Effect of stimulus intensity on the rising phase of
the nerve action potential in healthy subjects
and in patients with peripheral nerve lesions

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The nerve action potential is the most usual
indicator of the presence of a nerve impulse in
a peripheral nerve. The impulses travel along the axons
as brief electrical waves. The essential shape
characteristics of the nerve action potential (a bi-
or triphasic wave) are determined by the distribution
electric current in a volume conductor during
bipolar recording (Lorente de Nó, 1947a, b; Lloyd,
1952; Kostyuk, 1956; and Bureš, Petrán, and
Zachar, 1960) and will not be considered here. Our
earlier papers (Podivínský, 1965a, b) described the
effect of stimulus intensity on the amplitude and
latency of the nerve action potential in healthy
subjects and in patients with a peripheral nerve
lesion. Recently, the relation of fibre diameter to
the rising and falling phases of the spike was studied
in medullated nerve fibres of cats (Paintal, 1966).

In this study, interest was centred mainly on the
relationship between stimulus intensity and rate of
rise of the potential amplitude. On purely physio-
logical grounds, the rate of rise of a potential seems
to be just as important a parameter of the conducted
response as is amplitude. The problem raised by the
present experiments is whether this type of modifi-
cation of the nerve action potential can give some
information about pathophysiological conditions
and so contribute to detecting the early stages of a
nerve lesion.

METHODS AND MATERIAL

The technique employed was that reported by Dawson
and Scott (1949) and Gilliatt and Sears (1958). Details of
the method used in this study were similar to those
previously described by Podivínský (1965a, b).

Bipolar surface electrodes were used for recording and
stimulating. Nerve action potentials were recorded from
the ulnar nerve, at the elbow, after electrical stimulation
at the wrist. As the rise time of the nerve action potential
recorded with bipolar electrodes varies according to the
separation of the electrodes, for comparative purposes,
the interelectrode distance should be maintained constant.
In order to ensure a constant separation of 3 cm. surface
recording electrodes of the type originally described by
Dawson and Scott (1949) were used in this study.
Amplified potentials were displayed on one beam of a
double beam cathode-ray oscilloscope for photographic
recording above a time scale registered on the second
oscilloscope beam. Rectangular stimuli of 0-2 and 0-5
msec. duration were delivered at 0-3 and 1-0 per second
from an electric stimulator with low output impedance
(100 ohms) through an isolating unit.

The steepness of the rising face of the action potential
spike (Fig. 1) may be measured as the rise time of the
negative (upward) deflection of the triphasic response
(ΔT) or as tangent of an angle between the rising face of
the negative phase and the baseline (tan α). In addition
to these parameters the length of rise of the negative
potential deflection λ can be measured. From a purely
physical aspect the rise length λ may be defined as the
shortest distance between the not yet excited point of the
nerve and that of maximum depolarization. It is directly
proportional to the conduction velocity (v) and the rise
time of the negative deflection of the nerve response (ΔT),
according to equation

\[ \lambda = v \cdot \Delta T \]

The stimulating voltage varied from a threshold value
to a supramaximal electric stimulus (up to 150 volts),
thus permitting evaluation of the influence of stimulus
intensity on the time course of the nerve action potential.
Observations were performed in 50 healthy subjects
with an age range of 18 to 51 years and in 25 patients,
aged 20 to 55 years, suffering from slight peripheral nerve
lesions. In all patients, mild sensory disturbances were
present, mainly in the region innervated by the tested
ulnar nerve. Ten had painful conditions of the upper limb
due to intervertebral disk herniation in the cervical
region. Four showed initial damage to the ulnar nerve at
the elbow. Three had circumscribed arachnoiditis in the
cervical region. In eight patients, the diagnosis was
diabetic neuropathy. Investigations were carried out at
room temperature, maintained between 22°C. and 24°C.
The mean skin temperature of the examined limbs in the
control group was 31-2°C.; in the patients' group it was
30-6°C.
In normal people the rise time histogram (Fig. 2) showed the peak distribution of rise times of the action potential amplitudes of the ulnar nerve at supramaximal stimulation at 0·65 to 0·85 msec. (with a mean of 0·728 ± 0·022 msec.), whereas in patients with a peripheral nerve lesion the distribution of rise times was in marked contrast to this. There was a shift to the right, towards higher values, with a peak at 1·4-1·6 msec. (the mean value was 1·52 ± 0·057 msec.). The distribution of rise times in control subjects is significantly different from that of patients with nerve lesions (P<0·001).

The rise length (λ) of the action potential in a damaged nerve was found to be prolonged as compared with that of a healthy one. For example (Fig. 3, A), distance (D) between the stimulating cathode at the wrist and lower recording electrode at the elbow is 28·0 cm., latency (L) from onset of the stimulus artefact to the junction of the negative inflection potential and the baseline is 4·8 msec., and conduction velocity (v) in the healthy ulnar nerve is thus 

\[ v = \frac{D}{L} = \frac{28.0}{4.8} = 5.83 \text{, or } 58.3 \text{ m./sec.} \]

If the rise time (ΔT) is 0·7 msec., the rise length (λ) is then

\[ \lambda = v \cdot (\Delta T) \text{ mm.} \]
\[ = 58.3 \times (0.7) \text{ mm.} \]
\[ = 40.81 \text{ mm.} \]
\[ = 4.081 \text{ cm.} \]
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FIG. 4. Effect of stimulus intensity on the rise time of nerve action potential (n. ulnaris) in a healthy subject (M.D., age 18). Oscilloscopic tracings of nerve action potential (only the rising phase of potential amplitude is shown) at increasing intensity of stimulation (40, 50, 60, 70, 80, 90, 100, and 110 V). Top trace, potential at 110 V; bottom trace, potential at 40 V. The diagram was plotted according to data obtained from the oscilloscopic tracings shown in the upper part of the figure. It shows changes of amplitude (ordinate) and rise time (abscissa) of the action potential at increasing stimulus intensity. The maximum point on each line is the peak of potential amplitude (spike). The topmost line represents the rising phase at supramaximal stimulation (110 V); the effect of near threshold stimulation (40 V) is shown by the bottom line.

In the damaged nerve (Fig. 3, B) conduction distance (D) is 23·0 cm., latency (L) is 5·6 msec., and conduction velocity (v) is thus \[ v = \frac{23 \times 10}{5.6}, \]
or 41·0 m/sec. If ΔT is 1.7 msec., then \[ \lambda = \frac{41 \times 1.7}{10}, \]
or 6.97 cm.

The relationship between stimulation intensity and time course of the action potential of an intact nerve is illustrated in Figure 4. In each of these experiments the nerve responses to electrical stimuli of progressively increasing intensity from near threshold to supramaximal and vice versa were recorded on the multiple-exposure photograph made by displacing the base line upwards or downwards after each change of stimulus strength. In Fig. 4 the rising phases of normal potentials recorded during a typical experiment are shown graphically. With decreasing strength of stimulation, the peak action potential amplitude becomes smaller and the rate of rise becomes slower. At near threshold stimulation, the effect of which is shown as the bottom line, the rise time attains the greatest value.

In peripheral nerve paresis, both of these effects become intensified: each decrease of stimulus strength, as in the experiment in Fig. 5, caused a greater decrease in rate of rise and lowering of
action potential amplitude than in healthy individuals.

The curves of Fig. 4 and 5 show that amplitude and rise time change as a function of stimulus intensity. When the current pulse is extremely small, as in cases with threshold stimulation, sometimes some modification may occur. The rise time paradoxically becomes shorter although both the amplitude and the slope (\(\tan \alpha\)) of potential decrease progressively, and attain their minimal value at an intensity of nerve stimulation which is just liminal (Fig. 6).

**DISCUSSION**

The main results of this investigation show that in normal subjects of different ages, the rise time (\(\Delta T\)) for the nerve action potential evoked by weak stimulation is typically prolonged when compared with that attained at maximal and supramaximal intensity of nerve stimulation. In patients with peripheral neuropathy there was slowing of the rate of rise even at supramaximal shock strength when compared with the normal group, and decrease in rate of rise with decreasing intensity of stimulation also becomes more prominent here than in the normal subjects.

These results were not unexpected because some physical aspects of the stimulus parameters and their relations to the tissue are well established. The stimulus effect is mainly given by ionic movements in tissue and hence it is determined not only by the intensity of the field but also by its duration (time course). The surface membranes of the nerve fibre, both the myelin sheath and the nodal membrane, represent relatively large capacities. Therefore, higher stimulus intensities are needed at shorter stimulus durations to raise the membrane potential by a constant amount, e.g., to the threshold level (Tasaki, 1959). However, it is also well known that the current strength required for impulse conduction in axons and muscle fibres increases with decreasing rate of rise in current (Lucas, 1917; Katz, 1939). At near threshold stimulation, ionic currents displace not only the resting potential of the membrane of the axons to the threshold (critical) depolarization more slowly than in response to stronger shocks resulting in prolonged latency, but they also cause a very slow rate of rise so that the peak potential amplitude is attained after a relatively long period of time. Accordingly, modification of the membrane potential caused by a near threshold shock is very similar to that classically associated with long stimulating pulses as described by Tasaki (1939, 1959) and Knutsson (1964). Both in animals with experimental demyelination in peripheral nerves

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**FIG. 5.** Effect of stimulus intensity on the rise time of nerve action potential (n. ulnaris) in a patient with lesion of the peripheral nerve (K.F., age 40, with polyradiculo-neuritis). The intensity of stimulation (from top to bottom) 110, 100, 90, 80, and 70 V. Same indications as in Figure 4.

**FIG. 6.** Changes in various parameters of nerve action potential during graded strength of stimulation in a normal subject (H.F., age 38). The rise time of action potential increases with decreasing intensity of stimulation from supramaximal shock (a) to supraliminal (b). On the other hand the rise time declines with liminal stimulus intensity (c) although both amplitude and slope (\(\tan \alpha\)) of potential continue to diminish, and achieve their minimal value at threshold stimulation.
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(Tasaki, 1955; McDonald, 1963a, b; Kaeser, 1963; Cragg and Thomas, 1964; Mayer and Denny-Brown, 1964) and patients with a mild nerve lesion (Bannister and Sears, 1962; Gilliatt and Willison, 1962; Mayer, 1963; Mawdsley and Mayer, 1965; Miglietta, 1966; and others) myelin destruction accompanied by relative preservation of axons was histologically demonstrated or clinically greatly suspected. The experimental results of Tasaki (1955) suggest that reduction in thickness of the myelin sheath increases its capacity and decreases its transverse resistance. This results in increased leakage of current through the damaged internodal myelin and will reduce the current density at the neighbouring nodes of Ranvier and thereby delay excitation at these still excitable nodes and slow down the reaching of the peak action current. The axon irregularities associated with some reduction in fibre diameter frequently seen in demyelinated nerve fibres will increase the longitudinal resistance of axons and thus contribute to the slowing of the rise in current at the nodes (Gasser and Grundfest, 1939; McDonald, 1963a, b). If the degree of the myelin disintegration is intensive and the length of such an abnormality very extensive, the membrane current then rises more slowly than a certain critical rate and fails to trigger conducted potentials. This phenomenon is closely related to the process of accommodation of the electrogenic membrane, in a large population of nerve fibres, to a slow, outwardly directed current from the area of the sink. Accordingly, such a membrane does not become depolarized to a critical level and blocking of conduction may occur in this pathological condition.

The pradoxical behaviour of the rise time at stimulus intensity which is just at the threshold level can only partly be due to fallacy in measurement, i.e., as a result of some difficulties in determining the exact point of the peak. This may be the case when potentials are too small, when the slope of their rise from the time base is very gradual and their top is rounded. Hodes, Gribetz, Moskowitz, and Wagman (1965) also gave a similar explanation for changes in peak latencies of muscle potentials at weak stimulation. But real changes in the rise time do exist, and may be explained on the basis of a strength-duration relation. When the duration of the current pulse becomes far shorter or longer than the time constant of the resting axon membrane, the phenomenon of abolition of an action potential occurs (Tasaki, 1959). In the case of a threshold stimulation, the current pulse is extremely small, and the uncharged membrane on both sides of the excitation locus may prevent a further rise in potential amplitude at the locus of excitation, e.g., under the lower (active) recording electrode, so that the peak level of such a potential is reached prematurely within a shortened period of time.

However, experiments have not yet been done on the relationship between rate of rise of the nerve action potential and the stimulus intensity in man. Hence, our discussion and conclusions concerning the stimulus dependence of the rate of rise can only be preliminary and tentative. On the basis of our experiments, we may assume that the slope of the potential rise is very sensitive to reduction of stimulus intensity and that this is especially pronounced in cases of peripheral neuropathy.

SUMMARY

Rise times of the negative (main) deflection of triphasic nerve response (ΔT) at threshold and at supramaximal stimulation of the ulnar nerve were studied in 50 healthy subjects and in 25 patients with nerve lesions. The nerve was stimulated at the wrist and the response recorded above the elbow.

Rise times in patients with peripheral nerve lesions were markedly prolonged as compared with those in control subjects (mean: 0.728 ± 0.022 msec. in controls; 1.52 ± 0.057 msec. in patients).

The distribution of rise times in control subjects was significantly different from that of patients with nerve lesions (P<0.001).

Accordingly, the rise length (λ) of the action potential in a damaged nerve was found to be characteristically prolonged in comparison with that of a healthy one.

With decreasing strength of stimulation, rise times become longer and reach the greatest value at near threshold stimulation.

In peripheral nerve paresis, this effect becomes much more prominent than in healthy individuuls.

The results involving the effect of stimulus intensity on rate of rise of the action potential suggest a marked sensitivity of the slope of rise to reduction of stimulus intensity, mainly in cases of peripheral neuropathy. Thus, changes in rate of rise provide a highly sensitive index of peripheral nerve damage and would be useful in detecting the early occurrence of a nerve lesion.

The author wishes to express his appreciation to Mrs. Pafková for her excellent assistance, to Ing. G. Hudáková for her advice on the statistics, and to the Medical Photography and Film Institute for the careful photography.

REFERENCES


