

Contractile properties of muscles in myotonic dystrophy

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SUMMARY A study has been made of the contractile properties of plantarflexor and dorsiflexor muscles in 25 patients with myotonic dystrophy and in the same number of closely-matched control subjects. As anticipated, the mean torques developed during maximal voluntary contraction and during the isometric twitch were significantly reduced in the patient population, as were the mean amplitudes of the respective maximum muscle compound action potentials (M-waves). There was considerable variation in weakness between patients, however, and in some there was a striking discrepancy between the results for the plantarflexor and dorsiflexor muscles. It was also found that, in both muscle groups, the mean twitch contraction times were significantly shorter in patients than in controls, but no differences could be demonstrated in relation to fatigability and post-activation of the twitch. Some patients had great difficulty in obtaining full activation of plantarflexor motor units but there was improvement with repeated effort.

Although several studies of muscle contraction have been carried out in human muscular dystrophy (for example¹⁻⁷) there has been only one investigation of this kind in patients with myotonic dystrophy.⁸ In attempting to examine this last type of dystrophy we have been preoccupied with three basic questions. First, is there any consistent difference in the involvement of fast-twitch and slow-twitch muscle fibres by the dystrophic process? Second, is the force generated by dystrophic muscles appropriate for the associated electrical impulse activity? Third, do patients with myotonic dystrophy make full use of their available muscle mass? In addition to addressing these problems, we have attempted to characterise two physiological features of the excitable muscle fibres remaining in dystrophic muscles, those of twitch post-activation potentiation and susceptibility to fatigue.

The study has been performed on the dorsiflexor and plantarflexor muscles of the ankle using techniques elaborated for healthy subjects.⁹ The advantage of using these two muscle groups is that they differ not only in their actions on the ankle joint but

also in their physiological properties. Thus, in comparison with the plantarflexor muscles, the dorsiflexors have faster twitches, greater post-activation potentiation and more susceptibility to fatigue;⁹ they are also more readily excited during voluntary contractions.¹⁰

Methods

Subjects and patients

Experiments were conducted on 25 patients with myotonic dystrophy (15 males and 10 females aged 19 to 63 years) and on 25 healthy subjects who were closely matched for age, sex, weight and height. The diagnosis was based on family history and clinical examination and was confirmed by comprehensive electromyographical investigations and in some cases by muscle biopsies. All patients and subjects volunteered for the experiments and were paid. The project carried the approval of the Ethics Committee at McMaster University.

Techniques and protocol

The experiments were performed on the dorsiflexor muscles, of which the tibialis anterior was studied in detail, and on the plantarflexor muscles of the ankle. The same leg holder-ankle torque measuring device and stimulating-recording arrangements were used as in earlier studies.⁹⁻¹¹ With the person sitting and with his/her knee kept at a right angle, the plantarflexor and tibialis anterior isometric twitches were recorded together with their respective muscle compound action potentials (M-waves). The skin overlying the muscles was kept at 34°-38°C with an infra-red

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lamp. All subjects and patients had their muscles tested in stretched positions, corresponding to 20° of plantarflexion for dorsiflexor and to 10° dorsiflexion for plantarflexor;^{11,12} in three male patients, however, plantarflexor muscles were tested at 0° (that is, with the foot at a right angle to the tibia) owing to Achilles tendon contractures. Following 5 seconds of voluntary dorsiflexion or plantarflexion, post-activation potentiation of the twitch was assessed. During the measurement of maximal voluntary torque we determined the extent of motor unit activation in the two muscle groups by means of the interpolated twitch technique.¹⁰ Finally, the time-course and possible sites of fatigue were investigated by monitoring the decline of voluntary torque, together with the twitch and M-wave responses before, and after, 60 seconds of maximal effort. We also looked at the extent of recovery of these various parameters one minute after the end of the fatiguing effort.

All measurements were made from photographs of oscilloscope displays. A correlation analysis was performed with the Pearson coefficient of correlation and significance between means was assessed with the Student *t* test at the 5% level. Corrections for cases of non-homogeneity of variance were made.¹³

Results

Twitch properties

Figure 1 illustrates the typical twitch and M-wave responses obtained from a 45-year-old patient and from his matched control. In none of the patients was there evidence of myotonic after-discharges, which could have influenced the twitch values; valid comparisons could therefore be made between dystrophic and matched control responses. As anticipated, both tibialis anterior and plantarflexor twitch torques tended to be smaller in the dystrophic patients than in control subjects but the range of

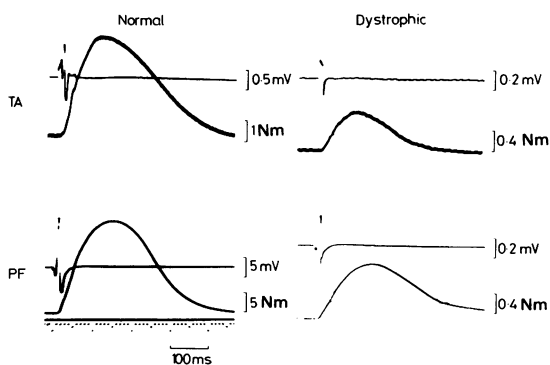


Fig 1 Twitch and M-wave responses obtained from plantarflexor and tibialis anterior muscles of a 45-year-old male patient and his matched control. Note in the dystrophic patient the significantly reduced twitch peak torque and M-wave, as well as the absence of myotonic after-discharge responses.

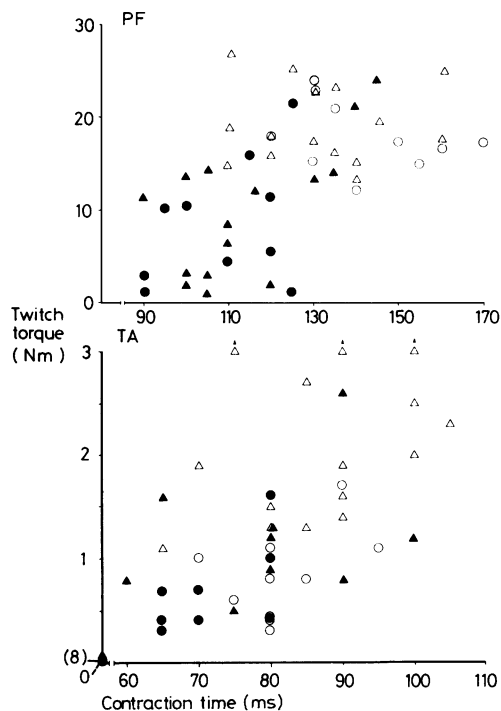


Fig 2 Twitch torque as a function of contraction time for plantarflexor and tibialis anterior muscles. Values for males and females are shown as triangles and circles respectively. Open symbols denote the control values while filled symbols identify results from patients with myotonic dystrophy. Arrows indicate tibialis anterior twitch torques greater than 3 Nm. Apart from the increased scatter of values in the dystrophic group, note the absence of twitches in the tibialis anterior muscles of eight patients (six males and two females) as well as the trend to reduced twitch torques and shorter contraction times in the remainder of the tibialis anterior and plantarflexor muscles.

values in the dystrophic population was much greater. Thus approximately one-third of the dystrophic plantarflexor responses and one-half of the tibialis anterior torques were within the corresponding control ranges, allowing for sex differences; at the other extreme, however, there were eight patients in whom it was impossible to record tibialis anterior twitches.

In fig 2 it can be seen that twitches tended to be faster in dystrophic plantarflexor and tibialis anterior muscles than in controls. Statistically significant correlations were found between twitch torque and contraction time for both tibialis anterior muscles and plantarflexor muscles in dystrophic patients, that is, the weakest muscles had the fastest twitches.

In order to assess the efficacy of impulse activity in eliciting contractile responses in dystrophic muscles, M-wave amplitudes were compared with the twitch torques. In both the tibialis anterior and plantarflexor muscles of dystrophic patients a significant correlation between two variables could be demonstrated ($r = 0.73$ and 0.72 , respectively); nevertheless, there were three dystrophic tibialis anterior muscles in which the M-waves were not associated with detectable contractions. Similarly, there was one dystrophic male patient in whom the plantarflexor muscles generated a large M-wave (19 mV) with very little twitch torque (fig 3); two female patients had normal-sized plantarflexor M-waves (7, 10 mV) associated with small twitches. However, the large variation in the twitch torque:M-wave ratios among subjects prevented any significant differences from emerging between the normal and dystrophic populations for either the tibialis anterior or plantarflexor muscles.

After the "resting" twitch had been recorded post-activation potentiation was assessed by measuring the twitch at the end of 5 seconds maximal voluntary contraction. No difference was observed between dystrophic and control subjects, the tibialis anterior showing, on average, eight times more potentiation than plantarflexors (for example, 90% and 11% respectively for dystrophic patients; see table). As with the normal group, the potentiated tibialis anterior and plantarflexor twitches in dystrophy showed briefer contraction and half-relaxation times, suggesting that the potentiation resulted from an increase in the intensity of the active state, rather than in its duration.^{9 14}

Voluntary contraction

In each patient and control subject a record was made of the greatest voluntary torque achieved dur-

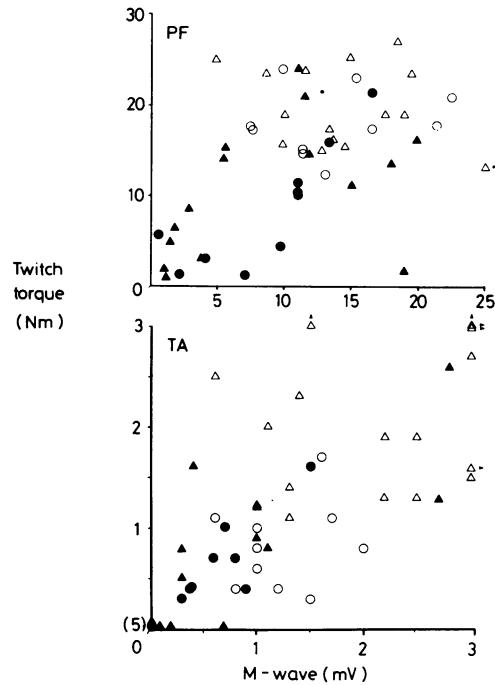


Fig 3 Twitch torque as a function of muscle compound action potential amplitude (M-wave) for plantarflexor and tibialis anterior muscles. Values for males and females are shown as triangles and circles respectively. Open symbols denote control values while filled symbols identify results from patients with myotonic dystrophy. Arrows indicate values beyond limits of axis. Note the greater variability of results in the dystrophic group. Of interest is the absence of tibialis anterior twitches and M-waves in five patients, and the absence of tibialis anterior twitches in a further three patients in whom M-waves were present.

Table Summary of mean contractile properties of plantarflexor and dorsiflexor muscles, obtained from control and dystrophic populations. Values of twitch peak torque (PT), contraction time (CT), half relaxation time (1/2 RT), muscle compound action potential (M-w), twitch post-activation potentiation (PAP), maximum voluntary contraction (MVC) and motor unit activation (MUA) are shown. Significance was assessed at 5% level, using independent t tests. (S, significant; NS, not significant)

		PT Nm	CT ms	1/2RT ms	M-w mV	PAP %	MVC Nm	MVC/PT —	PT-M-w Nm/mV	MUA %
Plantarflexors	Control	(x) 18.2	134.2	120.6	14.7	17	132.1	7.5	1.47	94.3
		(SD) 4.5	16.1	19.7	5.3	21	30.2	1.9	.92	8.9
	Dystrophy	(x) 10.2	112	113.6	8.6	11	73.6	9.9	1.72	83.9
	(SD) 6.9	15.5	28.4	6.1	26	49.1	6.9	1.87	22.4	
Significance		S	S	NS	S	NS	S	NS	NS	S
Dorsiflexors	Control	(x) 1.8	84.8	102.8	1.89	130	40.8	13.8	1.09	100
		(SD) 1.4	10.2	24.1	1.12	82	11.1	7.9	.92	—
	Dystrophy	(x) .65	76.2	92.3	.74	90	22.2	15.8	1.2	100
	(SD) .66	10.8	17.9	.71	58	15.3	10.3	.86	—	
Significance		S	S	NS	S	NS	S	NS	NS	NS

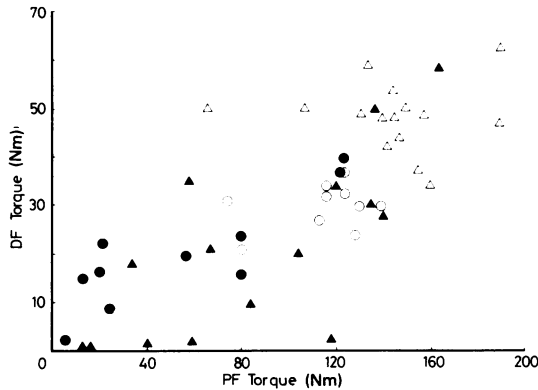


Fig 4 Maximum voluntary dorsiflexor torque as a function of plantarflexor torque in patients with myotonic dystrophy (filled symbols) and in their matched control subjects (open symbols). Values for males and females are shown as triangles and circles respectively. Note the considerable disproportion between plantarflexor and dorsiflexor torque in some male patients. Among the control subjects, men are shown to be stronger than women and, as expected, the patients were weaker than their matched controls.

ing three attempts, each lasting approximately 4 seconds. Figure 4 shows the dorsiflexor and plantarflexor torques plotted against each other; the results for normal subjects fell into two clusters, reflecting the greater strength of the males. In the dystrophic population there was a much greater range of observations, with some patients still possessing normal values and others having very little torque; in two cases there was complete paralysis of dorsiflexion. Among the dystrophic patients the loss of strength in one muscle group was often not proportional to the weakness in the other. The most extreme example was a 39-year-old man in whom dorsiflexion was only 5% of the control mean value whereas plantarflexion was 90% of the respective control mean.

In general, there was a tendency for dorsiflexion to show the greater relative impairment in the male patients and plantarflexion in the females (fig 4), but this impression may have been the result of the size of the sample. It was observed that six of the eight patients with absent tibialis anterior twitches developed measurable dorsiflexor torque during maximal voluntary effort; we believe that the latter was achieved mostly, or entirely, through use of the long extensors of the toes. Because of this last factor no significant correlation could be found between the tibialis anterior twitch and voluntary dorsiflexor torques in the patient population ($r = -0.04$), although such correlations were present for the same muscles in controls ($r = 0.60$) and for plan-

tarflexor muscles in both patients ($r = 0.79$) and controls ($r = 0.42$).

During maximal isometric strength testing we employed the twitch interpolation technique¹⁰ to establish whether or not the dystrophic patients were making full use of their surviving motor units. The dystrophic patients resembled controls in fully activating their tibialis anterior muscles but they showed a significantly reduced plantarflexor motor unit activation ($p < 0.05$; table). Full plantarflexor motor unit activation was achieved in only 28% ($n = 7$) of patients as opposed to 48% ($n = 12$) of control subjects. During the course of the testing session, we noticed in some patients an increasing ability to generate voluntary tension over repeated trials. Figure 5 shows the results obtained in a 20-year-old male patient who required five attempts before his plantarflexor torque became maximal; that this increase in strength was not artefactual but resulted from better motor unit activation was revealed by the decreasing interpolated twitches (fig 5).

Muscle fatigue

The susceptibility of dystrophic muscles to fatigue was tested by measuring the decline in isometric torque during 60 seconds of maximal voluntary dorsiflexion and plantarflexion. As in a previous study,⁹ the dorsiflexor muscles of healthy subjects were found to fatigue twice as rapidly as the plantarflexor group and this distinction was clearly evident in the dystrophic patients also (fig 6). At the end of each 20 seconds epoch the mean torque for the dystrophic muscles, expressed as a percentage of the initial value, was not significantly different from

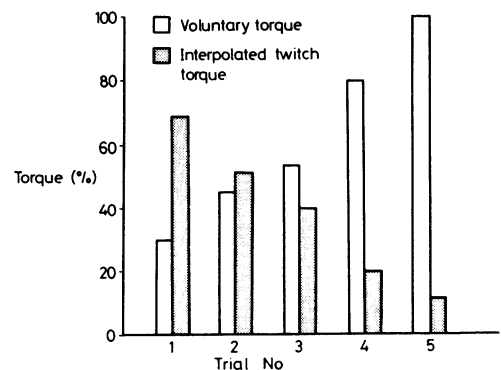


Fig 5 Evidence for increased plantarflexor muscle strength as a result of better motor unit activation in a 20-year-old male dystrophic patient (see text). There was no further increase of voluntary muscle strength following the fifth trial.

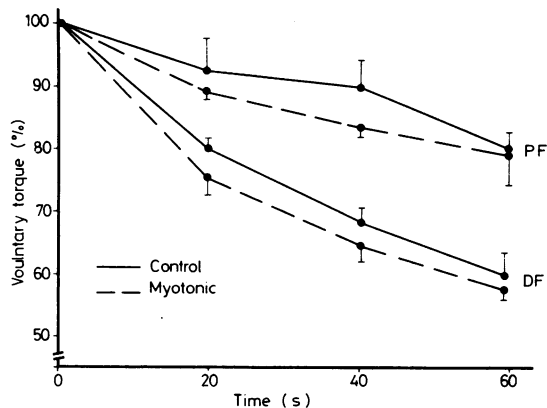


Fig 6 Decline of maximum voluntary torque of dorsiflexor and plantarflexor muscles of patients with myotonic dystrophy and their matched control subjects. Means and standard errors of the mean are shown. No significant differences were found between the results for dystrophic patients and controls. In patients with myotonic dystrophy and in control subjects, dorsiflexor muscles showed a greater susceptibility to isometric fatigue than plantarflexor muscles.

the mean for the control subjects. In both the normal and dystrophic subjects a maximal stimulus was interpolated before the conclusion of voluntary contraction to establish whether any of the decline in torque was due to failing motor unit activation. In none of the tibialis anterior muscles could a superimposed twitch be detected while, if one was present for the plantarflexor group, it was, on average, no larger than that present during short intense effort (see above). While these observations clearly indicated that the site of fatigue was peripheral, they did not distinguish between a failure of muscle fibre excitation, on the one hand, and one of excitation-contraction coupling or of the contractile machinery, on the other. For this reason a single maximal stimulus was delivered within two seconds of the end of effort and the amplitude of the M-wave was compared with that of the twitch torque. It was found that, in both the control and the dystrophic populations, tibialis anterior M-waves were not measurably different from those recorded in the resting state; in contrast the mean twitch torques were reduced from the initial potentiated values by 62% and 40% for the control and dystrophic populations respectively. These results showed that fatigue in dystrophic tibialis anterior muscles resembled that in normal ones in resulting from failure in some step beyond the excitation of the muscle fibres. In the plantarflexor muscles, which showed less fatigue than tibialis anterior, the results were in the same direction though less striking. The recovery of tibialis

anterior twitch torque followed a similar time course in the normal and dystrophic populations.

Discussion

As stated above, we have used the data gained in this study to address three fundamental aspects of myotonic dystrophy:

(1) Fibre type involvement in myotonic dystrophy

Evidence of preferential involvement of slow-twitch fibres in myotonic dystrophy was first reported by Engel and Brooke¹⁵ who noted that, in approximately half of their cases, the type I fibres had subsarcolemmal pads of non-myofibrillar material. In keeping with this observation we found the twitches to be significantly faster in the tibialis anterior and plantarflexor muscles of dystrophic patients than in controls. In theory, a stiffening of the series elastic component could also have caused a speeding-up of the twitch but the fact that the MVC:twitch ratios were not significantly altered in dystrophy suggested that such a factor was unimportant. However, far more striking than the altered twitch speeds was the disproportionate involvement of the two muscle groups in individual patients. In some patient, usually male, dorsiflexor torque was virtually abolished while plantarflexor torque was still appreciable; in other patients, usually women, the trend was in the opposite direction. The conclusions to be drawn from these observations are, first, that within a single muscle there is a tendency for fast-twitch elements to predominate. Secondly, and more importantly, in an individual patient at a given stage, the dystrophic process is capable of virtually destroying one muscle while sparing another, regardless of the component fibre types.

(2) Impulse:force proportionality

In a normal muscle much of the cross-sectional area is occupied by myofibrils but this is not necessarily true in myotonic dystrophy, in which some fibres have subsarcolemmal masses devoid of contractile material.¹⁵ There are also reports of abnormal transverse and sarcoplasmic tubular systems, ring fibres, prominent chains of central nuclei, and of fibres undergoing necrosis or regeneration.^{16,17} Any or all of these changes might be expected to diminish the contractile response of a dystrophic muscle fibre to a propagated impulse.

In the present study we have approached this problem by comparing the twitch torque with the M-wave amplitude. While the mean torque:M-wave ratios were very similar for tibialis anterior and plantarflexor muscles in the normal and dystrophic subjects, six patients showed disproportionately small

contractile responses. Although there have been no previous reports of mechano-electric disproportion in myotonic dystrophy, the present findings are similar to those of Desmedt and Hainaut¹⁴ who studied the twitch responses of adductor pollicis muscles in Duchenne muscular dystrophy (see also ref. 18). Also relevant are the findings of reduced tensions developed by skinned muscle fibres obtained from patients with Duchenne muscular dystrophy.^{19,20}

(3) Motor unit activation

Although the reduced twitch torques observed in the dystrophic patients were anticipated, it was possible that, during maximum voluntary contraction, motor units were not activated as fully as in normal subjects. This possibility was explored using the interpolated stimulus technique, previously exploited by Merton²¹ and by Belanger and McComas.¹⁰ In the case of tibialis anterior the dystrophic patients resembled controls in being able to activate their muscles fully. The results for plantarflexor differed in that only 28% of patients could develop all their potential torque; this value was significantly different from the value of 48% obtained for normal subjects. However, the true difference between the two populations of subjects was greater than this for some dystrophic patients were only able to develop a fraction of their ultimate torque at the first attempt and required several repetitions before achieving their maximal value. We believe that this situation is analogous to that in healthy subjects immobilised by plaster casts,^{22,23} in whom there appears to be a temporary failure of motoneuron excitation by descending motor pathways. In patients with moderately severe myotonic dystrophy the poverty of attempted movement throughout the day may well render motoneurons incapable of sudden, maximal activation. This finding has therapeutic implications for it offers dystrophic patients the possibility of better performance through the adoption of appropriate exercise regimens.

Physiological features of dystrophic muscle fibres

The final part of this study has been to explore two additional properties of the surviving muscle fibres in dystrophic muscles, namely their capacity for twitch potentiation and their susceptibility to fatigue. Despite the fact that the twitches were often diminished in the dystrophic muscles, the twitch potentiating capability in dystrophy remained appropriate for both muscle groups, being large for tibialis anterior and small for plantarflexors. This finding was unexpected, since electromicroscopic studies have shown marked abnormalities in the sarcoplasmic and transverse tubular systems of dys-

trophic fibres;^{15,16,24} both systems are known to be important in excitation-contraction coupling and probably, therefore, in the potentiating mechanism.^{14,25}

The fatigue characteristics of dystrophic muscles have not been adequately investigated in man, though there are reports of decreased²⁶ and normal²⁷ fatigability in dystrophic murine muscles. In an earlier study of myotonic dystrophy McComas and colleagues⁸ demonstrated decremental M-wave responses in extensor digitorum brevis muscles following indirect stimulation at modest rates and, on the basis of this observation, excessive fatigue might have been anticipated in the present study. Increased susceptibility to fatigue in dystrophy might also have been predicted from the contraction time results in the present study, which suggested preferential involvement of slow-twitch fibres by the dystrophic process. Contrary to expectation, however, the fatigue properties of patients with myotonic dystrophy were not significantly different from those in controls, being more marked for the dorsiflexor group than for plantarflexor muscles; the recovery of the tibialis anterior twitches from fatigue were also similar in the normal and dystrophic subjects. The fatigue results, and post-activation findings, indicated that the excitable fibres remaining in the dystrophic muscles retained at least some of their normal physiological properties.

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