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Review article

Antidromic vs orthodromic sensory median nerve conduction studies

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ABSTRACT

Objective: Median sensory nerve conduction studies are arguably the most often performed electrodiagnostic tests worldwide. Routine tests in clinical practice are done using either antidromic or orthodromic techniques type of stimulation, with no universal agreement on the use of one or the other technique.
Methods: We review the advantages and drawbacks of antidromic and orthodromic as well as their particularities for clinical application and research.
Results: The two techniques differ on how physical and physiological changes affect the action potential. Near-nerve recording is better suited for the orthodromic than for the antidromic technique, while studies of nerve excitability are better suited for the antidromic than for the orthodromic technique.
Conclusion: Both techniques are equally suitable for routine tests but research studies may specifically demand one or the other.

Contents

1. Introduction

Sensory nerves of the hand are commonly examined in routine practice of electrodiagnostic testing. The study of median and ulnar nerves is not only useful for the diagnosis of entrapment neuropathies but also for the assessment of suspected polyneuropathy, plexopathy or radiculopathy as well as for physiological studies in healthy subjects. The most frequent request for electrodiagnostic assessment of sensory nerve conduction in the finger-to-wrist segment of human hands is undoubtedly carpal tunnel syndrome (CTS). Many of us have begun to practice electrodiagnostic testing by determining median nerve conduction in healthy subjects and patients with CTS. Still, even if it is one of the most studied syndromes in neurology, our knowledge of its pathophysiology and of the correlation between neurophysiological testing and clinical aspects is incomplete (Werner and Andary, 2002). The neurophysiological study of CTS is not fully standardized but, instead, many

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methods have been described and are being used without consensus. To begin with, there is no universal agreement on whether to use antidromic or orthodromic techniques and no advice on that matter has been issued in various guidelines published so far (Jablecki et al., 2002; Sandin et al., 2010; Basiri and Katirji, 2015).

Orthodromic testing of sensory nerves has a long history. Dawson and Scott (1949) were the first to show that it was possible to record sensory nerve action potentials through the skin. Later on, Dawson (1956) used for the first time ring finger electrodes to obtain the orthodromic sensory nerve action potential (SNAP) in proximal nerve segments. Gilliatt and Sears (1958) were the first to use the method for clinical purposes in patients with entrapment syndromes and polyneuropathies. Antidromic testing was first described by Sears in 1959, as quoted in papers in which the authors used the antidromic technique to examine a large number of patients with suspected carpal tunnel syndrome (Campbell, 1962) or a single patient with polyneuritis (Bannister and Sears, 1962).

Each of the two techniques has its advantages and drawbacks but clinical neurophysiologists favor either one or the other. In an unofficial poll among physicians and technicians in Barcelona (Spain) and Lisbon (Portugal), we found that, in most occasions, the choice of one or another technique depended mainly on the school and training experience or convention than in theoretically based arguments, even though most people preferred the antidromic technique, considered to be easier to perform. Confidence in the results of an examination depends largely on technical ability, knowledge of the methodological variants and recognition of possible pitfalls and errors intrinsic of a specific technique. Therefore, we thought to review the advantages and drawbacks of orthodromic and antidromic testing of sensory nerve fibers over the finger-to-wrist segment of the median nerve for the practitioners to have material to choose from when deciding which technique suits their purposes better.

2. Technical aspects

Clinical neurophysiological assessment of hand sensory nerves is rapidly performed many times a day in most electrodiagnostic centers around the world. It is one of the easiest nerve conduction studies to perform and it is commonly the first technique for beginners to learn. Once the machine is set and the patient is in a quiet and comfortable environment, it takes only a few minutes to perform suitable antidromic or orthodromic recordings from one nerve that would serve the purposes of the study.

The examiner should be aware of the changes in waveforms, latency and amplitude that relate to the position of the electrodes and be consistent with the setup chosen for clinical work. Most authors would agree in keeping a standardized distance between the stimulating cathode and the recording active electrode of 14 cm in normal sized hands. It is also generally accepted that the study of short segments of the nerve across the site of compression increases the sensitivity of the study (Jablecki et al., 2002). In fact, one of the most sensitive tests recommended for the assessment of compression of the median nerve at the wrist is stimulation at the palm and recording over the wrist at a distance of 8 cm (Jablecki et al., 2002; Sandin et al., 2010).

The SNAP, obtained with whatever technique, is measured according to the conventional parameters of latency and amplitude. Duration is less commonly reported in clinical studies, possibly because of the difficulties in determining the true end of the SNAP. In fact, the analysis of duration reveals not only the eventual dispersion of the volley but also interesting physiological aspects related to the recording site. In a bipolar recording, the SNAP results from the summation of the activity reaching both electrodes and, therefore, inter-electrode distance significantly affects the SNAP waveform. Onset latency, usually measured at the beginning of the negative phase, depends on the fastest conducting fibers, while peak latency is an expression of the mean conduction velocity value among all fibers participating in the SNAP. No significant differences in diagnostic yield have been reported for conduction velocity calculated after onset or peak latency (Kasius et al., 2014). However, Pyun et al. (2005) have drawn attention to the fact that onset latencies may give more false positive results than peak latency measurement with both orthodromic and antidromic techniques. Amplitude can be measured from baseline to the peak (negative phase) or peak to peak (including negative and positive phases).

2.1. Antidromic technique

For this, the stimulating electrode activates the median nerve at the wrist and the response is recorded over digital nerves of the index or middle fingers. The stimulating electrodes should be placed longitudinally over the median nerve, to avoid unintended concomitant activation of the ulnar or radial nerves in transversally oriented stimuli. Typically, the cathode is placed distal with respect to the anode, even though no anodal block occurs with stimuli of high intensity (Dreyer et al., 1993). The exact distance between cathode and anode is not usually considered an important factor with antidromic stimulation because a response to cathodal stimulation can be obtained similarly using monopolar and bipolar montages. However, the inter-electrode distance is very important at the recording side (Wee and Ashley, 1990). This aspect is discussed more thoroughly below.

Supramaximal intensities used for the stimulation of sensory fibers at wrist level will unavoidably also activate motor fibers and, therefore, generate movements because of contraction of hand muscles (lumbricalis and thenar muscles). These movements may cause some interference with the recording and it may be adequate to hold tight the patient's hand when recording, mostly if there is any clinically based suspicion that the action potentials will be of small amplitude. A single stimulus is usually enough to obtain a sizeable action potential. However, it is good practice to average at least 8 or 10 epochs time-locked to the stimulus to smooth the waveform for an easier measuring of amplitude and latency.

2.2. Orthodromic technique

Stimulating electrodes are usually ring electrodes placed around the proximal and middle phalanxes of the 2nd or 3rd digits and the recording electrodes are placed on the ventral aspect of the wrist, over the median nerve, usually at about 1–2 cm proximal to the proximal wrist crease. For the stimulation, the electrodes do not need any special preparation but the characteristics of the stimulus are important.

For recording, as with the antidromic technique, it is recommendable to use a fixed distance between the active and reference recording electrodes to avoid electrode-related changes in SNAP amplitude and duration. For this purpose, wet pad electrodes mounted on a plastic case and attached with a Velcro strap or held manually over the nerve are a good option because the inter-electrode distance is already set and they can be slightly repositioned to get the largest response amplitude. Obviously, other types of electrodes would yield equally good results provided they are consistently used in any study requiring comparison among subjects. The orthodromic SNAP is of smaller amplitude than the antidromic one and its amplitude but not its latency is affected by wrist size (Lim et al., 1995). However, this is apparently also the case with antidromic recording, where amplitude of the finger

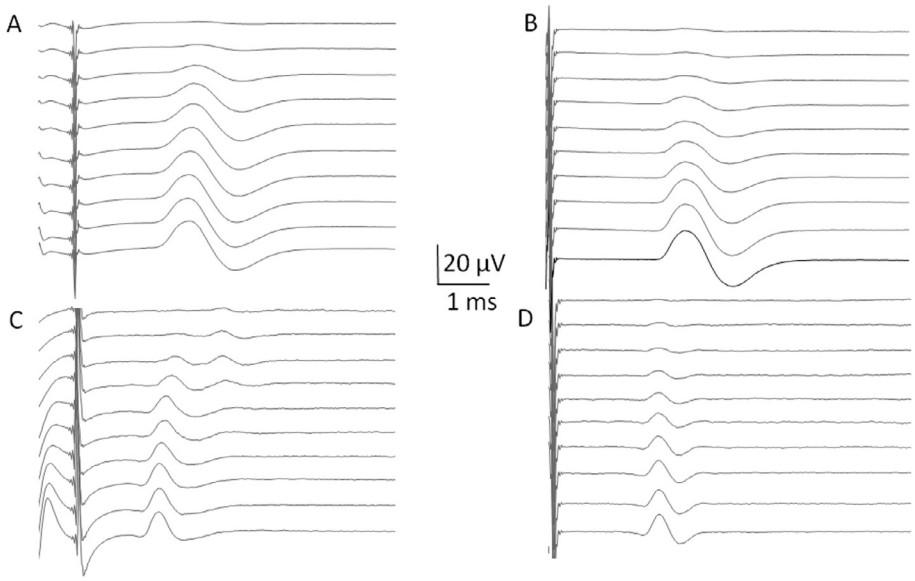

Fig. 1. Recordings of antidromic (A and B) and orthodromic (C and D) sensory nerve action potentials of the 3rd finger, at progressively increasing stimulus intensity. Antidromic testing with stimulation at the wrist over the median nerve and recording with ring electrodes on the 3rd finger. Orthodromic testing with stimulation at the finger with ring electrodes and recording at the wrist. Distance between stimulating cathode and active recording electrodes: 14 cm. Inter-electrode distance for stimulation and recording with both techniques: 3 cm. At each graph, the top traces are recorded at threshold intensity for eliciting a recognizable action potential and the bottom traces are those corresponding to a supramaximal stimulus intensity.

SNAP was found to be inversely proportional to the circumference of the finger (Bolton and Carter, 1980; as well as to the thickness of the wrist Chira-Adisai et al., 1999). In any case, orthodromic responses are more reliably measured after averaging some 8–10 traces. While recording at the palm is rather problematic due to the interference of activity from deep interossei and lumbricalis muscles and the proximity of the stimulus artifact, recording at the wrist yields clean and reproducible action potentials, with little noise from surrounding structures.

3. Differential influence of technical factors on antidromic and orthodromic SNAPs

Examples of representative recordings of antidromically and orthodromically generated SNAPs are shown in Fig. 1. The recordings were obtained to progressively increasing stimulus intensity, from barely perceptible to supramaximal, with electrodes placed in the exact same position and keeping the same interelectrode distance for stimulation and recording with both techniques. A series of details are evident in the graphs shown in this figure, with clear differences when comparing waveforms generated by antidromic and orthodromic stimuli. These are worth detailing for their consequences for applicability to clinical and physiological studies.

3.1. Effect of stimulus duration

There is a progressive shortening of latency with increasing intensity with both types of stimulation when stimuli are of long duration. Although the possibility exists that stimuli of higher intensity activate the axons at a progressively more distant site, the main reason for latency shortening relates to the characteristics of the stimulus waveform. We used constant-current stimulation, which implies taking into account the capacitive properties of the tissue under the stimulating electrodes to reach a given intensity. Because of that, the actual stimulus intensity is lower at the onset of the stimulus than at the end of it, as the current has to overcome the absorption of charges by the human tissues (Pereira et al., 2016). Activation of axons occurs according to the strength–duration properties, when the charge of the stimulus overcomes resistance. Low-intensity stimuli need to build up a sufficient increase in voltage to activate the minimum number of axons that generate recognizable action potentials, and this is more likely to occur after some hundreds of microseconds. This time is not available with short duration stimuli, which do not generate action potentials until the voltage has increased enough for them to be recognizable within the short time that the current is injected. In our experience, using stimuli of 1 ms duration, the time difference between the peak latency of the first recognizable action potentials to low intensity stimuli and the SNAP obtained with the same settings to supramaximal stimulation is about 0.5 ms for the antidromic stimulation and slightly more (0.6 ms) for the orthodromic stimulation. This difference is significantly reduced in patients with nerve lesions, because reduced nerve excitability makes low threshold fibers hypoexcitable, and loss of conducting axons results in a decrease in SNAP size. Whether separation of these two factors is possible and whether this would be of any value for the differential assessment of small fiber vs large fiber neuropathies is still unknown.

Some subjects do not tolerate supramaximal stimulus intensities well, and the question arises whether a low intensity stimulus would be sufficient for clinical assessment. In a study using various stimulus intensities, Nashed et al. (2009) have concluded that reliable action potentials can be obtained in antidromic recordings at 25% of the stimulus intensity that would generate a maximal response. However, as shown in Fig. 1, this is true only for short duration stimuli (0.1 ms), while displacement of latency is evident for longer duration stimuli when constant-current stimulators are used.

In the case of orthodromic stimulation, low intensity stimuli of 1 ms duration generate not only a delayed action potential but, also, a second action potential that follows the first one by a bit more than 1 ms. This is evident in the first 4 traces of C in Fig. 1 and forms a double peak potential (two peaks with the same amplitude) in the third trace. The second peak appears to be generated under the anode (anAP, to distinguish it from the caAP,

the potential generated by depolarization under the cathode; see Aprile et al., 2003, 2007; Therimadasamy et al., 2015; Leote et al., 2016). The mechanism of its generation is anode-break excitation at the switching off of the stimulus (Therimadasamy et al., 2015; Pereira et al., 2016). Even though this action potential has received some attention in recent years, not everything in its physiological mechanisms is completely understood yet. In practical terms, the examiner has to take into account the possibility that the nerve is depolarized under the anode rather than under the cathode. When using orthodromic stimulation, the examiner should not be misled by the anAP, which can be identified for its small amplitude and delayed latency with respect to the expected SNAP. The increase in intensity makes it disappear because of antidromic blocking from inputs generated under the cathode. The anAP is present only with constant current stimuli that have a sharp switch off (Pereira et al., 2016). Unfortunately, the design of the stimulator differs in the various machines available in the market. It is the responsibility of the examiner to know which type of stimulation is set in the electromyograph used to recognize the technical and physiological possibilities of the equipment.

3.2. Size of the action potential

The antidromic potential is significantly larger and wider than the orthodromic potential at all intensities. This can be attributed at least in a large part to the proximity of the nerve, which is closer to the skin surface in the finger, where the antidromic SNAP is recorded, than at the wrist, where the orthodromic SNAP is recorded. While it is convenient to think of the recording electrode closest to the stimulating electrodes as the "active" electrode, this is not so with differential recordings using bipolar electrodes placed along the nerve. The action potentials recorded non-invasively in humans with a short interelectrode distance result from the difference between the action potentials generated at the active and reference electrodes. This will result in summation or phase cancelation, depending on the interelectrode distance (Eduardo and Burke, 1988; Dumitru and Walsh, 1988). Typically, peak amplitude and duration grow with separation of electrodes. The reasoning is that, with short inter-electrode distance, the activity that is inevitably picked up at the reference electrode can influence the shape of the action potential generated in the active electrode because of phase cancelation (Dumitru and Walsh, 1988; Eduardo and Burke, 1988; Evanoff and Buschbacher, 2004). The minimum inter-electrode spacing that allows for the action potential to pass the active electrode before any appreciable electrical activity is generated under the reference electrode is 4 cm, provided a conduction velocity of 50 m/s and an action potential duration of 0.8 ms (Gitter and Stolov, 1995). With a 3 cm distance, a small loss of amplitude and slight changes in duration can be observed but this should still be tolerable for clinical studies (Walker, 1996).

Peak-to-peak amplitude is affected more than negative peak amplitude by variations in the distance between active and reference recording electrodes in both antidromic and orthodromic recordings (Gitter and Stolov, 1995; Andersen, 1985). Consistency in the method of amplitude determination is therefore compulsory since this parameter indicates how synchronized is the volley reaching the recording electrode per unit of time. The expert examiner should consider that, if changes in amplitude are due to technical factors, they usually go with complementary changes in duration (i.e., if amplitude decreases, duration increases and the other way around) and, therefore, the goal should always be to have the maximum possible SNAP peak amplitude when performing sensory nerve conduction studies. We take great care in using the same interelectrode distance of 3 cm between cathode and anode, as well as between active and reference electrodes, for all recordings with both techniques. In spite of that, and in agreement with most authors, we find a significantly larger antidromic than orthodromic SNAP (however, see Cohn et al., 1990 for an observation on similarity of antidromic and orthodromic responses). Certainly, examiners should use fixed distances between active and reference recording electrodes if they want to have comparable results among subjects and avoid over-interpretation of slight differences in SNAP amplitude and latency.

3.3. Differences in waveform

A conspicuous look at the waveforms in Fig. 2 reveals that the antidromic potential does not show an approaching positive phase. In fact, a SNAP should be triphasic, as it is a traveling potential, i.e., an action potential generated by the passage of current nearby but at a certain distance from the recording electrode (Gilliatt and Sears, 1958). The three phases are a small positive approaching phase, a large negative peak and a long positive tail. In fact, though, the initial positive phase, which is well defined with orthodromic recordings, is missing with antidromic recordings. The absence of this phase can be seen along the various recordings shown in the articles publishing recorded action potentials to antidromic stimulation (Bannister and Sears, 1962; Murai and Sanderson, 1975; King et al., 2001; Masakado et al., 2011). This is a striking difference with the orthodromic SNAP which permits speculation on the precise origin of the action potential recorded in the fingers to median nerve stimulation at the wrist. It is good practice to place the active recording electrode away from the base of the

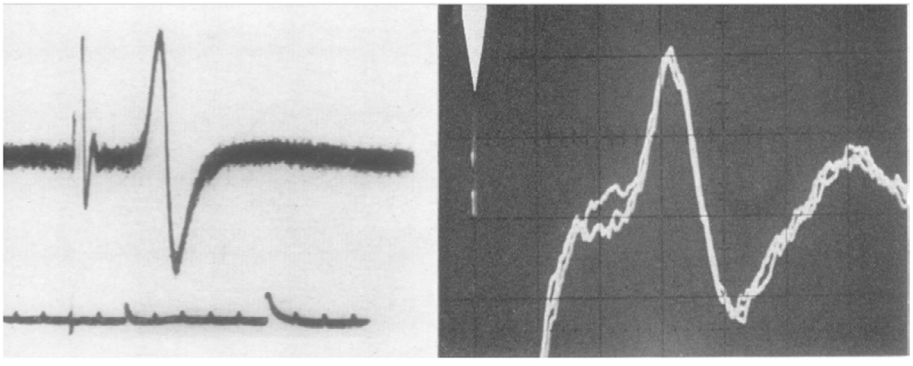

Fig. 2. Traces reproduced from the articles published by Bannister and Sears (1962) and Murai and Sanderson (1975) showing antidromic action potentials. See the absence of the approaching phase.

finger to avoid contamination of the action potential by volume conduction originated in the change of volume from hand to finger (Dumitru and Walsh, 1988; Deupree and Jewett, 1988; Kimura, 1999). However, Masakado et al. (2011) demonstrated that volume conduction may spread a long distance, suggesting a common onset for the compound muscle action potential of the second lumbricalis and the SNAP recorded at the base of the finger. It is therefore possible that the initial part of the antidromic SNAP includes the recording of distant volume conduction. This is another reason to support measuring peak rather than onset latency for the assessment of antidromic SNAPs in clinical practice (Pyun et al., 2005).

The larger and wider waveform of the antidromic than the orthodromic potential may explain some of the observations reported above. For instance, it may explain the absence of an anAP because the large antidromic potential may engulf the eventual generation of it. A number of factors may be responsible for the differences in waveforms. Factors such as age, gender and body mass index affect the amplitude of the action potentials (Fujimaki et al., 2009). These and skin temperature, impedance and depth of the nerve may affect differently antidromic and orthodromic recordings. Interestingly, no differences have been reported with the use of various types of recording electrodes in the obtained action potentials (Mondell et al., 1986; Athar et al., 2013). These observations stress the importance of the care that has to be taken with recording and analyzing orthodromic and antidromic SNAPs.

4. Particularities of each technique for clinical and physiological studies

The SNAP obtained with both techniques comes mainly from depolarization of sensory axons although there can be some interference by motor responses in the antidromic SNAP, as reported above and considered by Masakado et al. (2011). Undoubtedly, the most common application of the study of median sensory nerve conduction is the assessment of nerve compression in CTS. In this regard, comparison of the two techniques goes beyond the simple recording shown in Fig. 1. Seror (2000) examined reliability, sensitivity, and specificity of the inching test in the wrists of 20 controls and 20 CTS patients, performed orthodromically and antidromically on sensory nerve fibers of the third digit in preselected mild CTS patients. The sensitivity and specificity were both 100% with the orthodromic technique and 45% and 85% respectively with the antidromic technique. Therefore, this author recommended only the orthodromic technique for confirming the diagnosis of mild CTS in the few cases in which the inching technique is required, which Seror (2000) considered helpful in 6%–8% of all CTS cases.

Many tests can be done using either type of stimulation. Some are easier or more appropriate to perform with one or the other technique. As an example, near-nerve recordings are better suited for the orthodromic than for the antidromic technique (Smith, 1998), while studies of nerve excitability are better suited for the antidromic than for the orthodromic technique (Kiernan et al., 2001). Physical and physiological particularities that differ between the two techniques are summarized in Table 1. Unquestionable physical and physiological differences between the two techniques are: (1) With the antidromic technique, the nerves are close to the skin surface for recording at the fingers and relatively deep for stimulation at the wrist. This is the other way around for the orthodromic technique. (2) The site of nerve depolarization with the orthodromic technique, the digital nerves, lies more distal than the site of nerve depolarization with the antidromic technique. As a result, the fibers activated with the orthodromic technique may be thinner and less excitable, have lower temperature and may be more readily affected by distal neuropathies than those activated by the antidromic technique. (3) The digital nerves contain cutaneous sensory afferents (and joint afferents), whereas the median nerve at the wrist contains, additionally, motor fibers and muscle afferents. This physiological difference may affect excitability of the nerve because of different properties of sensory and motor fibers (Kiernan et al., 1996, 2004). As stated, the possibility exists that distal neuropathies affect more the recordings done with one technique than with the other. Distal axons can have a raised threshold but still are able to conduct action potentials generated upstream. As a result, the antidromic potential could be preserved when no responses are observed with orthodromic stimulation, as in the example of Fig. 3 taken from a patient with severe chemotherapy-induced polyneuropathy. Similar observations were reported by Tsaiweichao-Shozawa et al. (2008) in patients with severe CTS. A specific study of this possibility has not yet been done.

Table 1
Physical and physiological differences between antidromic and orthodromic techniques to examine median sensory nerve conduction between finger and wrist.

		Antidromic	Orthodromic
Recording	Nerve location	Superficial	Deep
	Nerve size	Thin	Thick
	Nerve length	Proximal	Distal
	Size of the SNAP	Large	Small
Stimulation	Fiber type	Mixed	Sensory
	Movement artifact	Present	Absent
	Relevance of stimulus duration	Little	Great

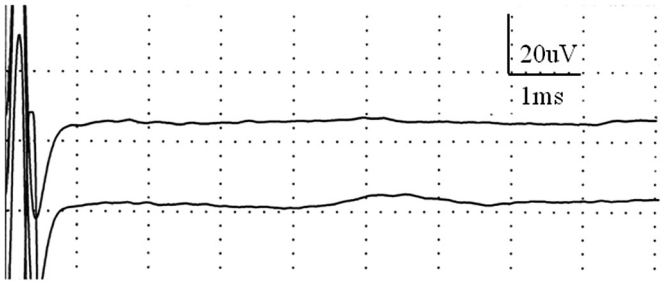

Fig. 3. Orthodromic (top) and antidromic (bottom) action potentials obtained in the segment wrist to 3rd finger in a patient with severe chemotherapy-related sensory neuropathy. Observe the absence of any recognizable action potential in the top trace (orthodromic) and the preservation of a low amplitude long latency response in the bottom trace (antidromic).

4.1. Observations reported using antidromic testing

Most authors have reported that the latency of the SNAP recorded with antidromic technique is longer and, therefore, the calculated conduction velocity would be slower than with the orthodromic technique (Murai and Sanderson, 1975; Tashjian et al., 1987). Bolton and Carter (1980) reported on differences between genders in the size of the antidromic SNAP, larger in females than in males likely because of females' thinner fingers. This may be a confusing factor when determining normative values if both genders are included in the same pool.

The antidromic SNAP has been used for the assessment of nerve excitability by various authors (Bostock et al., 1994; Kiernan et al., 1996, 2001, 2004; Kuwabara et al., 2006). A stable baseline and a sizeable action potential are needed for the assessment of membrane excitability using threshold tracking techniques, which makes these studies more suitable for antidromic than for orthodromic testing. Although the study of sensory nerves requires longer time than that of motor nerves, determination of sensory nerve excitability measures was considered feasible for routine clinical studies of sensory neuropathies (Kiernan et al., 2001) and

it has nowadays its place among slightly sophisticated techniques for the thorough study of sensory nerves. At physiological level, excitability studies have provided clear clues on differences in membrane properties between motor and sensory axons. Indeed, Kiernan et al. (2004) found greater activity-dependent hyperpolarization in motor than sensory axons, which was suggested to be due to less inward rectification as a result of less activity of the hyperpolarization-activated cation conductance in motor than in cutaneous afferents. Other differences are the greater persistent Na current in sensory than motor axons (i.e., greater current through Na channels that do not inactivate or do so very slowly) and increased greater membrane depolarization by about 4 mV in sensory than in motor axons (Howells et al., 2012). These findings may explain the different susceptibility of sensory and motor axons in peripheral nerve lesions. Fujimaki et al. (2012) have also shown that membrane excitability properties differed between median and radial superficial nerves (the membrane potential was more negative in median sensory axons than in superficial radial axons). This may mean that responses to disease may differ between the two nerves.

4.2. Observations reported using orthodromic testing

The application of stimuli in a rather distal segment of the nerve, as in the fingers, allows for recording not only at one point but in many along the nerve. Stimulation at proximal sites with recording distally implies unavoidable activation of motor fibers that would create artifacts and, therefore, assessment of segmental conduction velocity in the forearm or even more proximal segments is better done with the orthodromic than with the antidromic technique. This would be more difficult with the antidromic technique because of the artifact caused by simultaneous activation of forearm muscles. Using these possibilities of orthodromic testing, Valls-Sole and Llanas (1988) documented the sliding of the median nerve suggested by McLellan and Swash (1976) after observation of the microneurography needle moving with distant joint movements. Valls-Sole and Llanas (1988) recorded on the upper arm from the median and ulnar nerves simultaneously stimulated at the fourth finger and saw that what was just one action potential when recording with the upper limb stretched changed into two action potentials with the elbow flexed at 90°, maintaining the same stimulation and recording electrodes in their sites. This was interpreted as the median nerve sliding in one direction and the ulnar nerve in the other. This sliding was limited for the median nerve in patients with CTS (Valls-Solé et al., 1995). To this date, this remains as the only electrophysiological evidence of normal and limited sliding of the nerves with joint movements, a condition that can certainly cause dysfunctions because of angulation, stretching or anchorage of the nerve caused by soft tissues or bones in the nerve's vicinity (Wright et al., 2001, 2005). Recently nerve sliding has been assessed with a more appropriate tool for measuring aspects related to mechanical properties of the nerve sheaths, such as echography (Erel et al., 2010), which may open a new line of studies in search for evidence of dysfunction in syndromes presenting with pain and paresthesia, in which conventional EMG and nerve conduction studies are unable to demonstrate a lesion.

Inadvertent activation to a neighboring nerve may happen with orthodromic stimulation, but is less common than with antidromic stimuli. The unwanted activation of axons from the superficial radial nerve innervating partially the index finger has been described as a pitfall of the orthodromic study (Sonoo et al., 2006). However, this transforms into an interesting observation of simultaneous activation of two nerves that can give rise to a graphical comparison of two different action potentials, with a normal radial SNAP and an abnormal median SNAP in the diagnosis of focal lesions, such as CTS.

The anomalous distribution of sensory fibers in the median and ulnar nerves has been studied in a case of Martin–Gruber anastomosis using the orthodromic technique with near-nerve recording electrodes (Simonetti, 2001).

As stated above, the orthodromic technique facilitates the recording of the anAP with low intensity long duration stimuli. The anAP is an interesting phenomenon that is largely influenced by various technical aspects. In spite of that, though, it may have some clinical applicability as a measure of excitability of sensory axons (Leote et al., 2016; Pereira et al., 2016). Although the first hypothesis that the anAP was generated in nerve terminals and intradermal nerve endings or even skin receptors at the fingertip (Aprile et al., 2003, 2007) has proven to be wrong (Therimadasamy et al., 2015), it is still possible that the decreased nerve excitability characteristic of peripheral neuropathies can be indirectly demonstrated with such a simple technique (Joa and Kim, 2013; Leote et al., 2016). However, for that to occur, many more physiological studies are required to understand better the complex mechanisms of generation of nerve action potentials with electrical stimuli in intact human nerves. In fact, the potential clinical applicability of anAP recording may come from the complete understanding of its physiological mechanisms. It is indeed an expression of axonal membrane excitability, although much more work is still needed before it can be used with confidence as a nerve excitability marker.

5. Antidromic and orthodromic testing of carpal tunnel syndrome

There are many techniques available for the assessment of CTS, and reviewing them would be out of the scope of this paper. However, whatever the technique used, the examiner has to bear in mind the importance of the clinical context. If technicians are in charge of performing nerve conduction tests, they should be aware not only of the published quality requirements of standard performance (Neal and Katirji, 2008), but also of all details of technical aspects and their relation to the patient's symptoms and signs. Not all symptoms involving the hand derive from median nerve compression at the carpal tunnel and even if electrodiagnostic testing demonstrates a delay of nerve conduction in the median nerve, these observations do not necessarily provide full explanation for the patient's symptoms. Non-neurological disorders, such as arthropathic lesions of metacarpal bones, can contribute to pain, reduced strength and even numbness because of swelling-induced deformity of the joint and surrounding tissues. Angulation, stretching and displacement of digital nerves may cause ectopic discharges that manifest as paresthesiae (Wright et al., 2001, 2005).

No differences have been reported on the assessment of palm-to-wrist segment using either antidromic or orthodromic testing (Tackmann et al., 1981; Pyun et al., 2005). One of the key tests for the determination of a focal lesion in the median nerve is the comparison with another nerve (i.e., the radial or the ulnar) using either the same recording or the same stimulation site. This has been done by various authors using either antidromic or orthodromic techniques, with the fourth finger for the comparison to ulnar nerve and the thumb for comparison to radial nerve action potentials (Loong and Seah, 1971; Johnson et al., 1981, 1987; Carroll, 1987; Pease et al., 1989; Uncini et al., 1990). This method has been found to have 90% sensitivity in differentiating nerve compression from polyneuropathy in diabetic patients (Imada et al., 2007; Gazioglu et al., 2011). Some improvement of the technique may be obtained with the combination of various sensory recordings. Robinson et al. (1998) and Lew et al. (2000) defined the combined sensory index made up as the summation of the difference between median-ulnar ring finger antidromic latency

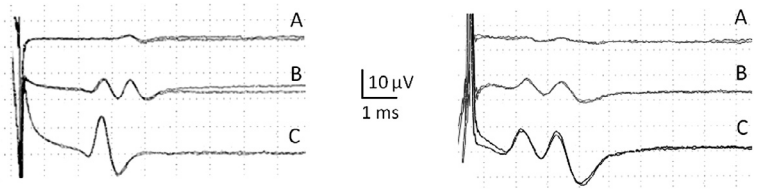

Fig. 4. Differences between double peak potentials of different origin. The traces of the left show the anAP and caAP recorded at the wrist with orthodromic stimulation of the thumb in a healthy subject. The traces in the right show the double peak potential recorded at the wrist to orthodromic simultaneous stimulation of the superficial radial nerve and the median nerve at the thumb in a patient with carpal tunnel syndrome. Note the difference in behavior of the second action potential with increasing the stimulus intensity, disappearing when it is the expression of an anAP and maintaining the amplitude when it is the expression of a delayed median nerve.

difference at 14 cm (ring-diff), median-radial thumb antidromic latency difference at 10 cm (thumb-diff) and median-ulnar mid-palmar orthodromic latency difference at 8 cm (palm-diff). These authors found this combination a consistent and reliable method for diagnosing CTS.

Stimulation or recording, depending on which technique is used, is done at the wrist over the median and ulnar nerves in two different series of stimuli. However, using an intermediate electrode position for either stimulation (Cassvan et al., 1988) or recording (Valls-Sole and Llanas, 1988) saves time and discomfort to the patient because only one stimulus series is used, and gives rise to a convincing graphical evidence of the dysfunction in the median nerve with respect to the nerve with which it is compared (Fig. 4). This was described as the 'bactrian sign' by Cassvan et al. (1988), who considered this sign recorded in the thumb to intermediate stimulation of median and radial nerves at the wrist as the most sensitive sign (83.7% positivity) for the diagnosis of CTS.

A double peak action potential due to activation of two nerves should be distinguished from a double peak potential generated by the combined recording of the anAP and the caAP with orthodromic testing. This can be done by just observing the effects of increasing the stimulus intensity. If this is the anAP, i.e., an action potential generated in the same nerve as the caAP, it would decrease amplitude with increasing stimulus intensity because of antidromic conduction block, while it will be maintained if the action potential is generated in a separate nerve in the case of a delayed median nerve action potential. There is also a physiological trick that reveals the different mechanisms of generation of the two types of double peak potentials, which is the study of the refractory period. As shown in Leote et al. (2016), the anAP recovers sooner than the caAP with inter-stimulus intervals of 2–3 ms. This is not the case with the action potentials generated in two different nerves, in which the two action potentials have parallel recovery.

Not all practitioners recommend the use of electrodiagnostic techniques for the assessment of CTS (Lane et al., 2014). Surgeons may still operate on the wrist to free the median nerve of compression based on history and physical examination and no electrophysiological evidence of lesion. The weakness of this situation may become clear when patients who fail to respond adequately to surgery are then referred for electrodiagnostic studies and signs of a different disorder are found. At present, it is clear that nerve conduction studies have an important role for the assessment of focal nerve damage and differential diagnosis of other potentially confounding neurological syndromes. They may also help with deciding on the best treatment option and predict the benefit. Upon request, the examiner has the choice of many possible techniques and, even if overall recommendations have been issued (Jablecki et al., 2002; Sandin et al., 2010), these do not deal with the small details reported in this study that can sometimes make a difference. As in many other clinical neurophysiology studies, the examination of a hypothesized compression of the median nerve in CTS patients should not be a routine study but a physiological test. Indeed, the examiners are requested to apply their physiological findings to clinical assessment and this implies mastering two different skills: technical and clinical. Only an intelligent combination of these two will make worthy an apparently simple and dull study of median nerve conduction in healthy subjects and patients with CTS.

Conflict of interest statement

The authors declare no conflict of interest.

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