Original Article

Force Assessment in Periodic Paralysis After Electrical Muscle Stimulation

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• *Objective*: To obtain an objective measure of muscle force in periodic paralysis, we studied ankle dorsiflexion torque during induced paralytic attacks in hyperkalemic and hypokalemic patients.

• *Subjects, Patients, and Methods*: Dorsiflexor torque after peroneal nerve stimulation was recorded during provocative tests on 5 patients with hypokalemic or hyperkalemic disorders and on 2 control subjects (1995-2001). Manual strength assessment was simultaneously performed in a blinded fashion. Standardized provocation procedures were used.

• *Results*: The loss of torque in hyperkalemic patients roughly paralleled the loss of clinically detectable strength, whereas in the hypokalemic patients, pronounced torque loss occurred well before observed clinical effects. No dramatic changes occurred in the control subjects. Torque amplitude decreased more than 70% in all patients during the provocation tests; such decreases were associated with alterations induced in serum potassium concentrations.

• *Conclusions*: Stimulated torque measurement offers several advantages in characterizing muscle dysfunction in periodic paralysis: (1) it is independent of patient effort; (2) it can show a definitely abnormal response early during provocative maneuvers; and (3) characteristics of muscle contraction can be measured that are unobservable during voluntary contraction. Stimulated torque measurements can characterize phenotypic muscle function in neuromuscular diseases.

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CMAP = compound muscle action potential; ECG = electrocardiogram

Hypokalemic and hyperkalemic periodic paralysis disorders are characterized by intermittent episodes of muscle weakness.[1] These episodes can be attributed to a primary muscle disorder or can occur secondary to systemic disease (eg, chronic potassium imbalance or hyperthyroidism). The primary disorders can be either sporadic or inherited as an autosomal dominant condition.[2-9] Recent studies have provided more direct information regarding the genotype-phenotype associations in these disorders.[10-16] In addition, a slowly progressive vacuolar myopathy that accompanies either condition may be exacerbated by frequent paralytic attacks.[1] Hence, early diagnosis can facilitate treatment that may decrease permanent muscle damage. However, the paralytic attacks are frequently brief and occur when the patient is far from a medical center, making the study of spontaneous attacks difficult. To diagnose periodic paralysis, previous clinical protocols have provoked attacks (by potassium manipulation, systemic drug administration, or rest after exercise) while assessing muscle strength or motor nerve conduction.[9,17-23]

Voluntary strength, measured either manually or with force transducers, is commonly used to diagnose neuromuscular diseases, determine disease progression, and/or monitor treatment efficacy.[24-28] The Medical Research Council scale commonly used for manual strength measurement is highly nonlinear (with mild to moderately weak muscles being rated between 4 and 5) and is thus unreliable for measuring modest changes. Quantitative voluntary strength assessment with use of a force transducer substantially increases measurement precision and has been used frequently to monitor patients in treatment trials.[24-30] However, because this approach depends on patient effort, unreliable results are often obtained if the patient is in pain or systemically ill.[9,26,31] Several investigators have measured the ankle torque produced by activation of the dorsiflexor muscles by percutaneous stimulation of the common peroneal nerve to monitor various neuromuscular conditions.[32-37] Our laboratory has described the further automation of this approach with online analyses of recorded responses.[32] The present study was performed to determine whether such an approach could aid in the phenotypic characterization of either hyperkalemic or hypokalemic periodic paralysis.

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SUBJECTS, PATIENTS, AND METHODS

The University of Minnesota Committee on Human Subjects approved the investigational protocols used in this study (1995-2001). All study participants were informed of the potential risks of the tests and signed informed consent forms. They all had a physical examination, an electrocardiogram (ECG), and serologic testing to rule out diabetes and renal, liver, and cardiac disease before enrolling in the study. Testing was performed in the early morning on well-rested study participants who had not exercised and had fasted for 12 hours. Study participants discontinued any medications that could interfere with paralytic attacks (eg, carbonic anhydrase inhibitors, potassium, diuretics, and sodium channel blockers) 1 week before the test.

Five patients previously diagnosed with periodic paralysis participated in the study. The 3 patients with hyperkalemic periodic paralysis came from families possessing the *T704M* mutation of the adult skeletal muscle sodium channel gene on chromosome 17. One patient with hypokalemic periodic paralysis had an *R528H* mutation in segment S4 of repeat II of the skeletal muscle L-type Ca^{2+} channel. The mutation in the other hypokalemic patient was not identified.

Two control subjects underwent each provocation protocol (potassium loading or depletion) on separate days. They also participated in 4-hour control recording sessions in which no manipulations of their serum potassium levels were made but during which their stimulated force was assessed continually.

Torque Measurements

Changes in isometric ankle torque after either voluntary activation or involuntary nerve-stimulated activation of the dorsiflexor muscles were recorded with use of an aluminum frame device that held the study participant's leg securely.[34] Force was measured by a strain gauge attached to an aluminum bar that restrained movement of the footplate.[32,34] A preamplifier (Grass Medical Instruments, Quincy, Mass) amplified the output of the strain gauge; output was then digitized and stored on an IBM-compatible personal computer.[32] The computer provided online measurement of torque magnitude, rise time, and duration. The footplate position was rotated for each study participant to stretch the dorsiflexor muscles for maximal force generation. All data acquisition and analysis programs were written with Lab VIEW 2 (National Instruments, Austin, Tex).[32]

For involuntary contractions, the peroneal nerve was stimulated supramaximally by surface electrodes with use of 100 to 150 V with 0.3-millisecond pulse durations at the fibular head with use of a stimulator (S11, Grass Medical Instruments).[32,34-37] Torque measurements were recorded for single twitch (after 1 stimulus), tetanic contraction (after 4 stimuli delivered at 50 Hz), and maximal voluntary contraction.

Provocative Maneuvers

Provocative testing was performed in a hospital room with emergency equipment and personnel readily available (clinical research center). Serum electrolyte and glucose values were available within 5 minutes of blood being withdrawn.

For all provocative studies, the patients and control subjects had their left legs inserted into the ankle torque measuring device and were seated in a chair adjusted to keep their thighs parallel to the floor. Intravenous catheters were placed in both of their arms; one was used only to obtain blood samples, while the other was available for administration of glucose, insulin, or potassium. The ECGs were monitored continually throughout each study, and traces were printed every 15 minutes. To maintain cutaneous leg temperatures above 30°C, convective air-warming coverlets (model 525, Augustine Medical, Inc, Eden Prairie, Minn) were wrapped around their legs and warm air (41°C) was continuously delivered via an air heater–blower unit (Bair Hugger model 500, Augustine Medical, Inc). The surface temperatures of their legs were monitored with use of a cutaneous probe (Yellow Springs Instrument, Yellow Springs, Ohio).

Manual strength testing (of right elbow flexion, wrist extension, hip flexion, ankle dorsiflexion, and great toe dorsiflexion) and single-pulse ankle dorsiflexor twitch torque measurements (done on the left legs) were performed approximately every 15 minutes, while 4-pulse tetanic torque and voluntary torque of the left ankle dorsiflexors were alternately measured every 15 minutes. Four-pulse stimulation was occasionally done more frequently during periods of rapid loss of strength. Testing continued until the serum potassium normalized and the study participants were asymptomatic; hence, the length of the study periods varied among the study participants.

Potassium Depletion

To test for hypokalemic periodic paralysis, glucose and insulin were administered to lower serum potassium. Each study participant drank a solution containing 1.5 g/kg of glucose (maximum, 100 g) over a 3-minute period at the onset of the test. Electrolytes (sodium, potassium, and bicarbonate) were measured every 30 minutes for 2 hours. If no weakness had developed and no contraindications occurred, glucose (3 g/kg, maximum of 200 g, in a solution of 2 g/5 mL) was infused intravenously over 1 hour with regular insulin (0.1 U/kg) administered intravenously 15 minutes and 45 minutes after the start of the glucose infusion. Serum glucose and electrolyte levels were measured

Table 1. **Stimulated Force Measurements During Potassium Loading Protocol**

		Baseline values					Values during potassium loading					
	Age (y)	Force 1-pulse (nm)	Force 4-pulse (nm)	Voluntary force (nm)	Time to peak (ms)	Half-maximal duration (ms)	Force 1-pulse (nm)	Force 4-pulse (nm)	Voluntary force (nm)	Time to peak (ms)	Half-maximal duration (ms)	Time during protocol (min)
Control subjects												
1	44	3.8	13.3	38.6	160	252	3.1	11.0	40.9	160	256	75
2	37	5.3	22.1	56.0	148	194	5.6	19.4	56.6	160	200	75
Mean ± SD		4.6±1.1	17.7±6.2	47.3±12.3	154±8	233±41	4.4±1.7	15.2±5.9	48.7±11.1	160±0	228±40	75±0
Patients with hyperkalemic periodic paralysis												
1	16	2.3	8.1	16.4	136	188	1.8	4.6	9.7	128	212	30
2	17	2.0	10.7	22.0	128	196	1.2	2.9	5.0	120	208	45
3	36	3.4	13.1	29.0	140	224	3.1	9.7	21.9	140	228	60
Mean ± SD		2.6±0.7	10.6±2.5	22.4±6.3	135±6	203±19	2.1±1.0	5.7±3.6	12.2±8.7	129±10	216±11	45±15

every 15 minutes for 2 hours after the glucose infusion began and then every 30 minutes for the next 2 hours. Because maximal potassium decreases and weakness occurred within 3 hours after the initiation of the glucose infusion, patients were given a meal containing complex carbohydrates 2 to 3 hours after completing the glucose infusion to help prevent symptomatic hypoglycemia. The potassium-lowering protocol was reversed by oral and intravenous potassium chloride administration if (1) potassium level decreased below 2.5 mEq/L, (2) marked weakness developed indicative of a severe attack, or (3) potentially serious ECG changes developed (prominent T waves or ST-segment depression).

Potassium Loading

To test for hyperkalemic periodic paralysis, study participants drank an unsweetened solution of 0.1 g/kg (1.3 mEq/kg) of potassium chloride over a period of 2 to 3 minutes at the onset of the test. Electrolytes (sodium, potassium, chloride, bicarbonate) were measured every 15 minutes for the first 2 hours, then every 30 minutes for the subsequent 2 hours. These studies were terminated by a glucose infusion of 50 mL of 50% glucose with 10 U of regular insulin if urgent treatment was needed because of (1) serum potassium level exceeding 7 mEq/L, (2) profound weakness, and/or (3) a serious change in the ECG signal (ie, bradycardia, atrioventricular block, QRS widening, QRS T-wave fusion).

Analyses

Torque amplitudes and timing parameters were automatically determined via software. Statistical analyses of the data were based on analyses of variance and *t* tests as appropriate. Statistical significance was inferred if $P<.05$.

RESULTS

Effects of Potassium Manipulation on Measured Force

Tables 1 and 2 detail the measured features of stimulated torque in control subjects and patients. For patients, the values during the protocol were those at which the torque amplitude produced by 4-pulse stimulation first decreased below 75% of baseline; values for 1-pulse and voluntary amplitudes were those that had been determined immediately before the chosen 4-pulse response. Points chosen later in the protocol would have shown a more dramatic amplitude decrease, but the time to peak and half-maximal duration values become less meaningful for such lower amplitude responses. Values for control subjects in the tables were chosen at 75 minutes into the protocol to provide a meaningful comparison for patients; at this time, torques were dramatically affected in the patients.

As seen in Tables 1 and 2, there was a trend for lower baseline torque measurements in hyperkalemic patients compared with both control subjects and hypokalemic patients. Although this was true for 1-pulse, 4-pulse, and voluntary torque measurements, the difference was not statistically significant for any of these determinations individually. There was no statistically significant difference in baseline time to peak or half-maximal duration for either patient group compared with control subjects.

For the points during the protocol that are reported in Tables 1 and 2, the 4-pulse stimulated force amplitudes of the patients showed moderate loss of force, being less than 75% of baseline by definition. The data for control subjects showed 4-pulse stimulated force amplitudes that were 89% to 102% of baseline amplitude after 75 minutes of both potassium manipulation protocols. Other than amplitude, the only statistically significant change in muscle response at the time of

Table 2. **Stimulated Force Measurements During Potassium Depletion Protocol**

		Baseline values					Values during potassium depletion					
	Age (y)	Force 1-pulse (nm)	Force 4-pulse (nm)	Voluntary force (nm)	Time to peak (ms)	Half-maximal duration (ms)	Force 1-pulse (nm)	Force 4-pulse (nm)	Voluntary force (nm)	Time to peak (ms)	Half-maximal duration (ms)	Time during protocol (min)
Control subjects												
1	44	4.1	13.9	37.4	164	248	3.4	12.5	34.8	160	244	75
2	37	6.1	23.7	60.4	156	208	5.2	21.1	59.0	156	200	75
Mean ± SD		5.1±1.4	18.8±6.9	48.9±16.3	160±6	228±28	4.3±1.3	16.8±6.1	46.9±17.2	158±3	222±31	75±0
Patients with hypokalemic periodic paralysis												
1	21	5.1	14.2	28.8	140	232	6.0	10.1	30.2	128	248	30
2	34	5.0	25.7	45.0	116	176	3.6	13.5	45.0	132	208	15
Mean ± SD		5.1±0.1	19.9±8.2	36.9±11.5	128±17	204±40	4.8±1.7	11.8±2.4	37.6±10.5	130±3	228±28	22±11

moderate loss of force was for time to peak in both hypokalemic and hyperkalemic patients, which were shorter than in control subjects (*t* test values .01 and .02, respectively).

Time Course of Torque Changes During Potassium Manipulations

Control Subjects.—In the same setting that was used for the potassium manipulation protocols, the 2 control subjects had torque and strength measured every 15 minutes for 4 hours. The control subjects remained asymptomatic and retained normal strength, as assessed via manual testing throughout the study. Twitch (single stimuli), 4-pulse (tetanic), and maximal voluntary torque amplitudes varied by less than 10% in each control subject throughout the study (data not shown), with a slight trend toward decreasing amplitude as the study progressed.

There was no substantial change in the manually assessed strength of control subjects at any time during either potassium loading or potassium depletion studies. Torque measurements varied little for the first 2 hours of the experiment; however, loss of amplitude that was less than 25% of baseline did occur in 1 control subject after 2 to 3 hours (Figures 1 and 2).

Patients.—All 3 patients with hyperkalemic periodic paralysis experienced a substantial decrease in left ankle dorsiflexor torque that preceded or paralleled the decrease in manually assessed strength of every muscle tested (Figure 1). The 2 patients with hypokalemic periodic paralysis showed a dramatic decrease in ankle dorsiflexor torque that greatly preceded any recognizable change in strength (Figure 2). The dorsiflexor torque decreased rapidly after the onset of the provocation studies in patients with both conditions, but the peak changes were well delayed in the hypokalemic patients (Figure 3). Additionally, the temporal relationship between the maximal change in serum potassium levels and loss of force differed in the 2 disorders (Figure 3); torque diminution paralleled the decrease and subsequent increase in potassium in hyperkalemic patients but substantially preceded the changes in hypokalemic patients.

Systemic Effects of Potassium Manipulation

In the potassium depletion study, the initial ingestion of glucose was associated with mild to moderate nausea without vomiting in all study participants (including the 2 control subjects). Three or 4 hours after intravenous infusion of glucose and insulin, all study participants became symptomatic (diaphoretic, tachycardic, nauseated, presyncopal) in association with transient hypoglycemia. A meal provided 2 to 3 hours after glucose infusion ameliorated but did not eliminate the symptoms. In 1 patient with hypokalemic periodic paralysis, an attack of severe weakness was precipitated, and potassium was administered orally and intravenously to terminate the study. No study participants experienced appreciable ECG changes, and in no study participants did potassium concentration fall below 2.5 mEq/L. Weakness was typically maximal within 2 to 3 hours of glucose infusion.

In the potassium loading study, nausea without vomiting and a flushed sensation occurred for 15 to 30 minutes after potassium ingestion. In 1 patient with hyperkalemic periodic paralysis, the potassium increased to 7 mEq/L; subsequently, the study protocol was terminated by glucose infusion. No study participants experienced substantial ECG changes. Weakness was typically maximal within 1 to 2 hours of potassium ingestion.

DISCUSSION

Clinical measurement of strength is a cornerstone of disease management in neuromuscular clinics. An accurate

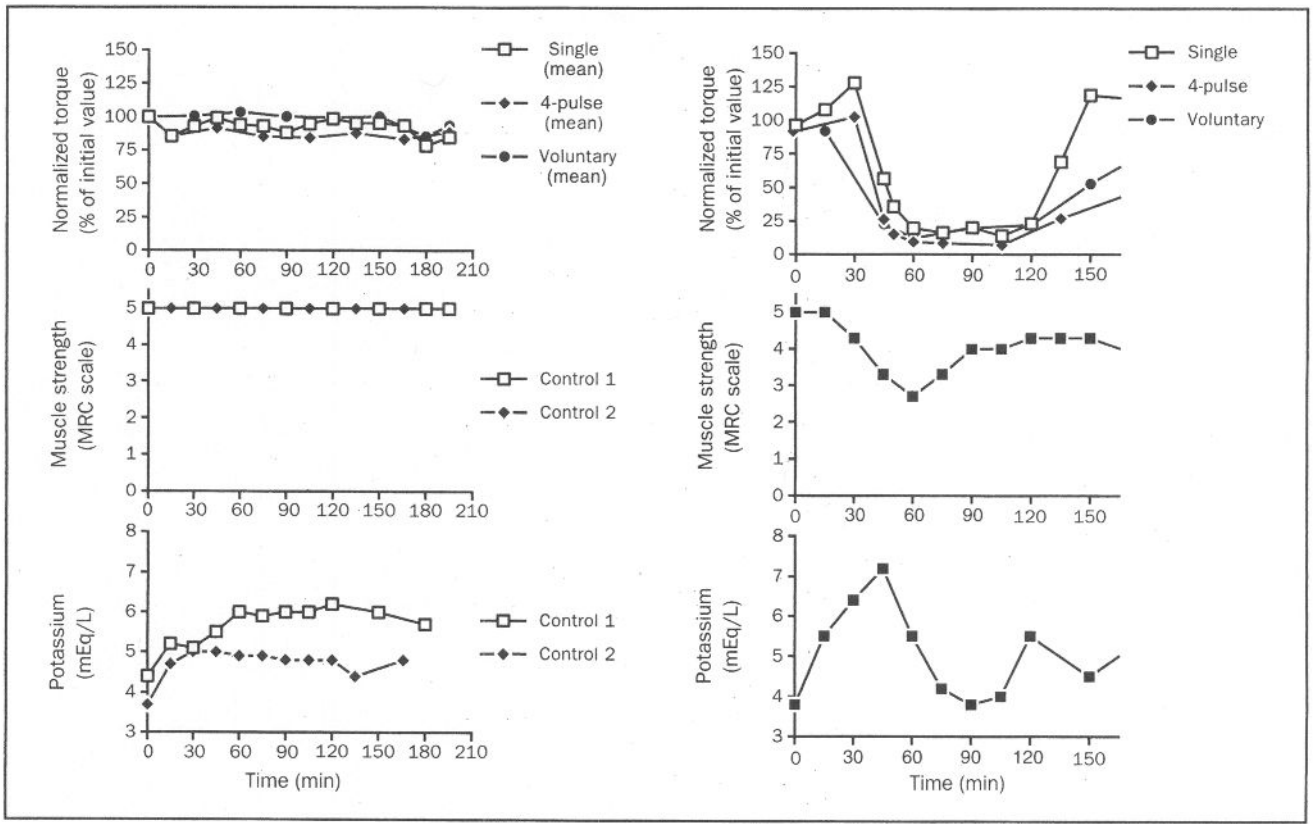

Figure 1. Force during potassium loading in control subjects and 1 patient with hyperkalemic periodic paralysis. Upper graphs represent left ankle dorsiflexor torque after single stimuli (twitch contractions), 4-stimuli at 50 Hz (tetanic contractions, labeled 4-pulse), and maximal voluntary contraction in 2 control subjects (left) and in 1 patient with hyperkalemic periodic paralysis (right). Middle graphs show the right ankle dorsiflexor strength assessed manually (Medical Research Council [MRC] scale). Lower graphs illustrate the simultaneous serum potassium concentration. Note that the 4-pulse and voluntary contractions were alternated every 15 minutes.

record of variable or progressive weakness can aid in correctly diagnosing a disease or phenotypically characterizing a genetic mutation. In addition, precise measurement of strength is often essential for accurate assessment of treatment efficacy and development of an appropriate therapeutic regimen.

Periodic paralysis is a clinical feature associated with multiple point mutations of genes encoding either (1) skeletal muscle tetrodotoxin-sensitive voltage-gated Na^+ channels, (2) the skeletal muscle L-type Ca^{2+} channel,[2-8,10,12,13,15,16,38] or (3) proteins that regulate potassium channel function. Published methods used to demonstrate periodic paralysis[1,9,17,19,21,22] either induce attacks of paralysis in vivo by exercise, potassium manipulation, or drug injection, or they measure muscle function in vitro.[1,17-19] Alternatively, exercise-induced changes in serum potassium levels have been reported in hypokalemic and hyperkalemic patients.[21] Muscle fiber conduction velocity can be used to distinguish affected from unaffected family members and can be abnormal even in affected individuals without attacks of periodic weakness; however, this test is nonspecific, being abnormal in many myopathic disorders.[9,22,23] Nevertheless, none of these tests is completely sensitive. Postexercise shifts in serum potassium may be mild, and absolute values may remain within the reference range, making assessment difficult. Manipulation of serum potassium may induce systemic effects, as in our control subjects, making elicitation and interpretation of mild voluntary weakness difficult. The ability to provoke an attack by potassium manipulation alone makes the findings more specific than provocative tests that use muscle exercise alone because exercise can induce an attack of weakness in both hypokalemic and hyperkalemic periodic paralysis. Similarly, changes in compound muscle action potential (CMAP) measurements can vary and are well defined for small distal muscles that may be least affected in a mild attack. Of note, twitch tension measurements are less sensitive in small distal

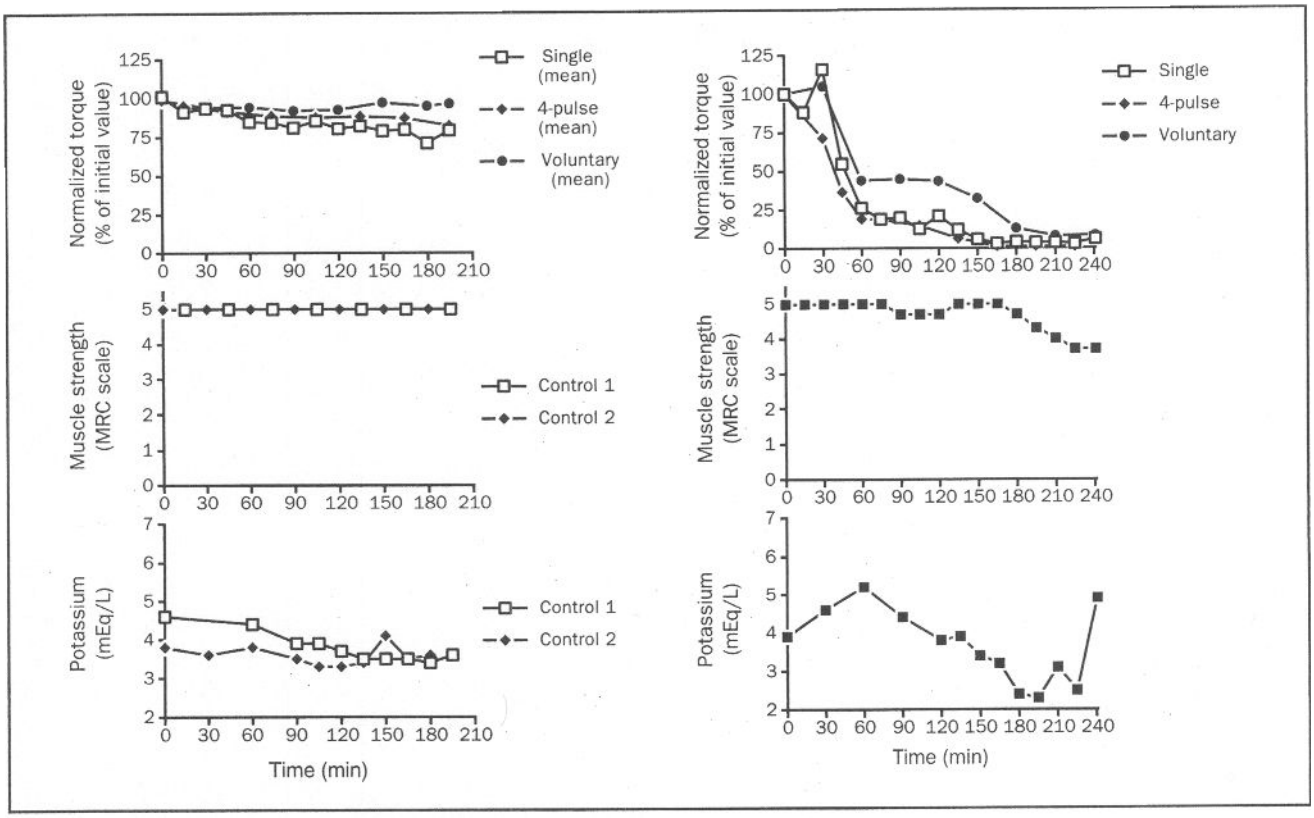

Figure 2. Force during potassium depletion in control subjects (left) and a patient with hypokalemic periodic paralysis (right). Graphs are organized as in Figure 1. Loss of force assessed with use of the torque measurements preceded weakness noted by the neurologist, who was unaware of the torque measurements. The initial rise in serum potassium was due to hemolysis. Note that the 4-pulse and voluntary contractions were alternated every 15 minutes.

muscles (low signal-to-noise ratios) relative to larger, more severely affected muscles.

In our study, stimulated torque measurements involved the tibialis anterior muscle, which is often affected early in an attack of periodic paralysis. The decrease in measured torque clearly preceded the decrease in strength as assessed manually in the hypokalemic patients. Furthermore, changes in simultaneously recorded CMAP amplitudes of distal muscles lagged behind changes in ankle dorsiflexion torque during manipulations of serum potassium (J. W. D., unpublished data, 2001). CMAP amplitudes measured after stimulation of either the peroneal or tibial nerves (measuring from extensor digitorum brevis or abductor hallucis muscle, respectively) decreased to 10% of initial values, but these changes could occur several hours after the observed maximal decreases in ankle torque. For example, for the data shown in Figure 2, right, at 40 minutes when ankle torque was minimal, the peroneal and tibial CMAP amplitudes were 54% and 114% of original values, respectively. Nerve compression may have occurred during these prolonged investigations, leading to potential alterations in CMAP amplitudes. In subsequent similar studies, torque recordings were performed while control subjects were supine; variations in CMAP amplitudes were then minimized.

Stimulated force measurement, being independent of subject effort, cannot be affected by the systemic symptoms that can substantially alter manual strength or voluntary force measurements. The decreased force observed in our study was not due to repeated stimulation of the muscle because it has been shown previously that in healthy controls the average peak tetanic torque generated by the dorsiflexor muscles varies by less than 4% with repeated testing.[32] In contrast, force amplitudes decreased by 10% to 25% in the control subjects during the study. Even though changes in control subjects were small compared with those in patients, they were greater than the typical 4% variation. Although observations in control subjects may reflect true change in muscle function produced by the potassium manipulations, continued op-

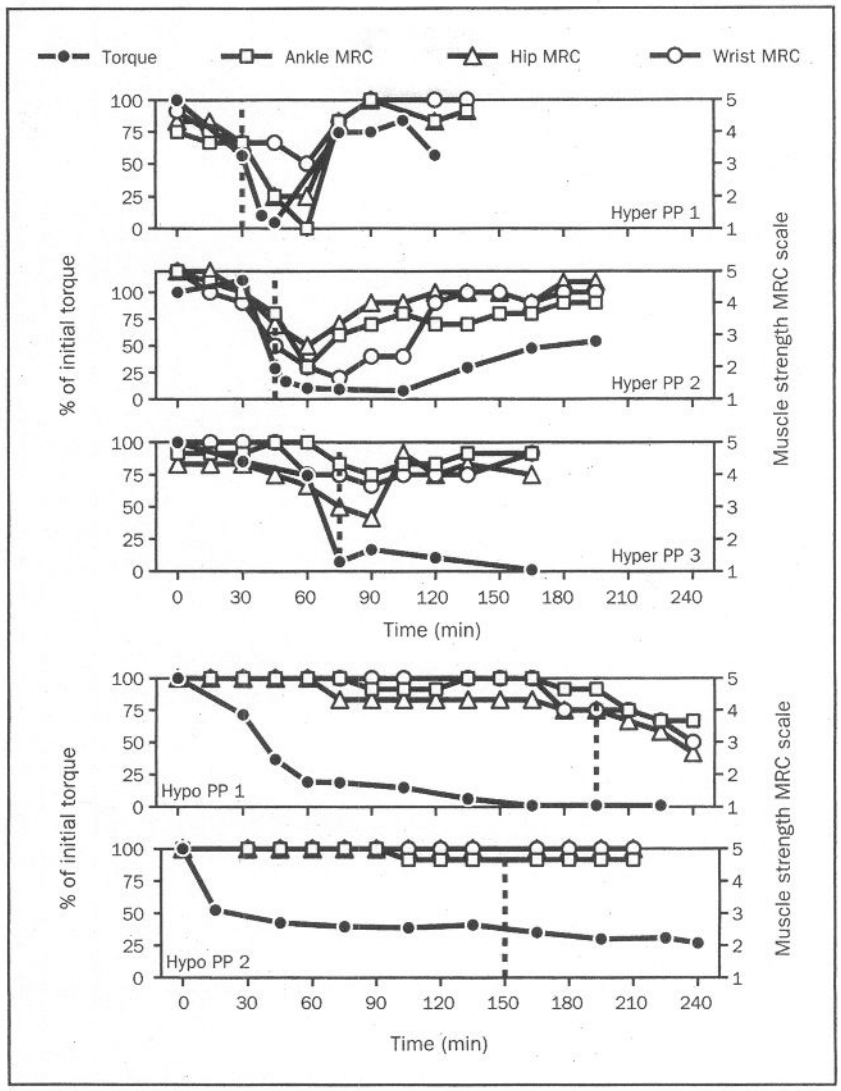

Figure 3. Time course of potassium manipulation effect on ankle dorsiflexor torque in all 5 patients. Upper 3 records are from 3 patients with hyperkalemic periodic paralysis (Hyper PP). Lower 2 records are from 2 patients with hypokalemic periodic paralysis (Hypo PP). Shown for comparison are ankle dorsiflexion force amplitudes in tetanic contraction (torque, 4-pulse stimulation at 50 Hz) and Medical Research Council (MRC) strength assessments of multiple muscle groups (ankle, hip, and wrist) for each patient. Vertical dashed lines represent time points at which changes in serum potassium were maximal.

timization of our study methods (in part by performing tests in supine subjects for better control of limb temperature and comfort) is desirable to attenuate further the observed decreases in torque in control subjects. In general, the stimulated force procedure was well tolerated by control subjects and did not interfere with participation in the study; the pain of nerve stimulation was comparable to that of typical peroneal nerve conduction studies.

The loss of force in hyperkalemic patients roughly paralleled the loss of clinically detectable strength. Nonetheless, stimulated force measurements were valuable in these patients to determine that the strength loss was not due to diminishing effort in face of systemic adverse effects from potassium administration. The voluntary strength loss for hypokalemic patients lagged behind the loss of stimulated force much more dramatically than was seen in the hyperkalemic patients. This difference in volun-

tary strength is unlikely due to variable effort because voluntary responses in humans are generally considered reliable.[29,30] Somehow the cellular pathophysiology of hypokalemic periodic paralysis must affect muscle response to a 4-pulse stimulus more than it affects the longer stimulation responsible for voluntary contraction. The more abrupt onset of weakness and loss of force in hyperkalemic periodic paralysis may relate to the somewhat lower baseline force amplitudes seen in these patients. One can only speculate why muscle in hypokalemic patients can retain voluntary strength for a longer period, whereas muscle in hyperkalemic patients loses voluntary strength in parallel with the loss of stimulated force. Likewise, the shortened time to peak measurements at the point of moderate weakness for both conditions, with preserved length of half-maximal duration, may reflect changes in sarcolemmal excitability.

Stimulated torque/force assessment is a reproducible and sensitive method that is valuable in selectively studying neuromuscular function in situations in which voluntary strength is affected by other factors. For instance, it can measure lower motor neuron function and strength in amyotrophic lateral sclerosis, independent of upper motor neuron disease. We have used this method to monitor the onset and progression of skeletal muscle weakness during a provoked attack of periodic paralysis, which will help in completely characterizing the phenotype of each mutation that can produce periodic weakness. Stimulated skeletal muscle torque assessment may both substantiate the diagnosis of a specific form of periodic paralysis in a particular patient and further clarify the underlying genotype-phenotype associations in this class of disorders. Furthermore, stimulated force studies allow various physiological force parameters to be measured (eg, contraction time, peak force, or time to peak force development), which are unobservable in voluntary contraction and may be selectively affected in different disease states.[32]

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