Changing central nervous system control following intercostal nerve transfer

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Object. The goal of this study was to find which central nervous system (CNS) pathways are involved in volitional control over reinnervated biceps or pectoral muscles.

Methods. Intercostal nerves (ICNs) were coapted to the musculocutaneous nerve (MCN) or the medial pectoral nerve (MPN) in 23 patients with root avulsions of the brachial plexus to restore biceps or pectoral muscle function. The facilitatory effects of respiration and voluntary contraction on cortical motor-evoked potentials of biceps or pectoral muscles were used to study CNS control over the reinnervated muscles. The time course of the facilitatory effect of respiration and voluntary contraction differed significantly. In the end stage of nerve regeneration, the facilitatory effect of voluntary contraction was significantly larger than that of respiration, indicating that the CNS control network over the muscle comes to resemble that of the recipient nerve (MCN or MPN) rather than that of the donor nerve (ICN).

Conclusions. The strengthening of previously subthreshold synaptic connections in a CNS network connecting ICN to MCN or MPN neurons may underlie changing excitability.

Key Words • brachial plexus • excitability • facilitation • intercostal nerve • nerve transfer • plasticity

Severe traction lesions of the brachial plexus frequently result in root avulsions. In these instances, reconstructive surgery aimed at restoration of the original neural connections is not possible because proximal nerve stumps are not available. To regain at least some function, the nerve transfer technique can be applied, that is, a nerve with intact continuity to the central nervous system (CNS), the donor nerve, is transected and coapted to brachial plexus structures originating from the avulsed roots, the recipient nerve. It has been convincingly demonstrated that the transfer of intercostal nerves (ICNs) to the musculocutaneous nerve (MCN) results in useful elbow flexion (at least Grade 3 according the Medical Research Council scale) in approximately two-thirds of cases.23,12,14,19,20,24

Physiologically, ICNs are controlled by CNS mechanisms involved in respiration and posture control.4,25 This explains why early in the reinnervation process, biceps contraction is only effected by means of a volitional vigorous respiratory effort or by coughing and sneezing. At the end stage of reinnervation, however, voluntary contraction of the biceps muscle can be initiated and sustained independently of respiratory activity. Patients experience contraction as similar to that of the healthy arm, without the use of any tricks. Transfer of ICNs to the medial pectoral nerve (MPN) results in comparable control over the major pectoral muscle. Because the control of the reinnervated muscles appears to change with time, some kind of “rewiring” of CNS connections must take place.16 It is not yet known how and to what extent this plasticity of the CNS occurs. More specifically, it is not known whether the CNS pathways controlling ICN activity after transfer resemble the original connections of the biceps or major pectoral muscles or those of the physiologically controlling intercostal muscles.

Magnetic stimulation of a specific area of one hemisphere elicits motor-evoked potentials (MEPs) in the corresponding contralateral muscles.1 The amplitudes of MEPs increase and their latencies decrease by slight voluntary contraction of the target muscle, a phenomenon known as “facilitation”21,22 (Fig. 1). Although the operative mechanism of facilitation is not fully understood, it has been ascertained that neural elements in both the spinal cord and motor cortex are involved.18
In the present study, the facilitatory effects of respiration and elbow flexion and adduction, respectively, were used to study CNS control over the biceps or major pectoral muscles after ICN–MCN or ICN–MPN transfer (Fig. 1). Intercostal muscles contract during respiration. A facilitatory effect of respiration on MEPs of the reinnervated biceps or pectoral muscles would point to a close resemblance to the original CNS connections to the ICN, that is, the donor nerve. Conversely, facilitatory effects of voluntary contraction (flexion or adduction) would point to CNS connections with recipient nerve qualities. A difference between the facilitatory effects of these two separate conditions may, therefore, illuminate which CNS pathways are involved in the volitional control over the reinnervated muscles. To study possible differences during the course of reinnervation, the facilitatory effects of the two conditions were measured in time.

Clinical Material and Methods

Patient Population

A consecutive series of 23 patients who had suffered a brachial plexus traction injury (20 males and three females) were studied prospectively; 17 of the patients underwent ICN–MCN transfer and six underwent ICN–MPN transfer. The study design was approved by the Medical Ethics Committee of Leiden University Medical Center and all participants gave informed consent. The mean age of the patients at the time of injury was 21.3 ± 4.9 years and the mean interval between trauma and surgery was 2.9 ± 2.2 months. Before surgery, needle electromyographic (EMG) studies had been performed to document objectively the complete absence of activity at maximal voluntary effort, and computerized tomography myelography was used to detect root avulsions. In all cases, the entire trajectory of the brachial plexus was exposed, and the definitive diagnosis of root avulsion was determined at operation by the absence of a spinal nerve within the intervertebral foramen. Fifteen patients had total rupture or avulsion of spinal nerves from C-5 through T-1. Four patients had avulsion of C-5 and C-6 nerve roots, and four had rupture of the C-5 root combined with avulsion of the C-6 root. Some of the patients in both latter groups also had avulsions of one or more lower cervical roots. An ICN–MCN transfer was performed in 11 patients with C-5 and C-6 nerve root avulsion, and in six patients with a ruptured C-5 nerve and avulsion of the C-6 root in whom further resection of the ruptured C-5 stumps up to the intervertebral foramen yielded only a fibrotic aspect, which was confirmed by intraoperative frozen-section examination. Such findings made these patients ineligible for nerve grafting, which otherwise would have been preferable. An ICN–MPN transfer was performed in six cases in which there were avulsions of C-7 through T-1 roots as well as avulsed or ruptured C-5 and C-6 roots. We have previously described the applied operative technique of the ICN–MCN or ICN–MPN transfer. Briefly, ICNs 3 through 5 were dissected free, transected as closely as possible to the sternum, and tunneled to the axilla. The MCN or MPN was then cut and the ICNs were coapted directly to one of them. Postoperative EMG studies showed typical respiratory activity in the biceps or major pectoral muscles, which left no doubt about assigning the reinnervation to the surgical repair. Before each MEP study, the force exerted by the reinnervated muscles was measured in time.

In the present study, MEPs were recorded 4 to 6 months after surgery. MEPs were recorded to the reinnervated biceps and pectoral muscles at rest and during voluntary contraction of the donor muscle (Fig. 1). The MEP amplitude was measured from peak to peak of the rectified EMG, using a 100-ms window (centered on the peak of the wave). MEP latencies were measured from the peak of the stimulus to the peak of the MEP. MEP amplitudes and latencies were measured in response to 20 repetitions of each condition and the means and standard deviations were calculated. The facilitatory effects of respiration and voluntary contraction were compared using a paired t-test.

Fig. 1. Diagrams showing normal innervation of biceps and intercostal muscles (A) and ICN–MCN transfer and transcranial magnetic stimulation (B). Note the facilitatory effect on MEPS during contraction as compared with rest: MEP amplitudes increase and MEP latencies decrease.
TABLE 1
Summary of MEP studies, intervals between operation and investigational study, and muscle force*

<table>
<thead>
<tr>
<th>No. of MEP Studies</th>
<th>No. of Patients</th>
<th>Mean Interval (mos)</th>
<th>Median Interval (mos)</th>
<th>MRC Score (no. of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11</td>
<td>24.8 ± 14.6†</td>
<td>20</td>
<td>2 0 4 2 3</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>11.5 ± 5.4†</td>
<td>9</td>
<td>3 2 1 0 0</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>10.2 ± 2.3†</td>
<td>9</td>
<td>1 2 2 0 0</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>6†</td>
<td>—</td>
<td>1** 0 0 1**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13‡</td>
<td>19§</td>
<td>25</td>
</tr>
</tbody>
</table>

* Values given for mean interval are shown with standard deviation. Abbreviations: MRC = Medical Research Council; — = not applicable.
† Time from operation to first study.
‡ Time from operation to second study.
§ Time from operation to third study.
|| Time from operation to fourth study.
** One patient was evaluated four times and the muscle force was M1, M4, M4, and M4, respectively.

biceps or major pectoral muscles was assessed according to the Medical Research Council scale.23
In total, 42 MEP studies were performed between 6 months and 4.8 years after surgery. Eleven patients were tested once and 12 patients were tested two to four times. The number of MEP studies performed in an individual patient and the mean interval between operation and MEP study are shown in Table 1. Eighteen of the 23 patients underwent their last test in the final phase of reinnervation, at least 1.5 years after surgery. The results of these studies were used to examine the facilitatory effect (amplitudes and latencies) at the end stage of recovery. The results of the remaining 24 studies, 19 of which were conducted within 1.5 years of surgery, were used to assess the facilitatory effect over time.

Transcranial Magnetic Stimulation

During the MEP studies, the patients remained seated. Standard Ag/AgCl electrodes were taped symmetrically over the biceps or belly of the major pectoral muscles and over the tendons on both sides. Magnetic stimuli were delivered at maximum intensity by using a stimulator (model 200; The Magstim Co. Ltd., Whitland, Dyfed, United Kingdom) with a 90-mm high-power round coil centered over the vertex. Each study consisted of four parts. Under each of four conditions, stimuli were delivered in triplicate, resulting in a total of 12 stimuli. First of all, three stimuli were given at rest. Subsequently, the patients were instructed to inspire deeply while keeping their arms relaxed. During inspiration and just before maximum inspiration was achieved, a magnetic stimulus was delivered. This procedure was repeated three times, allowing the patient to rest in between stimulations. The third portion of the testing consisted of stimulation during deep expiration in a comparable way. The fourth and last part of the investigation was conducted during volitional, symmetrical, slight contraction of the biceps or major pectoral muscles. The patients received auditory feedback of EMG activity so that they could stabilize the degree of muscle contraction. The coil was held to achieve maximum stimulation of each hemisphere (that is, “A-side” up for the right arm and “B-side” up for the left arm).

Statistical Analysis

Latencies and amplitudes of MEPs were measured for each of the three trials per condition. The MEPs were often polyphasic in the reinnervated muscles. Amplitudes were measured peak to peak by using the largest peaks in the MEP. Stimulus artifacts were corrected for by measuring the amplitudes of the positive and negative peaks as they related to the visually estimated baseline. All measurements were made by technicians unfamiliar with the research questions. Latencies of absent MEPs were regarded as missing values and their amplitudes were entered as 0 mV. Values from the three MEPs recorded per condition were averaged and the means were used for further analysis.

Amplitudes measured at inspiration and expiration were pooled to form the respiration condition. Pooling was justified because needle EMG examination of reinnervated biceps muscles following ICN–MCN transfer shows both inspiratory and expiratory activity.16 This EMG activity reflects the composition of the ICN, which contains fibers formerly involved with inspiratory and expiratory action. The amount of EMG activity in both inspiration and expiration has been shown to be related to the clinical force. Both expiratory or inspiratory neurons can help regain elbow flexion.16 Therefore, the respiration condition can be represented by the combination of the amplitudes of inspiration and expiration.

Conventional descriptive statistics were used to illustrate results. The association among facilitation condition, interval between surgery and investigation, and MEP parameters was examined using multiple analysis of variance (MANOVA). Data obtained from the biceps and major pectoral muscles were pooled for this approach. The conditions (rest, respiration, and contraction) and patient identity number were entered as factors. Inclusion of the identity number in the model allowed for different numbers of measurements between patients to be analyzed, and the interval between surgery and testing was entered as a covariate. The difference between the conditions with respect to the degree of facilitation was tested with the interaction between interval and conditions. The analysis was pursued for latencies as well as amplitudes, and separately for affected and healthy arms. If an effect of condition became apparent, another MANOVA was performed in which the rest condition was excluded to assess any differences between the two facilitatory maneuvers. A significance level of 0.05 was applied.

Results

The force of the reinnervated muscles at the time of magnetic stimulation is shown in Table 1. Figure 2 shows MEP amplitudes on the affected and healthy sides during rest, respiration, and contraction. The mean MEP ampli-
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For affected arms, MANOVA revealed significant differences in amplitudes between patients ($p < 0.001$). At the end stage of recovery, MEP amplitudes measured during the three conditions (rest, respiration, and contraction) differed significantly ($p < 0.0001$). Amplitudes measured during respiration differed significantly from those recorded during the resting period ($p = 0.001$). Amplitudes measured during contraction were also significantly higher than those measured during the resting condition ($p < 0.001$). The mean amplitude during contraction was significantly larger than that recorded during respiration ($p = 0.003$). Figure 3 left shows the differences in amplitude between respiration and contraction compared with the resting condition at the end stage of recovery.

For healthy arms, a similar analysis showed differences between patients ($p < 0.001$). There was a significant difference in amplitudes between conditions ($p < 0.001$). Compared with the resting condition, amplitudes measured during respiration ($p = 0.002$) and contraction ($p < 0.001$) proved to be significantly higher. Amplitudes measured during respiration were significantly lower than those recorded during contraction ($p < 0.001$, Fig. 3 right).

TABLE 2

<table>
<thead>
<tr>
<th>Condition</th>
<th>Amplitude (mV)</th>
<th>Latency (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>affected side</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rest</td>
<td>0.79 ± 0.11</td>
<td>19.81 ± 1.13</td>
</tr>
<tr>
<td>respiration</td>
<td>1.54 ± 0.20</td>
<td>18.03 ± 0.85</td>
</tr>
<tr>
<td>contraction</td>
<td>2.93 ± 0.46</td>
<td>17.91 ± 1.01</td>
</tr>
<tr>
<td>healthy side</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rest</td>
<td>0.87 ± 0.15</td>
<td>13.72 ± 0.63</td>
</tr>
<tr>
<td>respiration</td>
<td>2.04 ± 0.34</td>
<td>13.07 ± 0.49</td>
</tr>
<tr>
<td>contraction</td>
<td>4.54 ± 0.73</td>
<td>11.19 ± 0.36</td>
</tr>
</tbody>
</table>

* Values are expressed as the mean ± SEM.

Postoperative Time Course

For affected arms, a relationship was found between amplitude and interval ($p = 0.05$): amplitudes increased with time postsurgery. There was a significant interaction between condition and interval ($p = 0.01$); further analysis performed using MANOVA, excluding the resting condition, revealed this to be caused by a difference between the resting condition, on the one hand, and the other two conditions, on the other hand (Fig. 4). The slope of the relationship between amplitude at rest and interval was virtually zero (0.002 mV/month, standard error of the mean [SEM] 0.012), whereas slopes of the other two conditions were higher (respiration 0.017 mV/month, SEM 0.008; contraction 0.039 mV/month, SEM 0.021). The slopes of the three conditions differed significantly ($p = 0.011$).

As expected, for healthy arms there was no significant relationship between amplitude and interval, that is, amplitudes did not change over time ($p = 0.84$).

Latencies of MEPs

For affected arms, latencies differed between patients ($p < 0.001$), but not between conditions ($p = 0.071$).

For healthy arms, latencies differed between patients ($p < 0.001$) and between conditions ($p < 0.001$). The latter proved to be caused by contraction in which the latency was approximately 2 msec less than that at rest ($p < 0.001$). There were no relationships between latencies and intervals ($p = 0.075$), and none between conditions and intervals ($p = 0.74$).

Discussion

Before nerve transfer the donor nerve serves a function different from that exhibited afterward. Therefore, a CNS change of control over donor nerve motor neurons is a prerequisite for recovery of function. The ICNs cause intercostal muscle contraction during respiration. The functional gain of ICN–MCN or ICN–MPN transfers would obviously be very limited if biceps or major pectoral muscle contraction was accomplished by respiratory efforts only. Empirically, the transfer improves the function of the arm by establishing voluntary control.14,15

Fig. 2. Tracings showing MEP amplitudes on affected and healthy sides during rest, respiration, and contraction. Note marked facilitation through contraction on the affected side.

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The major finding of the present study was that, at the end stage of recovery following ICN–MCN or ICN–MPN transfer, voluntary contraction had a larger facilitatory effect on MEPs of the ICN reinnervated muscles than respiration (Fig. 2). This indicates that CNS connections to the donor ICN have changed from those controlling respiration to those controlling volitional contraction. However, respiration still had a facilitatory effect on MEPs of reinnervated muscles (Fig. 3 left). From one point of view, this finding is inconsistent with a change in CNS connections, as it implies that the original respiratory CNS connections to the ICN (the donor nerve) have been at least partially preserved. Then again, the facilitatory effect of respiration also occurs on the healthy side (Fig. 3 right), and so it does not conflict with, and may even support, a change in CNS connections. The presence of typical respiratory EMG activity in ICN–MCN reinnervated biceps muscles, which cannot be found in healthy biceps, indicates persistent donor qualities of the CNS connections to ICNs following transfer. The continuing interference of CNS respiratory ICN connections need not exclusively be via corticospinal neurons. Bulbospinal neurons in the respiratory center probably account for this phenomenon. In addition, from the difference in the effect of facilitation (that of contraction being larger than that of respiration) it may be concluded that the quality of the CNS pathway to ICN α motor neurons has changed, tending toward the MCN or MPN recipient rather than to the ICN donor.

**Plasticity of the CNS**

The CNS alterations may be the result of structural plasticity, namely, the formation of new direct connections between ICN and MCN or MPN neurons. Motor cortex mapping showed a lateral shift in the area governing ICN reinnervated biceps in time; at the end stage of recovery it resembled the physiological biceps area. Axonal sprouting is an important element in plastic reorganiza-

**Facilitation Conditions**

The facilitatory effect of contraction is much more pronounced on the healthy side than on the surgically treated side, possibly reflecting the difference in muscle force between the two sides. Incomplete peripheral nerve regener-
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Fig. 4. Graph displaying increases in MEP amplitudes with time. The solid line represents the line of best fit of amplitudes during respiration with a slope of 0.017 mV/month. The hatched line represents the regression of amplitudes during contraction (slope = 0.039 mV/month) and the dotted line the resting condition (slope = 0.002 mV/month). The slopes of the three conditions differed significantly (p = 0.011).

On the side of reinnervation, MEP amplitudes increased with time. This increase reflects both the number of growing peripheral axons and the enlargement of motor units. Clinically, an increase in muscle force was found. The slope of the relationship between amplitude and interval was significantly larger during contraction than during respiration (Fig. 4), suggesting that the facilitatory effect of contraction developed differently from that of respiration. However, the presumption that amplitudes increase linearly with time is not necessarily true. Directly after surgery, axons have not yet reached their target organs. At this stage, amplitudes must be zero, regardless of the facilitation condition. In addition, amplitudes cannot keep on increasing with time. The selected 6- to 60-month period represents the period during which clinically detectable changes occur.

A comparison between the CNS motor conduction times of the healthy and surgically treated sides might have been helpful for additional study of the CNS connections after nerve transfer. Unfortunately, however, differences in the length of CNS pathways to the α motor neurons make CNS motor conduction time measurements inaccurate. Motor neurons for the biceps muscles on the surgically treated side. Functional motor units on the surgically treated side. This increase reflects both the number of growing peripheral axons and the enlargement of motor units. Clinically, an increase in muscle force was found. The slope of the relationship between amplitude and interval was significantly larger during contraction than during respiration (Fig. 4), suggesting that the facilitatory effect of contraction developed differently from that of respiration. However, the presumption that amplitudes increase linearly with time is not necessarily true. Directly after surgery, axons have not yet reached their target organs. At this stage, amplitudes must be zero, regardless of the facilitation condition. In addition, amplitudes cannot keep on increasing with time. The selected 6- to 60-month period represents the period during which clinically detectable changes occur.

Conclusions

In the present study we demonstrated that, following an ICN–MCN or ICN–MPN transfer, the facilitatory effect of flexion/adduction (related to the MCN or MPN recipient) clearly exceeded the effect of respiration (related to the ICN donor). Apparently the site of excitability of the CNS connection to ICN α motor neurons was changed from the ICN donor to the MCN or MPN recipient. The capacity of the CNS to achieve such changes may affect functional outcome of repair, especially after nerve transfer.

References

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Manuscript received November 7, 1997.
Accepted in final form May 4, 1998.
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