Is postural tremor size controlled by interstitial potassium concentration in muscle?

M Lakie, N R Hayes, N Combes, N Langford

**Objective:** To determine whether factors associated with postural tremor operate by altering muscle interstitial K⁺.

**Methods:** An experimental approach was used to investigate the effects of procedures designed to increase or decrease interstitial K⁺. Postural physiological tremor was measured by conventional means. Brief periods of ischaemic muscle activity were used to increase muscle interstitial K⁺. Infusion of the β₂ agonist terbutaline was used to decrease plasma (and interstitial) K⁺. Blood samples were taken for the determination of plasma K⁺.

**Results:** Ischaemia rapidly reduced tremor size, but only when the muscle was active. The β₂ agonist produced a slow and progressive rise in tremor size that was almost exactly mirrored by a slow and progressive decrease in plasma K⁺.

**Conclusions:** Ischaemic reduction of postural tremor has been attributed to effects on muscle spindles or an unexplained effect on muscle. This study showed that ischaemia did not reduce tremor size unless there was accompanying muscular activity. An accumulation of K⁺ in the interstitium of the ischaemic active muscle may blunt the response of the muscle and reduce its fusion frequency, so that the force output becomes less pulsatile and tremor size decreases. When a β₂ agonist is infused, the rise in tremor mirrors the resultant decrease in plasma K⁺. Decreased plasma K⁺ reduces interstitial K⁺ concentration and may produce greater muscular force fluctuation (more tremor). Many other factors that affect postural tremor size may exert their effect by altering plasma K⁺ concentration, thereby changing the concentration of K⁺ in the interstitial fluid.

**Definition of terms**

Postural tremor is a fine shaking of the limbs. It is classically studied by recording the inadvertent motion of a limb (usually the hand) when the subject attempts to hold it in a stationary posture. When hand tremor is recorded by conventional accelerometry it can be seen to possess a more or less rhythmic component, usually with a peak frequency between 7 and 11 Hz. There are several views concerning the reason for this predominant frequency of oscillation, but as far as we know there is only one way of altering the frequency of tremor and that is by changing the mechanical properties of the limb. In this paper we do not concern ourselves with the frequency of the oscillation. However, as will be seen, there are many ways of altering the size of the shake. In this paper we do not address the question of overt pathological tremors, such as those caused by Parkinsonism or cerebellar disease. Our findings may, however, have implications for one form of essential tremor and its pharmacological treatment.

**Methods**

**Subjects**

We carried out β₂ agonist infusion experiments on 12 subjects (eight male, four female), mean (SD) age 21.4 (1.7) years. Ischaemia experiments were done on six subjects (five male, one female), mean age 37 (9.0) years. Permission was obtained from the local ethics committee, and written informed consent was obtained from the subjects. The experiments conformed with the declaration of Helsinki. All subjects declared themselves to be in good health and none had overt neurological symptoms or were taking β agonist or β blocker drugs.

**Correspondence to:**

Dr Martin D Lakie, Applied Physiology Research Group, School of Sport and Exercise Sciences, University of Birmingham, Birmingham B15 2TF; m.d.lakie@bham.ac.uk

Received 7 July 2003

Revised 28 November 2003

Accepted 29 November 2003

**See end of article for authors’ affiliations**
Apparatus
Hand tremor was recorded using a miniature accelerometer (5.0 g; Eurosensor, Towcester, Northants, UK) attached by a tight Velcro® strap above the nail bed of the middle finger of the right hand. Subjects were seated in a comfortable chair which had a shaped polyether foam cradle which supported the right forearm as far as the wrist joint. The unsupported pronated hand was extended and the subject was instructed to maintain it in an approximately horizontal position with the fingers slightly separated. The method and tremor measurements made with it have been described previously. The acceleration signal was dc amplified so that 1.0 g = 3.75 V, and an offset was subtracted to null the effects of gravity on the accelerometer. The resulting signal was further amplified with a gain of 2.5 to 25 (to accommodate the subjects’ tremor size) and filtered with a passband of 2–40 Hz. The signal was converted by an analogue to digital interface (CED 1401, 12 bit resolution, sampling rate 1000 Hz) and stored on a personal computer for subsequent analysis. In these experiments an electromyogram (EMG) was routinely recorded from the active extensor digitorum communis muscle, using surface electrodes with an inbuilt gain preamplifier and a passband of 20–350 Hz.

Procedures
In separate experiments, tremor was recorded after limb ischaemia and following infusion of the β2 agonist drug terbutaline (Bricanyl sulphate). For the drug trials, cannulae were inserted into the overnight fasted subject, who was allowed to relax for a period of at least 45 minutes, during which three control measurements were made. The drug was infused at a rate of 8 µg kg⁻¹ h⁻¹ through a cannula inserted into the left antecubital vein, over a period of 45 minutes. Venous blood samples were periodically taken from a second cannula implanted in the right antecubital vein. Blood samples were processed and stored at −80°C and were subsequently analysed for plasma K⁺ (indirect ion specific electrode). In these experiments there were infusions of different drugs, dosages, and placebos, with each subject being infused on five occasions. The subject was blind to the agent being infused. We only report here the effects of the terbutaline infusion. In the ischaemia experiments, the recording arrangements were the same. Ischaemia was produced by inflating a cuff placed around the upper right arm to a pressure of 200 mm Hg. The duration of the ischaemic period was two minutes.

Analysis
Various procedures can be used to quantify the size of a shake. In these experiments, fast Fourier transform (FFT) analysis was used to calculate the amplitude spectrum of the tremor. The duration of the epoch that was analysed was variable. It was normally ~30 seconds (ischaemia control measurements) or ~60 seconds (terbutaline) but was shorter (~15 seconds) when tremor size was likely to be changing relatively rapidly (that is, in the ischaemia and muscle activity experiments). The total amplitude in the spectrum between 4 and 14 Hz was computed and used as an index of tremor size. Most of the power in the tremor acceleration signal lies between 4 Hz and 14 Hz, and time domain measurements made using root mean square (RMS) values of the waveform, low pass filtered at 40 Hz, revealed a very similar pattern of change. Tremor size commonly reduces in the first few seconds after adopting a posture. To discount this effect we always allowed a period of at least five seconds between adoption of posture and the start of the analysis period. EMG was quantified by determining the area under the spectrum between dc and 45 Hz. Plasma concentration of K⁺ was expressed as mmol/litre.

RESULTS
Ischaemia
Figure 1 shows the change in the tremor (raw acceleration signal) in a typical subject. When a posture was maintained continuously during ischaemia, tremor size started to decline progressively after cuff inflation and was strikingly reduced after two minutes. However, when posture was not maintained continuously during ischaemia, there was only a small reduction in tremor size when posture was readopted by the arm after two minutes. When postural activity was restarted after ischaemia under resting conditions, the tremor size again showed a slow progressive decline as the posture was maintained. A substantial reduction in tremor was only apparent when muscular effort was combined with the ischaemia. In contrast to the mechanical record, the visual appearance of the raw EMG signal changed little, suggesting no change in the level of activation.

Figure 2 shows the power spectrum of the tremor signal recorded in the control period compared with the spectrum obtained two minutes after ischaemia, with and without concomitant postural activity. This figure also shows how the size of the tremor signal was quantified for use in the subsequent data analysis. This frequency domain analysis shows that all frequencies of tremor are substantially reduced...
ischaemia on its own causes only a small reduction. Ischaemia causes a considerable reduction of the tremor size, whereas ischaemia with or without postural effort reduced tremor size without a concomitant change in neural drive.

Figure 3 shows that for all our subjects the decline in tremor size over a two minute period was related not to ischaemia itself but to ischaemic muscle activity. The overall reduction in tremor size was large, consistent, and rapid when the ischaemic arm is active (mean (SD) reduction, 60 (10)% and much smaller and more variable (24 (18)%) when it was relaxed between measurements. The gross EMG necessary to generate the posture was not significantly different in the two conditions. The envelope of the EMG signal will contain components with similar frequencies to the tremor. The rectified and integrated (leaky integrator 20 ms time constant) EMG signal was subjected to FFT analysis. The resulting spectrum was divided into three bands, and the power in each was quantified (table 1). There was no significant change in the power in the band associated with tremor frequencies, or in the other two following ischaemia with or without postural effort. Peripheral ischaemia combined with postural effort reduced tremor size without a concomitant change in neural drive.

**DISCUSSION**

**Ischaemia**

Ischaemic reduction of tremor size was originally attributed to changes in muscle spindle sensitivity. However, the role of muscle spindles in the genesis of this form of physiological tremor is debatable. For example, an artificially produced “tremor” (a small movement of the hand produced by repetitive ∼10 Hz electrical stimulation at low intensity) was also rapidly attenuated by ischaemia. Thus the effect appeared less likely to be a reflex action and more likely to be a muscular phenomenon, but these investigators were unable to explain its basis, although they suggested it might be a form of “fatigue.” Our present observations provide an explanation. The reduction in tremor size is not produced by

![Figure 2](image.png)

**Figure 2** The amplitude spectrum of the tremor acceleration signal for a typical subject. Tremor was quantified by calculating the mean height of the frequency lines between 4 Hz and 1.4 Hz. In this example the mean size for the baseline condition was 5.85 cm s⁻². Maintained posture and ischaemia causes a considerable reduction of the tremor size, whereas ischaemia on its own causes only a small reduction.

![Figure 3](image.png)

**Figure 3** Ischaemia experiments. Tremor and rectified electromyogram (REMG) were measured in the windows shown in fig 1. The size of the tremor and REMG is shown. Ischaemia and a maintained posture produced a large, consistent, and significant reduction (mean (SD), 60 (10)% in tremor size (t = 13.43, p < 0.05). Ischaemia on its own (posture-relax-posture) produced only a much smaller, less consistent, and non-significant reduction (24 (18)%). The reduction produced by maintained posture was significantly greater than that produced by posture-relax-posture (t = −4.518, p < 0.05). The REMG was not changed by ischaemia and posture or by ischaemia alone. The data were compared by repeated measures tests (Bonferroni adjusted). Error bars = SEM.

<table>
<thead>
<tr>
<th>Band (Hz)</th>
<th>Maintained posture and ischaemia</th>
<th>Posture-relax-posture</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>4–13.9</td>
<td>102.85</td>
<td>11.64</td>
</tr>
<tr>
<td>14–24.9</td>
<td>97.05</td>
<td>13.12</td>
</tr>
<tr>
<td>25–40</td>
<td>98.95</td>
<td>9.82</td>
</tr>
</tbody>
</table>

The figures are the percentage values where the baseline electromyographic spectrum power has been set to 100% in each of the three bands. Data from the six subjects were combined. None of the bands is significantly different from the baseline in the maintained posture and ischaemia condition or in the posture-relax-posture condition (paired t tests).
the ischaemia itself but rather by muscular activity in the presence of ischaemia. This has the hallmark of an effect produced by depletion of a substrate or accumulation of a metabolite. We suggest this substance may be K⁺ which accumulates in the ECF of the active muscle. There is no change in the EMG size or frequency spectrum. This further suggests that the reduction mechanism is muscular rather than neural. There was some reduction in tremor in the limb under resting conditions, but in general it was difficult for subjects to maintain the arm in a completely relaxed state.

**Infusion of terbutaline**

Terbutaline is a β₂ adrenergic drug and is strongly tremorogenic. The classic experiments by Marsden and coworkers⁶,⁷ revealed a considerable increase in postural tremor and a slight decrease in the twitch time of slow muscles when adrenaline was infused. These workers concluded that it was the increase in the fusion frequency of the muscle that led to the great increase in tremor size observed. Thus a frequency of motor unit firing that would normally produce a fused force output would result in an output with much more ripple in the presence of an adrenergic drug. Adrenaline mediated changes in contractile characteristics had earlier been reported in animal studies.⁴ β₂ Agonists are thought to activate membrane located β₂ receptors (first described by Bowman and Nott'), altering the twitch properties of muscle as a result of cyclic 3′,5′AMP released into the muscle cytosol. However, as far as we are aware there is no direct evidence that this pathway is actually involved in the alteration of contractile characteristics. The increase in tremor is uncharacteristically slow. Abila et al commented that “processes taking up to one hour to develop would be unusual for mechanisms expected to be mediated via adenyl cyclase”.⁹

The tremorogenic effect in the present experiments was slow (fig 4). The tremor that can occur when these drugs are used to treat respiratory problems develops some time after the therapeutic effect. The rate constant of the tremorogenic effects of isoprenaline and the tremolytic effects of the selective β₂ blocker propanolol are very much slower than the heart rate responses.¹⁰

The delayed increase in tremor after a frightening experience which causes an immediate release of adrenaline will be familiar to most people. Also, tremor is the final symptom to appear following the adrenergic response to an insulin induced hypoglycaemic crisis.¹¹ We suggest (see below) that the contractile characteristics may be altered not by a specific direct adenyl cyclase mediated action of the drug on muscle β₂ receptors but by the more generalised reduction in K⁺ concentration that it produces by its well established effect on the muscle membrane located Na⁺/K⁺ pump (see for example, Bengtsson¹²). Two recent studies¹ ² and this one (fig 4) show that tremor size varies reciprocally and simultaneously with plasma K⁺. This relation might be even clearer were it not for the facts that tremor size is likely to be affected by the rate of change in K⁺ concentration as well as the absolute concentration, and that plasma K⁺ is not a precise indicator of muscle interstitial concentration, although it will reflect it.

**The proposed mechanism linking potassium concentration and tremor size**

As excitable cells are relatively permeable to K⁺ ions their membrane potential is close to the equilibrium potential for that ion. Consequently, alterations in extracellular K⁺ will have a profound effect on membrane potential and excitability. As far as the cells of the nervous system are concerned this effect is minimised by the presence of the blood–brain barrier, which is impermeable to K⁺, and by glial cells which “mop up” K⁺ and distribute it over a larger area (“spatial buffering”). Muscle cells have no such protective mechanism. Muscle fibres represent an enormous reserve of K⁺ which can
leak into the interstitium. Although the muscle cell membrane (sarcolemma) is relatively permeable to $K^+$, accumulation in the interstitium does not normally occur at rest because, first, the resting membrane potential is close to the equilibrium potential for potassium; and second, the $Na^+/K^+$ pump (which is active at $\sim 5\%$ of its maximum level in resting muscle) can prevent accumulation by returning $K^+$ into the cell. In active muscle the situation is very different. Because, first, the resting membrane potential is close to the equilibrium potential for potassium, accumulation can occur at rest because the pump is not active. The electromotive force for potassium is similarly high in resting and active muscle, $E_{K} = -80$ mV in resting muscle and $E_{K} = +80$ mV in active muscle. When the $Na^+/K^+$ pump is active, as in the T tubule, the electromotive force for potassium is $E_{K} = 0$ mV. The $Na^+/K^+$ pump mechanism is responsible for maintaining the transmembrane potential of $90$ mV in resting muscle, and it is this electromotive force that drives the $Na^+/K^+$ pump, as illustrated by the equation:

$$ E_{K} = -zF \frac{RT}{V} \cdot \ln \frac{[K]}{[K]^*} $$

where $z$ is the charge of the ion, $F$ is the Faraday constant, $R$ is the gas constant, $T$ is the temperature, $V$ is the volume, and $[K]$ is the concentration of potassium in the extracellular fluid and $[K]^*$ is the concentration of potassium in the intracellular fluid. The $Na^+/K^+$ pump mechanism also maintains the transmembrane potential of $90$ mV in active muscle, and it is this electromotive force that drives the $Na^+/K^+$ pump, as illustrated by the equation:

$$ E_{K} = -zF \frac{RT}{V} \cdot \ln \frac{[K]}{[K]^*} $$

where $z$ is the charge of the ion, $F$ is the Faraday constant, $R$ is the gas constant, $T$ is the temperature, $V$ is the volume, and $[K]$ is the concentration of potassium in the extracellular fluid and $[K]^*$ is the concentration of potassium in the intracellular fluid. The $Na^+/K^+$ pump mechanism also maintains the transmembrane potential of $90$ mV in active muscle, and it is this electromotive force that drives the $Na^+/K^+$ pump, as illustrated by the equation:

$$ E_{K} = -zF \frac{RT}{V} \cdot \ln \frac{[K]}{[K]^*} $$

where $z$ is the charge of the ion, $F$ is the Faraday constant, $R$ is the gas constant, $T$ is the temperature, $V$ is the volume, and $[K]$ is the concentration of potassium in the extracellular fluid and $[K]^*$ is the concentration of potassium in the intracellular fluid.
We suggest that under postural conditions the local concentration of K⁺ may reach a level where it changes function in that part of the muscle. Postural conditions involve repetitive activation of a small population of small motor units, lack of movement of the muscle, and reduced or absent perfusion. The combination of increased K⁺ efflux and diminished circulatory washout may produce a sufficiently high local interstitial K⁺ to impair the force generation of the muscle fibres that are active. This impairment would act to reduce tremor as a posture is maintained, so in that respect it is not an undesirable feature, but rather an asset. Thus for the small forces associated with tonic postural maintenance the response of the muscle fibres involved will become very much less brisk and the response of the muscles will be blunted.

A depression of plasma K⁺ will be associated with a generally decreased interstitial K⁺ concentration. As a result, muscle function will be less easy to compromise and tremor size will be high. Therefore any factor that reduces plasma K⁺ should be associated with large tremor size. Conversely, any factor that allows plasma K⁺ to rise should blunt the muscle response and decrease tremor size. A search of published reports shows that many, if not all, conditions associated with changed tremor size have been found to involve altered plasma potassium (table 2). This provides considerable circumstantial evidence in support of our theory.

Conclusions

Many factors that affect tremor size are also known to affect plasma K⁺ concentration, and by inference, interstitial K⁺ concentration. This correlation has been reported previously but a cause and effect mechanism has not been proposed. A simple mechanism may link the two factors. By partial blockade of the T tubule, an increase in interstitial K⁺ can cause muscle function to become changed in such a way that the fusion frequency is reduced. This will produce a much smoother, less pulsatile output of force from the muscle and less tremor in a postural role. This is the mechanism we propose for the reduction in tremor size that is produced by the combination of activity and ischaemia. Conversely, tremorgenic substances and conditions are associated with a reduced plasma and extracellular K⁺. In these conditions the muscular output will be brisker and force generation will be more pulsatile, predisposing to increased tremor. Our novel suggestion is that, in general, postural tremor size is inversely and causally related to plasma K⁺ concentration.

ACKNOWLEDGEMENTS

We would like to thank the subjects of these experiments.

REFERENCES


4 Lippold OCJ. Oscillation in the stretch reflex arc and the origin of the rhythmical 8–12 c/s component of physiological tremor. J Physiol (Lond) 1970;206:359–82.


