Cuff Electrodes for Long-Term Recording of Natural Sensory Information

Studying the Relationship Between Nerve Damage and Electrophysiological Parameters in Long-Term Implants

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Cuff electrodes for recording of the electro-neurogram (ENG) from peripheral nerves were introduced by Hoffer [20] and Stein, et al. [51]. The cuffs were used to obtain higher signal amplitudes than previously possible, at least in chronic recordings, and to decrease the pick-up of noise, especially from muscles. Cuff electrodes are relatively stable in long-term recordings [52], but the stability has never been quantified in terms of input-output relationships; i.e., in terms of responses to repeatable stimuli over time. Moreover, the relationship between nerve damage and electrophysiological parameters has never been assessed.

In this article, after reviewing the development of cuff electrodes and their applications, we present a long-term study of tactile peripheral nerve signals, electrically activated nerve signals, and impedance measurements. We show how the recordings vary over a 16-month period after implantation of nerve cuff electrodes in rabbits, and how nerve damage is reflected in the recorded signals.

Development of Nerve Cuff Electrodes for Recording

About 150 years ago, Du Bois-Reymond [3] showed that nerve fibers conduct electrical impulses. But it was not until 1910 that Garten [5] published the first clear recordings of the compound action potential (CAP) elicited by electrical stimulation. The difficulty in recording was not only that the signals were small, but also that their bandwidth was several kHz, which was too large for the string galvanometer used by Garten and others to record without significant distortion of the wave shape. High-fidelity recordings did not appear until Gasser, Newcomer, and Erlanger were able to record CAPs with a home-built cathode-ray oscillograph [4, 6], which readily solved the bandwidth problem.

Low signal amplitude is still a problem, not so much in recording of electrically evoked volleys, in which case the amplitude can be several millivolts, but when recording natural activity of the nerve extraneurally. For example, with hook electrodes the signal amplitude is no more than a few microvolts, which is not much higher than amplifier and thermal electrode noise.

Physiologists quickly discovered that when the nerve is lifted into the air or placed in oil, so as to provide a "locally restricted extracellular space," the amplitude of the recorded signal is increased since the resistance of the extracellular return path of the fibers' action currents is increased. This phenomenon was analyzed mathematically by Stein and Pearson [50]. It was then shown that with a silicone cuff around a nerve, and electrode contacts at the inner side of the cuff wall, a similar restriction of the extracellular space could be obtained, making possible long-term recording from nerves in situ [51]. From experimental work, the optimal cuff length was shown to be between 20 and 30 mm; the signal amplitude strongly decreased for cuff length below 15 mm [26, 51]. From a modeling study, Struijk [57] obtained similar results, and also showed that the amplitude decreases with the square of the cuff diameter for small diameters (up to 4 mm), in accordance with experimental results from, for example, Davis, et al. [2]. This latter result implies that cuff electrodes are most effective for small-diameter nerves. Hoffer, et al. [20, 26], used

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cuffs of 0.3 mm diameter to record from small rabbit nerves to obtain single-fiber potentials of more than 20 μV, whereas Stein, et al. [52], recorded single-fiber action potentials with an amplitude of around 3 μV using a cuff of 2.6 mm inner diameter.

As in all extraneural recording methods, the fibers with the largest diameters dominate the recorded signal. Stein, et al. [52], showed a power relationship between conduction velocity (which is approximately linear with fiber diameter) and amplitude of the recorded signal: $V \propto D^p$, where V is the amplitude, D the fiber diameter, and p a constant with measured values of 1.6 and 1.7. These values are close to the value of 1.8 that was obtained by Struijk [57] in the aforementioned modeling study.

Rejection of noise from sources external to the cuff is best obtained by the use of a balanced tripolar configuration with short-circuited end-contacts (see Fig. 1). Originally, noise rejection was attributed to the short-circuiting of the end-contacts, which prevents current from flowing through the cuff by reducing the potential difference between the cuff-ends [51, 52]. However, since the equivalent shunting resistance of the fluid and tissue around the cuff is no more than a few hundred ohms [26, 41], whereas the electrode-tissue impedance measured at the outer cuff contacts is in the order of one or more kohms at 1 kHz [59] and will be even higher at the lower frequencies of muscle noise, short-circuiting of the end-contacts will have negligible effect on the voltage between the cuff-ends [59]. The short-circuiting would only be effective if the impedance measured between the end-electrodes was less than a few hundred ohms. Instead, by short-circuiting the end-contacts, a terminal is created that gives the average potential of the two end-contacts, as long as the two contact impedances are equal. The same average potential is also recorded by the central contact, as long as the cuff is perfectly sealed, has a small diameter as compared to its length, has its central contact exactly midway between the end-contacts, and the tissue impedances inside the cuff are symmetrical. Differential recording between the center contact and the connected end-contacts will then cancel the potential difference between the cuff-ends [56].

Cuff Construction

Typically, cuffs are made from silicone tubes. Originally, deinsulated multistrand wires, made of Teflon-coated platinum-iridium or stainless steel, were sewn through the cuff wall in such a way as to cover most of the circumference of the inside of the cuff. But space was left for a longitudinal opening, needed to put the cuff around the nerve. Closure was obtained by simply tying sutures around the cuff. This kind of cuff was used by Hoffer and coworkers and Stein and coworkers in the cited studies. Julien and Rossignol [28] presented a different approach, useful only for acute experiments. A prefabricated nerve cuff with stranded copper wires and with a longitudinal slit was put around a nerve. A liquid polymer was then injected into the cuff to fill the remaining space around the nerve, and thus to fit the nerve tightly.

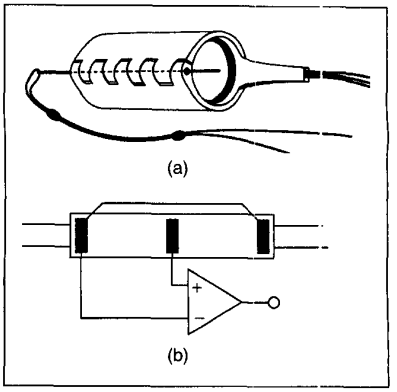
A spiral nerve-cuff design [39], intended for stimulation and recording, was developed to fit snugly, while at the same time able to expand in case of nerve swelling. This cuff was manufactured by bonding stretched and unstretched silicone sheets, with contacts sandwiched between them. The cuff is cut out and then self-spirals in a tubular shape.

Recently, new fabrication techniques made it possible to use Pt-foil contacts molded in dip-coated silicone cuffs [19], and to use interdigitating tubes, invented by Kallesøe, et al. [29], as a closing mechanism (see Fig. 1).

Applications of Nerve Cuffs for Recording

A peripheral nerve contains many thousands of nerve fibers, each of them transmitting information, either from the periphery to the central nervous system (afferent fibers) or from the central nervous system to the periphery (efferent fibers). Efferent fibers transmit information to actuators, mainly muscles, whereas afferent fibers transmit sensory information about the state of the organ and events such as muscle length, touch, skin temperature, joint angles, nociception, and other modalities of sensory information.

Most peripheral nerves contain both afferent and efferent fibers, and can thus be seen as a bidirectional information channel. Since nerve fibers are excitable by electrical stimuli, it is possible to influence the neuromuscular system artificially; e.g., to activate muscles by electrical stimulation of nerves.



1. (a) The silicone cuff electrode as described in the text (courtesy Dr. M.K. Haugland); the cuff's closure mechanism was developed by Kallesøe, et al. [29]. (b) Tripolar configuration with short-circuited end-contacts.

There are numerous applications of nerve cuffs for recording, divided into three groups:

1. *Studies of the neuromuscular system (patho)physiology, in particular, chronic studies in freely moving animals.* Examples of this kind of application include Hanson, et al. [11], who recorded the "central respiratory drive" from the phrenic nerve in fetal sheep; Hoffer, et al. [23, 24], who estimated conduction velocities to assess the order of motor unit recruitment in walking cats; Marshall and Tatton [38], who recorded from joint receptors in the cat; Milner, et al. [40], who recorded cutaneous afferent activity from the median nerve of a monkey during grasping and lifting; Little [34], who recorded spinal reflexes after spinal cord transection in cats; Loeb, et al. [35], and Loeb and Peck [36], who recorded motor activity during locomotion; Palmer, et al. [42], who obtained cutaneous receptor activity from median nerves in cats; and Stein, et al. [54], who used cuffs to classify sensory patterns during locomotion. Sahin, et al. [46], used the spiral cuff to record respiratory output in cats from the hypoglossal and the phrenic nerves.

2. *To monitor the state of the nerve, especially regeneration after induced damage.* Examples of studies of axotomized nerves and regeneration of nerve fibers can be found in [2, 8, 9, 22, 30, 31, 32].

3. *To use sensory signals as feedback information to control neuroprosthetic devices.* Studies in animals include [12, 13, 14, 25, 41, 43]. Woodbury and Woodbury [61] stimulated and recorded with cuff electrodes around the vagus

In humans, cuff electrodes have been used for the control of drop-foot and hand-grasp.

nerve in rats to study electrostimulation as an anticonvulsive treatment. Jezernik, et al. [27], recorded signals from bladder afferents to use for bladder control.

In humans, cuff electrodes for sensory recordings have been used in hemiplegic subjects for the control of drop-foot stimulation [15, 60] and for characterization of nerve signals during standing [1], and in quadriplegic subjects for the control of hand-grasp [18, 47-49].

Nerve Damage

With the use of nerve cuff electrodes in human subjects, the cuff-induced nerve damage becomes an important matter. Obviously, the presence of the nerve cuff induces changes in the tissues: connective tissue covers the cuff electrode, and the shape of the nerve changes as to completely fill the cuff (see, e.g., Larsen, et al., [33]).

According to Hoffer [26] the cuff should be at least 20% larger than the diameter of the nerve to prevent compression neuropathy caused by postsurgical edema [2, 55]. Compression neuropathy affects the larger fibers most severely [7, 58]. An effort to minimize compression neuropathy was made by Naples, et al. [39], by the use of the self-spiraling cuff.

Stein, et al. [52], observed in a nine-month implant in the hindlimb of a cat (lateral gastrocnemius-soleus nerve) that there was a small reduction in the number of larger fibers as compared with the same nerve in the contralateral leg. No associated changes in electrophysiological recordings were reported.

Experimental Methods

Electrode Description

Electrode contacts were made of platinum foil (25 μm thick) and Teflon-coated, multistranded stainless steel wires were spot-welded to the contacts. For the tripolar electrodes, three such contacts were wrapped around a Teflon-coated mandrel of 2.0 mm diameter. The mandrel with the contacts was dipped in silicone (Medical Adhesive Type A, Nusil) diluted with heptane, to form silicone tubes with embedded platinum contacts. After curing of the silicone, the tube was taken off the mandrel, cut to its final length, and an interdigitating locking mechanism [29] was cut out at one side of the cuff. See Haugland [19] for a detailed description of electrode fabrication. A platinum contact was added to the outside of the cuff to serve as a reference electrode.

The resulting cuffs had a length of 24 mm, an inner diameter of 2.0 mm, and an outer diameter between 3 and 4 mm. The ring-shaped contacts were 2.0 mm wide. One contact was placed in the center of the cuff, and the other contacts were 1 mm from the cuff ends. The contact separation (between centers) was thus 10 mm.

A subcutaneous connector was made by spotwelding the stainless-steel wires to gold-covered contacts and then placed in a Teflon case. The contacts were then covered with undiluted silicone and the connector was dipped in diluted silicone. The silicone could afterwards be perforated with a male connector to make contact.

The electrode and the connector were cured in demineralized water for a week. Then, they were cleaned in an ultrasonic cleaner, first in ethanol and subsequently twice in sterile demineralized water.

Implantation Procedure

The cuff electrodes were implanted in 20 female, 6-month-old, New Zealand white rabbits, under general anesthesia (Hypnorm/Dormicum) and under sterile conditions. There were 14 animals assigned to a long-term implant group (480 days), and six animals to a short-term implant group (14 days). The cuff electrodes were placed on the tibial nerve, just distal to the knee (Fig. 2). Pulling of the wires on the electrode was minimized by having the wires exit the electrode distally and routing them, via a loop just proximal to the knee, to a subcutaneous connector placed in the groin. Each animal was isolated in a cage of 1 × 1 m floor area for 10 days after the operation. Thereafter, the animals were housed in groups of five per cage (2.1 × 1.3 m). The postsurgical analgesic consisted of 0.3 ml Temgesic (0.3 mg buprenorphin/ml) twice a day for three days. The same procedure was used after each subsequent surgical intervention.

Five animals were excluded from the study, leaving 10 animals in the long-term implanted group and five animals in the short-term implant group. Reasons for exclusion were removal of lead wires by the animals during the first days after surgery (3×), one animal developed infection around the implant, and one animal died for unknown reasons.

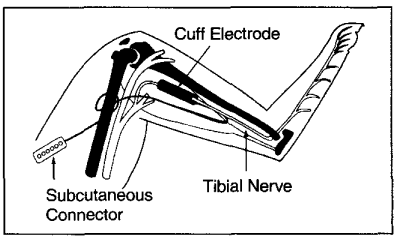
Experimental Procedure

Electrophysiological measurements were made on the day of implantation and 5, 60, 180, 360, and 480 days after implantation in the long-term implant group, and at days 0, 5, and 14 for the short-term implant group. All measurements were made with the animal under general anesthesia (Hypnorm/Dormicum). The animal was placed on a water-heated mattress, and in a wrapped thermo-blanket. The skin temperature of the lower leg was kept constant at 29 ± 0.5°C by using an infrared lamp. Central body temperature was monitored with a rectal probe and was constant at approximately 34°C during the entire experiment.

The subcutaneous connector to the lead wires was taken out via an incision through the skin. A male connector was pinched through the insulating silicone layer to make connection to the electrode. Nerve signals detected by the cuff electrodes were amplified with a differential preamplifier with a transformer-coupled input stage (Microprobe AD1). The signals were then further amplified (total gain of 80,000) and bandpass filtered (cut-off frequencies of 200 Hz and 10 kHz; 4th order). The signal was then sampled with a frequency of 30 kHz.

Mechanical Stimulation

Tactile sensory signals in the nerve were evoked by mechanically stimulating



2. The rabbit hind leg, showing the position of the cuff electrode, the subcutaneous connector, and routing of the wires. (Courtesy Dr. M.K. Haugland.)

Most peripheral nerves contain both afferent and efferent fibers, and can thus be seen as a bidirectional information channel.

the foot-pad. Indentations of controlled velocity were made with a linear moving coil motor driving a hard plastic 20 mm diameter probe, which was attached to a force transducer. The leg of the animal was fixated such that the probe made a perpendicular indentation (Fig. 3). Prior to indentation, the probe just touched the uncompressed foot-pad. During indentation, both the cuff signal and indentation force were recorded. Seven different indentation velocities were applied in 10 repeated cycles of increasing velocity.

In Fig. 4(a), $V_{mech}(t)$, a typical response to mechanical indentation, is shown. A background noise with a root mean square (rms) amplitude of about 0.6 μV is present. From power-density spectra, it can be shown that the background noise is of non-neural origin. When the force on the foot-pad increases, the nerve signal increases [Fig. 4(b)], reaching its maximum where the time derivative of the force (dF/dt) is maximal (compare with [12]). When the force reaches a constant level, the recorded signal again approaches its background level. Not shown here is that when the probe is released, there is again a transient nerve response (off-response), though smaller than the "on-response" (see also [12]).

From the force curve, we estimated a 5 msec duration time window where the slope (= dF/dt) was most constant, and calculated the rms value of the ENG-response in that same time period. In this way, we obtained one rms ENG value (averaged from ten indentations) for each of the seven different indentation velocities. In Fig. 4(c), this rms value is shown as a function of dF/dt for a single measurement day (day 60 postimplantation) in one animal. The solid curve is an exponential fit to:

$$\text{rms}(V_{mech})\big|_{indentation} = \text{rms}(V_{mech})\big|_{background} + a \cdot (1 - e^{-b \cdot dF/dt}) \quad (1)$$

From this equation, we calculated a rms value for each animal at each day of measurement for an indentation force of 800 N/s, as indicated by the vertical line in Fig. 4(c). We refer to this value as $\text{rms}(V_{mech})$.

The mechanically induced ENG was used to calculate power-density spectra and to calculate the median frequencies from these spectra. Because sometimes muscle reflexes contaminated the signal, and because this muscle activity appeared in the spectrum below 900 Hz, we used a trimmed median frequency, calculated from the spectrum between 900 Hz and 5 kHz, instead of the median frequency.

Electrical Stimulation

Electrical stimulation was applied to the tibial nerve at the ankle, using needle electrodes approximately 3 cm from the distal cuff end. Rectangular constant current pulses of 100 μs duration and 1.5 times the amplitude needed to evoke maximal responses were used. The peak-to-peak amplitude of the recorded signal was denoted V_{el}.

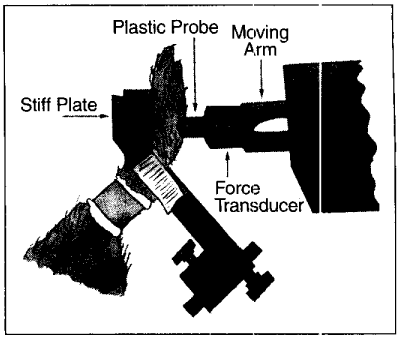
Before the measurements were made, first the magnitude $|Z|$ of the impedance Z between the central contact and the short-circuited end-contact was measured with a current of a few nA, at a frequency of 1.0 kHz, which is in the frequency range of the nerve signal. This gives the series impedance of the tissue between the contacts (i.e., the impedance between the central contact and one end-contact in parallel with the impedance between the central contact and the second end-contact) in series with the contact impedances.

According to Stein, et al. [50], the cuff signal is proportional to the extracellular resistance. Struijk [57] has shown that the 1D model they used holds for cuff diameters up to several millimeters. A relevant measure for the source strength is then the recorded signal divided by measured impedance, to remove the influence of the extracellular impedance:

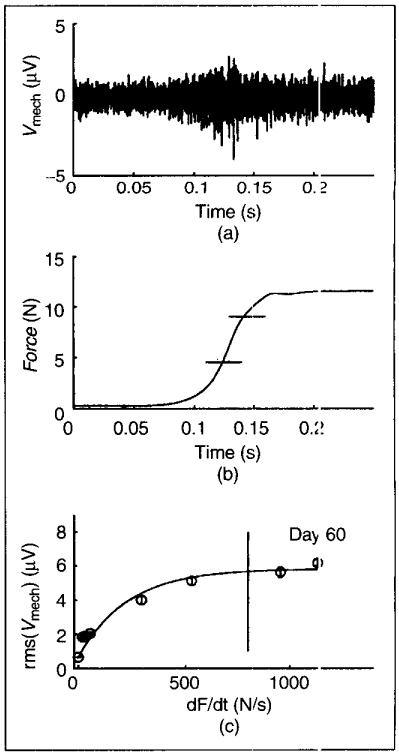
$$I_{mech} = V_{mech} / |Z|, \text{ and } I_{el} = V_{el} / |Z|.$$

Histological Study

For the histological study, the results of which are presented by Larsen, et al. [33], a total of 40 rabbits were used, including the ones described above. Apart from these experimental animals, a con-



3. The mechanical part of the experimental setup. The rabbit's lower leg is placed in a holder; the foot-pad is indented with a probe instrumented with a force transducer and mounted on the arm of a linear motor.



4. (a) Example of mechanically induced nerve signal, V_{mech}; (b) the applied force on the foot-pad of the rabbit; (c) the rms value of the recorded nerve signal, rms(V_{mech}), as a function of rate of change of the applied force dF/dt.

Cuff electrodes may be a valuable component to providing sensory feedback information in fully implantable FES systems.

trol group (n = 10) and a sham-operated group (n = 10) were also used. Six experimental animals, five sham-operated animals, and five control animals were sacrificed on day 14 after surgery, whereas the other animals were sacrificed on day 480 postsurgery. Transverse nerve sections were made at levels proximal to the cuff, at the mid-cuff level, and distal to the cuff, and from the nerve in the contralateral leg. Diameter histograms could thus be obtained at various places with respect to the nerve cuff (see [33] for details).

The results that are most relevant for comparison of the electrophysiological measurements with the histological findings will be quoted from [33] and will be used in the following section.

Results

Nerve Signal and Impedance

Figure 5(a) shows the rms ENG evoked by mechanical stimulation, rms(V_{mech}), for all 10 animals as a function of time. In Fig. 5(b), the mean values with standard errors are drawn. A statistically significant (p = 0.01) decrease in amplitude by 50% was seen from day 0 to day 5, after which there was no further significant change. (In Fig. 5(a) it can be seen that most of the increase and subsequent decrease of the mean rms(V_{mech}) was due to one animal.)

The same course of events (i.e., a sharp initial decrease in amplitude and a subsequent stabilization) was also observed in the electrically evoked peak-peak CAP (V_{el}).

In the five animals that were sacrificed after 14 days, we saw the same decrease in amplitude from day 0 to day 5, and no further change from day 5 to day 14.

In Figs. 5(c) and 5(d), the mean compound action currents, rms(I_{mech}) and I_{el}, are shown for mechanical and electrical activation. The initial decrease in amplitude is now only observed in I_{el} (approx. 30%, p = 0.02) and not in rms(I_{mech}). No further statistically significant trends are present beyond day 5.

In Fig. 6(b), we see the measured impedance, |Z|, for all animals and all measurement days. In the impedance curve, we see the same pattern as in the compound action potentials: an initial decrease by approximately 50%, with subsequent stabilization.

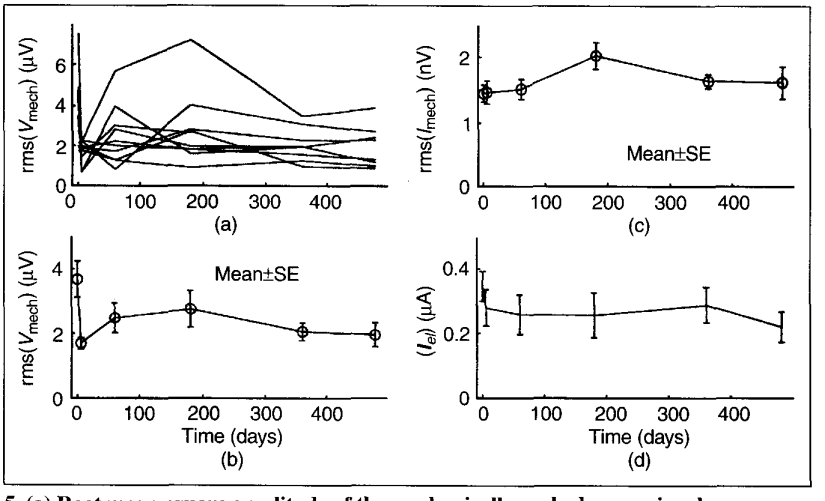
A scatter plot of rms(V_{mech}) versus $|Z|$ for all measurement days in all animals in Fig. 6(a), shows a high and statistically significant correlation between those variables (r = 0.80, p = 0.001). A similar statistically significant correlation was seen between V_{el} and $|Z|$ (r = 0.78, p = 0.001).

Figure 7(a) shows the normalized power-spectral densities of the mechanically evoked ENG for one animal and for different dF/dt, at the day of implantation. It is clear that there are no significant differences among the curves for different values of dF/dt, so there seems to be little spectral information about indentation speed in the ENG. This finding is also true at day 180, as shown in Fig. 7(b). However, the frequency distribution shows a striking difference between day 0 and day 180: the spectrum shifts to lower frequencies. This is reflected in the trimmed median frequency (calculated between 900 Hz and 5 kHz) versus time, as shown in Fig. 7(c), averaged for all 10 animals. The figure shows a statistically significant decrease in median frequency by 15% (p = 0.02), which mainly seems to take place between day 60 and day 180. No initial change in median frequency was observed. There was no change in median frequency of the background noise, indicating that the change is of true neural origin.

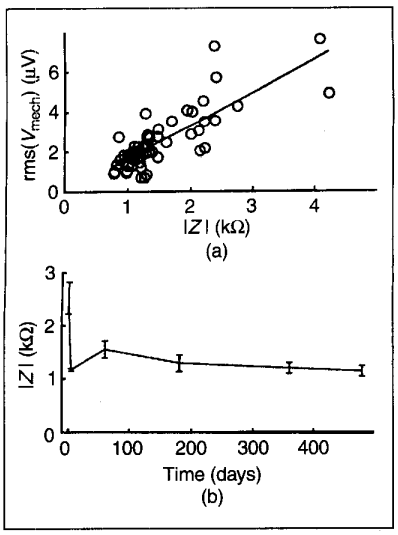
Nerve Damage

The histological study (see Larsen, et al., [33] for details) showed a statistically significant loss of myelinated fibers inside the cuff of 27% (p = 0.002) and distal to the cuff of 24% (p = 0.01), 14 days postsurgery; whereas the numbers of fibers proximal to the cuff and in the contralateral leg were unchanged (all numbers compared with the 14-day control group). The sham-operated animals showed no significant loss of fibers. After 16 months postsurgery there was no longer any significant decrease in the total number of myelinated fibers.

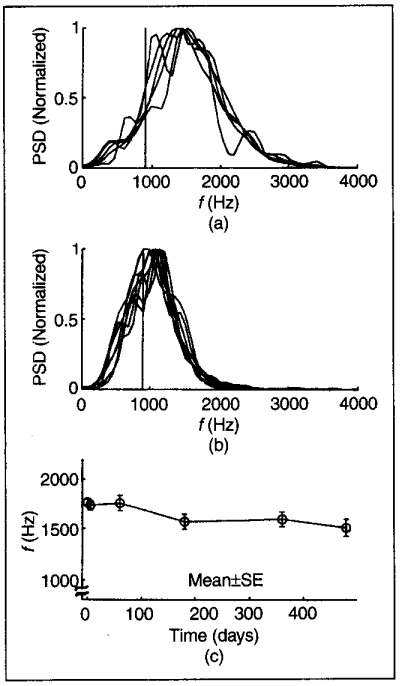
The initial loss (after 14 days) appeared to be nonspecific for fiber size, except for sparing of the smallest fibers. After 16 months, although the total number of fibers was the same as in the control group, there appeared to have been a shift



5. (a) Root mean square amplitude of the mechanically evoked nerve signal, rms(V_{mech}), for all animals as a function of time; (b) the average and standard errors of the curves in (a); (c) the same data as in (b) but divided by the measured impedance; (d) I_{el}, the averaged peak-peak amplitude of the electrically evoked compound action potentials, divided by the measured impedance, as a function of time.



6. (a) Scatter diagram of the rms of the recorded mechanically evoked nerve signal versus the measured impedance; the solid line is the best linear fit (regression line, $r = 0.8$). (b) Measured impedance as a function of time.



7. (a) Normalized power-density spectra of the mechanically evoked nerve signal, for one animal, for different rates of change of indentation force (*dF/dt*), at the day of implantation (the vertical line is at 900 Hz); (b) Same as in (a) for the same animal but now 180 days after implantation; (c) trimmed median frequency (using the power-density spectra above 900 Hz) as a function of time, averaged over all animals.

from the largest fiber group (the largest 20% of fiber diameters) toward smaller fibers, probably indicating that the fibers are regenerating but not to their original diameter. This effect was most pronounced distal to the cuff, but also clearly visible inside the cuff. There were no changes proximally and contrallaterally.

Discussion

In bioelectric measurements, the "bioelectric system" can be thought of as consisting of three subsystems: 1) the bioelectric source that generates currents in 2) the bioelectric medium or volume conductor, and 3) the measurement system, in particular the electrodes. In long-term recordings, each of these subsystems is subject to change. Often, changes in the electrodes are ignored, except for changes in electrode shape and position. We did not see any deformation of the electrodes, nor migration. We will not speculate about the possibility of changes in electrode properties, since we did not measure parameters such as electrode-tissue resistance and capacitance. Thus, assuming that the changes in measured impedances were not caused by changes of the electrode-electrolyte interface, we clearly observed changes in the bioelectric medium. The initial decrease in impedance between day 0 and day 5 was similar to the decrease by 76% (silicone rubber with Pt and stainless steel electrode contacts) and 55% (epoxy instead of silicone) from day 0 to day 4 after implantation in cats, as reported by Grill and Mortimer [10]. In contrast, Stein, et al. [53], did not report any initial change of impedance in mice and cats (silicone cuffs with Pt-Ir contacts). Grill and Mortimer attributed the initial change to fluid accumulation resulting from an increase in vascular permeability in response to the surgical procedure.

Grill and Mortimer [10] found an increase in apparent resistivity after day 5, whereas Stein, et al. [53], also saw a slow increase in impedance, due to encapsulation of the electrode by connective tissue. Figure 6(b) indeed shows this increase between days 5 and 60, but in contrast to the other two studies, the impedance again decreases to the level of day 5.

Upon seeing the initial change in amplitude of the recorded signals, one might ascribe this to nerve damage (change of the bioelectric source). However, the strong linear relationship between amplitude and impedance, as shown in Fig. 6 and derived theoretically by Stein and Pearson [50] and Marks and Loeb [37], implies that the recorded potential divided by the impedance gives a better estimate of the true bioelectrical source strength. The measured impedance, however, is not just the parallel impedance of the two tissue cylinders between the central contact and the two end-contacts, but also includes the electrode-electrolyte interfaces and the impedance of the tissue just around the ring shape contacts. Thomsen [59] estimated that the influence of the last two impedances may be even larger than the impedance of the tissue cylinders inside the cuff. A better way of measuring the impedance inside the cuff would thus be needed to obtain a true measure of the bioelectric source strength. This would, however, require a four-point measurement inside the cuff, and thus an additional contact and lead wire. For future experiments focusing on the relationship between nerve damage and electrophysiological measurement, this may be a worthwhile improvement.

Nevertheless, the initial loss of nerve fiber seems to be reflected in the electrically evoked signal divided by the impedance I_{el}. The peak-peak amplitude V_{el} of the electrically evoked CAP is defined by the activity in the fastest fibers, and thus the fibers with the largest diameters (> 10 μm). Action potentials in fibers with smaller diameters have a larger delay and do not contribute to V_{el}. This may explain the higher sensitivity in I_{el} to the decrease in the number of fibers after 14 days, as compared with the mechanically evoked signal rms(I_{mech}), where all active fibers contribute to the signal—even though larger fibers generally give higher signal amplitudes than smaller fibers, the largest fibers, which are I_a muscle afferents, are not activated by skin indentations.

The fact that fiber regeneration is not reflected in I_{el} is then explained by the fact that the fibers did not regenerate to those larger diameters. Thus, the regenerated fibers did not contribute to the peak-peak amplitude of the electrically evoked signals.

The (trimmed) median frequency, however, showed a change after 60 days postimplantation. This could well be attributed to the regeneration of smaller myelinated fibers, which shifts the relative contribution of fiber activity toward those regenerated fibers. They have a lower frequency content than larger fibers, because of their lower conduction velocity.

The initial change in the number of fibers (at day 14) could not be detected in the median frequency because, initially, all fiber diameters were equally affected, except for the very small fibers, which, however, contribute little to the signal.

For applications in functional electrical stimulation (FES) systems, response characteristics to tactile events are important. No information about the rate of the change of force was present in the spectral distribution of the measured signal, but there was a clear increase in amplitude with increasing *dF/dt* (see also [12]). This means that FES systems relying on measured amplitudes have to be adaptive to the changes in time, such as observed in this study.

Conclusions

Future developments of cuff electrodes will focus on fabrication methods, such as the use of thin-film electrodes, addition of electronics on the cuff, improvement of signal-to-noise ratio, and cuffs for fascicle selective recordings. Application of the cuff in FES systems is not limited to recording of tactile sensory information as feedback for control systems. Cuffs can also be used for sensing of proprioceptive information from, for example, muscle afferents [44, 45] or from bladder afferents to control bladder stimulation [27]. Cuff electrodes may thus be a valuable component to providing sensory feedback information in fully implantable FES systems.

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