Scandinavia goes St. Gallen

Treatment effects of IVIG in CIDP and variants

Christoph Neuwirth
Muskelzentrum/ALS Clinic

St. Gallen, 1st April 2023

Kantonsspital
St.Gallen

Monitoring of treated dysimmune neuropathies

- First step is to diagnose inflammatory neuropathies as early as possible (guidelines?)
- EDX is crucial, especially in atypical variants (very slow progression, pure motor/sensory, multifocal etc.)
- Clinical improvement with therapy is most relevant for patients, but also stopping further deterioration
- Needed dosage if IVIG for stabilisation can reasonably vary between patients and underlying diseases
- Relapses can occur silently or suddenly (half-life IVIG 3-4 weeks)
- How do you monitor disease activity or when deciding to taper off IVIG?

EAN EDX guidelines 2021 for diagnosing CIDP

TABLE 2 Motor nerve conduction criteria

(1) Strongly supportive of demyelination:

At least one of the following:

(a) Motor distal latency prolongation ≥50% above ULN in two nerves (excluding median neuropathy at the wrist from carpal tunnel syndrome), or

(b) Reduction of motor conduction velocity ≥30% below LLN in two nerves, or

(c) Prolongation of F-wave latency ≥20% above ULN in two nerves (≥50% if amplitude of distal negative peak CMAP <80% of LLN), or

(d) Absence of F-waves in two nerves (if these nerves have distal negative peak CMAP amplitudes ≥20% of LLN) + ≥1 other demyelinating parameter[a] in ≥1 other nerve, or

(e) Motor conduction block: ≥30% reduction of the proximal relative to distal negative peak CMAP amplitude, excluding the tibial nerve, and distal negative peak CMAP amplitude ≥20% of LLN in two nerves; or in one nerve + ≥ 1 other demyelinating parameter[a] except absence of F-waves in ≥1 other nerve, or

(f) Abnormal temporal dispersion: >30% duration increase between the proximal and distal negative peak CMAP (at least 100% in the tibial nerve) in ≥2 nerves, or

(g) Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) prolongation in ≥1 nerve[b] + ≥1 other demyelinating parameter[a] in ≥1 other nerve

- (LFF 2 Hz) median > 8.4 ms, ulnar > 9.6 ms, peroneal > 8.8 ms, tibial > 9.2 ms
- (LFF 5 Hz) median > 8.0 ms, ulnar > 8.6 ms, peroneal > 8.5 ms, tibial > 8.3 ms
- (LFF 10 Hz) median > 7.8 ms, ulnar > 8.5 ms, peroneal > 8.3 ms, tibial > 8.2 ms
- (LFF 20 Hz) median > 7.4 ms, ulnar > 7.8 ms, peroneal > 8.1 ms, tibial > 8.0 ms

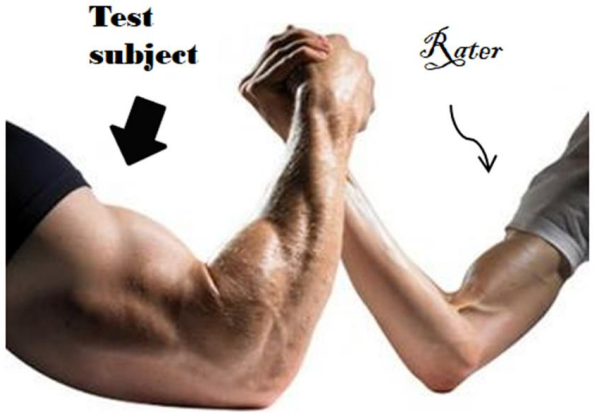
(2) Weakly supportive of demyelination

As in (1) but in only one nerve.

Monitoring of treated dysimmune neuropathies

- PROMs (patient reported ourcome measures)
  - do they feel better? Regional tingling? Walking distance/ climbing stairs?
  - are the symptoms stable between and around infusions? Yes = good
  - do they feel some wearing-off before and improvement days after infusions? Yes = bad → ongoing inflammatory activity → adjust intervals/dosage

- Neurological examination
  - e.g. improvement foot-drop, arm abduction etc
  - Beware! Manual testing and interpretation is highly rater dependent! → same rater recommended



- Electrophysiological monitoring
  - Select moderate-affected nerves for longitudinal assessments → same rater and EMG machine recommended

Monitoring of treated dysimmune neuropathies

› Electroencephalogr Clin Neurophysiol. 1997 Oct;105(5):385-9. doi: 10.1016/s0924-980x(97)00037-4.

The influence of active electrode placement on CMAP amplitude

M B Bromberg [1], T Spiegelberg

Affiliations + expand

PMID: 9363004 DOI: 10.1016/s0924-980x(97)00037-4

Abstract

The compound muscle action potential (CMAP) is a measure of the number of axons in a nerve. Placement of the active recording electrode over the motor point of a muscle is thought to give the maximal response, but there is considerable variation in amplitude among initially negative CMAP wave forms. Ten examiners of varied training backgrounds and experience placed the active electrode as they usually do over the thenar, hypothenar, abductor hallucis, and extensor digitorum brevis muscles in the same normal subject. There was variability of the CMAP amplitude recorded over each muscle; the lowest value recorded from a muscle was 57% of the maximum value, and the lowest median value was 77%. There was no relation between examiner background or level of training and recording the maximal response. Higher amplitude CMAPs were associated with steeper wave form slopes, but the range of correlations between amplitude and slope was 0.42 to 0.92. We conclude that when it is important to record the maximal CMAP response, empirical assessment by moving the active electrode is necessary.

Monitoring of treated dysimmune neuropathies

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Electrophysiological testing in chronic inflammatory demyelinating polyneuropathy patients treated with subcutaneous immunoglobulin: The Polyneuropathy And Treatment with Hizentra (PATH) study

Vera Bril [a,b,*], Hans-Peter Hartung [c], John-Philip Lawo [d], Billie L. Durn [e], Orell Mielke [d]

[a] Ellen and Martin Prosserman Centre for Neuromuscular Diseases, Division of Neurology, Department of Medicine, University Health Network, University of Toronto, Toronto, Canada
[b] Institute for Research and Medical Consultations, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia
[c] Department of Neurology, UKD and Center for Neurology and Neuropsychiatry, LVR Klinikum, Medical Faculty, Heinrich Heine University, Düsseldorf, Germany
[d] CSL Behring, Marburg, Germany
[e] CSL Behring, King of Prussia, PA, USA

See Article, pages 204–206

ARTICLE INFO

Article history:
23 June 2020
12 August 2020
Accepted 7 September 2020
Available online 14 September 2020

HIGHLIGHTS

- NCSs were conducted in the PATH study of maintenance SCIG (IgPro20) in CIDP.
- Conduction velocity decreased with placebo but increased with SCIG.
- Nerves showed increasing dysfunction with placebo but remained stable with IgPro20.

Monitoring of treated dysimmune neuropathies

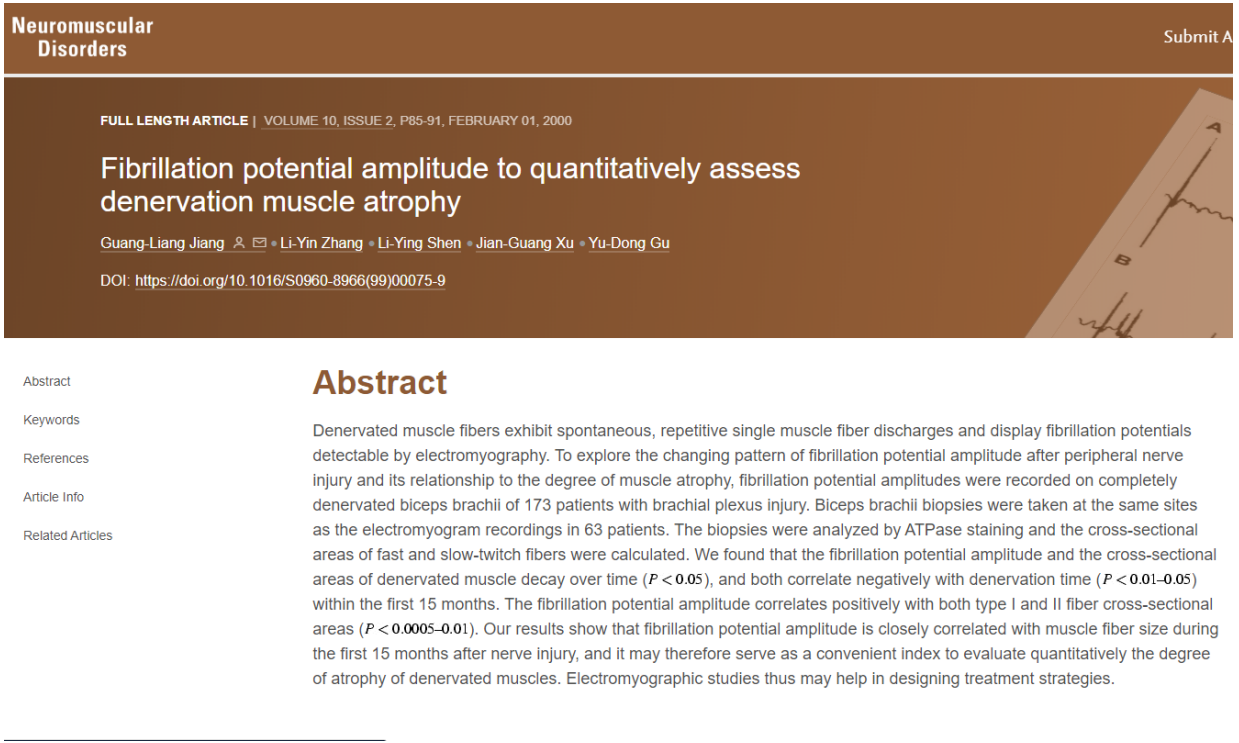
- Recommended EDX strategy dependent on clinical features
  - Suggestion: selection motor NCS with F-waves (!) at arm and leg
  - Select medium-affected nerves
    - → Severely affected nerves with secondary axonal damage unlikely to improve
    - → Non-affected nerves can only show deterioration
  - Sensory nerves can be prone to variability (oedema etc)
    - Beware of «Sural-sparing» in CIDP
  - EMG? Denervation and reinnervation (instable potentials) can be still visible on EMG over several months (even years)

Monitoring of treated dysimmune neuropathies

Fibrillations potentials are seen up to 5 years

Amplitude and duration of Fib's decrease with fibre atrophy → «old denervation»

However, quantification for outcome purposes remains troublesome



Neuromuscular Disorders

Submit A

FULL LENGTH ARTICLE | VOLUME 10, ISSUE 2, P85-91, FEBRUARY 01, 2000

Fibrillation potential amplitude to quantitatively assess denervation muscle atrophy

Guang-Liang Jiang • Li-Yin Zhang • Li-Ying Shen • Jian-Guang Xu • Yu-Dong Gu

DOI: https://doi.org/10.1016/S0960-8966(99)00075-9

Abstract

Denervated muscle fibers exhibit spontaneous, repetitive single muscle fiber discharges and display fibrillation potentials detectable by electromyography. To explore the changing pattern of fibrillation potential amplitude after peripheral nerve injury and its relationship to the degree of muscle atrophy, fibrillation potential amplitudes were recorded on completely denervated biceps brachii of 173 patients with brachial plexus injury. Biceps brachii biopsies were taken at the same sites as the electromyogram recordings in 63 patients. The biopsies were analyzed by ATPase staining and the cross-sectional areas of fast and slow-twitch fibers were calculated. We found that the fibrillation potential amplitude and the cross-sectional areas of denervated muscle decay over time ($P < 0.05$), and both correlate negatively with denervation time ($P < 0.01$–0.05) within the first 15 months. The fibrillation potential amplitude correlates positively with both type I and II fiber cross-sectional areas ($P < 0.0005$–0.01). Our results show that fibrillation potential amplitude is closely correlated with muscle fiber size during the first 15 months after nerve injury, and it may therefore serve as a convenient index to evaluate quantitatively the degree of atrophy of denervated muscles. Electromyographic studies thus may help in designing treatment strategies.

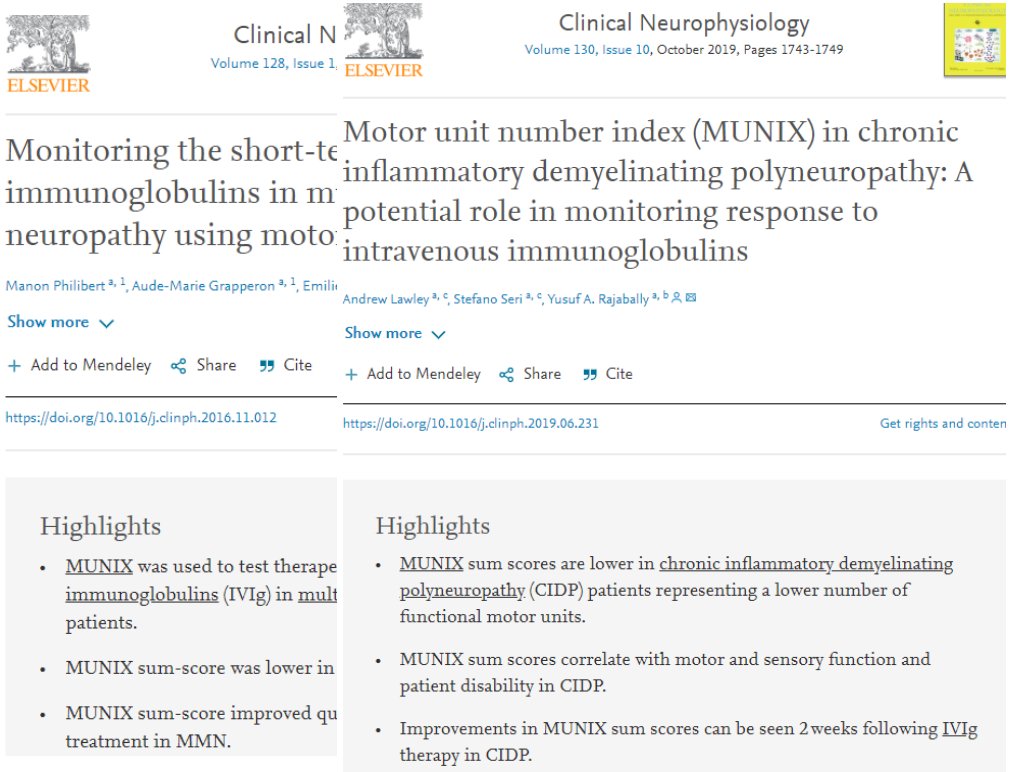
Monitoring of treated dysimmune neuropathies

Motor Unit Number Index (MUNIX) as a measure of treatment effects in MMN and CIDP has been proven sensitive to change

However, this was in acute, not chronic treatment → patients improved already clinically

Long-term changes due to reinnervation unknown (increase of motor unit size)

→ Feasible as a long-term biomarker?



ELSEVIER

Clinical N

Volume 128, Issue 1,

Monitoring the short-te
immunoglobulins in m
neuropathy using moto

Manon Philibert [a, 1], Aude-Marie Grapperon [a, 1], Emili

Show more

+ Add to Mendeley Share Cite

https://doi.org/10.1016/j.clinph.2016.11.012

Highlights

- MUNIX was used to test therape immunoglobulins (IVIg) in mult patients.
- MUNIX sum-score was lower in
- MUNIX sum-score improved qu treatment in MMN.

ELSEVIER

Clinical Neurophysiology

Volume 130, Issue 10, October 2019, Pages 1743-1749

Motor unit number index (MUNIX) in chronic inflammatory demyelinating polyneuropathy: A potential role in monitoring response to intravenous immunoglobulins

Andrew Lawley [a, c], Stefano Seri [a, c], Yusuf A. Rajabally [a, b]

Show more

+ Add to Mendeley Share Cite

https://doi.org/10.1016/j.clinph.2019.06.231 Get rights and conten

Highlights

- MUNIX sum scores are lower in chronic inflammatory demyelinating polyneuropathy (CIDP) patients representing a lower number of functional motor units.
- MUNIX sum scores correlate with motor and sensory function and patient disability in CIDP.
- Improvements in MUNIX sum scores can be seen 2 weeks following IVIg therapy in CIDP.

Monitoring of treated dysimmune neuropathies: example 1

- 69y old male, 3 months on statins (after muscular side effects on other statins years ago)
- Realized new difficulties climbing stairs at vacation in Cyprus, muscle cramps, lower weights in his fitness program. No sensory symptoms complained, no pain.
- CK 460U/l (<170), Myoglobin 150ug/l (<105) → statin side effect was suspected by patient and family physician
- Clinical mild proximal weakness legs > arms, preserved reflexes arms, vanished ATR

  →Statin-induced necrotizing autoimmune myopathy?

- EMG legs 2 months after symptom onset: acute denervation dist>prox, chronic reinnervation >6mV (?), only slight early reinnervation

Monitoring of treated dysimmune neuropathies: example 1

Nerv	Distanz mm	Latenz ms	NLG m/s	Amplitude mV	Stimulus mA	F-Latenz ms	Temp. °C
Medianus Motorisch Rechts							
Handgelenk - APB	75.0	3.94		11.3	37.0	34.3	
Ellenbeuge-Handgelenk	240	8.56	51.9	10.7	42.6		
Oberarm-Ellenbeuge	105	10.5	54.1	10.0	42.6		
Peroneus Motorisch Links							
OSG - EDB	95.0	5.29		6.5	52.0	59.9	
Dist. Cap. fib.-OSG	290	12.5	40.2	5.1	54.2		
Kniekehle-Dist. Cap. fib.	110	15.1	42.3	4.8	54.2		
Tibialis Motorisch Links							
Med. mal - Abd hal	105	6.26		10.2	55.6	61.5	
Kniekehle-Med. mal	390	16.6	37.7	8.3	55.6		
Tibialis Motorisch Rechts							
Med. mal - Abd hal	75.0	4.74		10.1	57.8	63.3	
Kniekehle-Med. mal	410	15.5	38.1	7.2	64.8		
Ulnaris Motorisch Rechts							
Handgelenk - ADM	70.0	2.96		13.9	10.7	34.2	
Dist. Sulcus-Handgelenk	245	7.94	49.2	11.3	22.8		
Prox Sulcus-Dist. Sulcus	120	10.1	55.6	10.7	25.4		
Oberarm-Prox Sulcus	100	12.0	52.6	10.4	25.4		

Nerv	Distanz mm	Latenz ms	NLG m/s	Amplitude uV	Stimulus mA	Temp. °C
Peroneus superfic Sensorisch Links						
Unterschenkel - Sprunggelenk	95.0	2.39	39.7	10.0	13.1	
Suralis Sensorisch Links						
Wade - Lat. Malleolus	130	3.41	38.1	7.0	15.7	26.9
Ulnaris Sensorisch Rechts						
Handgelenk - Dig V	140	2.75	50.9	8.6	11.9	

Example 1: 3 months later…

Nerv	Distanz mm	Latenz ms	NLG m/s	Amplitude mV	Stimulus mA	F-Latenz ms	Temp. °C
Medianus Motorisch Rechts							
Handgelenk - APB	75.0	3.87		11.8	36.2	33.1	
Ellenbeuge-Handgelenk	240	8.31	54.1	10.6	43.8		
Oberarm-Ellenbeuge	115	10.4	55.0	10.2	43.8		
Ulnaris Motorisch Rechts							
Handgelenk - ADM	80.0	3.45		15.3	18.3	33.7	
Dist. Sulcus-Handgelenk	235	7.96	52.1	14.1	29.0		
Prox Sulcus-Dist. Sulcus	110	9.93	55.8	13.4	31.6		
Oberarm-Prox Sulcus	80.0	11.3	58.4	13.1	31.6		

Nerv	Distanz mm	Latenz ms	NLG m/s	Amplitude uV	Stimulus mA	Temp. °C
Ulnaris Sensorisch Rechts						
Handgelenk - Dig V	155	2.83	54.8	9.8	11.4	

Nerv	Distanz mm	Latenz ms	NLG m/s	Amplitude mV	Stimulus mA	F-Latenz ms	Temp. °C
Medianus Motorisch Rechts							
Handgelenk - APB	75.0	3.94		11.3	37.0	34.3	
Ellenbeuge-Handgelenk	240	8.56	51.9	10.7	42.6		
Oberarm-Ellenbeuge	105	10.5	54.1	10.0	42.6		
Ulnaris Motorisch Rechts							
Handgelenk - ADM	70.0	2.96		13.9	10.7	34.2	
Dist. Sulcus-Handgelenk	245	7.94	49.2	11.3	22.8		
Prox Sulcus-Dist. Sulcus	120	10.1	55.6	10.7	25.4		
Oberarm-Prox Sulcus	100	12.0	52.6	10.4	25.4		

Nerv	Distanz mm	Latenz ms	NLG m/s	Amplitude uV	Stimulus mA	Temp. °C
Ulnaris Sensorisch Rechts						
Handgelenk - Dig V	140	2.75	50.9	8.6	11.9	

After booster treatment, improvement of proximal arm weakness and some degree leg weakness.

Standing on toes was possible for 2 seconds

NCS in legs and arms remained stable over years as well as clinical deficits

Monitoring of treated dysimmune neuropathies: example 2

- 61y old female, GBS 8 years earlier, relapse GBS 2 months ago, both treated with IVIG
- After last treatment 2 months ago improvement, but deterioration after 6 weeks
- Tingling in hands and feet, walking difficulties, problems doing the gardening (endurance)
- Clinically vanished DTR (only weak pectoralis-reflex), hypaesthesia hands and feet, no significant weakness in MMT, M. extensor digitorum brevis was visible and palpable, but no active contraction , positive Lasègue-sign. Walking-on toes and heels possible

Monitoring of treated dysimmune neuropathies: example 2

Nerv	Distanz mm	Latenz ms	NLG m/s	Amplitude mV	Stimulus mA	F-Latenz ms	Temp. °C
Medianus Motorisch Rechts							
Handgelenk - APB	80.0	17.1		5.6	27.4	46.2	
Ellenbeuge-Handgelenk	205	21.1	51.3	5.4	29.2		
Oberarm-Ellenbeuge	90.0	22.6	60.0	5.4	29.2		
Peroneus Motorisch Rechts							
Ankle - EDB	85.0	6.93		3.7	48.6		
Dist. Cap. fib.-Ankle	290	14.6	37.8	2.7	50.8		
Kniekehle-Dist. Cap. fib.	120	17.5	41.4	2.7	50.8		
Tibialis Motorisch Rechts							
Med. mal - Abd hal	95.0	8.50		2.5	61.0	73.8	
Kniekehle-Med. mal	380	17.8	40.9	2.1	61.0		
Ulnaris Motorisch Rechts							
Handgelenk - ADM	70.0	5.38		7.4	28.0	34.4	
Dist. Sulcus-Handgelenk	205	9.40	51.0	5.8	31.0		
Prox Sulcus-Dist. Sulcus	110	11.3	57.9	5.3	31.0		
Oberarm-Prox Sulcus	110	13.2	57.9	4.7	40.2		

Nerv	Distanz mm	Latenz ms	NLG m/s	Amplitude uV	Stimulus mA	Temp. °C
CTS Mixed Nerve Sensorisch Rechts						
Palm Med - Wrist Med	80.0	4.24	18.9	1.18	15.0	
Medianus Sensorisch Rechts						
Dig II - Handgelenk	165	8.28	19.9	1.08	14.0	
Peroneus superfic Sensorisch Rechts						
Unterschenkel - Sprunggelenk	85.0	2.13	39.9	5.0	8.3	
Suralis Sensorisch Rechts						
Wade - Lat. Malleolus	75.0	2.17	34.6	5.8	4.6	
Ulnaris Sensorisch Rechts						
Handgelenk - Dig V	135	2.91	46.4	1.37	11.2	

- EMG: slight chronic neurogenic changes
- No relevant acute denervation
- Long-term IVIG
- Several relapses due to patient initiated dose reductions / cancellations
- Finally, higher dosages and frequent intervals where accepted → sustained improvement

Example 2: 2.5 years later…

Nerv	Distanz mm	Latenz ms	NLG m/s	Amplitude mV	Stimulus mA	F-Latenz ms	Temp. °C
Medianus Motorisch Rechts							
Handgelenk - APB		5.81		16.6	31.8	32.9	
Peroneus Motorisch Rechts							
OSG - EDB	70.0	4.77		11.1	39.2	54.5	
Dist. Cap. fib.-OSG	302	12.5	39.1	8.2	46.8		
Kniekehle-Dist. Cap. fib.	100	14.8	43.5	8.9	46.8		
Tibialis Motorisch Rechts							
Med. mal - Abd hal	90.0	5.48		7.8	73.6	59.2	
Kniekehle-Med. mal	385	15.0	40.4	5.6	50.0		

Nerv	Distanz mm	Latenz ms	NLG m/s	Amplitude uV	Stimulus mA	Temp. °C
CTS Mixed Nerve Sensorisch Rechts						
Palm Uln - Wrist Uln	80.0	1.58	50.6	10.1	22.6	
Palm Med - Wrist Med	80.0	3.17	25.2	8.9	16.4	
Suralis Sensorisch Rechts						
Wade - Lat. Malleolus	98.0	2.79	35.1	6.9	12.2	

Comments? Suggestions? Questions…?