Sequential MR Imaging of Denervated and Reinnervated Skeletal Muscle as Correlated to Functional Outcome

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Chapter 4

Sequential MR Imaging of Denervated and Reinnervated Skeletal Muscle as Correlated to Functional Outcome

Abstract

Object: To prospectively assess the short inversion time inversion recovery (STIR) magnetic resonance (MR) signal intensity changes of denervated and reinnervated skeletal muscle over time in clinical patients.

Methods: This study was approved by the institutional review board, and informed consent was obtained from all patients. Twenty-three patients with complete traumatic transection of the median or ulnar nerve in the forearm were prospectively followed for 12 months after surgical nerve repair. STIR MR images of selected intrinsic hand muscles were obtained 1, 3, 6, 9, and 12 months after nerve repair, and signal intensities of denervated and reinnervated muscles were measured semiquantitatively. After 12 months, hand function was assessed. Signal intensity ratios were correlated to functional outcome with analysis of variance.

Results: Of the 23 patients, 10 had good function recovery, while 13 had poor recovery. For the group with good function recovery, mean signal intensity ratios of $1.267 \pm 0.060$ (standard deviation), $1.357 \pm 0.116$, $1.297 \pm 0.111$, $1.205 \pm 0.096$, and $1.086 \pm 0.104$ were found at 1-, 3-, 6-, 9-, and 12-month follow-up, respectively. In the group with poor recovery, mean signal intensity ratios of $1.299 \pm 0.056$, $1.377 \pm 0.094$, $1.419 \pm 0.117$, $1.398 \pm 0.111$, and $1.342 \pm 0.095$ were found at 1-, 3-, 6-, 9-, and 12-month follow-up, respectively. Comparison of the group with poor function recovery and the group with good function recovery showed significant differences at 6-, 9-, and 12-month follow-up ($P = .035$, $P = .001$, and $P < .001$, respectively), with normalizing signal intensities in the group with good function recovery and sustained high signal intensity in the group with poor function recovery.

Conclusions: STIR MR imaging can be used to differentiate between denervated and reinnervated muscles for at least 12 months after nerve transection.
4.1 Introduction

Several magnetic resonance (MR) imaging sequences have been shown to be useful in the diagnosis of muscle denervation (1–14). After a motor nerve lesion, various histochemical changes occur in denervated muscle, such as an increase in extracellular fluid and an increase in the capillary bed (10,13,15). MR imaging has been used to successfully depict these changes, as affected muscles display higher signal intensity than that of normal muscle on images obtained with T2-weighted short inversion time inversion-recovery (STIR) and gadolinium-enhanced MR imaging sequences, thereby providing a useful aid in the diagnosis of nerve injuries.

After traumatic transection of a peripheral nerve in the forearm, it is important to monitor regeneration after nerve repair, as the chance for successful reintervention is best in the first 6 months after trauma (16–20). Currently, other than clinical evaluation, needle electromyography is the method of choice in the early monitoring of nerve regeneration (21–23). Electromyography can depict subtle electrophysiologic changes in the target muscle, thus giving an indication as to whether regenerating axons have reached it (24). However, electromyography is time consuming, painful, invasive, and both operator dependent and temperature dependent, and the results are sometimes difficult to interpret (25–27).

MR imaging could provide the clinician with a noninvasive and objective tool with which to evaluate motor nerve regeneration by enabling him or her to compare muscle signal intensity over time. Studies in rodent models of denervation and reinnervation have shown that muscle T2 signal increases within the first weeks after denervation, with sustained high signal in the case of irreversible neurotmesis, and returns to normal after successful nerve repair (3,4,13,28,29). However, it is not yet clear how these experimental findings translate to humans. Also, in these studies, T2 relaxation times were measured, while it has been reported that STIR sequences have higher sensitivity in the depiction of muscle denervation (6,12,28,30). Furthermore, there is some ambiguity, as STIR is a variant of fat-suppressed imaging, and fat cell invasion occurs in denervated muscle (31–34).

Hence, the purpose of this prospective clinical study was to determine the extent and time course of STIR signal changes in denervated and reinnervated intrinsic hand muscles in the first 12 months after complete transection and subsequent nerve repair of ulnar or median nerves in the forearm.
4.2 Materials and methods

4.2.1 Patients

In this prospective study, patients were followed for 12 months after traumatic transection of the median or ulnar nerve in the forearm and subsequent surgical repair. Patients were recruited at the department of Plastic and Reconstructive and Hand Surgery of the ErasmusMC University Medical Center between September 1999 and September 2003. We previously established the long-term reproducibility of our semiquantitative measurement and postprocessing method (35).

A total of 27 consecutive patients were recruited, of which four were lost to follow-up (one patient died of unrelated causes, the other three patients changed their address without notice). Functional outcome could not be determined in these four patients, so their results were excluded, which left us the data of 23 patients. In these patients (21 male, two female), mean age was 26.9 years, with an age range of 14–75 years (female patients: mean age, 32 years; age range 24–40 years; male patients: mean age, 28.5 years; age range, 14–75 years). Thirteen patients had surgically confirmed complete transection of the median nerve, and 10 patients had complete transection of the ulnar nerve. In all patients, surgical exploration and nerve repair were performed within 24 hours after trauma.
This study was approved by the institutional review board of ErasmusMC University Medical Center, and informed consent was obtained from all patients.

4.2.2 Acquisition technique

STIR images of the affected hand were obtained 1, 3, 6, 9, and 12 months after nerve repair (at means of 31, 94, 181, 276, and 368 days, respectively) by using a standardized imaging and postprocessing protocol (35). All images were obtained with a 1.5-T MR imager (Gyrosan Intera Powertrak 6000; Philips Medical Systems, Best, the Netherlands), with the standard 20-cm quadrature non-phased-array knee coil. For all examinations, the same fat-suppressed STIR turbo spin-echo sequence was used (repetition time 1693 ms / echo time 15 ms / inversion time 170 ms; 256x256 matrix; field of view, 16 cm; turbo spin-echo factor, five; number of signals acquired, two; section thickness, 3 mm; intersection gap, 0.3 mm; imaging time, 4 minutes) (6,14,28,30). In all subjects, transverse sections of the midhand were obtained parallel to the plane through the first and fifth metacarpophalangeal joints.
and the middle of the second metacarpal bone, with the thumb in neutral position. For this purpose, a subject’s hand was placed in the center of a 20-cm knee coil by using a custom-made wrist cushion (Fig 4.1 A) and was placed as close as possible to the center of the MR imaging bore without causing patient discomfort and without leading to pressure on the affected site or the local nerves and tendons.

Within the wrist cushion, three sealed plastic test tubes were embedded with standard calibration fluid (Philips Medical Systems, aqueous 4.8 mmol/l copper sulfate solution), liquid paraffin, and olive oil, respectively. These substances were chosen because of their inert nature, ample availability, and imaging characteristics. With the imaging parameters used, these substances result in signal intensities that are far apart from each other and from the background. This forces automatic transmitter adjustments to be in the same range with every examination, thereby facilitating postprocessing. All acquired images were stored in 16-bit Digital Imaging and Communications in Medicine format for further processing.

**Figure 4.1:** A, Photograph of the knee coil, wrist cushion, and embedded calibration tubes used in this study. B, STIR MR image shows the contour drawing protocol in a patient with ulnar nerve injury. Two contours are drawn of the thenar muscles innervated by the median nerve and of the adductor pollicis and first interosseous muscles innervated by the ulnar nerve. Note the normal signal intensity of the thenar muscles and the increased signal intensity in all muscles innervated by the ulnar nerve.
4.2. Materials and methods

4.2.3 Post-processing

A common and robust correction method with which to compensate for location-dependent signal variation is to scan a uniform phantom and divide the images obtained in patients by the acquired phantom images (36–38). A phantom that exactly fitted the radiofrequency (RF) coil and that was filled with the aforementioned standard calibration fluid was examined with the same imaging parameters used for clinical imaging. To compensate for the influence on signal intensity of left-right positioning of the RF coil in the MR imaging bore (39), images of the phantom at 11 left-right positions were acquired once.

In-house software written in C (Visual C/C++ 6; Microsoft, Redmond, Wash) was then used to automatically detect the calibration tubes on the patient images on the basis of their shape and signal intensity. From the tube positions, the center of the coil was calculated, which in turn was used to select the phantom image closest to this position. The patient image then was automatically corrected for nonuniformity by dividing it by the phantom image that most closely matched the left-right position of the arm. Previous research has shown that long-term reproducibility of this method is similar to that of T2 relaxation time measurements (35). Total postprocessing time was 5 seconds per examination on a standard personal computer.

4.2.4 Signal intensity measurements

To measure nonuniformity corrected signal intensity in the intrinsic hand muscles, contours were drawn by using our dedicated analysis software and a drawing tablet (Graphire; Wacom, Saitama, Japan). On all images, the intrinsic hand muscles were identified, and two regions of interest were defined (A.R.V., 4 years of clinical experience). The first region of interest included the thenar muscles (abductor pollicis, opponens pollicis, and superficial head of the flexor pollicis brevis), which were innervated by the median nerve. The second region of interest included the adductor pollicis muscle and the first interosseous muscle. These groups were chosen to further minimize the influence of image intensity nonuniformity because with the used imaging settings, these regions of interest were situated very close to each other. Also,
the chosen regions were comparable in size, and the muscles were easily accessible for hand function tests. The other interosseous muscles and the hypothenar muscles were not considered for this study. For both regions of interest, contours were drawn approximately 1 mm within the muscle boundaries to minimize the influence of partial volume effects. The used contour drawing protocol is shown in Figure 4.1 B.

For both regions, the mean signal intensity was computed. Subsequently, a signal intensity ratio was calculated by dividing the signal intensity of the denervated muscle group by that of the nonaffected muscle group. This signal intensity ratio was then used for comparisons in time and correlation to functional outcome.

4.2.5 Functional outcome

Hand function tests were performed 12 months after trauma (A.R.V., 4 years of experience). As it is known that axons of the median and ulnar nerves have a growth rate of approximately 1 mm per day (40), testing 12 months after nerve transection in the forearm ensured that the sprouting axons had enough time to bridge the forearm and reach the target muscles. Muscle strengths of the affected thenar muscles (abductor pollicis and opponens pollicis muscles) or muscles innervated by the ulnar nerve (first interosseous muscle and adductor pollicis muscle) were scored according to the Medical Research Council scale (41). This scale is used to distinguish muscle contraction into one of six grades: grade 0 indicates no contraction; grade 1, flicker or trace of contraction; grade 2, active movement, with gravity eliminated; grade 3, active movement, against gravity; grade 4, active movement, against gravity and resistance; and grade 5, normal strength. Mean scores for the muscle group innervated by the median nerve and the group innervated by the ulnar nerve were then calculated.

Patients were divided into two groups: a group with good function recovery, defined as a mean grade of 4 and higher, and a group with poor function recovery, defined as a mean grade of less than 4. For this study, a cutoff point of grade 4 was chosen, as this defines muscle strength against resistance, which is the minimum requirement for daily living activities.

4.2.6 Statistical analysis

First, normal distribution of the data was ensured by using the Shapiro-Wilk test. Then the signal intensity measurements in the groups with good and
poor function recovery were compared at the five different time intervals by using analysis of variance. Analysis of variance was also used to compare in-group measurements at different intervals. \( P < .05 \) was considered indicative of a significant difference. For all statistical analysis, SPSS 14.0 for Windows (SPSS, Chicago, Ill) was used.
4.3 Results

After 12 months, hand function tests were performed in all remaining 23 patients. Of these patients, 10 showed good hand function recovery, and 13 showed poor recovery. During the 12 months after nerve repair, a total of 84 standardized STIR examinations were performed (35 in the group with good function recovery, 49 in the group with poor function recovery), which yields an average of 3.7 examinations per patient. At 1-, 3-, 6-, 9-, and 12-month follow-up, a total of 10, 18, 19, 19, and 18 patients, respectively were examined.

In the group with poor function recovery, signal intensity ratios of 1.299 ± 0.056 (standard deviation), 1.377 ± 0.094, 1.419 ± 0.117, 1.398 ± 0.111, and 1.342 ± 0.095 were found at 1-, 3-, 6-, 9-, and 12-month follow-up, respectively. For the group with good function recovery, signal intensity ratios of 1.267 ± 0.060, 1.357 ± 0.116, 1.297 ± 0.111, 1.205 ± 0.096, and 1.086 ± 0.104 were found at 1-, 3-, 6-, 9-, and 12-month follow-up, respectively. The highest signal intensity ratio found in all patients was 1.57; the lowest maximum signal intensity encountered in a patient within the first 6 months after nerve repair was 1.22. The results of the muscle signal intensity measurements are listed in Table 4.1 and Figure 4.2.

The results of statistical analysis for comparison of STIR signal intensity ratios at different intervals in the group with poor function recovery and the group with good function recovery and comparison between these groups are shown in Table 4.2 and Figure 4.3. In the group with poor recovery, a significant difference was found between measurements at 1-month follow-up.

![Figure 4.2: Graphs show STIR signal intensity measurements in the groups with (a) poor and (b) good function recovery.](image)
4.3. Results

**TABLE 4.1**: Mean signal intensity of denervated muscle relative to non-denervated muscle.

<table>
<thead>
<tr>
<th>Months after nerve transection</th>
<th>1</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor function recovery (n=13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of examinations</td>
<td>6</td>
<td>9</td>
<td>11</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Mean relative signal intensity ± SD</td>
<td>1.299±0.056</td>
<td>1.377±0.094</td>
<td>1.419±0.117</td>
<td>1.398±0.111</td>
<td>1.342±0.095</td>
</tr>
<tr>
<td>Good function recovery (n=10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of examinations</td>
<td>4</td>
<td>9</td>
<td>8</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Mean relative signal intensity ± SD</td>
<td>1.267±0.060</td>
<td>1.357±0.116</td>
<td>1.297±0.111</td>
<td>1.205±0.096</td>
<td>1.086±0.104</td>
</tr>
</tbody>
</table>

and those at 6-month follow-up (P = .033). For comparisons between other time points, no significant changes were found in this group. In the group with good function recovery, however, significant differences were found between measurements at 3-month follow-up and those at 9-month follow-up (P = .010). At 12-month follow-up, all measurements were significantly lower than measurements obtained at previous time points (P < .046).

Comparing the groups with poor and good function recovery at the different time points yielded no significant differences at 1- and 3-month follow-up (P = .406 and P = .696, respectively). However, measurements at 6-, 9-, and 12-month follow-up differed significantly between groups (P = .035, P = .001, and P < .001, respectively), showing normalizing signal intensities in the group with good function recovery and sustained high signal intensities in the group with poor function recovery. No relationship between functional outcome and age was observed (P = .39). Also, no differences in functional outcome were found between the group with ulnar nerve lesions and the group with median nerve lesions (P = .28).
**Figure 4.3:** Graph shows mean signal intensity ratios for different groups at different time intervals, with 95% confidence intervals (error bars). At 6-month follow-up and thereafter, significant differences (p<.035) were found between the group with good function recovery (■) and the group with poor function recovery (▲).

**Table 4.2:** Comparison of mean muscle signal intensities at different time intervals (analysis of variance (ANOVA), p values).

<table>
<thead>
<tr>
<th>Months after nerve transection</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Poor function recovery group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.092</td>
<td>0.033</td>
<td>0.061</td>
<td>0.328</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>0.396</td>
<td>0.661</td>
<td>0.404</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>-</td>
<td>0.668</td>
<td>0.094</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.203</td>
</tr>
<tr>
<td><strong>Good function recovery group</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.172</td>
<td>0.623</td>
<td>0.276</td>
<td>0.014</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>0.292</td>
<td>0.010</td>
<td>0.001</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>-</td>
<td>0.099</td>
<td>0.004</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.046</td>
</tr>
</tbody>
</table>
4.4 Discussion

Monitoring of nerve regeneration after surgical repair is of the utmost importance, as additional surgery may be indicated if nerve regeneration fails (18). The chance of success for such a reintervention is best in the first 6 months after initial nerve repair (16–19), so it is important to obtain information on the regeneration process as early as possible. Currently, needle electromyography is the reference standard in the evaluation of early function recovery; however, electromyography has several disadvantages (25–27,42). MR imaging could provide the clinician with a new tool with which to monitor nerve regeneration by depicting axon growth and signs of reinnervation in the denervated end muscles. MR neurography has been used to visualize Wallerian degeneration in the distal stump and nerve regeneration after surgery (2,5,43–48). Similarly, MR tractography could prove useful in tracking the growing axons (49). However, the mere presence of newly sprouted axons in the distal nerve stump does not automatically imply successful function recovery, as sensory fibers could easily grow toward muscles, and motor neurons could take a wrong turn toward the sensory end organs. Thus, methods with which to assess reinnervation of the end muscles also are needed.

It is known that functional outcome after surgical nerve repair often is suboptimal (50,51). In the present study, 10 of 23 patients had good function recovery, whereas the other 13 patients had poor recovery. At first glance, the results of surgical nerve repair may seem poor. However, for this study, not all intrinsic hand muscles were considered, as was the case for the hypothenar muscles and the second, third, and fourth interosseous muscle groups, all of which were innervated by the ulnar nerve. Also, for quantitative comparisons, averages of muscle strengths and image intensities were used, which may have caused a discrepancy between our grading and the clinical point of view. For instance, in the case of a patient with an ulnar nerve lesion, if the first interosseous muscle was poorly reinnervated (MRC grade 2) and the adductor pollicis muscle showed perfect function recovery (MRC grade 5), the average muscle strength grade would be 3.5 and recovery would be classified as poor (mean MRC grade less than 4), even if this patient had almost-normal hand function from a clinical point of view (as the thumb function would be intact). However, because the image intensity measurements in the muscles were weighed in a similar fashion, this seemed the most objective strategy with which to correlate function outcome to signal intensity.

Recent experimental studies in animals have shown that sequential MR imaging examinations may enable one to predict the prognosis of nerve injury by
measuring and comparing T2 relaxation times and T2 ratios of target muscles over time (4,29). Our results in human subjects resemble those found in a rodent model by Yamabe et al (29), with an initial increase in muscle signal intensity after nerve damage, sustained high signal intensity in the case of irreversible neurotmesis, and a return to normal signal intensity in the case of complete recovery. However, the time course in humans appears different. In the present study, we found that the maximum signal intensity in patients with good function recovery was reached at 3 months; however, in patients with poor recovery, this peak was reached at 6 months. In rats, these peaks were reached 2 weeks after nerve repair in the group with good recovery and 4 weeks after nerve repair in the group with irreversible neurotmesis. In the patients in our study, two different forearm nerves were considered, the site of nerve transection varied between the wrist and the elbow crease, and hand positioning in some patients was suboptimal because of accompanying tendon injuries; therefore, it is to be expected that our results are more subject to variation. However, even in the clinical setting, our results show that MR imaging enables differentiation between poor and good function recovery, as signal intensity ratios differed significantly between the two groups at 6-month follow-up and thereafter. Nevertheless, more research is needed to assess the usefulness of STIR MR imaging in predicting functional outcome for individual patients, especially since the variation in maximum signal intensity ratios in the patient group is quite large, with values varying from 1.22 to 1.57.

Usually, when sequential semiquantitative signal intensity measurements are needed, T2 relaxation times are measured. However, in the case of muscle denervation, STIR sequences have been reported to have higher sensitivity (6,12,28,30). Thus, in the present study, we used only a STIR sequence. Previous research has shown that with the standardized imaging and postprocessing protocol used, long-term reproducibility of these measurements is similar to that of T2 measurements (35). When we compared our results with the results of an experimental study by Yamabe et al (29), we found that the maximum mean STIR signal intensity ratio was 1.419 in the present study, while the maximum mean T2 ratio reported in the experimental study was 1.335. Although it is not clear whether the results in humans and rodents can be readily compared, these results seem to indicate that the STIR sequence does indeed have higher sensitivity in the visualization of muscle denervation than do T2 ratio measurements, which enabled us to confirm the findings in previous reports (6,12,28,30).

STIR muscle signal intensities have been reported to be useful, especially in
4.4. Discussion

the acute stage of denervation; however, in the chronic stage of denervation (after 6 months), STIR signal intensities are generally expected to drop, as fatty degeneration of denervated muscle takes place (52). In the present study, it was found that STIR muscle signal intensity ratio was highest at 3-month follow-up in the group with good recovery and highest at 6-month follow-up in the group with poor function recovery. In the former group, signal intensity normalized during the subsequent months (Fig 4.4). In the latter group, after this peak, the signal intensity ratio slowly decreased after 6 months. However, this difference was not significant, and denervated muscles could easily be distinguished after 12 months in all patients with signal intensity ratios still comparable to those reported for T2 relaxation times (Fig 4.5). Thus, STIR MR imaging is able to depict muscle denervation at least during the first 12 months after denervation, and during these 12 months, fatty degeneration does not significantly influence signal. Further research is needed to assess the usefulness of STIR after the first 12 months, however.

![Figure 4.4: STIR MR images in a patient after complete ulnar nerve transection obtained 3 (left) and 12 (right) months after nerve repair. After 12 months, signal intensity of the reinnervated muscles normalized, and the patient had good hand function recovery.](image-url)
A possible limitation of the present study was the fact that not every patient was scanned at all intervals. In theory, the missing values could skew the results and influence the mean values found for the different intervals. It can be seen, however, that the signal intensities in the group with good function recovery show an overall tendency to return to normal, while the signals in the group with poor recovery show sustained elevation. Thus, it does not seem likely that these missing values would result in a significantly different outcome.

Another possible limitation may be the presence of anatomic variants, like the Martin-Gruber and Marinacci anastomosis, in which muscles can have double innervation (53). In these patients, muscles remain functional when one of the two supplying nerves is damaged, which could influence measurements. Thus, we took the utmost care to identify these variants. However, in all patients with median nerve injury, the denervated thenar muscles showed...
increased signal intensity, while in all patients with ulnar nerve injury, signal intensity of the denervated adductor pollicis and first interosseous muscles was increased. Thus, the presence of such an anastomosis in these patients seemed unlikely. In three patients, however, we encountered another anatomic variation in which the deep head of the flexor pollicis brevis was innervated by the median nerve instead of the ulnar nerve. However, since the deep head of the flexor pollicis brevis was not considered in the present study, this had no effect on outcome.

In conclusion, STIR MR sequences can be used to differentiate between denervated and reinnervated muscles by enabling comparison of signal intensities over time. Signal intensity of reinnervated muscle returns to normal, while signal intensity of denervated muscle remains high for at least 12 months after nerve transection. Thus, STIR MR imaging may provide a new method with which to monitor nerve regeneration.
4.5 References


49. Meek MF, Stenekes MW, Hoogduin HM, Nicolai JP. In vivo three-dimensional reconstruction of human median nerves by diffusion tensor imaging. Exp Neurol 2006;198(2):479-482.


