SHORT REPORT

ABSTRACT: The lack of a practical model has hampered attempts to study the pathophysiology of muscle cramps. We investigated the feasibility, efficacy, and reproducibility of repetitive magnetic stimulation in producing experimental cramps. In 14 healthy subjects, the tibial nerve at the ankle was stimulated with a magnetic stimulator at rates beginning at 4 Hz to a maximum of 20 Hz. The frequency was gradually increased until a cramp was produced. Ten of 14 subjects demonstrated a muscle cramp. All subjects rated the discomfort of the procedure to be mild or moderate. Repeat testing yielded values that were highly reproducible. This technique holds promise for clinical studies and therapeutic trials.

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A NOVEL METHOD OF INDUCING MUSCLE CRAMPS USING REPETITIVE MAGNETIC STIMULATION

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Muscle cramps are a common complaint in a variety of neuromuscular diseases, but their pathogenesis is controversial and therapy is largely empirical.[5] The spontaneous and painful nature of cramps and the absence of a satisfactory method to produce them in humans has hampered efforts to understand their pathophysiology. Previously described physiological[7] and electrical[1] procedures to produce muscle cramps are highly painful, making it problematic to use these techniques to evaluate study populations. Magnetic stimulation of deeply located nerves or nerve roots has been shown to be less painful than comparable electrical stimulation.[2] Magnetic stimulation offers a similar advantage when prolonged, high-frequency stimulation is required. We used high-frequency magnetic stimulation to produce muscle cramps in healthy volunteers.

SUBJECTS AND METHODS

Fourteen healthy subjects without complaints of cramps were studied. The protocol was approved by our institutional review board and informed consent was obtained. Silver disk electrodes, 10 mm in diameter, arranged in the standard belly/tendon array, were used to record motor activity from the abductor hallucis brevis. The foot was placed in a relaxed neutral position, as were the toes. Magnetic stimulation was performed using a Magstim Rapid magnetic stimulator (Magstim Ltd., Whitland, Wales, UK) with two power boosters providing the current necessary to generate powerful magnetic fields. Maximum field strength was 2 T. We stimulated the posterior tibial nerve at the medial aspect of the ankle using a circular coil with a 90-mm diameter. The stimulator output (80% of maximal), the pulse duration (0.1 ms), and duration of each train (2 s) were held constant during the protocol. The optimal orientation and position of the coil was determined by delivering single pulses and observing for the most vigorous twitch of the great toe. That position was maintained for the remainder of the protocol. Stimulation was begun at a frequency of 4 Hz. Muscle activity was monitored on the oscilloscope and by loudspeaker using a Nicolet Viking IV device (Nicolet, Madison, WI). If a cramp did not occur following the train of impulses, we increased the frequency by 2 Hz and applied the higher-frequency train after waiting 1 min. This process was repeated with increasing stimulation frequency until a cramp occurred or a frequency of 20 Hz was applied without producing a

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cramp. A cramp was defined as involuntary motor unit activity that persisted for 2 s following the last stimulus in a train. If a sustained cramp occurred and became painful, the great toe was passively extended until the cramp subsided. Once a cramp was achieved, the stimulation frequency was reduced to a subthreshold value and the train delivered with muscle activity being observed as before. If no cramp occurred, the frequency was again increased until a cramp was reproduced or until 20-Hz stimulation failed to provoke a cramp. Most subjects returned on one or two occasions, weeks to months later, for the protocol to be repeated on the same foot.

RESULTS

Cramps induced by magnetic stimulation were simple to identify by sound and by observing for slight toe flexion. The surface electromyographic appearance was identical to that of spontaneous cramps (Fig. 1). Subjects could verify that a small involuntary muscle contraction was occurring and found that the contraction was initially associated with minimal discomfort and did not become painful until after 5–10 s. Cramp duration was frequently sustained and the cramp was terminated manually by extending the great toe.

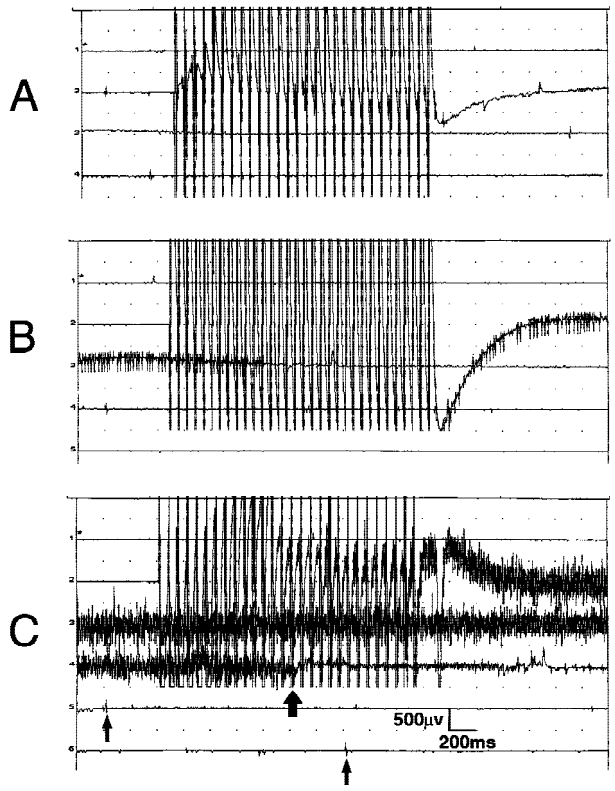

FIGURE 1. Surface EMG activity from abductor hallucis in a representative subject recorded continuously from top to bottom lines. Magnetic stimulation begins on the second line of each of the three tracings. The high-voltage signal at the onset of each stimulus is the stimulus artifact. (**A**) Stimulation at 8 Hz fails to generate a cramp. (**B**) Stimulation at 10 Hz results in a nonsustained contraction. (**C**) Stimulation at 12 Hz produces a sustained muscle cramp that is terminated by passive toe extension (thick arrow). Note the frequent fasciculations following the cramp (thin arrows).

Table 1. Cramp threshold frequencies in 14 normal subjects.

Subect	Age (yrs)	mCTF 1	mCTF 2	mCTF 3	eCTF
1	32	12	12	14	
2	33	11	12	12	13
3	47	14	14	18	
4	44	16	nc	16	15
5	33	18	18*		
6	44	13	13	14	13
7	31	14	12		
8	31	16	20	18	
9	35	14	14	12	
10	30	14	13*		
11	26	nc	nc		
12	39	nc			20
13	32	nc	nc	nc	
14	45	nc	nc	nc	
Mean	35.2	14.2	14.2	14.9	15.3

**These data were collected immediately after the initial measurement.*
mCTF = magnetic cramp threshold frequency.
eCTF = electrical cramp threshold frequency.
NC = no cramp.

A muscle cramp was produced in 10 of the 14 subjects with an average cramp threshold frequency of 14.2 Hz (Table 1). All individuals who experienced a sustained cramp did so between 12 and 20 Hz, but 4 subjects did not have a cramp within the outlined protocol. The technique yielded reproducible values over several trials for subjects with and without provoked cramps. The procedure was well tolerated as only 1 subject (data not included) elected not to complete the protocol. The technique was associated with mild-to-moderate discomfort, with the magnetic stimulation itself being the major source of discomfort rather than the induced cramp. Several subjects in whom cramps failed to develop underwent testing at higher frequencies (up to 30 Hz at 50% output) or longer durations (up to 3 s), but none experienced a cramp. Two subjects who demonstrated a cramp during the routine protocol also had a measurable cramp with reduced train duration (1.5 s) at the same frequency. Two of the investigators and two volunteers underwent electrical testing using Bertolasi's protocol[1] prior to the development of this magnetic method. For these individuals, the electrical cramp threshold frequency was similar to that produced by magnetic stimula-

tion. All found the electrical stimulation protocol to be extremely painful.

DISCUSSION

Experimental cramps in humans were first induced by high-frequency electrical stimulation of nerves by Lambert,[4] but the technique has not been widely used. A physiologic method[7] (sustained, forceful plantar flexion of the foot) proved to be unwieldy due to the difficulty in initiating a cramp and the intense pain that developed during the cramp. Bertolasi et al. studied cramps induced by electrical stimulation in healthy volunteers and developed a reproducible technique.[1] Unfortunately, the high-frequency electrical stimulation necessary to provoke a cramp is extremely painful, making this technique useful to study only the most motivated individuals.

Our magnetic technique offers a major advantage over the electrical protocol as described by Bertolasi et al. Magnetic stimulation of peripheral nerves is widely recognized to be less painful than comparable electrical stimulation.[2] This may be due to higher current density at the skin with electrical stimulation[3] or to preferential activation of motor fibers over sensory fibers with magnetic stimulation.[6] Magnetic stimulation has been widely used in stimulation of the cerebral cortex, cervical and lumbar nerve roots, and in deeply placed peripheral nerves, in part because it is better tolerated than electrical stimulation. Our technique also uses a 2-s duration of the stimulus train as opposed to the 4 s described in the electrical method, further reducing discomfort.

Magnetic stimulation has not replaced electrical stimulation in routine peripheral nerve conduction studies for a variety of reasons. These include difficulty in determining the exact point of depolarization, problems achieving supramaximal stimulation, and high-amplitude, long-duration stimulus artifact. The first concern is not relevant to the present application. Our inability to provoke cramps in certain individuals may be due to failure to achieve supramaximal stimulation rather than to inadequate stimulation frequency. This assumption was suggested by the data of Bertolasi et al.,[1] in which all individuals demonstrated a cramp within this frequency range at supramaximal stimulus. A related limitation with our technique is the inability to adequately determine and control for the number of nerve fibers being stimulated in a single subject and within groups of subjects. The stimulus artifact from the powerful magnetic field at a short distance from the recording electrodes often precludes accurate measurement of the evoked compound motor action potential. Variables particular to the Magstim instrument also influenced our protocol. The Magstim Rapid machine has limited output based on available current. In our experimental setting, the percentage output of the instrument was inversely proportional to the frequency within defined ranges. For instance, frequencies of >20 Hz require decreasing the output of the machine to <80% maximal as was used in our protocol. Similarly, increasing stimulus strength to >80% requires reducing the frequency. The addition of one or more power boosters to the experimental apparatus should minimize this problem. Despite these technical problems, we have demonstrated that the technique is quite reproducible for an individual subject, suggesting that similar numbers of motor axons are being stimulated each time. We believe the current protocol is valid to collect longitudinal data for an individual following pharmacologic or physiologic interventions.

Despite these defined limitations, we have shown that this technique is safe, simple, well-tolerated, and reliable. It shows promise as a technique for the study of human cramps and their response to physiologic and pharmacologic interventions.

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