Muscle After Spinal Cord Injury

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Course Description
The morphological and contractile changes of muscles below the level of the lesion after spinal cord injury (SCI) are dramatic. In humans with SCI, a fiber-type transformation away from type I begins 4–7 months post-SCI and reaches a new steady state with predominantly fast glycolytic IIx fibers years after the injury. There is a progressive drop in the proportion of slow myosin heavy chain (MHC) isoform fibers and a rise in the proportion of fibers that coexpress both the fast and slow MHC isoforms. The oxidative enzymatic activity starts to decline after the first few months post-SCI. Muscles from individuals with chronic SCI show less resistance to fatigue, and the speed-related contractile properties change, becoming faster. These findings are also present in animals. Future studies should longitudinally examine changes in muscles from early SCI until steady state is reached in order to determine optimal training protocols for maintaining skeletal muscle after paralysis.

Intended Audience
This course is intended for Neurologists, Physiatrists, and others who practice neuromuscular, musculoskeletal, and electrodiagnostic medicine with the intent to improve the quality of medical care to patients with muscle and nerve disorders.

Learning Objectives
Upon conclusion of this program, participants should be able to:
1. recognize the morphological and contractile changes of muscles below the level of the lesion after spinal cord injury (SCI).
2. recognize the progressive drop in the proportion of slow myosin heavy chain (MHC) isoform fibers and a rise in the proportion of fibers that coexpress both the fast and slow MHC isoforms.
3. determine optimal training protocols for maintaining skeletal muscle after paralysis.

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ABSTRACT: The morphological and contractile changes of muscles below the level of the lesion after spinal cord injury (SCI) are dramatic. In humans with SCI, a fiber-type transformation away from type I begins 4–7 months post-SCI and reaches a new steady state with predominantly fast glycolytic IIX fibers years after the injury. There is a progressive drop in the proportion of slow myosin heavy chain (MHC) isoform fibers and a rise in the proportion of fibers that coexpress both the fast and slow MHC isoforms. The oxidative enzymatic activity starts to decline after the first few months post-SCI. Muscles from individuals with chronic SCI show less resistance to fatigue, and the speed-related contractile properties change, becoming faster. These findings are also present in animals. Future studies should longitudinally examine changes in muscles from early SCI until steady state is reached in order to determine optimal training protocols for maintaining skeletal muscle after paralysis.


MUSCLE AFTER SPINAL CORD INJURY

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Spinal cord injury (SCI) is a devastating condition, and the pareses/paralyses of the skeletal muscles may cause inability to walk and, for cervical cord lesions, impairment of the upper extremities.

The purpose of this review is to evaluate the consequences of SCI on skeletal muscle. The articles assessed describe the morphological changes, both macroscopic and histological, including fiber-type transformation, as well as contractile changes in muscles following SCI. Changes over time after SCI are examined.

SEARCH STRATEGY

In PubMed, searches including “muscle,” “spinal cord injury,” and “spinal cord” were made. In all, 3013 titles of potential interest were identified. First, the titles were studied and, when the title was considered relevant, the abstract was reviewed. Following this, if the abstract was found to be of interest, the full text article was procured. In addition, reference lists from the obtained articles were scrutinized for relevant literature not retrieved from PubMed.

MACROSCOPIC AND MICROSCOPIC ATROPHY

Animal Studies. The macroscopic changes after SCI in animals have been studied primarily in rats, but also mice, rabbits, and cats. SCI in animals can be performed by transection, isolation, or contusion. In spinal cord transection the spinal cord is completely transected after laminectomy, resulting in a complete SCI. Spinal cord isolation is performed with transection of the spinal cord at two levels after laminectomies, combined with bilateral intradural severing of the dorsal roots between the transection points, resulting in complete
deafferentation. Spinal cord contusion is the result of applying a certain amount of compression or impact on the spinal cord after laminectomy. Four weeks after spinal cord transection, a decrease of between 20% and 40% in muscle mass is seen in hind-limb extensor muscles,1–3 with a tendency to return to control values after 30–60 days.1 Fibers start to atrophy in rats as early as 5 days after spinal cord transection,4 and cross-sectional area (CSA) continues to decrease for about 3 months, ending at values that correspond to approximately 45% of controls.5 After 6 months, the average fiber CSA increases to approximately 55% of control values, with a greater increase in type I fibers.5 The same initial degree of atrophy is observed in cats.6,7 In fast muscle the initial atrophy is less, especially in type I fibers,4 but it demonstrates the same tendency to recover after 1 year.8 Other slow and fast muscles of the hind-limb show the same pattern.9,10

Spinal cord isolation results in a 30–46% decrease in muscle mass in hind-limb extensor muscles after approximately 4 weeks,2,5,11,12 with the largest decrease occurring in the fast gastrocnemius muscle.2 The hind-limb flexor muscles decrease similarly in weight.11 The decrease is seen initially after spinal cord isolation but stabilizes after 15–30 days,11,12 except for the soleus muscle, which continues to decrease in weight after 90 days.12 The atrophy after spinal cord isolation is greater than after spinal cord transection.11

Spinal cord contusion also results in a decrease in muscle weight, with a maximum weight decrease of ~25% after 1 week. Three weeks later the muscle weight is normalized for the slow soleus muscle, but the fast gastrocnemius muscle displays a persistent 15–20% decrease, which does not normalize, even after 10 weeks.13

In conclusion, muscle fibers start to atrophy a few days after SCI. Furthermore, spinal cord isolation produces the greatest atrophy, followed by transection and then contusion, where, in the latter, muscle weight tends to normalize after several weeks.

Human Studies. Atrophy of muscle fibers precedes fiber-type transformation.14–17 An early study by Stilwill and Saghal18 investigated 4 traumatic tetraplegic patients at least 6 months after complete SCI at the sixth cervical level and 2 patients with amyotrophic lateral sclerosis, who were included to compare the effect of combined upper and lower motor neuron lesions. They showed that lower motor neuron lesions led to muscle fiber grouped atrophy and fiber-type grouping, whereas upper motor neuron lesions led to preferential atrophy of type II fibers with fiber-type grouping.

Studies that followed revealed that predominant type II fiber atrophy is seen during the first months after complete SCI, followed by type I fiber atrophy in the later stages.15,17 Following incomplete SCI, 6 weeks postinjury, thigh CSA was observed to be 33% smaller in the SCI group compared with controls, when corrected for intramuscular fat. At this time-point intramuscular fat was 126% greater in the SCI group compared with controls. After 3 months, thigh CSA had not changed significantly, but intramuscular fat had increased by a further 26% in the SCI individuals.19 It has been reported that adipocytes constitute up to 30% of the area in muscle biopsies after 8–10 years of denervation.20 SCI individuals, injured 1–16 years previously, have three times more intramuscular fat and almost four times more subfascial fat compared with able-bodied individuals.21

It has been shown that incomplete SCI individuals (5–37 months postinjury) undergo marked atrophy of all affected lower extremity muscles and have a 24% (tibialis anterior) to 31% (quadriceps femoris) smaller CSA in affected muscles compared with controls.22 The magnitude of atrophy after incomplete SCI is less than after complete SCI.22 The CSA of single fibers from chronic (4–17 years) SCI individuals was likewise significantly smaller compared with able-bodied individuals, although 3 of the SCI individuals had almost the same CSA as the able-bodied ones.23 The latter is in line with a study of chronic (>3 years) SCI individuals that showed no decrease in single-fiber CSA, compared with able-bodied individuals. The investigators suggested that the fibers that go through an early degenerative process might be destined to disappear after years of paralysis, and therefore the loss of muscle mass and force could be largely related to a loss of muscle fibers.24

Similarly, in individuals paralyzed up to 9 years, no relationship was found between the duration of paraplegia and the mean fiber area of the quadriceps muscles, even though the mean fiber area was slightly below the normal range in every case.16

Urso et al.25 studied the effects of SCI on alterations in gene expression and respective protein products in human skeletal muscle. They showed that transcriptional activity of the ubiquitin proteasome pathway increased 2 and 5 days post-SCI, and that the protein levels for the proteasome subunit
subsequently increased. The upregulation of the ubiquitin–proteasome pathway augments proteolysis and muscle protein breakdown. Increases in metallothionein gene expression and protease inhibitor (secretory leukocyte protease inhibitor, or SLPI) gene expression were observed to occur simultaneously. Metallothioneins exert protective effects on skeletal muscle, and SLPI inhibits proteolysis in skeletal muscle. These data suggest that the primary signalling networks activated in the days post-SCI are those involved in protein degradation and those that protect skeletal muscle from rapid degradation.25

**FIBER-TYPE TRANSFORMATION**

The energy demand of skeletal muscle contraction is indirectly reflected by myofibrillar adenosine triphosphatase (mATPase) activity.26 mATPase is the most widely used histochemical criterion for characterization of muscle fibers. Fibers are classified as type I (light staining intensity), type IIA (darker staining intensity), and type IIX (darkest staining intensity). The interpretation of this reaction is limited, however, to a relative (light vs. dark) relationship between the fibers from a single section and cannot be used to estimate the true activities of mATPase.27 With regard to nomenclature, type IIX fibers were originally called type IIB in humans, a term used originally called type IIIB in humans, a term used with regard to nomenclature, type IIX fibers were originally called type IIB in humans, a term used with regard to nomenclature, type IIX fibers were originally called type IIB in humans, a term used to estimate the true activities of mATPase.27 With regard to nomenclature, type IIX fibers were originally called type IIB in humans, a term used in some early studies.

The myosin heavy chain (MHC) molecule, the actin-based motor protein associated with muscle fiber contraction, plays a predominant role in specifying skeletal muscle properties.

In humans as well as in cats, three different MHC isoforms are expressed in adult skeletal muscles. These have been identified as MHC I, MHC IIA, and MHC IIX isoforms. The expression of each of these isoforms within a fiber results in the appearance of three different fiber types, that is, type I, IIA, and IIX fibers, respectively. However, in adult rodents, at least four different MHC isoforms are expressed in the limb muscles. These are isoforms MHC I, MHC IIA, MHC IIX, and MHC IIB, corresponding to fiber types I, IIA, IIX, and IIB, respectively. The order of progression of maximal contractile velocities of rodent muscle fibers is such that type I < IIA < IIX < IIB.28

The distribution of fiber types varies between individual muscles in both the upper and lower extremities, and some muscles are dominated by type I fibers (e.g., the soleus muscle), whereas others possess mostly type II fibers (e.g., the triceps brachii muscle). Within a single muscle, the relative distribution of the fiber types can vary, but probably not by more than 10–15% between regions in humans. The interindividual variation in muscle fiber-type distribution is primarily determined genetically in healthy individuals.29 The distribution of type I fibers (slow fibers)/type II fibers (both IIA and IIX, fast fibers) in healthy human individuals, calculated on the basis of the data from various studies cited by Saltin et al.,30 is approximately 40/60 in vastus lateralis and rectus femoris muscles, 50/50 in gastrocnemius, 60/40 in deltoid, 70/30 in tibialis anterior, and 90/10 in soleus muscle. Healthy individuals show no significant difference between female and male fiber-type distribution, or with regard to contractile properties.30,31 No studies have looked at possible gender differences in fiber types postinjury, but no significant differences have been demonstrated in neurological recovery or muscle strength between men and women following SCI.32–34 Studies on comparable gender differences in mice and rats following spinal cord contusion are rare.35,36 They show a difference between genders in percent tissue sparing of the spinal cord and in some locomotor motor scores, with females having more favorable outcomes.

The methods used to determine the MHC and fiber types has varied between studies. In human studies the methods used to examine the MHC isoforms and fiber types have generally been the same. Usually, a needle biopsy has been taken from selected muscles, and the muscle fiber types were determined by histochemical analysis using mATPase at distinct pH incubations. The MHC isoforms have been determined using sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE). Only one study, by Castro et al.,14 classified the fiber types based on both visual and optical density criteria, and one study by Burnham et al.37 used an immunofluorescence technique, as described by Jiang et al.,6,7 to determine the fast and slow MHC distribution. In animals the techniques have generally been the same.

**Animal Studies.** Spinal cord transection at the middle or low thoracic level results in a change toward a fast phenotype in slow flexor muscles such as the soleus muscle, where the MHC composition in normal rats is approximately 90–95% MHC I, 1–10% MHC IIA, 0–2% MHC IIX, and 0% MHC IIB (Table 1).5,12,13,28,38 After transection, a new steady state, as low as 6–20% for MHC I, is acquired,5,39,40
Table 1. Animal studies (rat, cat, rabbit) with paralyses after spinal cord injury, including determination of fiber type and myosin heavy chain (MHC) composition and fiber size.

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Observation time</th>
<th>Muscle(s) investigated</th>
<th>Animal and method of injury</th>
<th>MHC composition</th>
<th>Fiber-type composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grossman et al.11</td>
<td>4, 8, 15, 30, 60 d</td>
<td>SOL</td>
<td>Rat, spinal isolation</td>
<td>Type I 90% to 49%, Ila 18%, Ibx 1% to 33%</td>
<td>Type I from 90% to 6%, hybrid fibers I/II to 78%</td>
</tr>
<tr>
<td>Huey et al.12</td>
<td>4, 8, 15, 30, 60, 90 d</td>
<td>SOL, AL</td>
<td>Rat, spinal isolation</td>
<td>Type I 91% to 16%, Ila 4% to 12%, Ibx 0% to 69%, Iib 0% to 2%</td>
<td></td>
</tr>
<tr>
<td>Hutchinson et al.13</td>
<td>1, 3, 10 wk</td>
<td>SOL, EDL</td>
<td>Rat, spinal contusion</td>
<td>SOL: type Ibx 0% to 1.3%; EDL: type I 12.8% to 0%, Ila 9.7% to 4.2%, Ibx 36% to 48%, Iib 52% to 49%</td>
<td></td>
</tr>
<tr>
<td>Talmadge et al.26</td>
<td>15 and 30 d</td>
<td>SOL</td>
<td>Rat, transection</td>
<td>Type I -90% to 60%, Ibx and Iib increase to 30% and 4%, respectively</td>
<td></td>
</tr>
<tr>
<td>Talmadge et al.25</td>
<td>15, 30, 90, 180, 360 d</td>
<td>SOL, MG</td>
<td>Rat, transection</td>
<td>SOL: type I 95% to 10%, Ila 8% to 30%, Ibx 0% to 45%, Iib 0% to 5%; MG with fewer changes</td>
<td></td>
</tr>
<tr>
<td>Hiraizumi et al.2</td>
<td>4 wk</td>
<td>Q, G</td>
<td>Rabbit, transection and removal L7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Otis et al.5</td>
<td>1, 3, 6 mo</td>
<td>SOL</td>
<td>Rat, transection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Houle et al.104</td>
<td>90 d</td>
<td>SOL</td>
<td>Rat, transection</td>
<td>Type I 90% to 18%, Ila 10% to 65%</td>
<td></td>
</tr>
<tr>
<td>Talmadge et al.20</td>
<td>90, 180, 360 d</td>
<td>SOL</td>
<td>Rat, transection</td>
<td>Type I 90% to 15%, Ila 10% to 34%, Ibx 0% to 48%, Iib 0% to 8%</td>
<td></td>
</tr>
<tr>
<td>Talmadge et al.39</td>
<td>3 and 6 mo</td>
<td>SOL</td>
<td>Rat, transection</td>
<td>Type I 94% to 19%, Ila 6% to 33%, Ibx 0% to 46%, Iib to ~1%</td>
<td></td>
</tr>
<tr>
<td>Graham et al.60</td>
<td>6 mo</td>
<td>SOL</td>
<td>Cat, spinal isolation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Talmadge et al.62</td>
<td>6 mo</td>
<td>SOL</td>
<td>Cat, transection/spinal isolation</td>
<td>Type I from 98% to 68%, similar in type Ila and Iib</td>
<td></td>
</tr>
<tr>
<td>West et al.10</td>
<td>6–12 mo</td>
<td>TA, PI, RF, ST, VI</td>
<td>Cat, transection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lieber et al.1</td>
<td>1 y</td>
<td>SOL, EDL</td>
<td>Rat, transection</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The references are arranged according to observation time; that is, the earliest observation after injury is cited first. G, gastrocnemius; MG, medial gastrocnemius; SOL, soleus; Tr, triceps surae; Q, quadriceps femoris; RF, rectus femoris; VI, vastus intermedius; TA, tibialis anterior; EDL, extensor digitorum longus; PI, plantaris; ST, semitendinosus; AL, adductor longus; d, day(s); wk, weeks; mo, month; y, years (same time-measurement abbreviations apply for all tables); MHC, myosin heavy chain; SO, slow oxidative.
with the greatest rate of protein loss occurring during days 15–30, preceded by a drop in mRNA for MHC I. This correlates with the longer half-life of protein compared with mRNA. The proportion of MHC Ila starts to rise at day 15–30 and reaches steady state around day 100 at 30%.41 MHC IIx constitutes 45% after 6 months,39–41 after reaching steady state values as early as 90 days following transection,41 whereas MHC IIb constitutes only a few percent of the total MHC.39–41 In cats, MHC IIx reaches 17%42 and MHC IIb 14% at 6 months after spinal cord transection.42 MHC IIb is only seen in cats after SCI.41

Sixty days after spinal cord isolation and the resulting acquired flaccid paralysis in soleus in rats, the MHC I level is 49–65%, MHC Ila is 17–18%, MHC IIx is 18–33%, and MHC IIb is 0%.11,12 After another 30 days, a drop in MHC I to 16%, with a rise in MHC IIx to 69%, could be observed.12 This suggests a different time course of MHC changes in rat soleus muscle after spinal cord transection and spinal cord isolation. This may be due to the lack of neuromuscular function after spinal cord isolation, which results in fewer or no signalling pathways being activated.

Spinal cord contusion resulting in hind-limb paralysis with recovery of some locomotor function does not result in any significant changes in MHC composition in the soleus muscle after 10 weeks. The explanation could be an increase in neural activation during the paralysis due to the incomplete SCI.13

Ninety days after spinal cord isolation an increase is seen in type IIx (from 33% to 39%) and IIb (from 49% to 60%) in the medial gastrocnemius muscle (a fast extensor), whereas the tibialis anterior (a fast flexor) increases in IIx primarily (from 29% to 57%) and decreases in IIb (from 52% to 43%), with no type Ila present and 0–0.5% MHC I in both muscles, indicating a different effect on the fast extensor and the fast flexor muscles.43 After spinal cord transection, the medial gastrocnemius muscle shows a decrease in the initially low proportion of MHC I at day 90 with no other adaptations.40 The differences in MHC composition after isolation vs. transection could be caused by the low remaining level of electromechanical activity after transection.41 A fast flexor muscle such as the extensor digitorum longus muscle showed no significant changes 10 weeks after spinal cord contusion in one study.13 The differences between fast and slow muscles might be related to a greater absolute decrease in electromyographic activity in the soleus than in the gastrocnemius muscle, or it may be simply due to the fact that a fast muscle is more resistant to adaptations to reduced activity.41

Fiber-type composition in rat soleus muscle changes similarly 6 months after spinal cord transection in type I from 95% to around 5%, in type Ila from 1% to 13%, in type IIx from 0% to 51%, in hybrid fibers I/II from 2% to 0% (but 71% at 3 months), and hybrid II from 2% to 30%.5 The same tendency toward faster fibers and more hybrid fibers is seen in cats.42 Sixty days after spinal cord isolation in rats, the proportion of type I fibers in soleus muscle was decreased to 6%, Ila was unchanged at approximately 6%, IIx increased from 0% to 7%, and the proportion of hybrid fibers expressing MHC I/II increased up to 78%.11 This is consistent with the lack of change in MHC Ila levels observed after spinal cord isolation. In cats, the same changes were observed, but a small percentage of the fibers (~15%) also express an embryonic form of MHC, which is not seen in normal adult fibers.41 The finding of I/IIX hybrid fibers indicates that the transition from slow to fast muscle does not necessarily go in a direct order through gradually faster phenotypes.5 One year after spinal cord transection in rats the extensor digitorum longus muscle decreased significantly in the proportion of type I fibers from 5.5% to 0.43% and increased in type II fibers.42 If the muscles become spastic after spinal transection, as the segmental tail muscles of the rats do, no significant changes in fiber type are observed after 4 months, and fibers seem to recover. This is probably due to a comparable amount of neuromuscular activity caused in the spastic muscles.45

In conclusion, both spinal cord transection and isolation result in a progressive change in MHC and fiber type toward faster phenotypes, although there may be a different time course. Spinal cord contusion does not result in any significant changes after 10 weeks.

**Human Studies.** Generally, all studied individuals have had a traumatic spinal cord lesion reported as complete, but the definition of a complete injury has been different among the studies. For example, Shields46 considered a lesion to be complete if all three modalities tested, (sharp–dull distinction, position sense, and muscle strength) were absent below the level of the spinal cord lesion, whereas Gerrits et al.47 and Ditor et al.48 used the international standards for neurological classification of spinal cord injury, also called the ASIA (American Spinal Injury Association) classification.
In the ASIA scale, a lesion is defined as complete if there is absence of sensory and motor function in the sacral segments S2–4. Other groups simply indicated that their SCI individuals had a complete injury without explaining their definition of a complete injury. These discrepancies can be an important bias when comparing the studies, because the degree of paresis/paralysis of the muscles from where the biopsy is taken may influence the fiber-type transformation.

The methods used to examine the MHC isoforms and fiber types have generally been the same in all studies.

Pioneering work with regard to fiber-type transformation was done by Grimby et al. in 1976. They showed in 7 SCI individuals 10 months to 10 years after injury that the paralyzed muscles of vastus lateralis, gastrocnemius, and soleus were primarily dominated (estimated to be about 90%) by fibers stained darkly for alkaline stable mATPase (type II).

Since then, the transformations in different muscles and at various time intervals from the SCI have been examined. In particular, the vastus lateralis muscle has been used, but the rectus femoris, soleus, tibialis anterior, gastrocnemius, deltoid, and thenar muscles have also been examined. Tables 2, 3, and 4 present results obtained from the quadriceps femoris, the soleus, and other muscles.

The studies of vastus lateralis show no changes in fiber type or MHC isoform expression within the first few weeks following SCI. Castro et al. concluded that type I to type II fiber transformation does not occur within the first 6 months of injury. Nonetheless, they found a conversion among type II fiber subtypes within the first 6 months. They argued that the predominant response of mixed human skeletal muscle within 6 months of SCI is loss of contractile protein. Likewise, Talmadge et al. found no change in MHC I isoform expression between 6 and 24 weeks post-SCI.

Cramer et al. showed, in contrast to the results in most other studies, a marked decrease in type I fibers between 2–4 weeks and 18–20 weeks postinjury in the same patients followed over time. The type IIA fibers decreased slightly, whereas the type IIX fibers increased significantly between the two time periods. However, their results are based only on 2 individuals. Although the MHC isoform composition normally reflects the percentage of the different fiber types, the results of the study by Cramer et al. also showed smaller changes in the MHC isoform between the two time-points compared with the changes in fiber type.

Burnham et al. found that, within the first month after SCI, the MHC isoform composition remains relatively stable. A transitional period was detected between 1 and 20 months postinjury, where there was a progressive drop in the proportion of slow MHC isoform fibers and a rise in the proportion of fibers that coexpressed both the fast and slow MHC isoforms. They suggested that the MHC change may start as early as 4–6 weeks post-injury. The technique used to determine the MHC distribution was the immunofluorescence technique, and therefore it was different from most other studies. This may be of importance when comparing the studies. The coexpression of slow and fast MHC isoforms was also detected by Talmadge et al. The proportion of slow containing both MHC I and MHC II was small (3%), however, and first observed 24 weeks post-injury. In another study, a decrease in type I fibers was observed 7 and 9 months after injury, whereas no change in the relative percentage of type I and II fibers was seen in biopsies obtained 1–4 months post-SCI.

In the quadriceps muscle, the fiber-type transformation, with downregulation of type I fibers and upregulation of type IIA and IIX fibers, begins between 4 and 7 months post-SCI (Table 2).

The same was found for the soleus and gastrocnemius muscles (Tables 3 and 4). In a longitudinal study of soleus and gastrocnemius muscles, Lotta et al. reported that the MHC isoform and fiber-type percentage began to change toward fast fiber types at 7–8 months post-SCI. Shields found minimal change in fatigue properties of soleus muscle paralyzed for 4–6 weeks, consistent with a histochemical predominance of type I fibers, and thus no large change in fiber type during this time period.

In a transitional period postinjury there is a progressive decrease in the proportion of slow MHC isoform fibers and a rise in the proportion of fibers that coexpress both the fast and slow MHC isoforms. This indicates, like in animals, that the transition from slow to fast muscle does not necessarily go in a direct order through gradually faster phenotypes. The fiber-type transformation will continue until a steady state is reached approximately 70 months postinjury. However, this conclusion is based on cross-sectional observations on MHC isoform expression in two SCI individuals injured 20 and 73 months previously (see Table 2); that is, the new steady state might
### Table 2. Studies on human muscle fiber transformation in the vastus lateralis/rectus femoris/quadriceps muscle after spinal cord injury (SCI).

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Time since SCI</th>
<th>Muscle investigated</th>
<th>Number and lesion</th>
<th>Type I fiber findings</th>
<th>Type II fiber findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scelsi et al.(^{77})</td>
<td>1–17 mo</td>
<td>RF</td>
<td>22 complete paraplegics</td>
<td>1–2 mo: 60%, 4 mo: 60%, 7–9 mo: 43.7%, 10–12 mo: 51.1%, 17 mo: 27.5%</td>
<td>Predominant atrophy of type II fibers (first couple of months) followed by type I fiber atrophy</td>
</tr>
<tr>
<td>Stilwill and Sahgal(^{18})</td>
<td>&gt;6 mo</td>
<td>Q</td>
<td>4 C6 complete SCI</td>
<td>Group atrophy</td>
<td>Group atrophy</td>
</tr>
<tr>
<td>Grimby et al.(^{50})</td>
<td>10 mo to 10 y</td>
<td>VL</td>
<td>7 C5-T10 complete SCI</td>
<td>Decrease in fiber diameter</td>
<td>~90%; decrease in fiber diameter</td>
</tr>
<tr>
<td>Round et al.(^{16})</td>
<td>11 mo to 9 y</td>
<td>Q</td>
<td>7 T4–11 SCI</td>
<td>11 mo and 14 mo: 36% and 40%, &gt;3 y: 0–10%; atrophy</td>
<td>Predominantly type IIB fibers; atrophy</td>
</tr>
<tr>
<td>Greve et al.(^{53})</td>
<td>12–24 mo</td>
<td>VL</td>
<td>4 T4–10 complete SCI</td>
<td>IIA: 11.4–70.9%</td>
<td>IIA: 14.5–24.8%; IIB: 10.7–67.5%</td>
</tr>
<tr>
<td>Ditor et al.(^{48})</td>
<td>1–19 y</td>
<td>VL</td>
<td>6 T4–10 complete SCI</td>
<td>Decrease in fiber diameter</td>
<td>45%; muscle fiber area smaller than in able-bodied subjects</td>
</tr>
<tr>
<td>Gerrits et al.(^{47})</td>
<td>&gt;2 y</td>
<td>VL</td>
<td>6 C5-T9 complete motor SCI</td>
<td>MHC: 3 at 0–1%, 3 at 35–62%</td>
<td>MHC: 12–33%; IIX: 67%, 87%, 88% (low MHC I), and 6%, 30%, 38% (high MHC I)</td>
</tr>
<tr>
<td>Andersen et al.(^{53})</td>
<td>3–20 y</td>
<td>VL</td>
<td>5 C6-T4 complete SCI</td>
<td>MHC: 0.5%</td>
<td>MHC: 21.2%; IIB: 37.2%, coexpressing Ila and Iib: 40.7%, coexpressing Ila and Iib: 0.4%</td>
</tr>
<tr>
<td>Mohr et al.(^{55})</td>
<td>&gt;3 y</td>
<td>VL</td>
<td>6 C6-T4 complete motor SCI</td>
<td>MHC: 4.4%</td>
<td>MHC: 32.6%; IIB: 63%</td>
</tr>
<tr>
<td>Crameri et al.(^{54})</td>
<td>&gt;3 y</td>
<td>VL</td>
<td>6 C6-T7 complete SCI</td>
<td>4.9%</td>
<td>IIA: 9.6%, IICC: 2.0%, IIB: 83.5%</td>
</tr>
<tr>
<td>Burnham et al.(^{37})</td>
<td>0.5–219 mo</td>
<td>VL</td>
<td>12 C6–T8 complete SCI</td>
<td>Slow MHC: 0.5 mo: ~77%; 2.0 mo: 62%; 3.0 mo: 35%; 20 mo: 26%; 219 mo: 14%</td>
<td>Fast MHC: 0.5 mo: 23%; 20 mo: 34%; 3 mo: 33%, 20 mo: 66%; 73 mo: 100%, 219 mo: 85%; coexpressing fast and slow: 0.5 mo: 0%, 2.0 mo: 4%, 3.0 mo: 33%, 20 mo: 8%, 219 mo: 1%</td>
</tr>
<tr>
<td>Crameri et al.(^{52})</td>
<td>2–4 wk and 18–20 wk</td>
<td>VL</td>
<td>2 T5 and T11 complete SCI</td>
<td>2–4 wk: 50%, 18–20 wk: 9%, IIA: 26% to 6%; decrease in CSA of type I (62%)</td>
<td>IIX: 2–4 wk: 19%, 18–20 wk: 80%, IICC: small increase, IIA: small decrease; MHC IIX: large increase; decrease in CSA of type IIA and type IIX</td>
</tr>
<tr>
<td>Talmadge et al.(^{51})</td>
<td>6 and 24 wk</td>
<td>VL</td>
<td>6 C6-T10 complete SCI</td>
<td>MHC isoform: 6 wk: 40 ± 5%, 24 wk: 32 ± 5%</td>
<td>MHC isoform: Ila: 6 wk: 46%, 24 wk: 49%; IIX: 6 wk: 14%, 24 wk: 16%, coexpressing Ila and Iib: 6 wk: 0%, 24 wk: 3%</td>
</tr>
</tbody>
</table>

The references are primarily arranged with cross-sectional studies first followed by longitudinal studies, and subsequent according to time since SCI. C, cervical; T, thoracic; L, lumbar; VL, vastus lateralis; RF, rectus femoris; Q, quadriceps; MHC, myosin heavy chain; CSA, cross-sectional area.
be found anywhere between 20 and 73 months post-SCI. This information calls into question the often used term “chronic SCI” for individuals who have been injured more than 1 year.

When the “new steady state” is reached, all muscles, including the fast vastus lateralis and the slow soleus and tibialis anterior muscles, develop a fiber-type composition with almost exclusively fast type IIX fibers.16,27,37,46,47,53–55

In contrast to the aforementioned studies, others have shown that the magnitude of the decrease in type I fibers is not always correlated with the length of time following SCI. For example, Rochester et al.56 reported 2 individuals who had sustained their SCI 6 years previously. One had almost complete conversion to type II fibers with very few type I fibers remaining, whereas the other showed preservation of type I fibers within the normal range.56 Likewise, Hartkopp et al.57 observed almost exclusively (>99%) MHC I in the tibialis anterior muscle of a long-term paraplegic man. The reason for these observations is uncertain.

Ditor et al.48 studied 6 individuals with long-standing (1–19 years) complete paraplegia, and found that the vastus lateralis muscles had a higher proportion of type I fibers compared with literature values for healthy able-bodied individuals, and there was no significant increase in type II fibers. The reason for this was unclear, but they suggested that longstanding, persistent spasticity might preserve the expression of type I muscle fibers after SCI. A higher proportion of type I fibers in SCI muscles compared with able-bodied individuals was also found by Schantz et al.,58 when they examined anterior deltoid muscle from paraplegics and tetraplegics who had sustained their injury more than 2 years previously.

Gerrits et al.47 assessed the variability in MHC expression of paralyzed vastus lateralis muscles in 6 individuals who had sustained their SCI more than 2 years previously. They found that 3 individuals expressed predominantly MHC IIa and/or IIx, which is consistent with previous studies, whereas others expressed relatively high proportions of MHC I. It seems unlikely that the duration of the lesion was responsible for the high proportion of MHC I. All 3 individuals with high MHC I expression sustained their injury more than 10 years prior to the study, and a new steady state should have been reached. They also found that the muscle spasms could not explain the high level of MHC type I in these individuals, because they only occasional experienced muscle spasms.

Table 3. Studies on human muscle fiber transformation in the soleus muscle after spinal cord injury (SCI).

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Time since SCI</th>
<th>Number and lesion</th>
<th>Type I fiber findings</th>
<th>Type II fiber findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lotta et al.15</td>
<td>1–10 mo</td>
<td>10 C5–T1 complete SCI</td>
<td>1–2 mo: 88%, 5–6 mo: 84%, 9–10 mo: 66%; MHC: 1–2 mo: 83%, 5–6 mo: 80%; 9–10 mo: 70%; atrophy at 8–10 mo</td>
<td>IIa: 1–2 mo: 10%; 5–6 mo: 8%; 9–10 mo: 14%; IIb: 1–2 mo: 2%; 5–6 mo: 8%; 9–10 mo: 21%; MHC: IIa: 1–2 mo: 12%; 5–6 mo: 14%; 9–10 mo: 11%; IIb: 1–2 mo: 5%; 5–6 mo: 7%; 9–10 mo: 19%</td>
</tr>
<tr>
<td>Shields46</td>
<td>Acute &lt;6 wk; chronic &gt;1 y</td>
<td>3 complete SCI (acute); 10 complete SCI (chronic)</td>
<td>Acute SCI: minimal changes in fatigue and relaxation properties.</td>
<td>&gt;90% type II fibers in one chronic SCI, a large percentage being type IIb; chronic SCI: highly fatigable and relaxation properties consistent with predominance of type II fibers</td>
</tr>
<tr>
<td>Grimby et al.50</td>
<td>10 mo – 10 y</td>
<td>7 C5–T10 complete SCI</td>
<td>Decrease in fiber diameter</td>
<td>~90%; decrease in fiber diameter</td>
</tr>
</tbody>
</table>

References arranged according to time since SCI. C, cervical; T, thoracic; MHC, myosin heavy chain.
At the present time there are no explanations for the variation in fiber types just described, but it shows that there may be large interindividual variations. Still there is a consensus that SCI leads to fiber-type transformation toward type II fibers in all muscles in the majority of individuals after SCI below the level of the lesion. In Figures 1 and 2, timelines for the changes of type I and II muscle fibers/MHC after SCI are illustrated with information from the cross-sectional and longitudinal studies that could contribute to two or more points on the timeline.14,15,17,37,51,52

**OXIDATIVE AND GLYCOLYTIC CAPACITY**

Succinate dehydrogenase (SDH) activity is a marker enzyme for aerobic oxidative capacity of the cells, whereas α-glycerophosphate dehydrogenase (GPDH) is a marker enzyme for glycolytic capacity of the cells.14 Type I fibers are slow contracting and well equipped for oxidative metabolism with regard to both enzyme and substrate content. In contrast, type II fibers are fast contracting and contain more glycolytic enzymes and fewer oxidative enzymes than type I fibers.59

**Animal Studies.** Six months after spinal cord transection, oxidative capacity is significantly increased5 in the soleus muscle in rats when it is measured as mean SDH activity. It is stable in cats and has a tendency toward enhancement.7 There seems to be a gradual increase from 1 to 6 months after the injury without reaching a plateau.5 Citrate synthase as a marker of oxidative capacity is also elevated.5 GPDH levels in soleus muscle are stable and equal.

### Table 4. Studies on human muscle fiber transformation showing other muscles after spinal cord injury (SCI).

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Time since SCI</th>
<th>Muscle investigated</th>
<th>Number and lesion</th>
<th>Type I fiber findings</th>
<th>Type II fiber findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lotta et al.15</td>
<td>1–10 mo</td>
<td>MG</td>
<td>10 C5–T1 complete SCI</td>
<td>1–2 mo: 54%, 5–6 mo: 47%; 9–10 mo: 44%; MHC: 1–2 mo: 58%, 5–6 mo: 54%, 9–10 mo: 46%; atrophy at 8–10 mo postinjury</td>
<td>IIa: 1–2 mo: 21%; 5–6 mo: 20%; MHC: 1–2 mo: 25%; 5–6 mo: 33%; 9–10 mo: 36%; MHC: IIa: 1–2 mo: 20%, 5–6 mo: 15%, 9–10 mo: 16%; IIb: 1–2 mo: 22%, 5–6 mo: 31%, 9–10 mo: 38%</td>
</tr>
<tr>
<td>Stillwill and Saghal18</td>
<td>&gt;6 mo</td>
<td>Th</td>
<td>4 C6 complete SCI</td>
<td>Group atrophy</td>
<td>Group atrophy</td>
</tr>
<tr>
<td>Grimby et al.50</td>
<td>10 mo to 10 y</td>
<td>G</td>
<td>7 C6–10 complete SCI</td>
<td>Decrease in fiber diameter</td>
<td>~90%; decrease in fiber diameter</td>
</tr>
<tr>
<td>Rochester et al.56</td>
<td>1–14 y</td>
<td>TA</td>
<td>7 T4–12 complete SCI</td>
<td>Decrease in type I; atrophy less in type I than type IIa or IIb</td>
<td>Increase in type IIA and IIB</td>
</tr>
<tr>
<td>Martin et al.27</td>
<td>2–11 y</td>
<td>TA</td>
<td>5 C6–T4 complete SCI</td>
<td>~14%; CSA of fibers significantly lower compared with controls</td>
<td>~86%; CSA of fibers significantly lower compared with controls</td>
</tr>
<tr>
<td>Schantz et al.58</td>
<td>&gt;2 y</td>
<td>D</td>
<td>6 C4–6 and 8 T3–12</td>
<td>Paraplegics: 59%, tetraplegics: 66%, able-bodied individuals: 42%</td>
<td>Paraplegics: IIA: 25%, IIb: 15%; tetraplegics: IIA: 26%, IIb: 5%; able-bodied individuals: IIA: 17%; IIb: 41%</td>
</tr>
<tr>
<td>Harridge et al.96</td>
<td>2–22 y</td>
<td>TA</td>
<td>9 C7–T10</td>
<td>MHC: 26%</td>
<td>MHC Ila: 65%; Ilx: 10%; MHC Ila: 0.5%; Ilx: 0%</td>
</tr>
<tr>
<td>Hartkopp et al.57</td>
<td>14 y</td>
<td>TA</td>
<td>Th11 complete SCI</td>
<td>MHC: 99.5%</td>
<td></td>
</tr>
</tbody>
</table>

References are arranged according to time since SCI. G, gastrocnemius; MG, medial gastrocnemius; Th, thenar; D, deltoid; TA, tibialis anterior; C, cervical; T, thoracic; MHC, myosin heavy chain; CSA, cross-sectional area.
to control levels in light and dark fibers, respectively, but there is an increase in mean GPDH activity as a consequence of change in fiber composition due to a higher content of dark (fast) fibers. The highest value occurs at 3 months and declines afterward. The fact that the GPDH/SDH ratio is not increased demonstrates maintenance of the oxidative capacity of the soleus muscle.

Six months after spinal cord isolation, the mean SDH concentration per fiber is unchanged, but GPDH levels are significantly elevated. In the fast gastrocnemius muscle, SDH activity is decreased 6 months after transection, with a tendency toward elevated GPDH levels. This reflects a shift in the fast muscle toward a fast fatigable profile. After spinal cord isolation, significantly lower SDH and higher GPDH levels are found; that is, there is a change toward a fast glycolytic profile.

**Human Studies.** In vastus lateralis muscle it was found within 6 months of SCI that SDH and GPDH activity increase to above control values. This supports the conclusion that only long-term inactivation and consequent unloading of skeletal muscle can reduce aerobic–oxidative enzyme levels. The loss of ability to maintain force over repeated contractions during electrical stimulation early after SCI might therefore not be related to the content of enzymes that regulate energy supply.

On the other hand, the oxidative enzymatic capacity in paralyzed muscle from individuals with SCI who had sustained their injury more than 1 year previously is documented to be well below the level seen in able-bodied individuals. In the tibialis anterior muscle, SDH activity in type II fibers decreased by 67% and by 48% in type I fibers in 5 motor-complete SCI individuals who had sustained their injury at the C6–T4 levels, 2–11 years previously. In muscles paralyzed more than 2.5 years earlier, the enzyme activities (SDH and GPDH) were similar across fiber types. In long-term (>2 years) SCI individuals, a correlation is seen between total SDH activity and fatigue resistance.

To our knowledge, no longitudinal studies starting at the early stage of SCI and continuing past 6 months have examined the change in oxidative and glycolytic capacity. The time course for which the oxidative capacity starts to decline is therefore not known.

Low values of citrate synthase activity (reflective of nuclear expression of mitochondrial proteins) and mitochondrial DNA (mtDNA) content have been observed in vastus lateralis muscles of paraplegics when compared with healthy individuals. In addition, a positive correlation between citrate synthase activity and mtDNA content has been documented in SCI individuals.
mATPase ACTIVITY

Animal Studies. In cats, myosin ATPase (mATPase) activity has been reported to increase in whole muscle homogenate after spinal cord transection, probably as a result of an increase in type II fibers. Spinal cord transection had no significant effect on mean mATPase activity between fiber types.6,7 In kittens, 6 months after spinal cord transection, mATPase activity was seen to be elevated in the soleus and medial gastrocnemius muscles. The mATPase level was more closely related to maximum shortening velocity (Vmax) than to contraction time.63

Human Studies. The energy demand of contraction of skeletal muscle is indirectly reflected by mATPase activity.26 The average mATPase activity is not altered within the first 6 months after complete SCI, which is in concordance with the lack of plasticity of type I fibers in the first 6 months after injury.26,7

In a study by Martin et al.27 on tibialis anterior of 5 motor-complete SCI individuals 2–11 years post-injury, the absolute mATPase activity of type I and II fibers was reduced by approximately 40% when compared with controls. The relative mATPase activity was still higher in type II than type I fibers.

In human muscles after SCI, there appears to be a general reduction in absolute activities of metabolic enzymes, with a shift in the metabolic profile of fibers toward the fast glycolytic type. The fact that the SCI individuals were studied more than 2 years post-SCI can be a contributing factor to the reduced enzymatic activities.27

CONNECTIVE TISSUES CHANGES

Animal Studies. An increase in endomysial and perimysial connective tissue is seen in rat soleus and extensor digitorum longus muscles 1 year after spinal cord transection.44 In the rabbit, flaccid paralysis induced by removal of the spinal cord below S7 resulted in diffuse vacuolar, granular, and hyaline degeneration of muscle fibers after 4 weeks, and there was replacement with lipocytes and perimysial connective tissue.2

Human Studies. In long-term denervated human muscle, the atrophic myofibers are substituted with adipocytes and collagen.21,33,55,64,66 The accumulation of collagen in skeletal muscles from chronic SCI individuals is located particularly in the perimysial areas.54,55,64 The high total collagen concentration in paralyzed muscles is probably due to accumulation of types I and III collagen, which are found in epi-, peri-, and endomysium and are the major collagen types in skeletal muscle.64 Type IV collagen, which is located in the basement membranes only, showed no significant difference between controls and SCI individuals; however, Koskinen et al.64 suggested an accelerated type IV collagen turnover in skeletal muscle of SCI individuals, especially after functional electrical stimulation.

Increases in adipocytes and collagen are scarce in human skeletal muscle for up to 1 year after lower motor neuron denervation, but they increase thereafter despite a decrease in mean fiber diameter of the myofibers.20 According to Koskinen et al.64 hydroxyproline concentration, which represents the total collagen content, was two times higher in skeletal muscle (vastus lateralis) from long-term (>2 years) SCI individuals before training, and it was four times higher after functional electrical stimulation training compared with able-bodied controls. Electrical stimulation may increase collagen turnover in skeletal muscle, indicating an adaptive remodeling process of intramuscular collagen in response to training.

VASCULARIZATION

Following complete chronic (>1 year) SCI, arterial diameter, as well as arterial blood flow in the sympathetically deprived and paralyzed leg muscles, are significantly lower than in controls.65–69 However, these reductions are only evident for absolute values, as correcting for the reduced muscle volume following muscle atrophy in SCI individuals eliminates the differences in diameter and peak blood flow.67,68 Vascular atrophy after SCI appears to be closely linked to muscle atrophy. The capillary/fiber ratio of the tibialis anterior muscle from complete chronic paraplegic individuals was found to be within the control range. The capillary density (number of capillaries per mm²), which is independent of variation in fiber size, was within the control range.56 The mean arterial pressure showed no significant differences between individuals with T4–12 SCI and controls.65

Individuals with chronic incomplete SCI, who are mobile, show similar blood flow capacity at rest compared with those who are able-bodied, which is in contrast to complete SCI individuals.70 When muscles from individuals with chronic complete SCI are electrically stimulated and compared with able-bodied individuals, the magnitude of muscle blood flow...
response is similar between groups, but a prolonged time for blood flow to increase (approximately fivefold) is observed in individuals with SCI. Also, the half-time to recovery of blood flow after electrical stimulation is prolonged approximately threefold in individuals with SCI.67 Olive et al.68 showed, however, that increased muscle fatigue in individuals with SCI is not associated with prolonged time for blood flow to increase at the onset of exercise. After cuff occlusion there was significantly prolonged recovery of blood flow to baseline levels, suggesting reduced vascular reactivity in those with complete SCI.67

CONTRACTILE PROPERTIES

Contractile properties can be divided into force-, fatigue-, and speed-related properties. The latter can be subdivided into half-relaxation time and time to peak tension. In speed-related properties, the relationship between stimulation frequency and force production is typically a sigmoidal curve that differs between fast and slow muscles. Higher stimulation frequencies are required to obtain the same level of force production relative to maximum force in fast muscles as in slow muscles. The curve is said to shift to the left for slow muscles and to the right for fast muscles.

Following SCI, the contractile properties of the muscles change, most likely due to muscle atrophy, fiber-type transformation toward predominance of glycolytic type II fibers, and reduced levels of oxidative metabolism.

Animal Studies. As early as 20 days after spinal cord transection, a decrease in contraction time from 28 ms to 18 ms (an 36% drop) was observed in rat soleus muscle, and it stabilized after day 50 at 13.2 ms (Table 5).71

Three and 6 months after transection, faster speed-related properties were observed, with a shorter time to peak tension (45%) and half-relaxation time (55%) at both time-points. Maximum shortening velocities were significantly reduced. The force–frequency relationship shifted rightward as an indication of faster relaxation kinetics. Force generation, measured as maximal tetanic force, was reduced by around 44% (3 months) and 25% (6 months), respectively. For the majority of speed-related properties no significant differences were observed between 3 and 6 months. Fatigue-resistance was reduced by approximately 25% (3 months) and 45% (6 months). This suggests that force-related properties tend to return to starting levels after 3–6 months. Speed-related properties tend to plateau, whereas fatigue-related properties continue to decline.39 One year after spinal cord transection, time to peak tension is similarly seen to decline by 51% of baseline values, absolute peak tetanic tension is unchanged, and tension per square centimeter increases by >100%.8 The latter change may be explained by the higher level of fast myosin isoforms.39

In tail muscles of rats with spasticity as a result of sacral transection, a different effect is observed with a preservation/enhancement of slow properties, for example, prolonged time to peak, but with a loss of fatigue resistance, less tetanic force, and atrophy. Changes may be caused by altered intracellular calcium distribution.72

In mice, spinal cord transection results in an initial (day 7–14) increase in time to peak tension and half-relaxation time of 20–50% in the soleus muscle, but these properties return to starting values at about day 28. These initial changes toward a slower phenotype might not relate to a change in fiber type (which occur later) but rather to changes in intrinsic myofibrillar factors. These myofibrillar factors could be Ca2+-induced Ca2+-release mechanisms, ryanodine and dihydropyridine receptor expression, or free cytosolic Ca2+ concentration after disuse. Absolute peak tetanic tension relative to CSA is preserved. The force–frequency relationship shifted leftward initially, but at day 28 a rightward shift was observed, similar to the initial slower phenotype developing into a faster one.3

In cats undergoing spinal cord transection as kittens, there was a significant decrease (approximately 50%) in half-relaxation time of the soleus muscle after 9 months, whereas the medial gastrocnemius preserved these properties. The maximum shortening velocity was increased in both muscles, indicating different regulating mechanisms. The frequency–tension relationship shifted rightward, corresponding to a faster phenotype for both muscles.63

Measurement of individually dissected muscles (different method than above where in situ measurement was used) 1, 3, and 10 weeks after spinal cord contusion in rats showed a significant decrease in half-relaxation time after 3 weeks, but there were no changes in time to peak tension. Peak twitch and tetanic tension were decreased by the third week but recovered to normal after 10 weeks.13 A study using in situ force measurements of the soleus muscle 2 weeks after spinal cord contusion found a significantly decreased
peak tetanic force and an increased fatigability, but there was no significant difference in peak twitch force or time to peak tension. Also, a significant effect at 1 week of early locomotor training on improving motor recovery was observed. On the single muscle fiber level in the tibialis anterior of the rat, maximum force after spinal cord contusion was decreased by 25% after 2 weeks, but it recovered 4 weeks later. The specific force (force/CSA) remained impaired, indicating a reduction in muscle fiber quality.

Human Studies. The contractile properties of quadriceps, soleus, tibialis anterior, triceps brachii, and thenar muscles have been investigated in humans (Table 6). However, contractile properties more than 1 year postinjury in chronic SCI are almost the same in all muscles. This is likely due to the general transformation of fiber types toward predominantly fast glycolytic fibers in all paralyzed muscles.

That most investigators use the term “chronic SCI” for individuals who have been injured more than 1 year is problematic, because no studies have determined when the contractile properties reach a steady state. Fiber-type transformation is postulated to reach steady state around 70 months post-SCI, thus contractile properties might also not reach a new steady state until years post-SCI. This theory still requires longitudinal studies in order to be validated.

In the first couple of weeks following SCI, only small changes are seen in contractile properties. When the soleus muscle was repeatedly activated in SCI individuals who sustained their injury less than 1 year postinjury, a significant effect on improving motor recovery was observed.106

### Table 5. Studies on contractile properties in animals with spinal cord injury (SCI).

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Time since SCI</th>
<th>Muscle(s) investigated</th>
<th>Animal (number) and method of injury</th>
<th>Contractile properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Landry et al.3</td>
<td>7, 14, 28 d</td>
<td>SOL</td>
<td>Mice, transection</td>
<td>Force reduced, maximum tension is reached at lower stimulation frequency; Pt relative to CSA is preserved; initially a rapid conversion to slower contractile properties, but returning to control values around day 28; similar changes in 1/2RT</td>
</tr>
<tr>
<td>Hutchinson et al.13</td>
<td>1, 3, 10 wk</td>
<td>SOL, EDL</td>
<td>Rats, spinal contusion</td>
<td>At 1 wk, no changes, at 3 wk Pt and Po decreased, but these changes disappeared by week 10; no changes in 1/2RT faster at 3 wk</td>
</tr>
<tr>
<td>Davey et al.71</td>
<td>20–250 d</td>
<td>EDL, SOL</td>
<td>Rat, transection</td>
<td>SOL shows slower contraction time after 20 d, but is stabilized by day 50; twitch posttetanic and cooling potentiation (characteristics of fast muscle); EDL close to normal</td>
</tr>
<tr>
<td>Talmadge et al.39</td>
<td>3 and 6 mo</td>
<td>SOL</td>
<td>Rat, transection</td>
<td>Maximal power output maintained as a result of increased Vmax; reduced ability to sustain locomotor or movement function as a result of increased fatigability</td>
</tr>
<tr>
<td>Roy et al.63</td>
<td>6–12 mo</td>
<td>SOL, MG</td>
<td>Cat, transection</td>
<td>Relative tension (tension/CSA): SOL is maintained, MG is decreased; contraction time and 1/2RT: SOL is significantly shortened; MG is unchanged; maximum shortening velocity and myosin ATPase: both SOL and MG are increased; frequency–tension relationship: SOL and MG shifted toward a faster muscle</td>
</tr>
<tr>
<td>Lieber105</td>
<td>1 y</td>
<td>SOL, EDL</td>
<td>Rat, transection</td>
<td>Faster contraction/relaxation in SOL; maintenance of force-generating capacity in spite of a decrease in CSA; no changes in EDL</td>
</tr>
</tbody>
</table>

References are arranged according to observation time, with the earliest observation after injury cited first. EDL, extensor digitorum longus; SOL, soleus; MG, medial gastrocnemius; CSA, cross-sectional area; Pt, absolute peak twitch; P\text{\textsuperscript{\textcircled{t}}} absolute peak titanic tension; tPt, time to peak twitch; 1/2RT, one-half relaxation time.
<table>
<thead>
<tr>
<th>Investigators</th>
<th>Time since SCI</th>
<th>Muscle investigated</th>
<th>Number and lesion</th>
<th>Contractile properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shields et al. 74</td>
<td>Acute &lt;5 wk, chronic &gt;3 y</td>
<td>SOL</td>
<td>13 above T8 SCI complete: 4 acute, 9 chronic</td>
<td>Acute: minimal change in contraction speed, retained fatigue-resistant properties; chronic: slowing of the contractile speeds of twitch and tetanus; reduction in torque; time to peak and $\frac{1}{2}RT$ prolonged</td>
</tr>
<tr>
<td>Shields 46</td>
<td>Acute &lt;6 wk, chronic &gt;1 y</td>
<td>SOL</td>
<td>13 C5-T8 complete SCI: 3 acute, 10 chronic</td>
<td>Acute: no significant changes present, no significant changes to the M-waves; chronic: torque reduced within 30 s, $\frac{1}{2}RT$ prolonged and maximum rate of relaxation reduced, M-wave amplitude reduced, at 3 min</td>
</tr>
<tr>
<td>Gaviria et al. 75</td>
<td>Acute &lt;10 mo, chronic &gt;10 mo</td>
<td>Q</td>
<td>19 T4-9 complete SCI: 6 acute, 13 chronic</td>
<td>Acute greater fatigue resistance compared with chronic; smaller decline in contractile force and in the velocity by which this force declined; acute smaller alterations in amplitude of the M-wave and smaller decrease in the muscle fiber conduction velocity compared with chronic</td>
</tr>
<tr>
<td>Scott et al. 80</td>
<td>8–144 mo</td>
<td>Q</td>
<td>13 C5-T8 SCI</td>
<td>Lower peak twitch force and fatigue ratio; faster contraction and relaxation; twitch-to-tetanus ratios greater in both conditions</td>
</tr>
<tr>
<td>Rochester et al. 77</td>
<td>1–14 y</td>
<td>TA</td>
<td>7 T4–12 complete SCI</td>
<td>Less force; less able to generate torque; rise time of a twitch and tetanic contraction shorter; $\frac{1}{2}RT$ slower with repeated tetanic stimulation during the fatigue test</td>
</tr>
<tr>
<td>Gerrits et al. 31</td>
<td>1–21 y</td>
<td>Q</td>
<td>7 C5-T5 SCI</td>
<td>Force–frequency relationship shifted to the left; faster contractile properties; maximal rate of force rise greater; $\frac{1}{2}RT$ shorter</td>
</tr>
<tr>
<td>Thomas et al. 79</td>
<td>1–24 y</td>
<td>TB</td>
<td>72 C3–7 SCI</td>
<td>Weaker forces during maximum voluntary contractions; whole muscle strength reduced; peripheral motor conduction times similar for SCI and Ab</td>
</tr>
<tr>
<td>Gerrits et al. 87</td>
<td>1–27 y</td>
<td>Q</td>
<td>7 C5-T8 SCI</td>
<td>Fatigue resistance negatively correlated with the time since injury</td>
</tr>
<tr>
<td>Häger-Ross et al. 83</td>
<td>&gt;1 y</td>
<td>Th</td>
<td>12 C4–6 SCI</td>
<td>Strong twitch forces of paralyzed motor units; weak tetanic forces; half-maximal force achieved at low frequencies; slowing of conduction velocities, twitch contraction times, and EMG durations similarly</td>
</tr>
<tr>
<td>Klein et al. 89</td>
<td>&gt;1 y</td>
<td>Th</td>
<td>7 C4-C6 SCI</td>
<td>Unit force declined to 8–60% of initial after 2 min of stimulation; all motor units were influenced similarly</td>
</tr>
<tr>
<td>Yang et al. 82</td>
<td>1.5–16 y</td>
<td>Th</td>
<td>10 C5-6; 1 C1-2</td>
<td>Varying reduction in motor units; motor units greatly enlarged and produced an average of up to sixfold the normal force</td>
</tr>
<tr>
<td>Gerrits et al. 76</td>
<td>1.5–24 y</td>
<td>Q</td>
<td>7 C5-L1 SCI</td>
<td>Averaged over all angles, SCI torques 35% of those in controls; force–frequency relationship shifted to the left</td>
</tr>
<tr>
<td>Butler et al. 88</td>
<td>2–15 y</td>
<td>Th</td>
<td>15 C5–7 SCI</td>
<td>Larger force declines in paralyzed muscles (60%) compared with control muscles (15%)</td>
</tr>
<tr>
<td>Thomas 78</td>
<td>2–23 y</td>
<td>Th</td>
<td>17 cervical completely paralyzed Th</td>
<td>Half of paralyzed muscles weaker tetanic forces and higher twitch/tetanus force ratios; reduced frequency to produce half-maximal force, shift to lower frequencies of the overall force frequency relation; strong motor units in SCI; half of the paralyzed muscles lower M-wave amplitudes</td>
</tr>
<tr>
<td>Gerrits et al. 54</td>
<td>&gt;2 y</td>
<td>Q</td>
<td>8 C3-T12 SCI</td>
<td>Force–frequency relationship shifted to the left; force–response reduced; contraction speed increased; maximal rate of force rise higher 50–90% of motorneurons lost; size of remaining units increased; average twitch force of motor units increased by up to fivefold</td>
</tr>
<tr>
<td>Gordon et al. 81</td>
<td>No description</td>
<td>Th</td>
<td>11 C2–6</td>
<td>References arranged according to time since SCI. C, cervical; T, thoracic; TA, tibialis anterior; Q, quadriceps; SOL, soleus; Th, thenar; TB, triceps brachii; Ab, able-bodied; $\frac{1}{2}RT$, one-half relaxation time; CNS, central nervous system.</td>
</tr>
</tbody>
</table>
than 6 weeks earlier, the twitch and tetanus only showed minimal changes. The soleus muscle still responded as would be expected from a slow endurance muscle.46,74

Because the contractile properties change together with fiber atrophy, fiber-type transformation, and changes in oxidative metabolism, one might suggest that the changes start to occur around 3–7 months post-SCI. Further studies are required to confirm this possibility.

In the quadriceps muscle of SCI individuals who have sustained their injury less than 10 months (mean ~7 months—acute group) or more than 10 months (mean ~67 months—chronic group) previously, it was shown that the acute group had greater fatigue resistance, with a smaller decline in contractile force and velocity during stimulation, smaller alterations of M-wave amplitude, and a limited decrease in muscle fiber conduction velocity compared with the chronic group.75 These results suggest that the contractile properties continue to change 10 months after SCI.

The force-related changes seen in both complete and incomplete chronic SCI individuals more than 1 year post SCI show a decrease in force in all paralyzed muscles.76–79 Quadriceps muscle torque in individuals with SCI was 35%,76 and peak twitch forces were 62% of the values in controls.80 Atrophy is the factor responsible for the greatest loss of whole muscle strength—that is, the sum of voluntary and paralyzed muscle fractions.79 One study of thenar muscle showed that approximately half of the SCI individuals who had been paralyzed for up to 23 years were as strong as those of controls, whereas the other half were significantly weaker than controls. Atrophy was also less visible in the strong SCI individuals. There is no obvious explanation for the observation of strong thenar muscles.78 A study of single-fiber mechanics from chronic (>3 years) SCI individuals showed no difference in absolute fiber peak power between SCI and control individuals. Accordingly, the investigated fibers showed no signs of atrophy.24

There is a general reduction in the number of motor units in both completely and partially paralyzed thenar muscles of chronic SCI individuals.81,82 In one study, 50–90% of the motor units were lost. The size of the remaining units increased, and there was an inverse correlation between the number of surviving motor units and average twitch force of single units. The enlarged units produced up to six times the normal force.78,81,82 This enlargement probably occurs by extensive sprouting of motor nerve terminals to innervate more muscle fibers.83

A study of thenar muscles from chronic cervical SCI individuals showed strong twitch forces but weak tetanic forces. The lower tetanic forces for most paralyzed units suggest that fiber atrophy was severe enough to counteract any force enhancement from increases in innervation of more fibers by surviving axons. The thenar muscles paralyzed by SCI retain a population of motor units with heterogeneous contractile properties.84

In chronic SCI, the speed-related changes show faster contractile properties and shorter half-relaxation time in the examined muscles, most likely arising from changes in muscle fiber composition toward predominance of fast glycolytic muscle fibers.83,74,77,84 In one study, the maximal rate of force rise (isometric tetani) was about 50% faster, and half-relaxation time was about 20% shorter in paralyzed quadriceps muscle compared with normal control muscle.31 When compared with control muscles, faster contraction and faster relaxation of paralyzed quadriceps muscle is seen in both non-fatigued and fatigued conditions.86 In chronically paralyzed soleus muscle, the same results were confirmed by a 20-ms shorter time to peak twitch torque and a 25% shorter twitch half-relaxation time when compared with soleus muscle from individuals with acute paralysis.85 Investigations of single fibers from chronic SCI individuals have also shown increased contraction velocity.24

However, a study of thenar muscle from chronic SCI individuals showed no changes in the contractile speed, although the study group had significantly weaker tetanic forces.78 Chronic paralyzed quadriceps muscles had faster contractile speed but no changes in relaxation time.84

Furthermore, the torque–frequency relationship should be closely associated with the contractile speed of the muscle. In chronic SCI individuals there is a leftward shift in the force–frequency relationship. There is a significant reduction in the stimulus rates that can evoke half-maximal force compared with controls.31,78,84 This leftward shift in the force (torque)–frequency relationship in chronic SCI individuals is actually opposite to what might be expected. The paralyzed muscles of SCI individuals are typically composed of type II fibers, but the force–frequency relationship is shifted to the left, a feature that is normally associated with a slowing of contractile properties. Gerrits et al.76 investigated whether differences in torque–angle relationships between the quadriceps in SCI and able-bodied individuals could explain the shift.
Their results show that there was no difference between groups, but SCI normalized torques were lower at the extreme angles. At all angles, SCI muscles produced higher relative torques at low stimulation frequencies. There was no evidence of a consistent change in the length of paralyzed SCI muscles, and the anomalous leftward shift in the torque–frequency relationship was not the result of testing the muscle at a relatively long length.

To our knowledge, there is no explanation for the leftward shift in the force–frequency relationship, but one factor might be the lower temperature seen in SCI muscles. The influence of increasing temperature on contractile properties and fatigability of paralyzed quadriceps muscle has been studied. The resting temperature of the quadriceps muscle of individuals with SCI is reduced to approximately 31°C, compared with 36°C in able-bodied individuals. This is probably the result of impaired muscle blood flow. Heating the muscle to 36°C shortened the half-relaxation time, and low-frequency force responses became less fused. The maximal rate of increase in force remained unchanged. Heating had no effect on either force decline or slowing of relaxation during fatiguing contractions. The force–frequency relationship of the paralyzed quadriceps muscle was shifted to the right after the muscle was heated. The results indicate that reduced muscle temperature in SCI individuals may lead to an underestimation of the changes in contractile properties in terms of relaxation rate or the degree of fusion with low-frequency stimulation. In addition, the force–frequency relationship of paralyzed muscles does not accurately reflect the magnitude of the changes in contractile properties, even when the muscle is heated, and should therefore be treated with caution.

Scott et al. found that higher frequencies were required to produce the same normalized force output from fatigued quadriceps muscles as compared with a non-fatigued condition. This means that, relative to their non-fatigued conditions, the force–frequency relationship of both SCI and control individuals shifted to the right with fatigue.

Following chronic SCI, all muscles become less resistant to fatigue. This means there is a significant reduction in torque and significant slowing of the contractile speeds of both the twitch and tetanus during repetitive activation. A study of thenar muscle showed a force decline in the paralyzed muscles of as much as approximately 60% during a fatigue protocol with 18 Hz, whereas the muscles of control individuals only showed a decline of approximately 15%.

Gerrits et al. also showed that fatigue resistance between chronic SCI individuals was negatively correlated with the time since injury.

A study of single motor units in chronically paralyzed thenar muscles showed that thenar motor units are highly fatigable. The unit force declined to 8–60% of initial levels after 2 minutes of stimulation, and the study group demonstrated that this fatigability reflects impairments within muscle fibers and not failure of neuromuscular transmission or membrane excitability. The uniform shift in the force fatigue index distribution to lower values suggests that all motor units in paralyzed thenar muscles were influenced similarly as result of SCI.

These studies verify that human muscles, which have been paralyzed for a long time, show properties that are characteristic of fast fatigable muscles.

There may be several reasons for decreased resistance to fatigue. The most often used explanation is the transformation of fiber type toward fast fibers. Talmadge et al. determined the effect of SCI on the profile of sarcoplasmic reticulum calcium-ATPase and MHC isoforms in vastus lateralis muscle fibers. They demonstrated that the fast isoform of sarcoplasmic reticulum calcium-ATPase, which mammalian fast fibers contain, is upregulated soon after SCI in paralyzed human muscle. The proportion of fibers with the slow isoform of sarcoplasmic reticulum calcium-ATPase alone was decreased by 30% at 6 weeks and 65% at 24 weeks. At the same time, the hybrid sarcoplasmic reticulum calcium-ATPase fibers, containing both slow and fast sarcoplasmic reticulum calcium-ATPase, was increased nearly fivefold by 24 weeks. However, no significant difference was found in the proportion of fibers containing only MHC I between SCI and control individuals at either time-point (6 weeks and 24 weeks). The SCI resulted in high proportions of MHC I and MHC IIA fibers with both sarcoplasmic reticulum calcium-ATPase isoforms.

Adaptations in sarcoplasmic reticulum calcium-ATPase and MHC isoform expression therefore appear to be asynchronous, resulting in the generation of high proportions of fibers with mismatched sarcoplasmic reticulum calcium-ATPase and MHC isoforms, compared with muscles from control individuals. Because fibers containing the fast sarcoplasmic reticulum calcium-ATPase isoform are typically more fatigable than fibers with the slow isoform, it is reasonable to predict that the mismatched fibers (those containing fast
sarcoplasmic reticulum calcium-ATPase) may have an increased susceptibility to fatigue.\textsuperscript{51}

In individuals with SCI, 2–15 years after injury, the sarcolemmal lactate/H\textsuperscript{+} transport capacity in the thigh muscle is much lower than in the muscle of healthy, untrained individuals, which indicates that prolonged muscle inactivity decreases the muscle’s ability to transport lactate and H\textsuperscript{+}, which may be one of the reasons for muscle fatigue after SCI.\textsuperscript{90}

Another possible reason for reduced fatigue resistance of paralyzed skeletal muscle during stimulated contractions is the significant negative correlation between the Na\textsuperscript{+}, K\textsuperscript{+-}ATPase concentration in the paralyzed muscle and number of years since injury. However, the study that demonstrated this relationship did not investigate whether the activity of Na\textsuperscript{+}, K\textsuperscript{+-}ATPase was also reduced, or perhaps was enhanced, as a compensatory measure.\textsuperscript{48}

In conclusion, chronic SCI results in a decrease in force, faster contractile properties, and less resistance to fatigue in all paralyzed muscles.

**SUMMARY**

**Animal Studies.** The changes in the soleus muscle after spinal cord transection seem to follow a certain time course in rats.

Macroscopic atrophy of the muscles in the region of 20–40\% appears in the fourth week and thereafter returns to normal. Similarly, fiber CSA decreases starting from days 4–5, with decreases in type I and IIA fibers of 30\% and 40\%, respectively. The minimum CSA of around 40\% of control values for all fibers is seen after approximately 90 days, and thereafter a smaller increase is observed, especially in type I fibers, which return to approximately 70\% of starting values. For MHC levels, steady state is reached at about day 90, with MHC Ila and IIX fibers predominating.

There is an increase in glycolytic capacity that peaks after 3 months, after which it decreases, with the oxidative capacity stabilizing or even increasing.

The contractile properties of the soleus muscle change with changes in speed-related properties. A faster phenotype is evident in the early phase, and a plateau phase develops after 3–6 months. The force-related properties recover after an initial decline, whereas fatigue-related properties continue to decrease. A fast muscle shows a slightly different pattern of changes with only an initial decline in type I fiber CSA until day 5, whereas type II fibers continue to atrophy. A decrease in MHC I content is observed after 1 year.

**Spinal isolation** as a model of lower neuromuscular (electromechanical) activity induces a larger reduction in muscle weight of the hind-limb, and the soleus muscle does not reach a plateau, even after 90 days. The reduction in fiber CSA is initially greater after spinal isolation. There is a different time course for the fiber changes and a lower content of MHC IIa. The metabolic changes are similar with a stable oxidative capacity and an increased glycolytic capacity.

After spinal cord contusion, no changes are seen in MHC composition after 10 weeks, and a decrease in half-relaxation time, peak twitch, and tetanic tension recorded after 3 weeks recovers fully 10 weeks after the contusion.

**Human Studies.** With long-term inactivation, as in SCI individuals, an almost complete fiber-type shift occurs from type I and IIA to type IIX. Inactivity leads to a loss in muscle mass initially due to both increased degradation and decreased synthesis of myofibrillar protein, followed by a period dominated by increased degradation and, after 30 days of inactivity, a new and lower steady-state level for protein turnover is reached.\textsuperscript{59}

The fiber-type transformation begins 4–7 months post-SCI and reaches a new steady state with a predominance of fast glycolytic type II fibers 20–70 months after the injury. In the transitional period there is a progressive decrease in the proportion of slow MHC isoform fibers and a rise in the proportion of fibers that coexpress both the fast and slow MHC isoforms (hybrid fibers).

The oxidative enzymatic activity starts to decline after the first couple of months post-SCI and may reflect the transformation from slow to faster muscle fibers. The whole muscle strength of paralyzed muscles from chronic SCI individuals is significantly reduced. However, the size of the remaining motor units increases, and there is an inverse correlation between the number of surviving motor units and the average twitch force of single units.

Muscles from individuals with chronic SCI show less resistance to fatigue, and the fatigue resistance is negatively correlated with the time since injury. The changes in fatigue resistance will at some point stabilize, and at that time they will show properties that are characteristic of fast fatigable muscles. At the same time, the speed-related contractile properties change toward faster contractile properties in muscles.
ANIMAL SCI AS A MODEL FOR HUMAN SCI

When comparing human with animal studies, it is observed that fiber atrophy, fiber type, and MHC transformation following spinal cord lesion have a much faster time course in the animals investigated, independent of the method employed in the animal studies (transection or isolation), and independent of gender differences between animals. When a new steady state is reached, the soleus muscle in rats generally shows a lesser degree of reduction of MHC I compared with soleus muscle from humans, whereas the MHC proportions are almost identical between control animals and control humans. In addition, MHC IIx increases less in rat soleus compared with human soleus. MHC IIb expression represents only a small percentage of the total MHC in rat soleus. In SCI humans, fast and slow muscles follow almost the same time course with regard to transformation of MHC I to MHC Iia and IIx. At steady state, MHC composition in fast and slow human muscles is almost identical. However, in spinal cord–transected rats, the MHC transformation has a slower time course in fast muscles, and the changes are smaller in fast muscles than in slow muscles.

The changes in SDH activity during the first 6 months following injury are similar in rat slow muscle and human fast muscle, but not in rat fast muscle compared with human fast muscle. This suggests that the rat should not be used as a model for enzyme studies of fast muscles in humans.

In comparing studies performed on rats and cats, it was found that rats show a faster time course as well as a different proportion of fiber types and MHC expression at steady state.\(^{28}\)

Contractile properties show the same trend in changes in muscles from spinal cord–lesioned humans and animals, but there is a much faster time course in animals. In spinal cord–transected cats, the contractile changes have a much slower time course compared with rats, and the changes are smaller in fast muscles than in slow muscles. The force–frequency relationship is shifted to the right in mice (initially leftward shift), rats, and cats. In humans with chronic SCI, there is a leftward shift in the force–frequency relationship years after SCI. There is no explanation for this difference between humans and animals. The results indicate that the time course of changes in the contractile properties seems to follow the fiber-type transformation in both animals and humans.

The results indicate that different species of mammals show different patterns of changes following spinal cord transection, although the starting point may look almost identical. Nonetheless, all spinal cord–transected mammals show a transition in all muscles below the level of the lesion toward a higher expression of MHC Ila and IIx and a lower expression of MHC I.

CLINICAL PERSPECTIVES

SCI results in dramatic muscular adaptations below the level of the lesion. All of the described changes in paralyzed muscles can, to a certain extent, be reversed by electrical stimulation. Several factors may influence the search for the optimal training protocol, including time since injury, severity of injury, type of electrical stimulation (e.g., low- or high-frequency stimulation), type of training (high- or low-resistance training), and duration and frequency of training. Preventing musculoskeletal adaptations after SCI may be more effective than reversing changes in the chronic condition.\(^{91}\)

Following electrical stimulation, a significant increase in muscle tissue is seen, CSA increases, and atrophy is almost fully reversed.\(^{55,91–94}\) The muscle-to-adipose tissue ratio is increased; that is, the muscle CSA is increased without change in the adipose CSA.\(^{95}\) Electrical stimulation also induces a decrease in proportion of type IIX fibers and an increase in proportion of type IIA fibers.\(^{52,92}\) One study even showed an increase in type I fibers.\(^{27}\) In accordance with these findings, MHC IIx presence was found to significantly decrease, and MHC Ia significantly increase.\(^{20,52,53,59,92}\) The number of fibers that coexpress MHC Ila and IIx changes toward the number observed in normal muscle.\(^{53}\) The contractile properties also revert toward normal values. The muscles become slower contracting,\(^{77,96}\) there is an increase in muscle force,\(^{92,97,98}\) an increased fatigue resistance,\(^{27,77,96–100}\) and half-relaxation time returns to normal.\(^{77}\) Electrically induced stimulation increases the glycolytic and mitochondrial oxidative enzyme levels.\(^{29}\) There is an increase in both SDH activity\(^{27,56}\) and citrate synthase activity.\(^{27}\)

Recently, it has been shown that body weight–supported treadmill training (BWSTT) without any electrical muscle stimulation is able to induce an increase in muscle fiber size and increased muscle oxidative capacity in individuals with incomplete SCI [ASIA Impairment Scale (AIS) C].\(^{101}\) Interestingly, it has been documented in an individual with a motor-complete (AIS B) SCI nearly 5 years postinjury that BWSTT was able to induce an increase in muscle fiber size and increased muscle oxidative capacity.
increase the mean fiber area in the vastus lateralis muscle by 27%. Type I fibers increased to 24.6% from 1.3%, whereas type IIA and IIX decreased correspondingly.102 These results give hope for further treatment possibilities for prevention of the muscle atrophy and redistribution toward a less fatigue-resistant muscle fiber type. This may in turn help to prevent some of the complications commonly seen in individuals with SCI, including pressure sores and increased insulin resistance, and may thus improve their quality of life.

CONCLUSIONS

Future studies of humans with SCI should examine longitudinal changes in muscles from early SCI through when a new steady state is reached. These studies should look at the changes in fiber types, oxidative metabolism, and contractile properties in SCI individuals to determine when a new steady state is reached and if this steady state is reached at the same time with regard to the different changes. These future findings may have relevance in the search for an optimal training protocol.

REFERENCES


