The evaluation of peripheral nerve regeneration is of great interest in clinical as well as in experimental situations. However, there are few techniques that give early and quantitative information on the status of the regeneration process. If quantitative assays would be available, different surgical techniques and medications could be evaluated more accurately in relation to axonal ingrowth and functional recovery. The purpose of this study was to investigate the merits of nerve compound action signals (NCASs) recorded electrically and signals recorded with a novel magnetic recording technique. We compared the two techniques in the rabbit peroneal nerve, 2, 4, 6, and 8 weeks after a nerve reconstruction. Our conclusions are that the signals recorded with the magnetic sensor are far more reproducible and less prone to stimulus artifact than the electrically recorded signals. Furthermore, the magnetic recording shows that the number of axons that have regenerated increases with time. Previously, this could only be determined with histological studies. Other ingrowth parameters that can be quantified are the average ingrowth distance, and the variation between axons in ingrowth velocity.
Key words: nerve regeneration • nerve compound action signals • quantitative analysis • electrophysiology • magnetic recording
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A COMPARISON OF ELECTRIC AND MAGNETIC COMPOUND ACTION SIGNALS AS QUANTITATIVE ASSAYS OF PERIPHERAL NERVE REGENERATION

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One of the challenges in the field of peripheral nerve regeneration is the early and quantitative evaluation of the regeneration process in terms of number of active axons in the bundle. In clinical situations, the success rate of a second nerve reconstruction may increase significantly when failing regeneration can be detected early after the initial nerve repair.[11,14] The decision to attempt a second reconstruction can be justified only if it is based on accurate, i.e., quantitative, information on the present state of the nerve. Under laboratory conditions, it is equally important to have a quantitative assay of nerve regeneration, for example, when medications or microsurgical techniques are compared. The evaluation of nerve regeneration is just an example of a situation where quantitative measurements would be desirable. Such a diagnostic tool would also be helpful, for example, to evaluate the extent of peripheral nerve trauma and/or compression or to assess the severity of peripheral neuropathies.

The existing techniques to evaluate nerve regeneration do not meet the criteria of sensitivity and/or accuracy necessary for early and quantitative evaluation. For example, functional recovery may not occur until many months after the reconstruction. Although functional recovery should remain the ultimate proof of the quality of regener-

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ation, it cannot detect regeneration in an early stage. Standard, noninvasive transcutaneous electrophysiological techniques may be useful to demonstrate nerve activity qualitatively, but a quantitative interpretation of the signals is hampered by variations in tissue properties and geometry.[16] In addition, the relatively large distance between the nerve and the electrodes is the reason that this technique has insufficient spatial resolution to detect short regeneration distances on the order of millimeters.

Therefore, we investigated two other invasive techniques that may overcome these problems. Both methods require surgical exposure of the nerve bundle. The first method is the traditional measurement of the extracellular nerve compound action *potential* with a ring electrode.[8] This method is compared with a relatively new technique of measuring the intracellular nerve compound action *current* with a magnetic sensor.[17,20] In principle, both techniques offer greatly improved sensitivity and accuracy compared to transcutaneous measurements. They can be used to measure axonal ingrowth well before functional recovery can be observed.[9,10]

MATERIALS AND METHODS

The common peroneal nerve in 26 New Zealand White rabbits, 12–14 weeks old and 2.8–3.0 kg of weight, was unilaterally transected and reconstructed in accordance with the Erasmus University guidelines for animal research. The animals were divided into four groups of 4, 7, 5, and 10 rabbits that survived 2, 4, 6, and 8 weeks, respectively.

For the recording of the signals, the following sensors and stimulation electrodes were used:

1. The magnetic toroidal sensor. The sensor consisted of a ferrite core which was wound 150 times with 50-μm diameter, insulated copper wire. This toroidal coil was insulated with silicone paint. The sensor had an inner diameter of 2.0 mm, an outer diameter of 4.8 mm, and was 1.5 mm wide.[4] The toroidal sensor measures intracellular action currents, and it has been shown that the signals are relatively independent of surrounding tissues.[15] The recordings must be done with the sensor submerged in saline.
2. The electric sensor. On the proximal side of the magnetic sensor coil, we mounted a ring of 0.5-mm diameter silver wire. This was used as a monopolar electrical sensor. The ground electrode was placed in the saline bath between the electric sensor and the stimulation electrode.
3. The stimulation electrode was composed of two 0.5-mm diameter silver wires, which were embedded in a 2.5-mm diameter epoxy semicylinder, forming a stimulator hook on which the nerve could be mounted. The two wires were placed 2.5 mm apart.

The experiment involved two operative procedures that were performed under general anesthesia for which we used a mixture of nitrous-oxide, oxygen, and enflurane gas. The first operation was performed to create a standardized nerve lesion and reconstruction, and in the second operation we measured the NCASs (nerve compound action signals) in the regenerating nerve.

In the primary operation a lateral incision was made just proximal to the knee and the common peroneal nerve was dissected and separated from the vascular bed over a distance of 20 mm. The nerve was transected with a pair of "Millesi micro scissors" (Inox FD20) at a position 15–20 mm proximal to where it inserts into the peroneus longus muscle. The nerve ends were approximated with a temporary reinforcement suture that was placed between two points at 5 mm proximal and distal to the respective cut ends of the nerve. The nerve was reconstructed with a standardized procedure using three or four epineural microsurgical 10-0 ethilon sutures as described by Millesi[13] and used by many others.[12] After the reconstruction, the skin was closed and the anesthesia was ended. The entire procedure took an average of 40 minutes. No postoperative protection was used and automutilation, wound infection, or wound dehiscention were not observed. The rabbits survived for variable times after the reconstruction operation as described above.

For the terminal (recording) surgery, we exposed the reconstructed common peroneal nerve from the sciatic notch to the knee. This was done through a lateral incision from the sacrum to a point lateral and just distal to the knee. By dividing the insertion of the biceps femoris muscle we could displace the muscle and expose the nerve over its full length. The common peroneal nerve was mobilized and then cut at a distance of approximately 7 cm proximal to the primary lesion. The cut end of the nerve was threaded through the recording sensors and stretched to its original length. The

sensors could be moved freely over the nerve from the proximal cut end to the lesion. The stimulator hook was placed near the lesion at the distal end of *the nerve*. With this hook the nerve could be stimulated at a position varying from 10 mm proximal to 20 mm distal to the lesion. Because the sensors and the stimulator electrodes were all mounted on XYZ micromanipulators, their positions could be determined with a 0.5-mm accuracy. We recorded with four stimulator/sensor configurations as indicated in Figure 1: B_0/A_1, B_0/A_2, B_1/A_2, and B_2/A_2.

During the recording procedure, the tissues were kept moist by creating a bath with skin flaps. The bath was continuously perfused with 0.9% NaCl solution (20 mL/min) which was maintained at a temperature of 37 ± 1°C. In this way, we had good temperature control. The saline is also required for the magnetic recording of the NCASs.[15] When measured in saline, the electrically recorded signals will decrease by 3 orders of magnitude in comparison to signals recorded with the nerve suspended in air. However, the signals recorded in saline will be more reproducible since the amplitude and shape of signals recorded in air varies greatly depending on the amount of moisture surrounding the nerve and the electrode.

The nerves were stimulated with a 50 μs, monopolar, rectangular pulse, sufficient in amplitude to stimulate all viable fibers in the bundle. The electric and magnetic signals were recorded simultaneously and in each recording session four batches of 256 consecutive NCASs were averaged. In this way we could evaluate the signal variability and eliminate artifacts in the recordings.

RESULTS

The results of this study can be divided into two topics. The first deals with a comparison between electrically and magnetically recorded NCASs in healthy nerves. We will focus on the merits of these signals for quantitative analysis, i.e., an analysis in terms of the number of active axons. The second topic deals with the actual evaluation of peripheral nerve regeneration.

Comparison between Electrically and Magnetically Recorded Signals. Figure 2 shows typical examples of magnetic (a) and electric (b) signals recorded in the configurations B_0/A_1 and B_0/A_2. The stimulator/sensor distances are indicated in the figure. Three aspects of these signals are of interest. The first aspect is the latency time, which is the main parameter traditionally extracted from electrically recorded signals. For example, the time of the signal onset is the time in which the fastest axons conduct a signal from the stimulation site to the recording site. Because the distance between the two is known, we can calculate a conduction velocity of these axons. This can be done with the magnetically as well as with the electrically recorded signals.

The second aspect of the signal that is of interest is the amplitude. Table 1 shows the average amplitude for both types of signals recorded in the

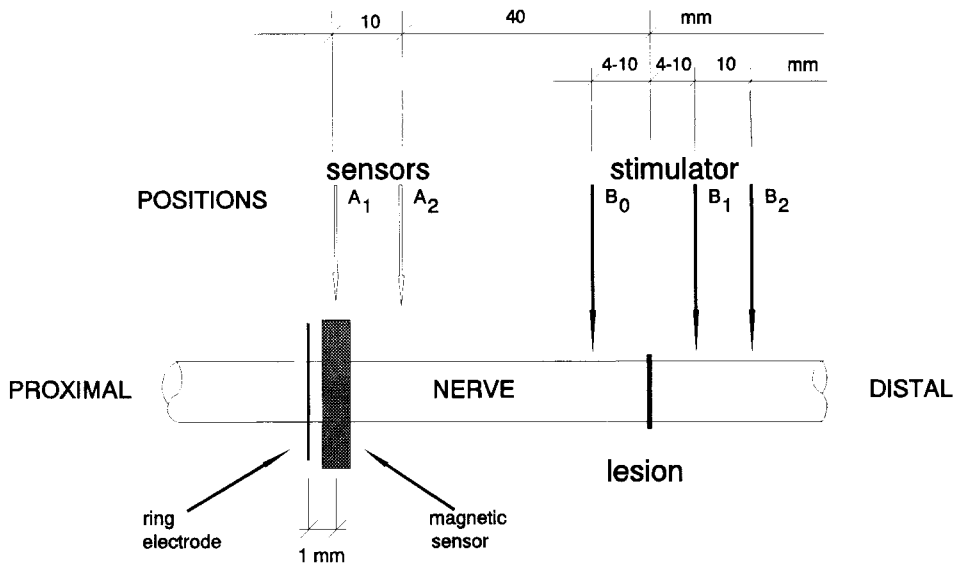

FIGURE 1. Schematic overview of the recording setup with typical locations of the recording **(A)** and stimulation **(B)** sites. The electric and magnetic sensors were mounted together at a fixed distance of 1.0 mm, with the electric sensor on the proximal side.

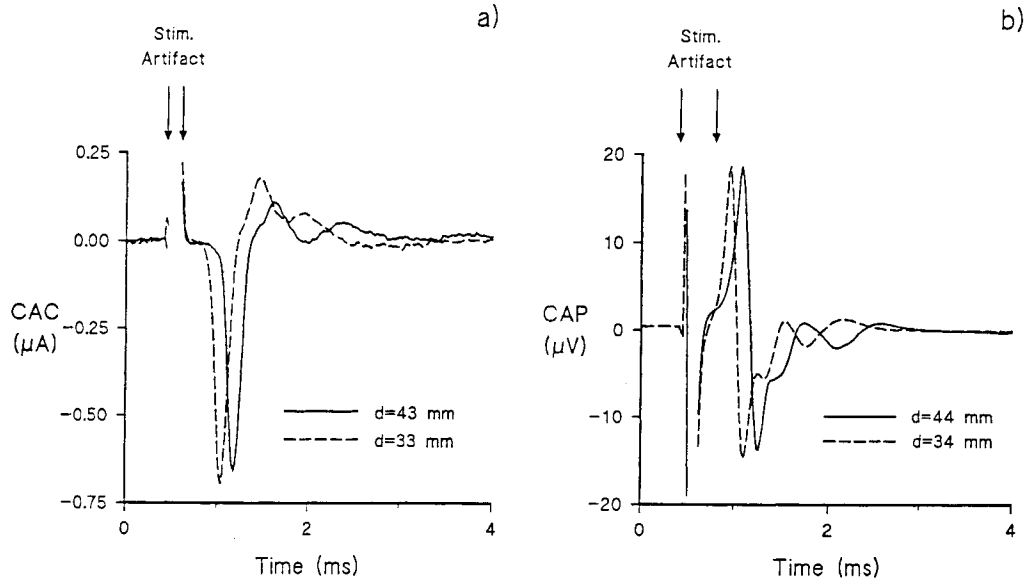

FIGURE 2. Representative examples of magnetically recorded compound action currents (CAC) **(a)**, and electrically recorded compound action potentials (CAP) **(b)** recorded from the same nerve in the B_0/A_1 and B_0/A_2 configurations. The distance, *d*, between the stimulator and recording sensors is indicated. As can be seen in Figure 1, the electric sensor was always 1 mm more proximal than the magnetic sensor.

B_0/A_1 and B_0/A_2 configurations. The relative variation in the magnetically recorded amplitude is less than in the electrical counterpart. Some variation may be expected due to differences between animals, but we expect a good correlation between the magnetic and electric signal amplitude when measured simultaneously in one animal. However, calculation of the correlation coefficient yields a low value of 0.5, demonstrating that the magnetic and electric signal amplitudes recorded in one animal are only weakly correlated. The following analysis shows that the magnetic recordings are more reproducible than the electric signals.

The magnetically recorded signals normally show a decrease in amplitude with an increasing distance between stimulator and sensor. This expected change in amplitude is the result of the differences in the conduction velocities of the axons which leads to more pronounced differences in latencies when the NCASs are conducted over a longer distance.[17] This dispersion leads to signals that are lower in amplitude and more stretched in time. The same argument should hold for the electrically recorded signals. Table 1 shows the average relative change in signal amplitude due to dispersion in percent per millimeter conduction distance for both signals. For this analysis, we used all B_0 recordings in the healthy proximal nerve segment with an average distance between the stimulus electrode and recording site of 40 mm. The average change in the magnetic signal amplitude is -1.4% per millimeter and, as expected, this value was consistently negative in all but one anomalous experiment. On the other hand, the equivalent value for the electric signals is positive (1.0% per millimeter), contrary to what is expected, and has a large variation between experiments. This is a well-known shortcoming of the electrically recorded signals, which are very sensitive to changes in the impedance of the surrounding tissues.[16] This parameter is hard to control under experimental conditions. The amplitude of the magnetic signal is determined mostly by the intracellular action current, and therefore, it reflects the number of active axons in the bundle.[18]

Table 1. Comparison of parameters derived from magnetically and electrically recorded signals in healthy nerves.

Parameter	Magnetic recording	Electric recording
Average signal amplitude	0.80 ± 0.32 μA (n = 26)	31.18 ± 18 μV (n = 19)
Average amplitude reduction due to dispersion (%/mm)	−1.4 ± 1.8 (n = 16)	1.0 ± 6.4 (n = 13)

A third aspect of interest that can be seen in Figure 2 is the duration of the stimulus artifact. In the magnetic recordings, the artifact is far shorter in time than in the electric recordings.

In conclusion, the timing parameters that can be extracted from the electric signal can also be

found from the magnetic signal. In addition, the magnetic signal has a reproducible amplitude that is virtually independent of the uncertain extracellular impedance under the given experimental circumstances.[4,15] Also, the stimulus artifact is smaller in the magnetic than in the electric signal.

The Evaluation of Nerve Regeneration. Figure 3 shows typical examples of magnetic and electric signals recorded in the B_0/A_1 and B_1/A_2 configurations (see Fig. 1). The conduction distance for both measurements was approximately equal. The solid line represents the B_0/A_1 measurement and looks similar to the signals in Figure 2a. However, the broken line was obtained with stimulation of the regenerating, distal nerve segment. There is a clear reduction of the amplitude of the magnetic signal of more than 50% and the latency of the first peak increased by 15%. Both effects were observed in all measurements. The amplitude reduction ranged from 30% to 100%, and the increase in first peak latency time varied from 0% to 30% when conduction distances were kept constant.

A 100% reduction, i.e., no signal, indicates that no excitable fibers have reached the stimulation point. Less severe reductions are due to two effects: (1) dispersion in the distal, regenerating part of the nerve is greater than in a healthy nerve; and (2) only a fraction of all proximal axons has reached the stimulation point. Dispersion does not only lead to amplitude reduction, but also to an increased width of the action signal. Comparing the two signals in Figure 3a, it is clear that the signal width has not increased greatly, demonstrating that the additional dispersion in the distal segment must be modest. Additional evidence that the dispersion effect is not the main factor causing the smaller signals comes from Table 1 which shows the average reduction in amplitude due to dispersion is 1.4% per millimeter conduction distance in a healthy nerve. If the entire amplitude reduction of 50% would be due to dispersion, this would correspond to an increase of conduction distance that is equivalent to 35 mm of healthy nerve. Especially in view of the fact that the first peak latency increased by only 15%, this seems a rather unrealistic situation. The large stimulus artifact and previously described irreproducibility of the electric signal do not allow such conclusions based on Figure 3b.

Figure 4 shows the results as recorded in configuration B_1/A_2 and B_2/A_2. Each dot represents the first peak amplitude of the magnetic signal of a recording in one animal normalized with the amplitude recorded from the same nerve when in the B_0/A_1 configuration (compare with Fig. 3). Each panel (a, b, c, and d) shows all signals recorded in one survival time group. The horizontal axis represents the distance, z, from the lesion to the distal stimulator. Due to the neuroma formed at the site of the surgically repaired lesion, the stimulator could not be moved closer than within 4 mm of the

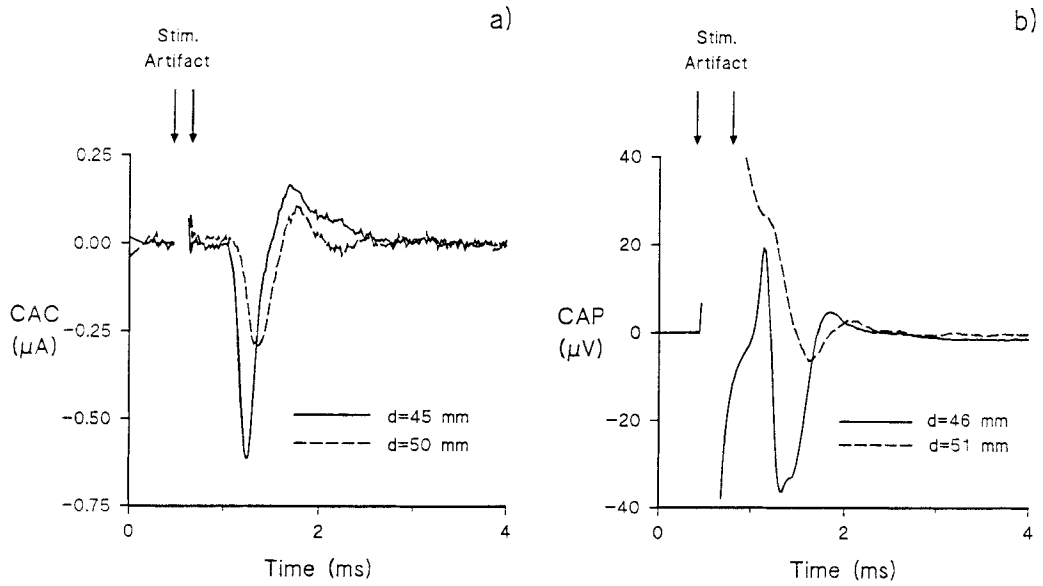

FIGURE 3. Representative examples of magnetically recorded compound action currents (CAC) **(a)**, and electrically recorded compound action potentials (CAP) **(b)** recorded from the same regenerated nerve in the B_0/A_1 (solid line) and B_1/A_2 (broken line) configurations. The distance, *d*, between the stimulator and recording sensors is indicated. The B_0 and B_1 positions were 5 mm proximal and 10 mm distal to the lesion, respectively.

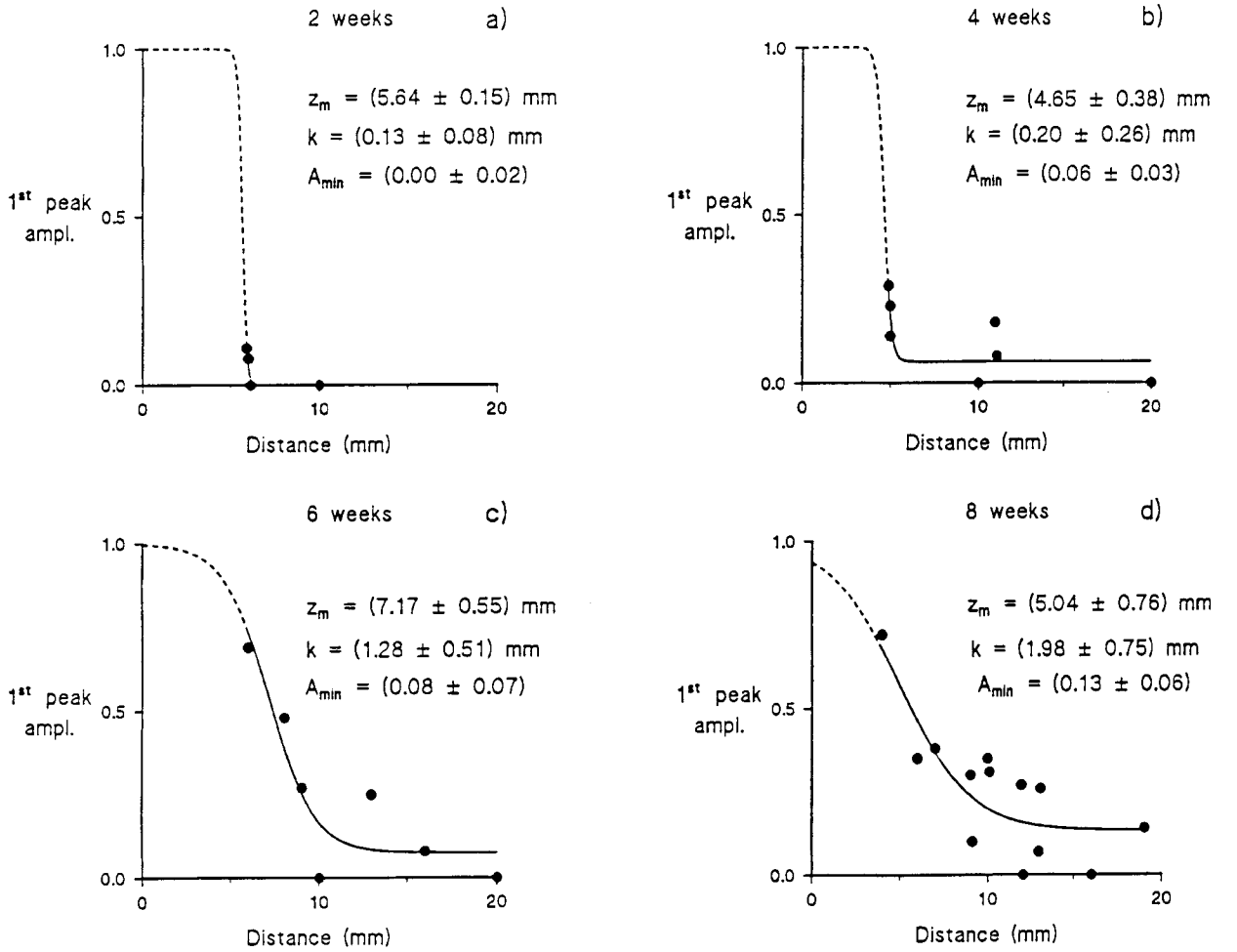

FIGURE 4. The normalized amplitude of the first peak of the magnetically measured compound action current in the regenerating common peroneal nerves of 26 rabbits as a function of the stimulus position. The lesion is at 0.0 mm. Due to neuroma, the stimulator could not be placed closer to the lesion than approximately 4 mm. Each panel gives all data recorded in one survival time group. Not all animals allowed two recordings with the stimulus distal to the lesion as indicated in Figure 1. The mean ingrowth distance, z_m, the variation of the ingrowth distance, k, and the fraction, A_{min}, of axons that have regenerated over the full 20-mm distance considered were used for the sigmoidal curves that were obtained as best fits to the data points.

lesion. The normalized amplitude of the first peak of the magnetic signal is plotted on the vertical axis. By choosing the B_0/A_1 configuration for normalization, the dispersion effect was kept minimal because the conduction distances are approximately equal for the B_1/A_2 and the B_0/A_1 configurations (see Fig. 1). A small error in the normalized amplitude, estimated at 15%, had to be accepted for the amplitudes recorded in the B_2/A_2 configuration (compare with Fig. 2).

To compare the results from the different survival time groups a curve was fitted to these data. This curve can be viewed as the fraction of all proximal axons that has grown a specific distance into the distal segment of the reconstructed nerve. In order to allow a comparison of the data, the equation describing the curve should contain a minimum number of parameters that are expected to vary with the survival time. We chose the following parameters: (a) the average distance that the axons have regenerated into the distal segment of the nerve; (b) the variation in ingrowth distance between axons, reflecting the fact that not all nerves grow with the same velocity; and (c) the number of axons that have regenerated over the full length of the nerve considered (20 mm).

Furthermore, the curve should have the property that the number of ingrown axons decreases with the distance distal from the lesion, independent of the choice of parameters. Since the number of axons distal from the lesion can be no more than a fraction of the number of axons on the proximal side, the curve should approach unity at the lesion. A curve that reflects all these properties

is the standard sigmoidal curve. The parameters in the equation for this curve are A, which represents the fraction of all axons proximal to the lesion that has grown into the distal segment of the reconstructed nerve. The parameter z_m represents the average regeneration distance of the axons, k represents the variation in the regeneration distance between axons, and A_{min} is a measure of the number of axons that has regenerated the full 20-mm length of the nerve.

$$A = A_{min} + \frac{1 - A_{min}}{1 + e^{\frac{z - z_m}{k}}}.$$

When the regeneration time increases from 2 weeks (Fig. 4a) to 8 weeks (Fig. 4d), the regeneration distance, z_m, initially increases, although at 8 weeks there seems to be a setback. As expected, the spreading in regeneration distance increases with time, which makes the curves less steep. Also, the number of axons that have completely regenerated increases with time. In the electrically recorded signals, the variations in amplitude, due to the changes in impedance of the interposing tissues, are so large that diagrams like the ones produced for magnetically recorded signals did not show any significant relationship between survival time, amplitude, and distance between the lesion and the stimulation site.

DISCUSSION

The goal of this study was to compare techniques that allow quantitative studies on peripheral nerves without taking histological sections, specifically after a nerve reconstruction. For example, the healing process after a nerve lesion can be subdivided into three steps: the reconstruction, the axonal ingrowth, and the reconnection with the proper target organs. Quantitative measurements of the ingrowth could be used as an indication of the probability of functional recovery. More detailed information on the ingrowth process may prompt specific interventions that eventually lead to improved results.

Quantitative assays would also be of interest in experimental research in which one would like to determine the effect of, for example, surgical techniques, nerve-growth-enhancing compounds, or other substances on ingrowing axons in a damaged nerve. The quantitative information needed consists of a fiber distribution diagram that would give absolute numbers of fibers for a number of fiber size classes. Electrically recorded NCASs have been used for this purpose,[2,8–10] but they can only provide the number of fibers in one fiber class relative to the number of fibers in other classes.[18]

Although this study does not present fiber distributions, we have demonstrated in this article that the magnetic technique is sufficiently reproducible to allow a quantitative analysis along the same lines as presented in the literature.[19] In this article, we have tacitly assumed that the amplitude of the magnetically recorded signal is a measure of the number of fibers in the bundle. This approach is valid as a first indication of the capabilities of this method. However, more accurate results may be expected from a more detailed analysis of the signals, for example, with a 2CAS method.[1,2,17–19] Our present efforts are directed toward this goal.

The electrically recorded signals do not only have irreproducible amplitude, but may also suffer from severe stimulus artifact interference. The stimulus artifact in our electrically recorded signals is between 0.4–0.6 ms in width, while the artifact in the magnetically recorded signals is only 0.2–0.3 ms wide. In order to avoid a coincidence of the nerve signal and the stimulus artifact, the stimulator must be placed at some distance from the recording site. When the stimulus artifact becomes very wide, such as in the electric signals, this distance may become impractically large. In human nerves this effect will be even more pronounced due to the higher conduction velocities.

With respect to the evaluation of the regeneration, several observations can be made from the magnetically recorded signals in the four survival time groups. The first observation is that the number of axons that can be stimulated decreases with an increasing distance between the lesion and the stimulation position. Second, the number of axons that have regenerated completely through the distal segment considered increases with time. These aspects of the nerve regeneration are well known and have been described based on histological studies.[5–7,11]

Furthermore, our data indicates that not all axons grow with the same velocity so that the variation in ingrowth distance increases with time. This is reflected by the parameter k in the fitted curves. The decrease of the average ingrowth distance, z_m, in the 8-week survival time group, compared with the 6-week group, seems paradoxical. However, this may be evidence of a degeneration of those axons that failed to reach the proper target organs.[3] Further research is required to elucidate this point.

In this study, we used antidromic stimulation and proximal recording for several reasons. First,

we found that the immature sprouts distal to the lesion produce considerably smaller signals than the healthy segments of the axons on the proximal side. Further, the signals of the ingrowing axons are probably not very well defined, which would hamper a 2CAS analysis mentioned earlier. Also, it is well-known that one proximal axon may produce more than one sprout in the distal segment[5–7] so that the functional number of axons could be overestimated when recording distally.

So far, the literature has not provided any method to evaluate nerve regeneration quantitatively in an electrophysiological way. This experiment shows that with the magnetic recording method it is possible to evaluate the regeneration of peripheral nerves without taking sections for histological studies.

The goal of this research project is to further develop this novel recording technique. Just recently, an openable magnetic sensor has been developed which can be clipped onto the nerve. This device has made it possible to record NCASs from nerves without having to transect the nerve to place them in the sensor. The characteristics of this device and its performance in comparison with the closed sensor are presently investigated. With this technique, the possibility has been created to do longitudinal in vivo studies in a single animal. In the near future, it should be possible to obtain diameter distribution histograms with absolute numbers of fibers in each fiber size class.

While this study indicates that magnetic measurements can be used to study the effects that different medication or surgical techniques have on regeneration, similar quantitative information would be useful under a variety of other conditions. For example, it would be possible to evaluate the state of nerves that suffer from neuropathies, physical trauma, or compression. When the magnetic recording techniques presented here progress to clinical application, both the physician and patient will benefit from this new, quantitative information.

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