Nerve Autografts, Allografts, Conduits, Wraps, and Glue. What Should I Do?

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Rothman Institute at Thomas Jefferson University
Outline

• Wallerian Degeneration
• Regeneration
• Direct Repair
• Gap Repair
  – Conduits
  – Allografts
  – Autografts
  – Wraps
• Algorithm
Wallerian Degeneration

• In 1849 Augustus Waller
  – Distal portion of nerve undergoes progressive degeneration
• WD begins with axon degeneration.
  – Blood-tissue barrier permeability increases
  – Myelin sheath breaks down
  – Influx of macrophages occurs,
• Myelin debris contains several inhibitors of axon regeneration
  – Clearance mediated first by Schwann cells and later by hematogenous phagocytes
Wallerian Degeneration

- **Acute axonal degeneration (AAD)**
  - 30 min post injury, axon segments at both the proximal and distal ends degenerate hundreds of micrometers

- **Granular disintegration of the axonal cytoskeleton (GDC)**
  - Breakdown of neurofilaments and microtubules
  - Committed step in Wallerian degeneration.
  - After onset axons disintegrate within an hour in an all-or-none fashion

- **Time lag of ~1–2 days in the rodent and up to 7 days in humans exists between injury and GDC**
  - Depends on the species, the distance of injury from cell body, and the diameter of the axon
Axonal Regeneration

• Following axon degeneration, SC proliferation is a key event in promoting axon regeneration
  – Provide structural guidance and growth-promoting substrates to regenerating axons.

• Grow in close association with SCs along the basal laminar tubes (endoneurium) and are thus able to retrace their former pathways
Axonal Regeneration

- 1-2mm/day
  - Same velocity of slow anterograde axoplasmic transport

Facial nerve grafting with sural

Timing determined by tinels

Braam-Microsurgery-1993
Axonal Regeneration

• Motor axons must reach the target muscle in a critical time window (12–18 months).
• In the case of neurotmesis (Sunderland Type V), it is estimated that there is a 50% loss of axons across each coaptation site.
  – Axonal Escape
  – Neurofibrosis
• Furthermore, of the small percentage of axons that do reach their target muscle, it is estimated that even a smaller percentage are able to remake functional connections.
• Nevertheless, our best option remains guiding axonal growth
Guided Growth:
Must be out of Zone of Injury

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**Fig. 3. Upper:** Excised left ulnar nerve graft 8 months after repair with a processed nerve allograft (Avance). **Dashed lines** specify the 3 areas (proximal stump, midpoint, and distal stump) that were embedded and cut for histological analysis. **Center:** Axial histological semithin cut sections (1 μm) stained with toluidine blue and imaged at ×10, corresponding to each of the 3 areas depicted by the dashed lines. Total number of myelinated axons (n) is shown for each section (midpoint, 1056 axons). Normal myelinated axon count of ulnar nerve: approximately 16,000. **Lower:** High-power view with detailed profiles of myelinated figures (oil immersion ×63).

Berrocal-J Neurosurg-2013
Guided Growth: Tension-free Repair

EXPERIMENTAL STRETCH NEUROPATHY

CHANGES IN NERVE CONDUCTION UNDER TENSION

ERIC J. WALL, JENNIFER B. MASSIE, MICHAEL K. KWAN, BJORN L. RYDEVIR, ROBERT R. MYERS, STEVEN R. GARFIN

From the University of California, San Diego

We developed an animal model of stretch injury to nerve in order to study in vivo conduction changes as a function of nerve strain. In 24 rabbits, the tibial nerve was exposed and stretched by 0%, 6%, or 12%, of its length. The strain was maintained for one hour. Nerve conduction was monitored during the period of stretch and for a one-hour recovery period.

At 6% strain, the amplitude of the action potential had decreased by 70%, at one hour and returned to normal during the recovery period. At 12% strain, conduction was completely blocked by one hour, and showed minimal recovery. These findings have clinical implications in nerve repair, limb trauma, and limb lengthening.

Traction of a peripheral nerve may be due to trauma, or occur during limb lengthening, nerve repair, or fracture fixation. The safe limits of nerve elongation are not well established, despite several basic scientific and clinical studies. Nerve ischaemia has been reported to occur at 15% elongation (Lundborg and Rydevik 1973; Ogata and Naito 1986), and histological changes at between 4% and 50% stretch (Highet and Holmes 1944; Highet and Sanders 1943; Liu, Benda and Lewey 1948; Hoen and Brackett 1956; Halte 1970). Mechanical failure of a nerve may take place at between 30% and 75% elongation (Sunderland and Bradley 1961; Halte 1970; Rydevik et al 1990). Failure to conduct is reported to begin at stretch levels ranging from 6% to 100% (Mitchell 1972; Denny-Brown and Doherty 1945; Turner 1951; Schneider 1952; Gray and Ritchie 1954; Tezir, Faibisoff and Williams 1975; Bora, Richardson and Black 1980; Yamada 1987; Brown et al 1989).

It is now common to monitor nerve conduction during operations involving potential traction injury, but little basic data is available on conduction changes with neural tension. We have studied the effect of stretching on nerve function in an animal model, controlling several biomechanical guidelines including strain rate, limb joint position, and in situ strain. We correlated conduction changes in the nerve with nerve stress and strain, and with histological changes.

MATERIALS AND METHODS

We used 24 mature New Zealand white rabbits, weighting 4.5 ± 0.5 kg (mean ± sd). Anaesthesia was induced with...
The Implication of Repeated Versus Continuous Strain on Nerve Function in a Rat Forelimb Model

Mitsunobu Watanabe, MD, Makio Yamaga, MD, Teiji Kato, MD, Junji Ide, MD, Toshio Kitamura, MD, Katsumasa Takagi, MD, Kumamoto, Japan

We studied the effect of repeated and continuous nerve strain using a rat forelimb model to investigate whether an innocuous level of strain applied continuously affects nerve function when applied repeatedly. We used the rat median cord of the brachial plexus and assessed the effects of strain by studying nerve histology (blood-nerve barrier), function (grasping strength), and electrophysiology. Continuous stretching was applied to the rat forelimb for 1 hour at 2 N. After this strain neither histologic analysis, grasping strength, nor electrophysiologic analysis revealed any effect. We then applied repeated strain at both 60 and 120 times per hour; after the latter strain abnormalities in histology, grasping strength, and nerve conduction were identified. These results suggest that a small nerve strain applied repeatedly results in nerve dysfunction. Our data may help explain the cause of nonspecific neural symptoms in the upper extremities of patients with no objective findings. (J Hand Surg 2001;26A:663–669. Copyright © 2001 by the American Society for Surgery of the Hand.)

Key words: Nerve implication, repeated strain, brachial plexus, rat.

Patients who complain of neurogenic symptoms such as pain and numbness of the neck, shoulder, and upper limbs are often encountered in daily clinical practice. With the recent progress in diagnostic techniques, the number of cases leading to confirmed diagnoses has increased but there are still many cases in which a definite cause cannot be established. Patients with frequent use of upper limbs because of nonspecific neurogenic symptoms in the absence of objective findings may be characterized as having an overuse syndrome. The pathogenesis, however, remains obscure.4 Because of the difficulty in understanding the cause of symptoms in such disorders, we have developed an experimental model to evaluate the effect of continuous and repeated nerve strain.
Direct Repair

- Suture vs. Glue
- Rat Model
- 8wks post repair

Histologic & Functional Outcomes:
- Crush > Suture = Glue

Felix-Microsurgery-2013
Direct Repair

• Suture vs. Glue

• Human Cadaveric Model:
  – Tibial nerve

• 2 sutures +/- various fibrin glues

Resistance to Gapping: All glues > No glue

Load to Failure: No difference

Isaacs-JHS-2008
Direct Repair Often Not Possible

- AAD
- Innate neural tension/retraction
- Zone of Injury
- Often Faced with a Gap
Gap Repair Options

Conduit

Allograft

Autograft

Allograft + Nerve Connector

Allograft + Nerve Protector
Conduits

• **Advantages**
  
  – Combat Axonal Escape
  
  – Can Aid in Repair Technique
  
  – Can be Filled with Pro-Regeneration substrates (SCs, ADSCs) [Animal Studies Only]

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<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>End-to-end alignment, no gapping, adequate tension and approximation, no fascicle extrusion</td>
</tr>
<tr>
<td>Good</td>
<td>End-to-end alignment gapping &lt; 1 mm, no fascicle extrusion, or End-to-end alignment, excessive approximation, no fascicle extrusion</td>
</tr>
<tr>
<td>Fair</td>
<td>End-to-end alignment gapping &gt; 1 mm, fascicle extrusion</td>
</tr>
<tr>
<td>Poor</td>
<td>Inadequate alignment regardless of tension, fascicle extrusion</td>
</tr>
</tbody>
</table>

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Conduit Assisted Repairs:
Inexperienced = Experienced

Suture Only:
Experienced > Inexperienced
Conduits

- Disadvantages
  - Lack Endoneurial Architecture
  - Lack Support Cells
  - Relies on Fibrin Matrix as Scaffold
    - Limited Length-Stability: Don’t yet know limits
  - Diameter Mismatch

14mm Gap

28mm Gap

6wks

12wks

Rat Sciatic Model

Whitlock-Muscle Nerve-2009
Acellular Allograft

• Advantages
  – Endoneurial Architecture
  – Varying Diameters
  – No Donor Morbidity
  – No WD debris mediated regeneration inhibition
Acellular Allograft

- Animal Data:
  - Superiority to Cabled Autograft

<table>
<thead>
<tr>
<th>Table 1. Functional Outcomes</th>
</tr>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Group A</td>
</tr>
<tr>
<td>Acellular allograft</td>
</tr>
<tr>
<td>Tibialis anterior</td>
</tr>
<tr>
<td>Muscle weight (%) Tibialis anterior</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Group B</td>
</tr>
<tr>
<td>Cabled autograft</td>
</tr>
<tr>
<td>Compound muscle action potential (%)</td>
</tr>
<tr>
<td>Gastrocnemius</td>
</tr>
<tr>
<td>Muscle weight (%) Tibialis anterior</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Group C</td>
</tr>
<tr>
<td>Reversed autograft</td>
</tr>
<tr>
<td>Max isometric tetanic force (%)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>A vs B</td>
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<tr>
<td>A vs C</td>
</tr>
<tr>
<td>B vs C</td>
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<tr>
<td></td>
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<tr>
<td>Functional outcomes are given as percentages, with the results normalized to the contralateral side. *P &lt; 0.05.</td>
</tr>
</tbody>
</table>

Force Transduction:
Reversed Autograft > Allograft > Cabled Autograft

Tang-Microsurgery-2013
# Acellular Allograft

## Table 2. Results of Histomorphometric Analysis at Mid-graft and Distal to the Graft at 6 Weeks

<table>
<thead>
<tr>
<th>Histomorphometry</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acellular allograft</td>
<td>Cabled autograft</td>
<td>Reversed autograft</td>
</tr>
<tr>
<td>Mid-graft</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fiber count</td>
<td>11,028 ± 2674</td>
<td>6754 ± 1001</td>
<td>13,375 ± 926</td>
</tr>
<tr>
<td>Fiber diameter (μm)</td>
<td>4.37 ± 0.15</td>
<td>4.14 ± 0.18</td>
<td>4.02 ± 0.02</td>
</tr>
<tr>
<td>Myelin thickness (μm)</td>
<td>0.42 ± 0.01</td>
<td>0.47 ± 0.02</td>
<td>0.36 ± 0.05</td>
</tr>
<tr>
<td>Fascicular area (mm²)</td>
<td>0.96 ± 0.16</td>
<td>0.37 ± 0.06</td>
<td>0.66 ± 0.08</td>
</tr>
<tr>
<td>Distal to graft</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fiber count</td>
<td>8392 ± 1691</td>
<td>5383 ± 395</td>
<td>12,034 ± 1899</td>
</tr>
<tr>
<td>Fiber diameter (μm)</td>
<td>3.49 ± 0.03</td>
<td>3.56 ± 0.05</td>
<td>3.91 ± 0.01</td>
</tr>
<tr>
<td>Myelin thickness (μm)</td>
<td>0.45 ± 0.04</td>
<td>0.43 ± 0.02</td>
<td>0.41 ± 0.03</td>
</tr>
<tr>
<td>Fascicular area (mm²)</td>
<td>0.88 ± 0.08</td>
<td>0.59 ± 0.15</td>
<td>0.94 ± 0.12</td>
</tr>
</tbody>
</table>

No statistical analysis was performed since only two animals in each group were used.

## Table 3. Results of Histomorphometric Analysis at Mid-graft and Distal to the Graft at 12 Weeks

<table>
<thead>
<tr>
<th>Histomorphometry</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>A vs B</th>
<th>A vs C</th>
<th>B vs C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acellular allograft</td>
<td>Cabled autograft</td>
<td>Reversed autograft</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid-graft</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fiber count</td>
<td>10,005 ± 784</td>
<td>6407 ± 967</td>
<td>15,101 ± 1575</td>
<td>0.112</td>
<td>0.023*</td>
<td>0.001*</td>
</tr>
<tr>
<td>Fiber diameter (μm)</td>
<td>4.23 ± 0.08</td>
<td>4.50 ± 0.11</td>
<td>4.39 ± 0.05</td>
<td>0.09</td>
<td>0.357</td>
<td>0.651</td>
</tr>
<tr>
<td>Myelin thickness (μm)</td>
<td>0.48 ± 0.02</td>
<td>0.52 ± 0.03</td>
<td>0.53 ± 0.03</td>
<td>0.598</td>
<td>0.433</td>
<td>0.955</td>
</tr>
<tr>
<td>Fascicular area (mm²)</td>
<td>0.68 ± 0.05</td>
<td>0.34 ± 0.04</td>
<td>0.86 ± 0.08</td>
<td>0.003*</td>
<td>0.101</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Distal to graft</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fiber count</td>
<td>9434 ± 974</td>
<td>11,229 ± 864</td>
<td>12,557 ± 2169</td>
<td>0.957</td>
<td>0.902</td>
<td>0.987</td>
</tr>
<tr>
<td>Fiber diameter (μm)</td>
<td>4.54 ± 0.09</td>
<td>4.20 ± 0.24</td>
<td>4.47 ± 0.25</td>
<td>0.499</td>
<td>0.962</td>
<td>0.644</td>
</tr>
<tr>
<td>Myelin thickness (μm)</td>
<td>0.58 ± 0.02</td>
<td>0.52 ± 0.02</td>
<td>0.53 ± 0.05</td>
<td>0.644</td>
<td>0.69</td>
<td>0.991</td>
</tr>
<tr>
<td>Fascicular area (mm²)</td>
<td>0.73 ± 0.06</td>
<td>0.88 ± 0.18</td>
<td>0.93 ± 0.18</td>
<td>0.813</td>
<td>0.661</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Mid-Graft Nerve Fiber Count (6 & 12 wks):
Reversed Autograft > Allograft > Cabled Autograft
Acellular Allograft

- Level III Evidence Demonstrating Promising Clinical Results

**Table 4. Summary of Results of Most Repaired Nerves in the Upper Extremity Reporting Quantitative Data**

<table>
<thead>
<tr>
<th>Factor</th>
<th>n</th>
<th>Age (y)</th>
<th>Preoperative Interval (d)</th>
<th>Follow-Up (d)</th>
<th>Gap (mm)</th>
<th>Complex</th>
<th>Lacerations</th>
<th>Neuromas</th>
<th>Meaningful Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digital nerves</td>
<td>35</td>
<td>46 ± 14</td>
<td>(23–68)</td>
<td>190 ± 349</td>
<td>(0–1,460)</td>
<td>306 ± 184</td>
<td>19 ± 9</td>
<td>5</td>
<td>24</td>
</tr>
<tr>
<td>Median nerve</td>
<td>8</td>
<td>28.2 ± 7</td>
<td>(20–38)</td>
<td>369 ± 278</td>
<td>(14–725)</td>
<td>230.5 ± 111</td>
<td>33 ± 13</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Ulnar nerve</td>
<td>3</td>
<td>42 ± 24</td>
<td>(25–70)</td>
<td>27 ± 38</td>
<td>(3–71)</td>
<td>323 ± 54</td>
<td>27 ± 6</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*Complex mechanisms include amputations, avulsions, and blast injuries.*

*Meaningful recovery is defined as S3-S4 or M3-M5 on the MRCC scale.*

Cho-JHS-2012
Acellular Allograft

- Disadvantages
  - No Support Cells
  - Cost
  - Limited Clinical Data
  - Length limited to 7cm
Autograft

• Advantages
  – Gold-standard since 1920’s with extensive evidence
    • Frykman & Gramyk
      – 80% median n recovery
      – 60% ulnar n recovery
  – Support Cells (Survive Devascularization)

Graft SCs labeled: 1 day 14 days

Trumble-JHS-1994
Autograft

• Advantages
  – Endoneurial Architecture
  – Non-immunogenic
  – Segments > 7cm
Autograft

• Disadvantages

• Donor Morbidity
  • Functional loss
  • Neuroma formation

• WD debris

• Diameter Mismatch
  • Cabled grafts < Single

• Animal Data
  • Source of graft matters

Motor Donor
Sensory Donor
Distal to Graft Nerve Fibers: Motor > Sensory
Wraps

• Advantages
  – Custom-sized conduit
    • Vein wraps, Synthetic wraps
  – Animal Data – XU-JHS-2000
    • Reduces adhesion/fibrosis formation
    • Improved functional and histologic outcomes

• Disadvantages
  – Possible to overtighten leading to compression
  – Some wraps limit neovascularization and diffusion
  – Limited Data
Algorithm

Nerve Gap Reconstruction: Repair Options

- **Primary Repair**: * Only if no tension at anastomosis site under full range of motion
- **Conduit** vs. **Allograft** vs. **Autograft**: Consider gap size and functional importance of reconstructed nerve
- **Allograft**: * Autograft donor site defect (<5 cm) can be reconstructed with allograft to minimize donor site morbidity
- - Nerve connector / protector cuff can be used to aid primary repair, allograft or autograft nerve reconstruction
- - Nerve transfers considered for proximal nerve injuries in addition or as alternative to other reconstructive options

Ducic-Annals Plastic Surg-2012
A, Traumatic injury to the radial sensory digital nerve in 65 year-old patient, resulting in pain at the injury site and finger numbness. B, Excision of pain-generating neuroma. C, Resulting 5 mm gap reconstructed with nerve conduit.
A, Peripheral nerve tumor requiring excision of associated fascicle. B, Reconstruction of 40 mm nerve fascicle defect with nerve allograft and anastomotic nerve connector.
A, Traumatic injury to a major peripheral nerve in a 25 year-old patient. B, Final defect size after stump debridement to healthy fascicular tissue. C, Reconstruction of 50 mm nerve defect with sural nerve autograft. (Donor medial and lateral sural nerve defect reconstructed with 50 mm nerve allograft and anastomotic nerve connector.)