

Computer method for the analysis of evoked motor unit potentials

1. Control subjects and patients with myasthenia gravis

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SYNOPSIS An on-line computer method is described for the isolation of single motor unit potentials, evoked by stimulation of the anterior tibial nerve at the ankle, from the compound action potential recorded from surface electrodes over the extensor digitorum brevis muscle. The latencies, durations, amplitudes, and areas of the potentials were measured in a group of control subjects and patients with myasthenia gravis. In myasthenic patients there is a significant reduction in the durations of motor unit potentials and a significant increase in latencies while their amplitudes and areas remain unchanged. The results are consistent with the presence of a 'terminal neuropathy' in myasthenia gravis.

In previous reports on motor unit potential configurations in patients with myasthenia gravis, concentric needle electrode recording of voluntary activity of motor units at minimal effort has been studied (Pinelli and Buchthal, 1953; Simpson, 1969; Oosterhuis *et al.*, 1972; Negri and Caraceni, 1973). These authors agree that the mean duration of motor unit potentials is reduced while unit amplitudes remain normal or nearly so. The problem of representative sampling arises when needle electrodes are used in studies of this type. The action potential obtained (APn) arises within a 0.5 mm radius of the tip of the needle from a small number of muscle fibres (Ekstedt and Stålberg, 1969, 1973) and occasionally from a single muscle fibre (Rosenfalck, 1969). Its dimensions are influenced by the spatial arrangement of the muscle fibres around the electrode tip and by the temporal dispersion of their action potentials. The APn is related to muscle fibre density or cross-sectional area (Buchthal *et al.*, 1955) and is a poor index of the total number of muscle fibres contained in the motor unit. The position of the needle electrode within the unit will also influence the APn so that many 'motor unit potentials' can be obtained from the same motor unit (Buchthal *et*

al., 1955; Buchthal and Rosenfalck, 1973). These factors limit the conclusions that can be drawn from studies of that type and the results obtained can be variously interpreted to support both a neurogenic and a myopathic influence in the aetiology of the disease. Simpson (1969) considered that the myasthenic motor unit potentials were compatible with either a postjunctional defect or a prejunctional defect in discrete branches of the telodendria of the motor axon.

We believe that additional and complementary information can be obtained in suitable muscles by the use of surface recording electrodes arranged to record from a greater number of the underlying muscle fibres. We have studied the motor unit potentials (APs) so recorded and evoked by stimulation of the motor nerve to the muscle. By the technique to be described, we have been able to isolate the electrical responses of individual motor units from the muscle compound action potential and to measure their latencies, amplitudes, durations, and areas. The purpose of this paper is to present the results obtained in the extensor digitorum brevis (EDB) muscle in a group of control subjects and patients with myasthenia gravis.

METHODS

Values are expressed as mean \pm 1 standard deviation.

Twenty healthy volunteers aged 38 ± 14 years were obtained from among the staff of the Department of Neurology. None had any history or clinical evidence of neurological disease.

Twenty-two patients with myasthenia gravis aged 38 ± 16 years were studied. Three patients were asymptomatic, 19 were symptomatic and/or had evidence of a decrementing response of the compound muscle action potential of the EDB evoked by tetanization with a train of supramaximal stimuli applied to the anterior tibial nerve at the ankle. Of the symptomatic patients, all were ambulant and none was severely disabled. The duration of the myasthenia gravis ranged from two months to 50 years. Eleven patients had undergone thymectomy six months to 14 years before the present study. In none of the patients was there evidence of other neurological disorders. All but two patients were

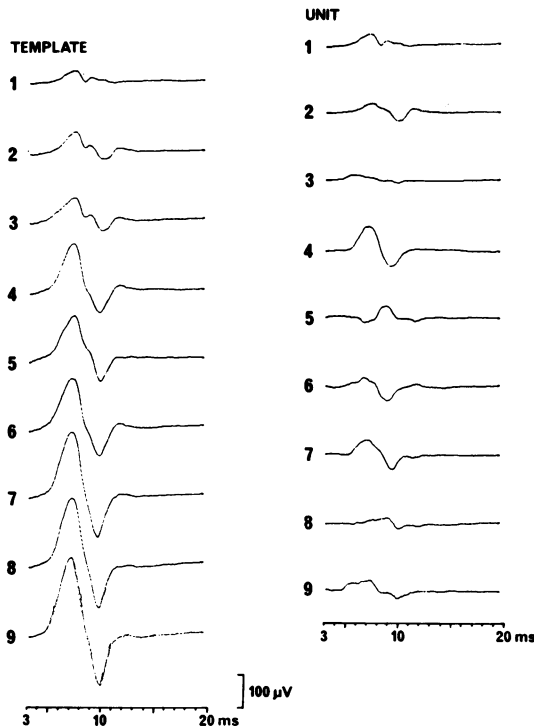


FIG. 1. M.C.G., aged 53 years. Computer printout of templates and units obtained by template subtraction in a normal subject.

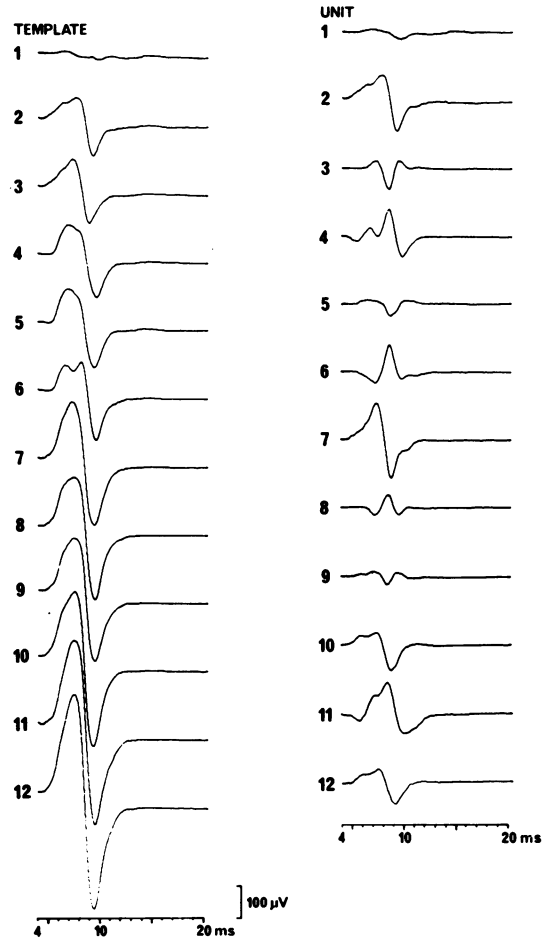


FIG. 2. E.S., aged 47 years. Computer printout of templates and units obtained by template subtraction in a patient with myasthenia gravis.

taking anticholinesterase drugs routinely. The technique employed for the sequential recruitment of motor unit potentials in the EDB muscle by stimulation of the anterior tibial nerve at the ankle, the placement and composition of the surface electrodes for stimulation and recording, and the properties of the amplification system have been described previously (McComas *et al.*, 1971a; Ballantyne and Hansen, 1974). The on-line computer handling of data for identification and storage of the evoked motor unit potentials has been reported (Ballantyne and Hansen, 1974). The electrical

responses of the first evoked motor unit, the first and second, the first, second, and third, and so on are each stored sequentially in up to 15 computer memory stores (templates). A computer printout of these templates in a control subject is shown in Fig. 1 where—

- template 1 = first evoked motor unit potential.
- template 2 = summated potentials of first and second evoked motor units.
- template 3 = summated potentials of first, second, and third evoked units, and so on.

It is apparent that the algebraic subtraction of template 1 from template 2 will yield the second evoked motor unit potential in isolation (Fig. 1, unit 2). Similarly, the third evoked potential is obtained by subtraction of template 2 from template 3 and so on. The first motor unit potential is common to both columns. Figure 1 right hand column is a printout of the first nine motor unit potentials in a control subject in the order in which they were recruited by graded incremental stimulation of the anterior tibial nerve.

Figure 2 shows a similar printout from a patient with myasthenia gravis. The distal latency, duration, area, and amplitude were measured for each potential. The distal latency was obtained by measurement of the time interval between the onset of the stimulus artefact and the appearance of the initial deflection of the potential on the oscilloscope. The duration of the potential was measured from the initial deflection to the return of the baseline to zero potential and included negative and positive phases. Both the latter measurements were assessed manually from the computer printout. The value for peak to peak amplitude was provided by the computer, as was the absolute area of the potential (Ballantyne and Hansen, 1974). The fastest motor conduction velocities and shortest distal motor latencies in the lateral popliteal nerves were also measured using an established technique (Hodes *et al.*, 1948) save that the

evoked response from the EDB muscle was recorded using surface electrodes as above. All studies were undertaken in a thermostatically controlled room and skin temperature of the limb maintained at $33^{\circ}\text{C} \pm 1^{\circ}\text{C}$.

RESULTS

All values are expressed as the mean ± 1 standard deviation. Statistical significances have been assessed using Student's *t* test.

TABLE 2
PARAMETERS OF EVOKED MOTOR UNIT POTENTIALS

Motor unit parameter	Potentials (no.)	Mean	SD	P
Latency (ms)				
Control	171	4.44	0.87	—
Myasthenia gravis				
NT	102	5.85	1.28	< 0.001
T	99	5.85	1.70	< 0.001
All	201	5.85	1.50	< 0.001
Duration (ms)				
Control	171	9.46	1.77	—
Myasthenia gravis				
NT	102	8.50	1.78	< 0.001
T	99	8.29	1.75	< 0.001
All	201	8.40	1.77	< 0.001
Amplitude (μV)				
Control	173	56.4	28.5	—
Myasthenia gravis				
NT	100	56.3	32.1	NS
T	98	56.2	35.0	NS
All	198	56.7	33.8	NS
Area (area units)				
Control	173	16.3	8.0	—
Myasthenia gravis				
NT	100	16.5	9.8	NS
T	98	16.2	8.7	NS
All	198	16.4	9.2	NS

NT = No thymectomy. T = Thymectomy.

TABLE 1
SHORTEST DISTAL LATENCIES AND FASTEST MOTOR CONDUCTION VELOCITIES

	Subjects (no.)	Mean	SD	P
Shortest distal latency (ms)				
Control	20	3.43	0.46	
Myasthenia gravis	22	4.22	0.83	< 0.01
Fastest motor conduction velocity (m/s)				
Control	20	51.7	3.56	
Myasthenia gravis	19	51.8	3.80	NS

In patients with myasthenia gravis, the fastest motor conduction velocities in the knee to ankle segment of the lateral popliteal nerve were similar to control values, but the shortest distal motor latencies were significantly prolonged (Table 1). The durations of individual motor unit potentials were significantly reduced in myasthenic patients (Table 2, Fig. 3), while both the amplitudes and the areas were comparable with control values (Table 2, Fig. 4). Previous thymectomy has not influenced the results obtained in this study (Table 2).

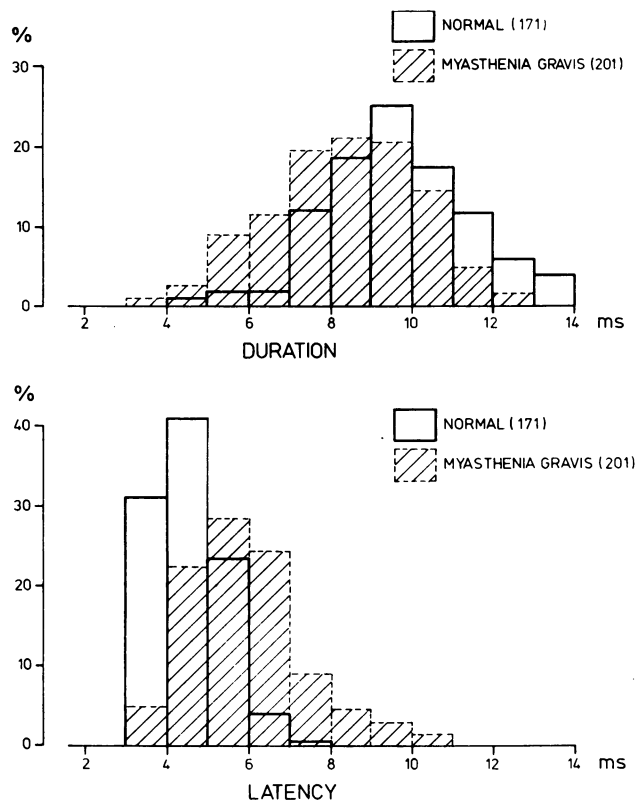


FIG. 3. Histograms of motor unit potential durations and latencies expressed as the percentage occurring in each group.

DISCUSSION

We have previously presented evidence that there is no loss of motor units in the EDB muscle in patients with myasthenia gravis (Ballantyne and Hansen, 1974) and suggested that the reduction in unit numbers reported in an earlier study (McComas *et al.*, 1971b, 1973) was due to the inability of the method employed adequately to quantify motor unit numbers when their potentials are qualitatively altered from normal. The results of the present study would support that suggestion by showing significant changes in both the latencies and durations of the evoked motor unit potentials in myasthenia gravis. When surface electrode recording is employed over the EDB muscle a greater number of muscle fibres in the motor unit can be expected to contribute to the recorded potential than when concentric needle electrodes are used (Simpson, 1974). For a critique of surface recording over this muscle see McComas *et al.* (1971a). We

would submit that the potential recorded (APs) is more representative of the electrical activity of the whole motor unit in these circumstances and is related more to the total number of muscle fibres in the unit than it is to fibre density.

We have found that the latencies of the supra-maximally evoked muscle action potentials are significantly prolonged in myasthenia gravis in agreement with previous reports (Preswick, 1966; Slomić *et al.*, 1968). The fastest motor conduction velocities in the proximal (knee to ankle) segments are within the normal range (Table 1). Slomić *et al.* (1968) also reported normal values for the proximal segment of the ulnar nerve. Since the motor axons appear to be conducting normally, we infer that the increase in the distal motor latency arises at or below the site of branching of the motor nerve fibres as they enter the EDB muscle. It is perhaps not surprising to find that the latencies of individual motor unit potentials are also prolonged (Table

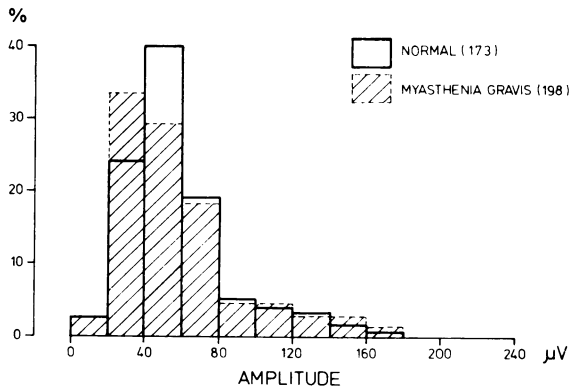
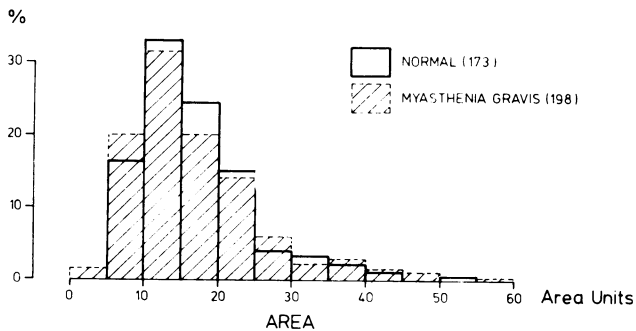


FIG. 4. Histograms of motor unit potential amplitudes and areas expressed as the percentage occurring in each group.



2, Fig. 3). Preswick (1966) proposed that the increased motor latency was due to a slowing of conduction in the fine intramuscular nerve fibres rather than to a delay at the neuromuscular junction as anticholinesterases did not reduce the

latency. Similarly, the increased jitter in myasthenia gravis is incompletely reversed by neostigmine (Ekstedt and Stålberg, 1973), indicating that it is in part due to alteration in the conduction velocity of either the muscle fibres themselves or of the intramuscular nerve fibres. In this context, it is of interest that Stålberg and Thiele (1972) found that the increased jitter occurring in neurogenic lesions is sometimes improved by edrophonium which they interpret as due to an action outside the endplate, possibly on the intramuscular nerve fibres. We, too, would consider that a reduction in conduction velocity in the fine intramuscular nerve fibres is the likely explanation of the increased latency of the motor unit potentials in myasthenia gravis. This 'terminal neuropathy' is also pertinent to the aetiology of the decreased duration of the motor unit action potentials that occur in that condition. Buchthal *et al.* (1955, 1957), using a multiple needle electrode, have shown that in normal subjects the duration of the motor unit potential is determined mainly by the varying

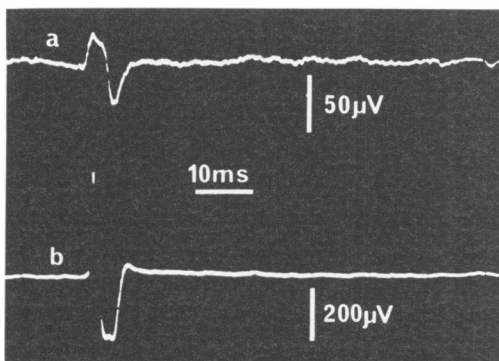


FIG. 5. Motor unit potential from EDB muscle recorded by (a) surface electrodes and (b) concentric needle electrode. Polarity, negative upwards.

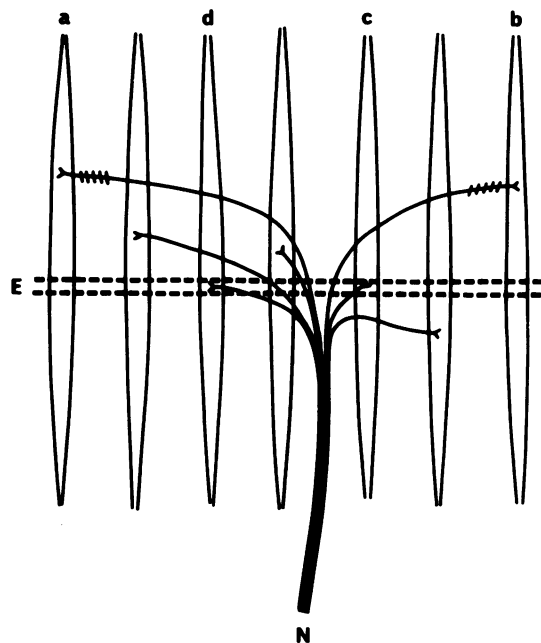


FIG. 6. *Schematic representation of a motor unit. (a) and (b) are muscle fibres whose endplates lie outside the main innervation zone. (c) and (d) are muscle fibres whose endplates lie within the main innervation zone. E: surface recording electrode. The muscle fibre action potentials from (a) and (b) take longer to reach the recording electrode than those from (c) and (d). Increased dispersion of the endplates relative to E will cause an increase in the duration of the motor unit action potential. In myasthenia gravis, a terminal neuropathy with 'dying back' of the intramuscular nerve fibres will lead to loss of response in (a) and (b) and shortening of the duration of the motor unit potential (see discussion).*

situations of the endplates on the individual muscle fibres of the unit, leading to the asynchronous arrival of their propagated action potentials at the recording electrode. Increased dispersion of the endplates is accompanied by an increase in the duration of motor unit potentials. They also demonstrated that factors causing an alteration in conduction velocity in the muscle fibres can lead to appreciable change in action potential duration but differences in conduction time in the terminal ramifications of the motor nerve add no more than 0.5 ms to an average motor unit potential duration. They measured not only the duration of the negative spike of the

unit potential but also that of the associated initial and terminal potentials of opposite polarity. These components appear to be derived by electrotonic spread from the region where depolarization is initiated and many more muscle fibres of the motor unit are thought to contribute to this portion of the motor unit potential than to its high amplitude negative part which contains the spikes. By our method of surface recording, volume conduction over the greater distance to the recording electrode will modify these potentials. A typical example is shown in Fig. 5 where simultaneous surface (a) and concentric needle (b) recordings of a motor unit potential are shown. By the surface method the amplitude of the negative phase is reduced absolutely and also relative to the terminal positive phase. The duration of the potential remains unchanged, but the duration of the negative phase (b) in Fig. 5 is relatively shorter, presumably due to the smaller number of active muscle fibres from which the needle electrode records.

Histological studies on myasthenic muscle (MacDermot, 1960; Bickerstaff and Woolf, 1960; Coërs *et al.*, 1966) have shown elongation of endplates and chains of endplates along muscle fibres connected by a single fine nerve twig suggesting that some anatomical dispersion of endplates does occur. This is either insufficiently great to manifest itself electrophysiologically as an increase in action potential duration or is obscured by other factors, which we will discuss later, exerting an opposing influence. The reduction in action potential duration in this study is in agreement with reports in the literature (Pinelli and Buchthal, 1953; Humphrey and Shy, 1962; Simpson, 1969; Oosterhuis *et al.*, 1972; Negri and Caraceni, 1973). Mean muscle fibre diameter is reduced in myasthenia gravis (Brooke and Engel, 1969) and action potential size is proportional to fibre diameter (Håkansson, 1956), so that theoretically a reduction in the size of individual fibre action potentials might be expected. Oosterhuis *et al.* (1972) have proposed that the reduced motor unit potential duration can be explained on this basis. Such changes should, however, also diminish the amplitude of the motor unit potential. We have found normal amplitudes (APs) as did Negri and Caraceni (1973) (APn). Neuromuscular block, intermittent

or complete, if occurring randomly throughout the unit territory would lead to a diminution in both dimensions of the potential, i.e. amplitude and duration. If, however, neuromuscular block is most marked at those endplates which lie furthest from the main innervation zone of the unit (Fig. 6) and presumably innervated by the longest intramuscular nerve fibres, there will be a loss of the late arriving fibre action potentials at the recording electrode leading particularly to a reduction in the duration of the unit potentials as follows: the peak amplitude of the unit action potential is determined by the summation of the largest group of fibre potentials having the closest synchronization. The progressive descent from peak amplitude is then due to the summation of successively fewer late arriving potentials. The loss of the later of these potentials will therefore have comparatively little effect on the peak amplitude, while their relatively small numbers leave the area under the unit potential comparatively unchanged but will produce a disproportionately large reduction in unit potential duration. The increase in motor unit potential duration (APn) in myasthenic subjects after anticholinesterase administration (Oosterhuis *et al.*, 1972; Negri and Caraceni, 1973) confirms the importance of neuromuscular block in this context. These authors do not state if the durations increase to normal values but examination of the data of Negri and Caraceni (1973) reveals that this does not occur. In some fibres, therefore, it is probable that neuromuscular block has progressed to the stage of complete denervation. Occasional fibrillation has been reported (Simpson, 1969) and denervated muscle fibres have been demonstrated histologically in myasthenia gravis (Brownell *et al.*, 1972; Oosterhuis and Bethlem, 1973). Engel and Warmolts (1971, 1973) noted the denervated fibres to be scattered singly in the biopsy specimens, although they later occurred in groups in the more chronic myasthenics. Type grouping of fibres is rarely seen, suggesting that collateral sprouting from other axons does not occur. Our electrophysiological results lead us to the same conclusion, as no abnormally large motor unit potentials occurred in myasthenic patients (Fig. 3 and 4) as would be anticipated had significant collateral reinnervation occurred. Thus the 'terminal neuropathy' which we consider is the cause of

the prolonged distal unit latencies also adequately explains the reduction in duration of the motor unit action potentials where the longest intramuscular nerve fibres innervating the most peripherally situated endplates are affected by a dying back process leading initially to a reversible neuromuscular block but later to complete denervation. Motor units will contain somewhat fewer muscle fibres but this does not progress to the stage where whole units are lost (Ballantyne and Hansen, 1974). In terms of this unitary hypothesis, a relationship between potential duration and latency may be anticipated and would appear to occur. We have found that an increase in the proportion of short duration potentials is accompanied by an increase in distal motor latencies. Oosterhuis *et al.* (1972) found that the shortest potentials occurred in their most severely affected patients, while Slomić *et al.* (1968) noted that the greatest prolongation of distal motor latencies also occurred in the most severely affected patients. There is, therefore, an inverse relationship between potential durations and distal motor latencies in myasthenia gravis explicable on the basis of a neurogenic influence acting at the most peripheral level. There is no need to invoke a myopathic hypothesis to explain the shortening of potential durations.

In conclusion, we believe that our results support the presence of a presynaptic dysfunction in myasthenia gravis taking the form of a terminal neuropathy in the fine intramuscular nerve fibres. This is responsible for both the increase in distal motor latencies and the reduction in motor unit potential durations found in that condition.

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