people with this condition. Recently, however, it was shown that the denervated muscles can undergo a remarkable recovery of mass, excitability and force if they are conditioned with a sufficiently intensive regime of electrical stimulation (KERN *et al.*, 2002*a*, *b*; 2004). Treating the muscles in this way will not restore normal mobility, but it may, at some future point, pave the way to neuroprosthetic approaches of the type that have been applied to patients with upper motor neurone lesions (HORCH and DHILLON, 2003). There are, in any case, potential secondary benefits, including: improved cardiovascular fitness; better skin condition and muscle cushioning, with a corresponding reduction in the risk of pressure sores; and improvements in cosmetic appearance and patient self-esteem.

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The present study forms part of a collaborative project designed to place this application of electrical stimulation on a secure scientific footing. In particular, the use of suitable animal models will enable us to devise protocols for clinical use that provide the maximum beneficial effects with the minimum intrusion into the patient's normal daily activities. For this purpose we needed a stimulator that would allow us to investigate the effects of long-term conditioning on the denervated tibialis anterior muscle of the rabbit.

The cell membrane of denervated muscle fibres is much less excitable than that of nerve fibres and activating it calls for high currents and long pulse durations. At the whole muscle level, the absence of functional nerve branches means that adequate recruitment depends on conveying electrical excitation directly to all parts of the muscle, and the active area of the electrodes must be large so as to create the necessary volume and intensity of the current field while minimising local heating. For these reasons, the pulse charge required to activate a denervated muscle is 100–500 times greater than that needed to activate an innervated muscle.

Our clinical studies in patients suffering from long-term flaccid paraplegia (KERN *et al.*, 1999; 2002*b*; 2004) were carried out with surface electrodes connected to a stimulator designed for external use (HOFER *et al.*, 2002). Surface electrodes have also been used in some chronic animal studies, but the need for restraint necessarily limits the daily duration of stimulation that can be applied (MOKRUSCH *et al.*, 1990).

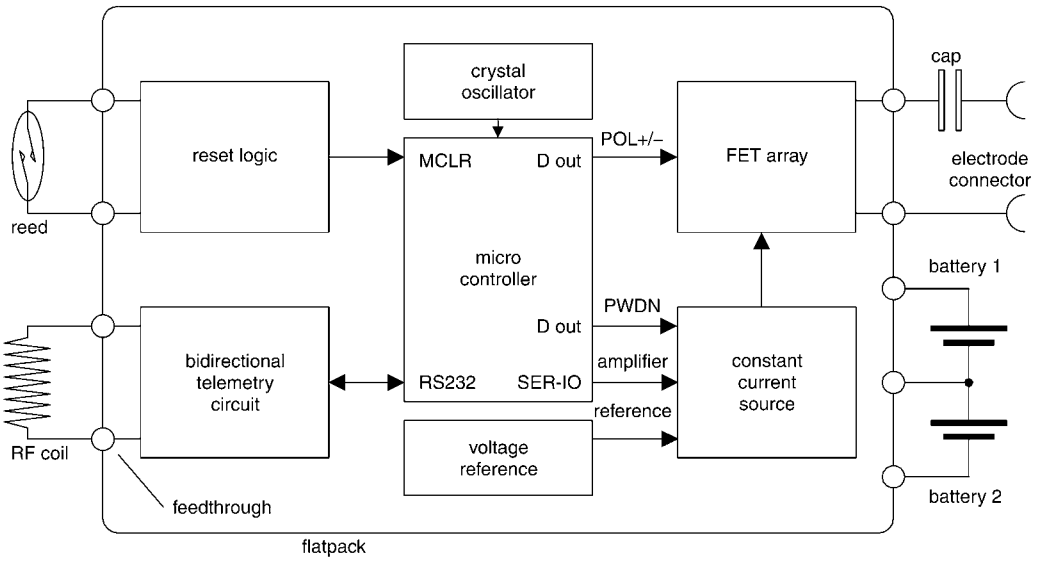

Fig. 1 *Block diagram of implantable stimulator. Sensitive parts of circuitry are sealed hermetically in flatpack and are connected to external components, such as radiofrequency coil, reed switch and batteries, by multiple feedthroughs*

To activate the denervated crycoarytenoid muscle in sheep, electrodes were implanted and connected to the stimulator by percutaneous leads (MAYR *et al.*, 2001). Similar solutions have been adopted for other studies (GORZA *et al.*, 1988; AL AMOOD *et al.*, 1991). Percutaneous leads are susceptible to damage, their use carries a risk of infection, and they still deny the subject full mobility.

To avoid these problems, implantable devices have been developed for studies in humans (WILLIAMS, 1996) and in animals (DENNIS, 1998; DENNIS *et al.*, 2003; ZEALEAR *et al.*, 2001). However, existing devices would not meet the requirements of the present study, which called for complete flexibility in the choice of stimulus parameters throughout the experiment, a high maximum pulse charge, the ability to programme burst and pause intervals, interrupted by adjustable periods of rest throughout a 24 h cycle, and a device lifetime of at least 12 weeks. Furthermore, to make full use of this functionality, we needed to develop a user-friendly interface, to incorporate safeguards in case of operating errors, and to provide features that would support and simplify the collection and analysis of data.

The implantable device that was developed to meet this specification has been used extensively and has proved stable and reliable in experiments that considerably exceeded the original design lifetime.

2 Methods

2.1 *System design and technology*

The implantable device consists of a battery-powered programmable stimulator connected by leads to a pair of epimysial electrodes. The external components are a notebook computer and a transmitter/receiver unit. The stimulator generates biphasic, constant-current pulses. All pulse and burst parameters can be specified on a graphical user interface on the notebook computer; the program is then transferred to the implanted device through a bidirectional radiofrequency link. Pre-programmed stimulation sequences can be initiated manually, or a training protocol with up to 16 independent stimulation sequences can be run automatically.

2.1.1 *Implantable stimulator (Fig. 1)*

The implantable pulse generator consists of a radiofrequency telemetry circuit, a microcontroller and a constant-current output stage. The telemetry circuit manages the transfer of data to and from the external components. This includes specification of the required pulse parameters (frequency, pulse duration, pulse amplitude) and stimulation sequence parameters (burst duration, burst pause, duration of sequence), which are stored in the onboard memory in the microcontroller.* Deviations from the desired settings are minimised by deriving all parameters from a crystal oscillator and a voltage reference.

The output stage includes a constant-current source, a FET array for polarity reversal and a decoupling capacitor to ensure charge balance. To conserve power during operation, the output stage is activated only during a burst. To extend shelf-life when the device is not in use, a logic circuit triggered by a reed contact resets the microcontroller and deactivates all of the circuitry (Fig. 1).

The stimulator will operate with either one or two lithium thionyl chloride batteries†, each of which has an open circuit voltage of 3.67 V and a capacity of 750 mAh. The choice of one battery or two is dictated by the required operating life and the stimulation parameters. The present application called for high driving amplitudes over an extended experimental period, a specification that was met with two batteries connected in series. Operating life is determined mainly by the electrical power delivered to the tissues; the power consumed by the control circuitry (130 μW during stimulation, 55 μW in standby mode) and data transmission (95 μW) is relatively insignificant.

The circuitry was fabricated with surface mount technology (SMT). The circuit was enclosed in an hermetically sealed (resistance-seam-welded) gold-plated flatpack.‡ The flatpack, together with the batteries, transmitter/receiver coil, output decoupling capacitor and electrode connector, were cast in a medical grade epoxy resin. A loop of Dacron mesh, attached to the wall of the stimulator with medical grade silicone adhesive, provided anchorage during implantation (see below). Finally the device was sealed in a gas-permeable bag for ethylene oxide sterilisation.

2.1.2 *Electrodes*

Each electrode consists of a 0.1 mm thick piece of stainless-steel sheet, with an active area of 150 mm^2, which was shaped

*PIC16F874, Microchip Technology Inc., Arizona USA
†LPC-7PN, Eagle-Picher Industries, Missouri, USA
‡Our Aegis, MA, USA

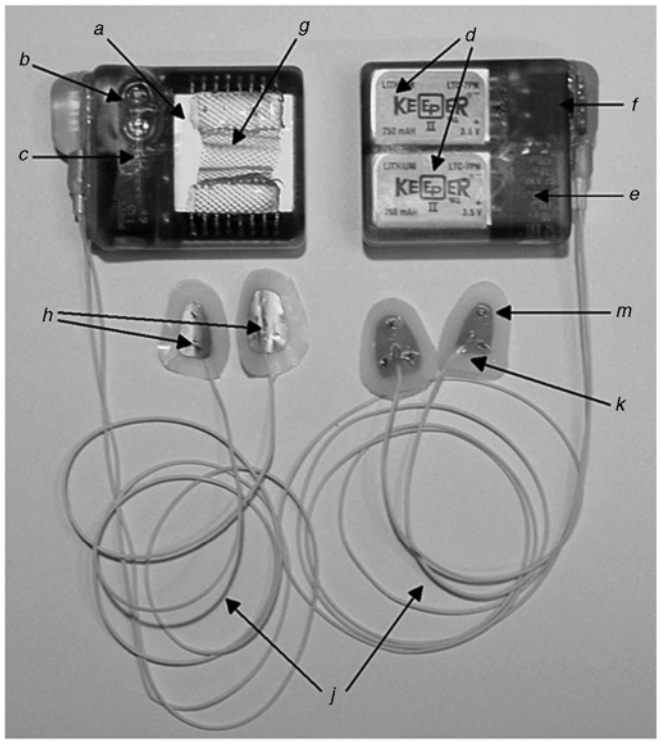

Fig. 2 *Photographs of both sides of implantable stimulator and epimysial electrodes. (a) Electronic circuitry sealed in flatpack; (b) RF coil; (c) reed switch; (d) batteries; (e) output capacitor; (f) electrode connector; (g) loop of Dacron mesh; (h) muscle-contacting surface of stainless-steel foil electrode; (j) electrode lead; (k) spot-welded connection between lead and electrode; (m) silicone rubber backing to isolate electrode from surrounding tissues*

to conform anatomically to the surface of the muscle (Fig. 2). The non-contacting surface was insulated by a thin sheet of silicone rubber, which extended beyond the boundary of the electrode by 0.5 mm in all directions to minimise stimulus spread to adjacent structures. A lead was attached to the electrode by spot-welding; a temporary pacing lead** was used for the first 15 implants, after which a more flexible lead†† was used for the remaining implants.

2.1.3 *Programmer and transmitter/receiver unit*

Detailed consideration has been given to the way the system will be used by personnel with limited engineering expertise. Stimulation parameters are entered or modified on a notebook computer (IBM PC or compatible) via a clean graphical user interface. The settings, together with an activity log, are written automatically to a plain text file (ASCII format) and can be further annotated by the user to create an individual study record for each animal. The protocols and measurements stored within this record are readily accessible for review.

During the course of the experiment, windows were added for determining threshold, rheobase and chronaxie; the resulting data can be exported directly to a Microsoft Excel spreadsheet for further analysis. The software was developed with the Integrated Development Environment Delphi 6‡‡ and is supported by both MS Windows 2000 and Windows XP*.

The data needed to specify the entire stimulation sequence are transferred to the implanted device by a radiofrequency transmitter/receiver unit linked to the serial port (RS-232) of the PC. Transmission reliability is increased by returning each individual data word and the serial number of the implant to the programmer for checking. In addition, the stimulation data are accepted only after a check sum transmitted from the programmer has been verified by the implant.

The telemetric link uses amplitude shift keying (ASK), with load shift keying (LSK) for back transmission, at a data rate of 1200 bits s^{-1} on a carrier frequency of 100 kHz. The transmission link operates within an axial displacement of 40 mm and a radial displacement of 30 mm.

2.1.4 *Quality control*

Critical components, such as the battery and the reed contact switch, are subjected to a limited incoming inspection. During production of the implantable device, the quality assurance procedure consists of functional tests performed after the electronic circuitry is completed, after the flatpack is sealed, after all the electrical components have been assembled, and after the assembly has been cast in epoxy resin. In each test, the power consumption, data transmission and stimulation parameters are examined. The welding seam on the flatpack was subjected to a helium leak test for the first ten implants but was checked subsequently by visual inspection with a microscope.

2.2 *Implantation technique and experimental design*

All procedures involving animals were performed in strict accordance with the Animals (Scientific Procedures) Act 1986, which governs animal experimentation in the UK. Male New Zealand White rabbits, of 2.5–3 kg body weight, were operated on under general anaesthesia with full aseptic precautions. The common peroneal nerve of the left hind limb was microdissected, and the motor branches were cut and diverted, denervating the dorsiflexor muscles of the ankle.

The stimulator was removed from its sterile pack and placed in the peritoneal cavity through an incision in the abdominal musculature. In closing this incision, we captured the loop of Dacron mesh with the sutures to prevent the device and its connecting leads from migrating within the abdominal cavity. The two electrodes were taken subcutaneously to the left hind limb and secured to the epimysium to overlie the proximal superficial and deep distal surfaces of the tibialis anterior muscle. All skin incisions were then closed, and the animals were allowed to recover from anaesthesia.

At predetermined intervals, the implanted stimulator was used to determine the rheobase and chronaxie of the denervated tibialis anterior muscle in the conscious animal. This required two operatives: one cradled the animal, held the transmitter/receiver and palpated the muscle for a contractile response; the other operated the software. The pulse duration was set to 100 ms per phase, and ten bipolar constant-current pulses were delivered to the muscle while the muscle response was assessed. A step change in amplitude was then implemented, and the test was repeated. In this way, the amplitude for threshold activation (rheobase) could be resolved to 0.04 mA. The amplitude was then set at 2× rheobase, and the corresponding pulse duration for threshold activation (chronaxie) was resolved to 0.5 ms per phase with a similar stepwise protocol.

After denervation for 10 or 36 weeks, the denervated muscle was stimulated for 1 or 5 h a day with one of several different patterns, so that the therapeutic effects of re-establishing contractile activity (conditioning) could be evaluated.

**Medtronic, Inc., Minneapolis, MN, USA
††Cooner Wire Inc., Chatsworth, CA, USA
‡‡Borland, Scotts Valley, CA, USA
*Microsoft Corporation, Redmond, WA, USA

3 Results

3.1 *Device specifications*

The implantable device measures 46 × 38 × 17 mm and weighs 45 g. Its operating life is determined mainly by the choice of stimulation protocol and can be estimated from

$$L = \frac{Q_{eff}}{I \cdot T \cdot N/3.6 \times 10^6 + \Delta} \quad (1)$$

where L is the operating life in days; Q_{eff} is the effective capacity of the battery in mAh (normally 600 mAh); I is the amplitude of the stimulus pulse in mA; T is the duration of both phases of the stimulus pulse in ms; N is the number of pulses per day, and Δ is the non-stimulus-related utilisation of capacity per day; which consists of the current needed to run the device and to operate the radiofrequency link, together with any internal leakage (approximate total 1 mAh d^{-1}). For example, the implantable device could theoretically sustain continuous stimulation at 1 Hz with an amplitude of 10 mA and a pulse width of 10 ms per phase for approximately 103 days (just less than 15 weeks).

Table 1 gives the range and resolution within which the individual stimulation parameters of the implantable stimulator can be specified.

3.2 *Production details*

The device borrowed to some extent from implant technology used in some of our earlier applications (LANMÜLLER *et al.*, 1999). For example, it was possible to employ materials and technological processes developed previously, as well as functional blocks such as data transmission. The additional development time associated with the present device and manufacturing tools amounted to approximately 1 man year.

Production and quality control occupied approximately 20 man hours per device. We have lost five units out of 55 during production owing to mechanical ($n = 2$) or electrical ($n = 1$) manufacturing faults and failure of individual electronic components ($n = 2$) that were not subject to incoming inspection.

3.3 *Implantation history*

Fifty-five units have been used in the rabbit study to date. Some were used only to determine the time course of changes in chronaxie and rheobase during periods of denervation of up to 36 weeks. Others were used both to take these measurements and to stimulate the denervated tibialis anterior muscle for either 2, 6 or 10 weeks, with a pattern that consisted of bipolar pulses of 20 ms duration per phase, amplitude 4 mA and frequency of 20 Hz, delivered either for 1s on, 2s off, or 2s on, 1s off. Stimulation was maintained for 60 min per day (the 'training period'), given in either a single session or two sessions separated by 12 h. The maximum duration of implantation was 36 weeks.

So far, the total number of implanted animal weeks is 964, and, excluding excitability measurements, a total of 109 200 000 impulses have been delivered.

Table 1 Pulse parameters and additional technical specifications of implantable stimulator. Figures in brackets are resolution with which each parameter can be set

Stimulation amplitude	max. 10 mA (40 μA)
Pulse duration per phase	0.5–40 ms (0.5 ms)*
Stimulation frequency	1–64 Hz (1 Hz)
Burst duration	0.1–10 s (0.1s)
Pause duration	0.1–10 s (0.1s)
Period of training	10–180 min (10 min)
Number of preset training sequences	1–16
Interval between sequences	1–42 h (1 h)
Maximum electrode impedance	500 Ω

*At maximum amplitude of 10 mA. Chronaxie measurements were conducted with amplitude less than 8 mA, at which impulses with duration per phase of 100 ms could be generated

3.4 *Problems*

There have been two device failures, one after 15 weeks and one after 29 weeks of implantation. In both cases, it was no longer possible to communicate with the device, even after explantation; the reason has not been identified. Even with these failures, the original specification, which called for a lifetime of 12 weeks, has been handsomely exceeded, enabling us to extend the experimental period as indicated.

To determine chronaxie and rheobase and to set parameters for longer-term stimulation, the rabbits had to be lightly restrained while the transmitter/receiver unit was placed on the abdomen over the implanted stimulator. In some cases, data transmission between the transmitter/receiver unit and the implanted device was interrupted during the procedure. The transmitter unit had then to be repositioned to re-establish contact between the two. We attribute these interruptions to movement of the animal or the transmitter unit; the stimulator had been secured to the abdominal wall during implantation and was unlikely to move.

The most frequent cause of implant failure was breakage of the more flexible leads.[†] This occurred in seven cases, none before 36 weeks of implantation. In a single animal, routine palpation of the stimulated muscle indicated that contraction was weaker during the final 3 days of a 42 day stimulation period. Post-mortem inspection of this device revealed a small defect in the insulation of the electrode lead, probably caused during surgical implantation 112 days before.

During the terminal procedure, the device and electrodes were explanted and examined. In several cases, the silicone rubber backing on the distal electrode had become partially detached from the stainless-steel foil. This had not posed a problem with stimulation of the muscle, although it may have increased current spread to surrounding tissues. In two cases, fluid was found between the electrode and the muscle, with a corresponding brown discolouration of the tissue and some corrosion of the stainless-steel foil. In neither case had stimulation been attenuated. No defects were observed at the lead–electrode junctions.

3.5 *Time course of changes in chronaxie and rheobase*

We exploited the bidirectional communications link with the implantable stimulator to investigate long-term changes in the excitability of denervated rabbit muscle. We observed a transient increase in rheobase during the 2 weeks following denervation; rheobase then declined to a level similar to, or lower than, that seen in control, innervated muscles. Chronaxie increased from 3.24 ± 0.54 ms ($n = 55$) to 15.57 ± 0.85 ms ($n = 55$) ($p < 0.0001$) per phase in the 2 weeks following denervation (Fig. 3), and remained at a similarly elevated level up to the maximum period for which observations have been made, currently 36 weeks.

A full strength–duration curve was constructed as part of the physiological evaluation conducted under terminal anaesthesia. The definitive values obtained for the rheobase and chronaxie in this way did not differ significantly from the last measurements made in the conscious animals.

[†]Cooner Wire Inc.

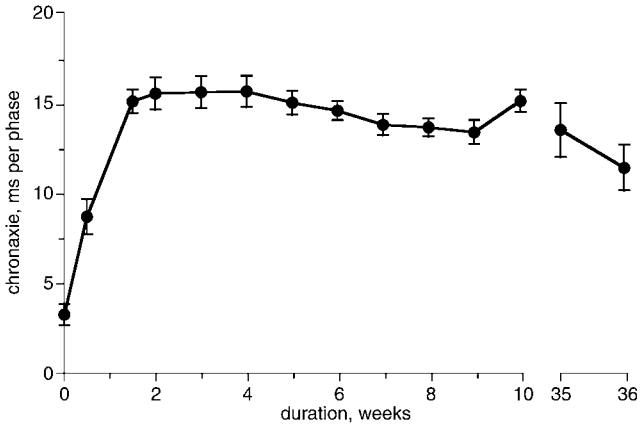

Fig. 3 *Time course of changes in chronaxie, measured in lightly restrained, conscious rabbits during first 36 weeks following denervation. Each point represents mean ± SEM. Numbers of animals: n = 7 at 35 weeks, n = 6 at 36 weeks; for all other time points, n is between 41 and 55*

4 Discussion

We describe here an implantable stimulator that is suitable for intraperitoneal implantation in experimental animals down to the size of laboratory rabbits. It allows the experimenter to select from a wide range of stimulation parameters and on–off patterns, and these can be set before or after implantation using a bidirectional radiofrequency link.

In the present experimental study, the device proved reliable and stable for periods of implantation as long as 36 weeks, with just two of the 55 implanted devices failing, and those only after 15 and 29 weeks. The loss of less than 10% of the implants during manufacture was considered an acceptable price for assured reliability under implanted conditions. The most common cause of failure was lead breakage, occurring at the end of the 36 week implantations; a more suitable lead is being sought.

In spite of the complexity of the patterns used in this study, the protocol never had to be modified on account of technical limitations of the stimulation device. The facility for programming periods of training and rest for several days in advance was particularly valuable, obviating the need for daily intervention and minimising any stress to the animal that could have been caused by excessive handling.

To make full use of the extensive range of user-specified functions, we needed to equip the system with a user friendly interface. This was evidently achieved, for no problems were experienced in conducting the animal studies in Liverpool, UK, despite the geographical separation from the technical team in Vienna, Austria. New features, needed by the experimental team during the course of the study, were readily incorporated, thanks to the modular structure of both the hardware and software, and this was achieved without interruption or loss of data.

In some animals, the range of the telemetry link was at the limit of usability, necessitating repositioning during the programming procedure. Although programming was eventually successful in all cases, this point needs to be addressed in the future.

The stimulation system described here provided a non-invasive way of obtaining a detailed time course for changes in the excitability of denervated skeletal muscle over an extended period within individual animals, something that has not been possible until now (ASHLEY *et al.*, 2004). The effects of conditioning on these and other physiological, biochemical and histological properties of denervated rabbit muscles are currently being analysed. A preliminary account of the findings has been published (SALMONS *et al.*, 2005).

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