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Hands-on Course 12

MUNIX and Phrenic nerve conduction studies (Level 3)

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MUNIX AND PHRENIC NERVE CONDUCTION STUDIES

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Introduction
Objective markers of disease progression in diseases affecting motor neurons are urgently needed. This is particularly relevant for ALS clinical trials. Ideally progression markers are easy to apply in a clinical setting, highly reliable and meaningful in terms of disease progression.
Quantification of motor unit loss by means of MUNIX has the great advantage that this measure directly reflects the underlying pathology. [1] [2] Likewise phrenic nerve conduction studies not only objectively reveal diaphragmatic function but also provide prognostic information.[3]
Both methods have gained a lot of scientific interest over the past few years and are at the forefront of ALS research.[4] [5]

Key learning objectives
This course will focus on practical issues. Participants will understand the applicability and limitations of these methods. MUNIX will be performed on APB, ADM, FDI, Biceps, TA, EDB. After the course attendees will be able to make high quality MUNIX recordings and compound muscle action potential (CMAP) recordings of the diaphragm.

MUNIX

General Procedure

MUNIX measurements can be performed from any muscle in which a maximum CMAP can be recorded. It is a three step procedure.
First the CMAP is recorded applying supramaximal nerve stimulation. To ensure consistency between repeat measurements the placement of the electrodes is standardized according to the provided photographic documentation**. The active recording electrode must be adjusted several times to achieve a maximal amplitude and risetime and a sharp negative take-off of the CMAP**. This is the most critical step and must be performed carefully.
Next the subject activates the tested muscle voluntarily against resistance given by the examiner. The contraction must be isometric, limb movement should be avoided. The force is increased from minimal to maximal at 5-9 different force levels. Once a stable contraction level is achieved the surface EMG interference pattern (SIP) is recorded.
Finally the area and the power of the CMAP and the SIP are used to make a calculation which is plotted on a regression curve. Munix results are calculated and updated with each SIP recording after the first three sweeps have been recorded. A minimum of 20 epochs is recommended.

Instructions (for automated method, e.g. Synergy EMG machines)

CMAP recordings
Record the compound CMAP using supramaximal stimulation (Figure 1). Change the position of the 'active' or 'E1' electrode several times to obtain the CMAP with highest amplitude. It should not have an initial positive deflection and the expected shape. The markers '1', '2' and '3' are placed at the onset, negative peak and baseline crossing of the CMAP. Adjust their positions using the mouse, if necessary. The gain can also be adjusted if needed. The results table will show the associated measurements of the CMAP. CMAP amplitude may not be less than 0.5 mV.

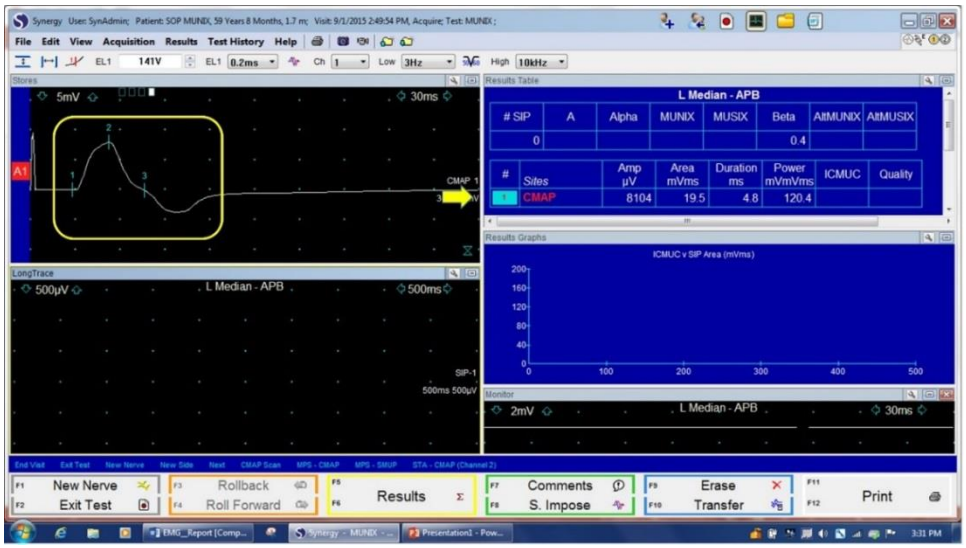


Figure 1

SIP recordings

After recording the CMAP, push the 'Next' or 'Trace ▼' key, as appropriate. The system will automatically change settings for the SIP recordings. Note the monitor trace in the bottom right corner. It should appear flat indicating no significant noise and interference (Figure 2).

- Push the 'Switch' or 'Acquire ON' button. You will see the EMG activity in the monitor trace (bottom right) and 'Long trace' (bottom eft) windows. The signal amplitude should be greater than 200 µV and contain spikes representing EMG activity. When a stable signal is seen, push the 'Acquire' or 'Switch' button to stop recording.
- Note the SIP measurements in the result table. The graph will display the data point of 'Ideal case motor unit count (ICMUC)' versus the SIP area.
- Push the 'Next' or 'Trace ▼' button to begin recording the next SIP epoch. Repeat the above 2 steps to get the necessary SIP epochs.

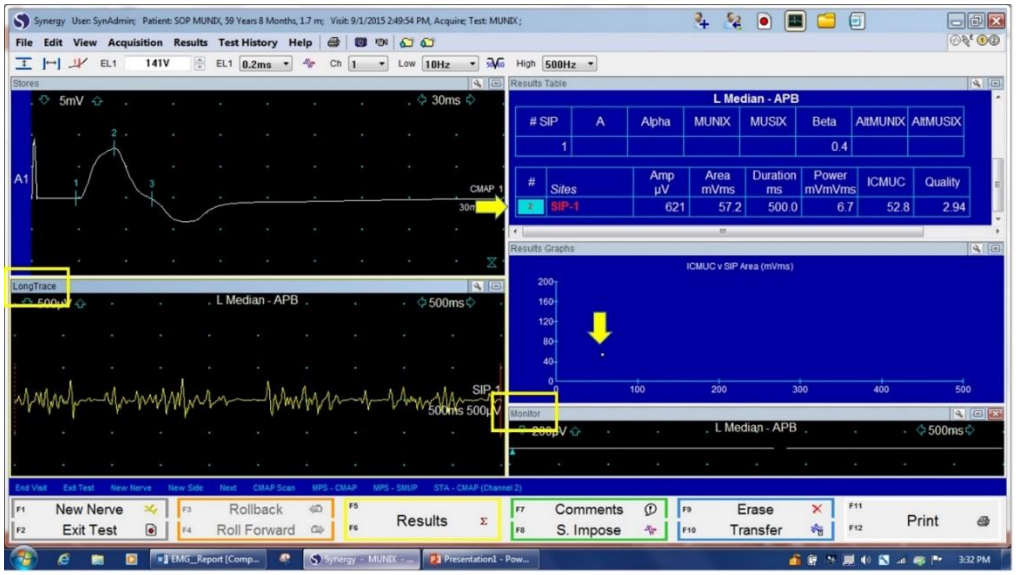


Figure 2

When the system has collected 3 SIP epochs that are accepted for analysis, the regression line is drawn, and the results of MUNIX calculations are updated (Figure 3).

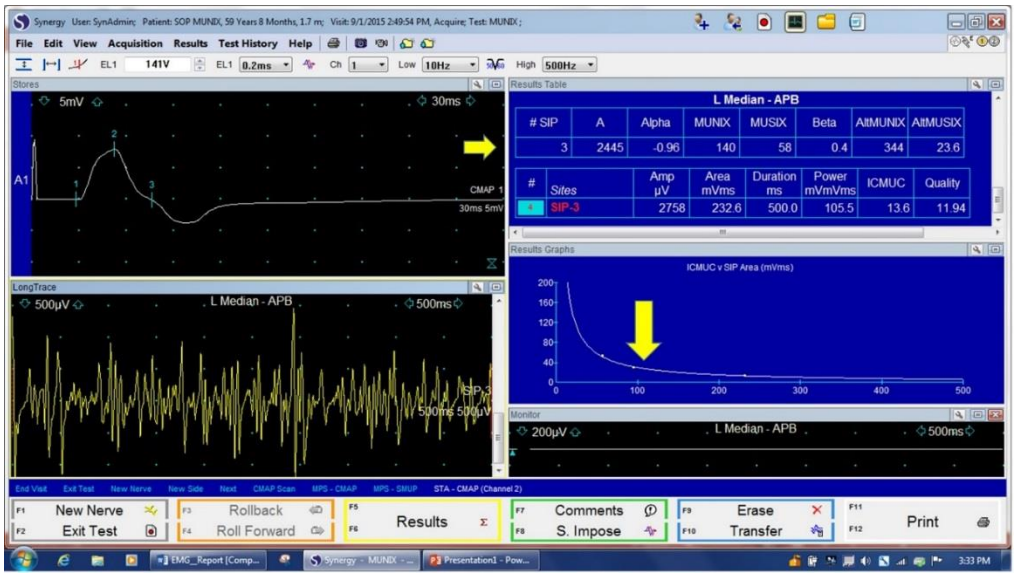


Figure 3

The system is capable of recording up to 29 SIP epochs (Figure 4). Record the SIP using 5-9 force levels ranging from slight to maximum force of contraction. It is more important to collect data in the low and mid-range of force. Perform 2 to 4 trials to collect at least 20 ***included*** SIP epochs or more.

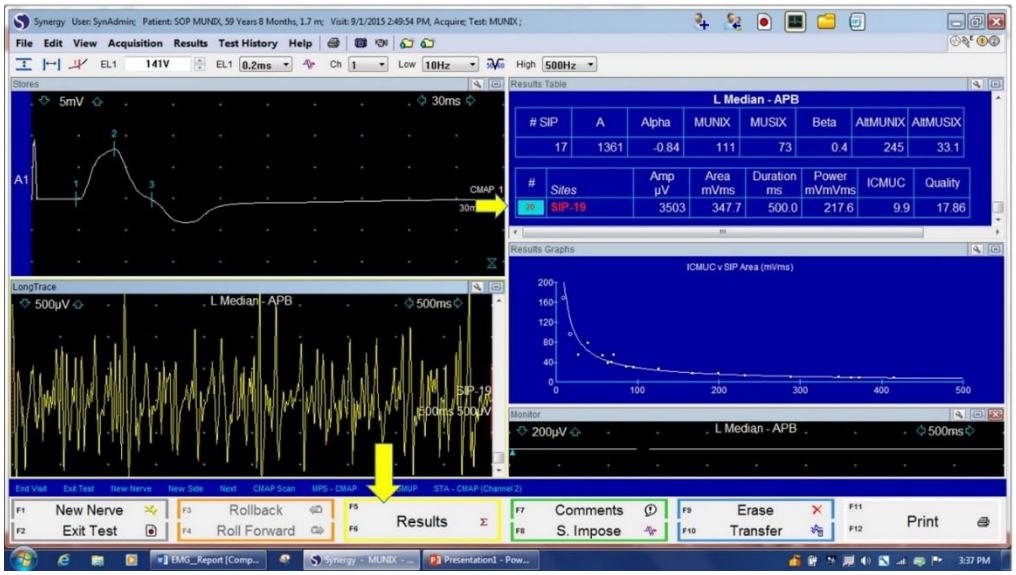


Figure 4

Generation of appropriate SIPs

To accurately calculate MUNIX for each muscle it is important to capture an appropriate range of force during collection of SIPs (see above). The subject is asked to gradually increase force, receiving acoustic feedback. Motor unit potential amplitude should gradually increase. The investigator provides resistance (see pictures below). The contraction must be isometric! Avoid any limb movements. Care should also be taken for the examiner not to touch the recording and reference electrodes. SIPs with a quality index below 1.0, ICMUC > 100 and SIP area < 20 mVms will be automatically rejected (empty circles in the graph) for the MUNIX calculation. SIPs with baseline shift, tremor or bimodal pattern with very low volume conducted activity should not be recorded or may exceptionally be deleted/excluded manually.

Hints

- SIP recordings that do not fulfil the quality criteria will be excluded automatically by the software and should not be manually included.
- Avoid measurements with tremor, baseline-shift, or obvious change of innervation/force level within the single SIP recording epoch (500ms).
- Do not record SIPs too fast, resulting in SIP epochs of<500ms.
- Try to get a wide range of measurements at distinguishable different force levels. This can be estimated with a wide range of the provided "quality index", starting at lower values above 1.0. Ideally data points are nicely distributed along the regression curve.
- SIP recordings at lower/intermediate force levels are more important for proper MUNIX calculation than maximal force levels.
- However, in the biceps, tibial anterior, and FDI muscles, initial higher force levels might be required to obtain appropriate SIP recordings. Minimal SIP amplitude should be > 0.2 mV.

Review results

Click on the 'Results' (Figure 5) key to review the tabulated data (Figure 5). The graph is shown under the table. The data points excluded from analysis are shown using open circles in the plot. Note the indication of exclusion in the result table. By default SIP signals that produce ICMUC > 100 and/or Quality (=SIP area/ CMAP area) < 1 are automatically excluded. User can manually include or exclude the various recordings. Exit the screen by clicking on the 'Results' key' in the bottom left of the screen.

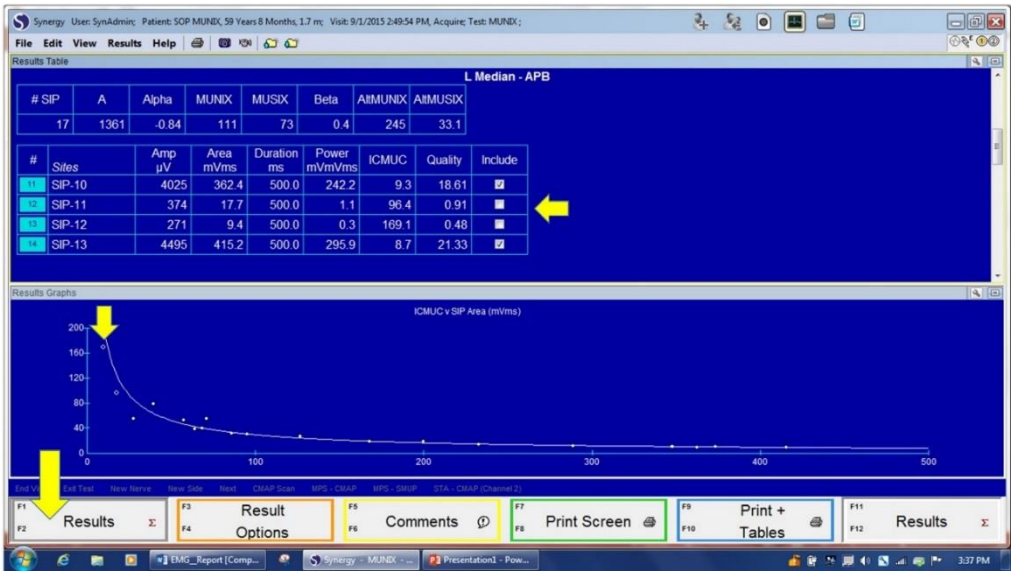


Figure 5

One can also review the recordings using the scroll bar in the long trace window. In Figure 6, the 'SIP 15' epoch has excessive power-line frequency interference. Exclude this by removing the checkmark in the 'Include' column of the result table. Need of excluding SIPs should be the exception and only applicable to clearly polluted or faulty SIP recordings!

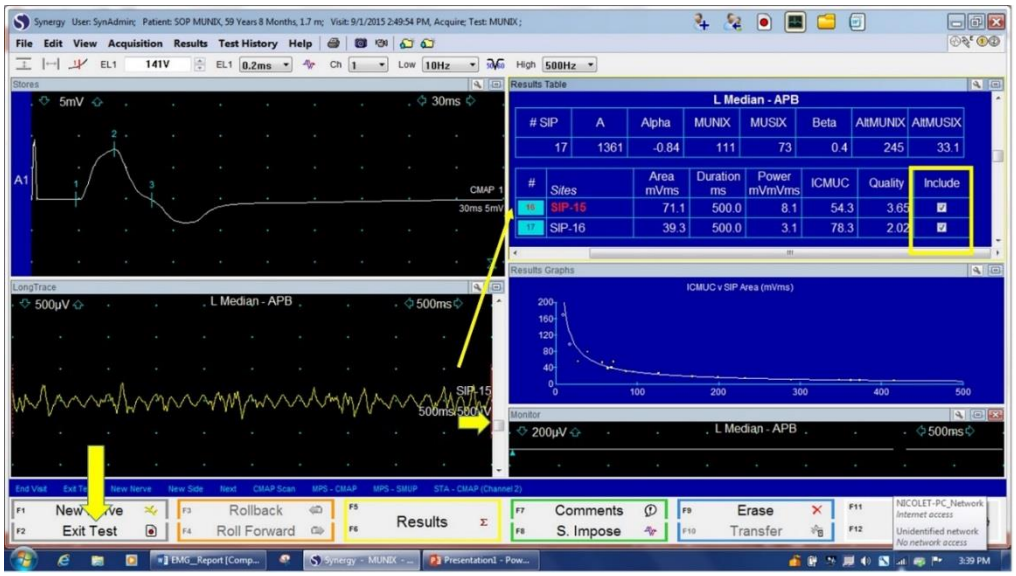


Figure 6

Click on 'Exit Test' to return to test menu of the system (Figures 10 and 11). Choose another muscle for testing.

3 Golden Rules:

1. ***Always carefully optimize the CMAP amplitude***

2. ***Get a nice distribution of at least 20 included (!) SIP measurements of 500ms duration at different force levels from minimal to maximal on the regression curve, starting around quality values with 1, not "patchy"***

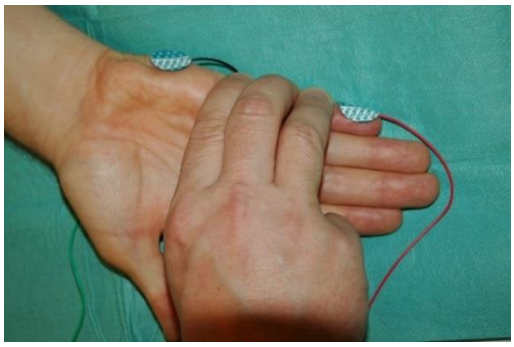
3. ***Avoid inconstant SIP recordings with bursts or increasing/decreasing force levels during the 500ms epoch; do not acquire SIPs too fast < 500ms***

Electrode Placement for Individual Muscles

Subjects should be lying comfortable on an exam table. This is especially relevant for positioning of the arm for the biceps measurements. However, patients may also be seated comfortably in a chair with table or chair with arms nearby for support of hands.

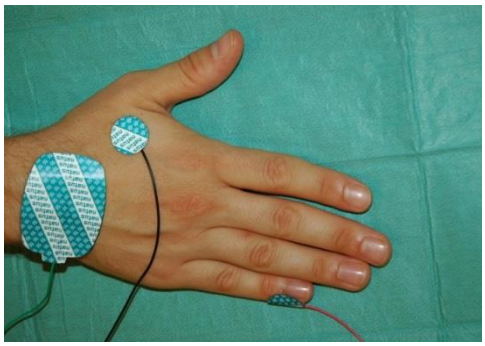
Abductor Digiti Minimi (ADM)

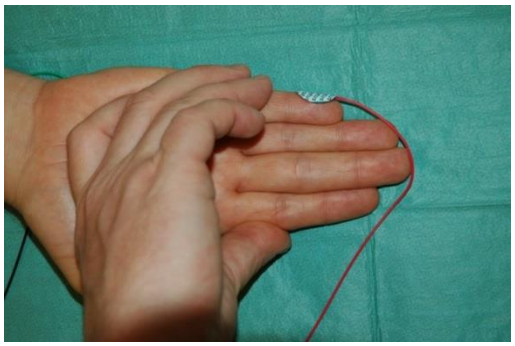
- Place hand upon flat surface, palm up
- Place recording electrode on ADM at midpoint fifth metacarpal
- Place reference electrode distally at the little finger
- Grounding electrode is placed on the dorsum of the hand
- Place stimulator at wrist adjacent to flexor carpi ulnaris tendon
- In some subjects, maximal CMAP is achieved with more proximal placement of the recording electrode
- Be aware of initial baseline shift due to electrode movement on the skin while increasing force levels
- Counter resistance: stabilize with your fingers/thumb. Do not allow abduction of digit V



First Dorsal Interosseous (FDI)

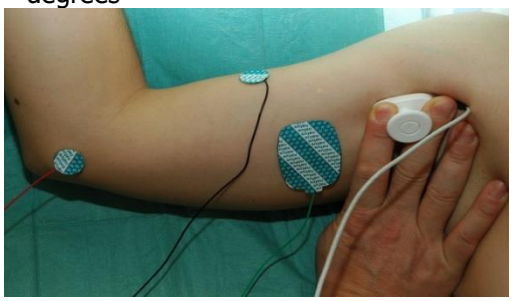
- Place hand on flat surface, for measurements palm upward, relaxed with no finger adduction/abduction
- Be aware, that position of the fingers/thumb abduction has an influence on CMAP
- Place recording electrode halfway between the first and second metacarpals, aligned with metacarpal. In some subjects, highest CMAP is obtained more proximal and next to the second metacarpal.
- Place reference electrode distally at the little finger to obtain highest CMAP (compared to the index finger) and to avoid positive take-off of CMAP.
- Grounding electrode is placed on the dorsum of the hand
- Place stimulator at wrist adjacent to flexor carpi ulnaris tendon
- Counter resistance: stabilize with your fingers/thumb. Do not allow abduction of digit II, avoid additional flection of the index finger.

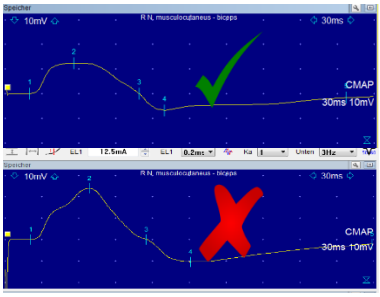




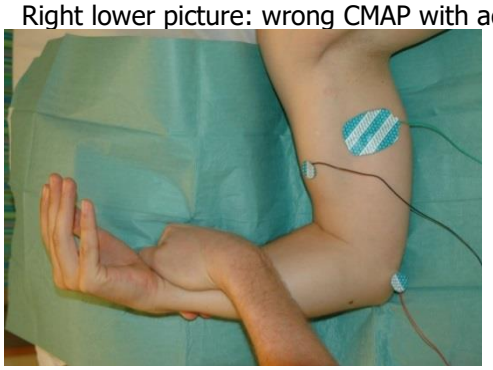
Biceps

- Place arm such that biceps tendon and attachment to coracoid may be easily palpated, with elbow flexion about 90 degrees
- A flat positioning of the subject with arm abduction and elbow flection (forearm on a pillow) might be most comfortable for subject and rater
- Place recording electrode on bulk of muscle between antecubital fossa and acromion, 1/3rd way up from antecubital fossa
- Place reference electrode over the medial epicondylus of the elbow
- Place stimulator just inferior to tendon of short head of biceps as the musculocutaneous nerve emerges from the axilla
- Isolated stimulation of the musculocutaneous nerve can be challenging. Verify visually that there is no additional wrist flection by median nerve co-stimulation and no double peak shape of the CMAP (see recordings below)
- Counter resistance: place your hand, forearm or elbow at the patient's wrist/distal forearm to avoid elbow flection. SIP measurements should be performed with elbow positioned at 90 degrees





Right upper picture: correct CMAP with single biceps stimulation
Right lower picture: wrong CMAP with additional wrist flexor stimulation



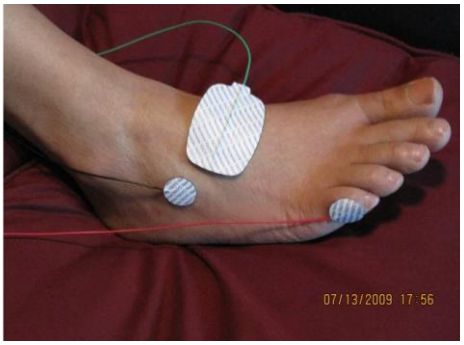
Tibialis Anterior

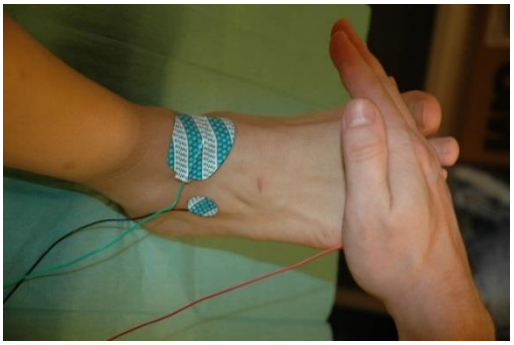
- Lower leg is positioned naturally with sole of the foot on the floor, knee flexed approximately 90 degrees.
- Place recording electrode lateral to tibial crest, one-third of distance between ankle and knee (closer to knee).
- Place reference electrode over the patellar tendon.
- Grounding electrode should be places above at the level of the fibular head.
- Place stimulator one to two fingerbreadths inferior to fibular head.

- Counter resistance: use your hand to give resistance with the foot positioned at 90 degrees. Avoid pronation/supination of the foot.

Extensor Digitorum Brevis (EDB)

- Lower leg is positioned naturally on a bed.
- Place recording electrode on dorsum of foot two to three fingerbreadths from lateral malleolus.
- Place reference electrode distally over the little toe.
- Grounding electrode should be places on the dorsum of the ankle.
- Place stimulator at ankle, just lateral to the tibialis anterior tendon.
- Counter resistance: place side of your hand or forearm on proximal phalanx of toes, foot in 90 degrees position.





Further reading[6-14]

Phrenic nerve conduction study

General Concept

Phrenic nerve conduction, as an electrodiagnostic method, was first described by Newson-Davis.[15] Subsequent authors showed that the electrical activity in the diaphragm could be reliably recorded from surface electrodes, when the contraction is evoked in the muscle by stimulating the phrenic nerve percutaneously at the neck.[3 16] Phrenic nerve stimulation is an accessible non-invasive test, which is non-volitional and well-tolerated. Its motor response size depends on the number of excitable motor units in the diaphragm.[17] It has been shown that a small motor response following phrenic nerve stimulation indicates impending respiratory failure in ALS[18] and is an independent prognostic factor for survival in ALS patients.[19] In addition it provides information about phrenic nerve lesion as occurs during thoracic surgery or trauma, helps to discern the reason of respiratory failure in intensive care setting, and has prognostic value in Guillain-Barré syndrome and other neuromuscular conditions. It is a non-volitional tool for testing respiratory impairment in patients unable to cooperate with

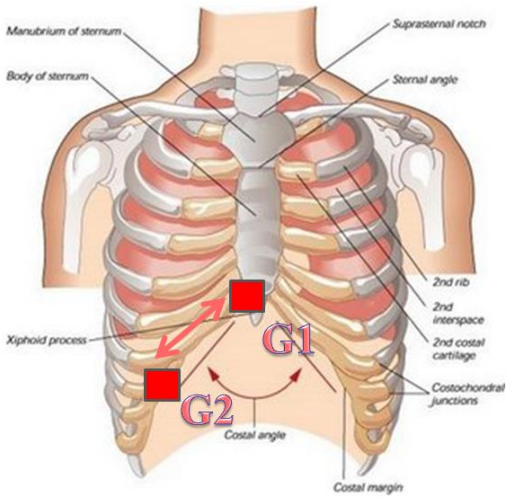
conventional tests (like patients with cognitive dysfunction). This simple test can offer relevant information about respiratory function if properly performed.

Instructions

Bilateral diaphragm motor responses are obtained by percutaneous bipolar electrical stimulation of the phrenic nerve at neck (posterior to the lateral border of the sternocleidomastoid muscle, immediately behind its mid portion, generally at the level of the superior limit of thyroid cartilage) and recorded through surface electrodes on the homolateral costosternal angle (active electrode), with the reference electrode ipsilateral, on the costal girdle, 16cm apart from G1, in a recumbent patient. A ground electrode can be placed around the homolateral wrist or on the thoracic region. The stimulus duration is set between 0.2-0.5 ms as necessary to obtain supramaximal stimulation. Brachial plexus stimulation artifact is avoided by changing stimulus duration, electrode position and stimulus intensity.[20]

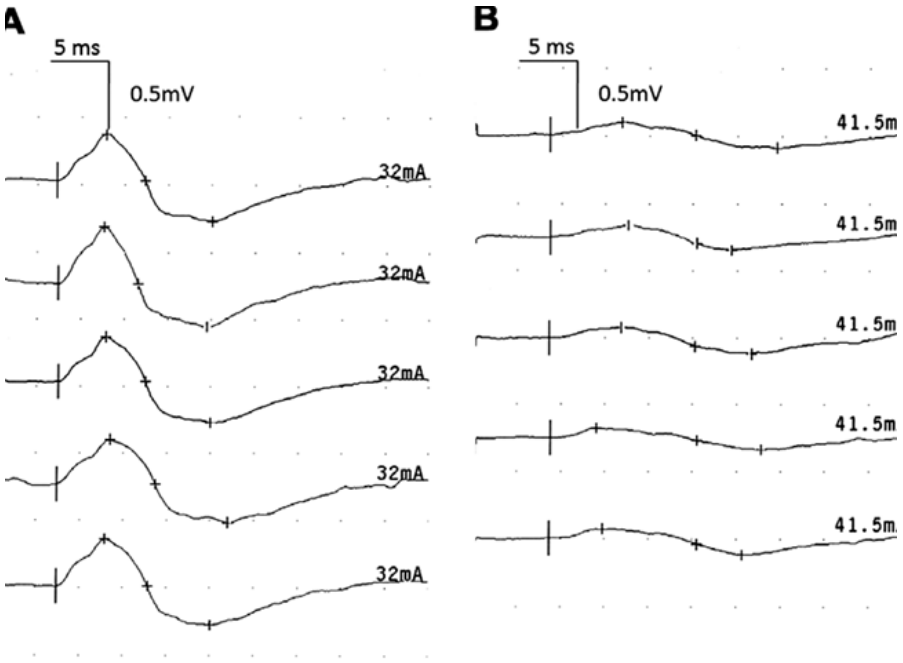
Responses should be recorded at the same moment of the respiratory movement, as the morphology of the motor response changes, we prefer at the end-of-expiration time (muscle relaxed).

We propose to record a minimum of five consistent motor responses from each side to ensure reliability. The response with the highest amplitude (or negative-peak area) should selected for analysis.



Both the size of the motor response and the distal latency should be considered. Amplitude or area of the diaphragm motor response is a more representative of the lower motor neuron pool.[17] However, latency tends to increase when motor response in small and can provide relevant information.[21] The terminal latency of the phrenic nerve correlates with respiratory symptoms in amyotrophic lateral sclerosis.[22]

In general inter-side correlation of the phrenic nerve motor responses is very high in ALS [23] Thus, a mean value from both sides and a single size motor response are valid alternatives to evaluate respiratory status and to monitor its progression in ALS. The figure below illustrates test-to-test reliability of the phrenic responses and the differences of amplitude that can be disclosed between ALS patients (A) and normal subjects (B).



Phrenic nerve response can be particularly useful in uncooperative ALS patients, as the ones with cognitive dysfunction. In addition, patients with marked lips paresis have major difficulty in performing technically satisfactory respiratory tests.
Care should be taken to avoid patients with pace-maker or implantable cardioverter defibrillator, otherwise no other contra-indication is usually considered.

Ideally, each laboratory should define its normative values. Generally a peak-to-peak amplitude < 0.4 mv and a latency > 9.0 is considered abnormal.

3 Golden Rules:

1. ***Patients should be relaxed with a quite respiration***
2. ***Always stimulate at the same respiratory phase during the respiratory cycle to optimize CMAP reliability***
3. ***Record a number of responses to confirm reliability.***

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Conflict of interest:
The authors have no conflict of interest in relation to this manuscript