Limbo temperature and human tremors

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Abstract
The changes in postural tremor of the hand produced by moderate cooling of the muscles of one forearm have been investigated in 16 normal subjects and in 16 patients with essential tremor. In both groups, cooling produced a profound long lasting decrease in tremor level of the ipsilateral hand. In normal subjects, although cooling reduced the tremor size, the EMG of the active muscle clearly increased. Warming the limb in normal subjects produced an increase in tremor level and decrease in EMG. Cooling or warming the limb did not, however, significantly change the peak frequency which was quite stable for each subject. The results of cooling were compared with a brief period of ischaemia, which also reduces tremor size. Local cooling may be a useful manoeuvre for patients with essential tremor, and for others who wish to reduce their tremor temporarily in order to improve dexterity.

The size of physiological tremor in any person varies from time to time and there are large differences in the size of tremor in different people. There is no sharp division between the size of tremor in normal subjects and in patients with essential tremor. Tremor size is a continuum, with essential tremor patients at the upper end of the range. Essential tremor is generally thought to be a monosymptomatic disease—its cause and central origin are uncertain.

It has long been known that β-receptor agonists increase tremor levels and that the emotional states of anger or fear can have considerable influence, probably through their actions in liberating adrenaline. The increased tremor of thyrotoxicosis is also well known. Apart from these causes, little seems to be known about other factors influencing tremor size in normal people. Mosso in 1896 heated one arm of a subject (his brother), and found that an accentuated tremor of the hand was produced.1 Conversely, cooling the arm has been shown to reduce action tremor,2 postural tremor14 and essential tremor.3 The effect of changed temperature on the relationship between tremor size and EMG has not been previously investigated.

One suggested mechanism for tremor is that an oscillation in a peripheral feedback circuit is responsible. The rate of oscillation is dictated by the delay in the circuit. Changing the temperature of the muscular and neural components of the circuit will alter the delay and thus change the frequency. There is a discrepancy in published reports on the influence of temperature on tremor frequency. Lippold1 found a reduction of peak frequency with cooling but this was not confirmed by Elble and Randall,4 although they did not publish the relevant data.

We aimed to explore the size and time course of these temperature-related effects in detail, to examine the changes in the relationship between tremor size and EMG activity, and to investigate whether cooling had a potentially therapeutic value in patients with essential tremor.

Methods
The subject was seated with the elbows flexed at 90°; the pronated forearms were held in cradles by 'Velcro' straps. The hands were held horizontally, with the fingers slightly abducted. Strain gauge solid state accelerometers (ICS 3021) each weighing 2.8 g were attached over the nail beds of the middle fingers on each side. The recordings on each side were simultaneous and lasted 80 s. Following amplification and low-pass filtering (~3 dB at 30 Hz), the signals were sampled at 100 Hz and stored on disc. The 80 s record was divided into 30 overlapping (10 s) "slices" which were subjected to Fourier analysis. A spectrum was constructed from the average of these 30 slices and used for the subsequent analysis. The peak frequency, size of the peak, and mean height of nine frequency bands from 3-6 to 15-3 Hz were obtained. For most purposes, the tremor spectrum for each hand was therefore reduced to a histogram with nine bands. Additional details are contained in fig 1. The method and some preliminary results have been briefly described elsewhere.5-7

A) NORMAL SUBJECTS
Thirteen male and three female subjects were tested, their ages ranged from 20 to 67 and the mean was 28. No subject had evidence of neurological disease and none was taking β-blocking drugs or β agonists. A standard protocol was followed for each subject. A measurement was made every five minutes for 20 minutes; the first one was disregarded, and the subsequent four acted as controls.
Tremor (80 s)

The temperature of the laboratory was between 20°C and 23°C. The hand and arm were immersed for a period of 5 minutes in stirred water which was maintained at 15°C (cooling) or 44°C (heating).

At the end of this period the arm was dried and tremor measurements made every five minutes for at least 30 minutes. In five preliminary experiments a tank with a watertight seal at the wrist was used so that the forearm only was immersed. This apparatus has been illustrated in an earlier publication. On all other occasions both hand and forearm were immersed. The two procedures produced identical results. Skin temperature was monitored by small disc thermometers (Yellow Spring Instrument Co) taped to the surface of the forearm.

In 12 experiments EMG recordings were simultaneously made with suction cup electrodes (SLE Ltd) over the extensor digitorum communis (EDC) muscle of the arm that was cooled or warmed. Such electrodes have previously been used satisfactorily under water.

For these observations the experimental sessions, as described above, were preceded by immersion of the hand and forearm in water at skin temperature for ten minutes to permit skin resistance to stabilise. We also always ascertained that the changes as a result of cooling could be reversed by re-warming and vice versa. A ‘Neurolog’ isolated pre-amplifier with a pass band of 5-150 Hz, fed the signal to one channel of a ‘Graphtec’ high speed chart recorder and to an analogue to digital converter and computer.

The computer permitted the rectified EMG envelope to be integrated so that it could be quantified. After changing the temperature of the limb, the changes were monitored for 30 minutes and then the converse procedure carried out. Five subjects were tested on repeated occasions. On six occasions, on four subjects, oscillographic recordings from a small number of individual motor units were made by implantation of fine insulated silver wires in the EDC muscle.

In 15 experiments on six subjects the effect of a period of ischaemia was investigated. The same tremor recording apparatus was employed, but instead of immersion in a water bath, one forearm was made ischaemic by a pneumatic cuff inflated to 175 mm Hg around the arm for a period of 8 minutes. Bilateral measurements of tremor were made during this period and after the circulation was restored.

The tremor waveform was composed of a range of frequencies. However, in all subjects that were tested, a prominent rhythmic com-
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Figure 2. The effect of cooling on the spectral components of hand tremor in 16 normal subjects. (A) control data at room temperature; the left and right sides are similar. In both sides there is a peak of activity between 7-5 and 9-9 Hz. In (B) the right forearm has been cooled for 5 minutes. These measurements were made 1 minute after cooling. There is a considerable decrease in the size of all the bands on the cooled side. The non-cooled side also decreases slightly. Means and SEM are shown. *p < 0.05 **p < 0.01

Figure 3. The time course in the reduction of hand tremor size following cooling. Values are the mean and SEM of the peak tremor size. The pre-cooling values (average of 4 measurements) are similar for left and right hands. After cooling the right forearm for 5 minutes, its tremor size is reduced and the reduction persists for 36 minutes. There is a slight tendency for the uncooled left hand tremor to decrease as time elapses. Skin temperature of the cooled forearm is shown. Temperature is reduced 13°C by the period of cooling, and after 36 minutes it is still depressed by 6°C. Full recovery of temperature has evidently not occurred.

Ponent was evident. Frequency analysis of control data obtained at room temperature revealed a clear peak frequency between 7-3 and 9-8 Hz in all the normal subjects. As has been previously shown, the frequency peak was quite characteristic for each individual and did not change much on repeated investigation. The peak frequencies of the left and right hands were also well matched. The size of the tremor, determined either by the acceleration at the peak frequency or the sum of the nine bands, was more variable, with a 15-fold variation between individuals. The day to day variation for the individuals who were tested on several occasions was less, typically a factor of two. These results are in good agreement with other observations.

Cooling

Immediately after cooling the right forearm for 5 minutes the tremor in that arm was diminished (fig 2). The decrease was very striking, with the level in several of the frequency bands falling to a third or less of the control values. The change was highly significant. There was a tendency for the tremor in the uncooled side to fall a little, although the decrease did not reach statistical significance. The peak frequency for each of the 16 subjects was determined. Before cooling the mean (SEM) for the right hand was 8.5 (0.8) Hz and after cooling 8.8 (1.3) Hz. There was no tendency for the peak frequency to decrease with cooling and the difference was not significant. The increase in SD after cooling reflects the increased difficulty of determining the precise peak in the spectrum, as the sharpness of tuning was reduced. The reduction in sharpness is also evident in the flattened shape of the average spectrum in fig. 2.

The effects of cooling were not transient, on the contrary the tremor was reduced for a long time after the period of cooling. Figure 3 shows the size of the tremor at the frequency peak for all the subjects up to 36 minutes after cooling. There is negligible recovery within this period. Some subjects were followed for up to 150 minutes, and even after this time the tremor size of the cooled limb was less than the other. Skin temperature did not reflect the change in tremor in a very obvious way. Temperature fell rapidly upon immersion of the arm and recovered progressively when the limb was removed from the water, although at the end of 36 minutes the temperature of the cooled limb was still usually 5–6°C colder than the control. The period of rising skin temperature was not accompanied by a progressive increase in tremor size.
There was a tendency for the size of the tremor to decrease in the non-cooled arm. Although the experiments were carried out in an air temperature of 20°C–23°C it was significant that most of the subjects complained of a general feeling of coldness after the procedure.

Tremor size in the cooled limb could be quite rapidly restored in two ways. First, the limb could be actively rewarmed by immersion in warm water. Second, quite lengthy periods of 'limbering up' restored tremor size. Repeated rhythmic flexion/extension movements appeared to be more effective than isometric efforts. However, the increases in tremor size produced by 'limbering up' were generally quite short-lived; the tremor size would quickly return to a sub-normal level.

**Electrical activity**

Figure 4A shows the instantaneous output of the accelerometer and EMG activity recorded by surface electrodes over the EDC muscle. The duration of recording is 80 s. The reduction in tremor size produced by cooling is accompanied by a clear increase in size of the envelope of the interference pattern of the surface EMG. This increase could be due to an increase in the firing of the units that were already active, to the recruitment of new units, or both. The changes in the surface EMG were confirmed by computerised integration of the rectified records. The mean integrated rectified EMG (10 s epoch, n = 25) was 0.88 (0.12) (V s) for the cooled arm,

![Figure 4A](image)

**Figure 4** A) (left) raw hand tremor, and (right) simultaneous EMG activity in the right EDC muscle. All traces are 80 s duration. The middle pair of traces was obtained at room temperature. The right forearm was warmed by immersion in water at 44°C for 10 minutes (bottom pair of records) and then cooled by immersion in water at 14°C for 10 minutes (top pair of records). The records were taken 3 minutes after warming and cooling. Cooling causes a large decrease in tremor size and a large increase in EMG. Warming increases tremor size with a slight reduction in EMG. The relationship between tremor size and electrical activity of the responsible muscle is clearly paradoxical; B) Action potentials recorded by intramuscular fine wires in the right EDC muscle. The middle record was obtained at room temperature (2 records are superimposed), the top record after cooling and the bottom after heating (details as in A). Cooling increases the duration of the action potential, whereas warming decreases duration and increases size. Calibration 20 ms/div, 1 mV/div.

![Figure 5](image)

**Figure 5** The effect of warming on the spectral components of hand tremor (mean and SEM). (A) control data at room temperature. As in fig 2, left and right hands are similar at room temperature. (B) shows the effect of warming the right forearm for 5 minutes. The measurements were made 1 minute after warming ended. There is a large increase in tremor in the warmed limb. Tremor in the non-warmed limb is not changed in size. Other details are as in fig 2.
for the control arm and 0.15 (0.08) for the warmed arm.

Inspection of single units recorded intramuscularly showed that the increase in activity was caused, in the main, by recruitment of new units. The duration of individual action potentials was increased by cooling, but their size was not changed (fig 4B). There did not appear to be a large increase in the firing frequency of individual motor units. This was in practice difficult to assess as wires which sampled typically only one or two units before cooling would sample more after the muscle was cooled.

**Warming**

Immediately after heating the forearm, the size of tremor was increased (fig 5). There was more individual variation with warming than with cooling, and one subject failed to show an increase. The increase with the others was up to three-fold. Warming caused an increase in tremor size in each band; the height of the rhythmic peak was increased. The mean (SD) increase for the 7.5–8.7 Hz band was 1.6. The peak frequencies before warming were 8.8 (0.8) Hz, and after heating 8.8 (0.7). There was no significant change in frequency. The increase in tremor did not last as long as the decrease produced by cooling (fig 6). After warming, the skin temperature returned quite rapidly and progressively towards its original value. Both in terms of skin temperature and tremor it was usually difficult to detect any difference between the control and heated limb after 20 minutes. In three of the subjects, warming caused the tremor to become visible; it might well have been thought to be 'symptomatic'.

The increased tremor was accompanied by a slight decrease in surface EMG (fig 4A). Individual motor units slightly increased their amplitude after heating (fig 4B) but it was common for a unit that was tonically active as the posture was maintained under normal conditions, to cease firing when the limb was warmed.

**Ischaemia**

The effects of 8 minutes of occlusion are shown in fig 7. Frequency analysis revealed that the amplitude of all the bands is reduced by ischaemia in a way that is very similar to the effects of cooling. Tremor size was reduced, and the peak became less prominent in the ischaemic arm. Tremor of the other arm was not changed. There was an increase in EMG of the EDC muscle of the ischaemic arm. Both effects were rapid, becoming noticeable after about 30 s with most of the change occurring in the first three minutes. When the cuff was deflated, there was always a rapid increase in tremor, sometimes with evidence of a rebound above the initial level for the first few seconds.

However, when a 5-minute period of moderate cooling was compared with a 5-minute period of complete ischaemia it was found that the reduction caused by cooling was consistently greater than that caused by ischaemia. This implies that the effects of cooling cannot be mediated purely by a reduction in blood flow.

B) PATIENTS WITH ESSENTIAL TREMOR

Five minutes of cooling greatly reduced the tremor size in all the patients with essential tremor. The decrease was usually quite obvious, both to the observer and the patient. In five of the patients a previously conspicuous
tremor became unnoticeable. The size of all the frequency bands was reduced on the cooled side (fig 8).

One patient with severe essential tremor was subsequently successfully treated by stereotactic surgery. The considerable reduction in tremor of the right hand produced by a thalamic lesion in the left ventralis intermedius nucleus was no greater than that produced by a longer period of cooling (10 minutes at 10°C). The ability of all the patients to write and draw was tested. The improvement was remarkable (fig 9). One patient was able to write legibly, albeit slowly, for the first time in 15 years.

Discussion

TEMPERATURE AND TREMOR FREQUENCY

In earlier work resting physiological tremor was recorded by an instrument in which the weight of the hand was supported by a light bar attached to an angular accelerometer. At rest a fine tremor with a peak of about 8 Hz was observed; this became much more conspicuous when the fingers were extended. Thus by changing from a resting tremor to a postural tremor the size of the oscillation increased, but the frequency did not change. With small mechanical inputs it was observed that the hand responded to a brief impulse with a decrementing transient oscillation at the frequency of the tremor. The passive properties of the wrist and associated tissues evidently form an underdamped resonant system. The relatively high frequency of this resonance is probably due to muscular thixotropy which is a reflection of the well documented short range stiffness of muscle.

Physiological tremor of the hand is probably due in large measure to the mechanical vibrations from the unfused contractions of motor units exciting this resonant system. If, alternatively, tremor occurs as a result of an instability in the peripheral feedback loops that are utilised in motor control, then the frequency of the tremor should be determined by the delay inherent in the loop. One effect of cooling would be to increase the delay, as muscle contraction and peripheral nerve conduction are slowed. In the present experiments no change in frequency with cooling (or heating) were observed. With cooling the size of each frequency component became less, but there was no shift in the pre-
dominant frequency. This was true of the normal subjects and the patients with essential tremor. Accordingly, it seems unlikely that a peripheral feedback loop is directly involved in the generation of physiological or essential tremor.

TEMPERATURE AND TREMOR SIZE
There is evidently a positive correlation between the temperature of a limb and the size of tremor. Thus immersion of the arm in warm water increases the size of the tremor and cold water decreases it. The effect is most likely to be caused by a change in muscle temperature. Other workers have studied the relationship of muscle temperature to the temperature of water surrounding the limb. Barcroft and Edholm,13 studied the temperature in the deep part of the brachioradialis muscle. Prolonged periods at 15°C were required to change significantly the temperature of this part of the muscle. Clarke, Helon and Lind,14 and Petrofsky and Lind,15 showed that there is an approximately linear relationship between muscle temperature in the brachioradialis muscle and the depth at which it is measured. The muscle that we studied (EDC) is smaller than the brachioradialis and is superficial. There will be a temperature gradient within the muscle. In the present experiments intramuscular measurements of temperature were not made, but any single value would not have been representative of the muscle as a whole. For the first dorsal interosseous muscle, skin temperature correlates quite well with muscle temperature at temperatures below 25°C.16 In the present experiments skin temperature is assumed to covary with the temperature of the underlying muscle (figs 3 and 6). In our experiments all subjects reported that the brief period of cooling was sufficient to produce reduced force output and also a difficulty in producing rapidly alternating movements. We have previously described this as a cold-induced adiadochokinesia.17 This is direct evidence that the mechanical output of the muscles has been changed.

Changing the temperature of mammalian muscle has profound effects on the dynamics of force generation. This is sometimes overlooked as much basic muscle physiology has been performed on amphibian muscle at low temperatures. Amphibian and fish muscles are relatively insensitive to the effects of temperature change. In contrast, mammalian muscle is greatly affected by change in temperature. Thus for a human muscle twitch, lowering the temperature will increase the latent period, the time to peak force, and most markedly increase the relaxation time.18-21 It has been shown that cooling a fast muscle (EDL rat)22 potentiates the twitch tension. However, in human studies, cooling produces a decrease in twitch tension in muscles that are physiologically slow (soleus)23 and fast (1st dorsal interosseous).14 The Q10 of these temperature-related effects ranges from 1.2–1.7. As cooling will reduce the force output of the muscle, more motor units must be recruited to maintain the chosen position. This is consistent with the changes in the EMG reported here. The increase in number of active motor units, and the decreased size and velocity of the twitch, will reduce the pulsatile input to the resonant system. Fusion of normally sub-tetanic impulses will be more complete. With heating the opposite changes occur; tremor increases and EMG diminishes. Raising the temperature of the muscles will increase tremor by increasing the size and velocity of the muscle twitch. In this sense, heating may increase tremor in the same way as a rise in circulating adrenaline, by producing a decreased degree of tetanic fusion.23 Thus with temperature changes, tremor and EMG vary paradoxically. Ranatunga24 has suggested that the recruitment order of motor units may be different after cooling. This suggestion is difficult to reconcile with the present observations as it implies the earlier activation of larger, faster motor units after cooling. On this basis, cooling would increase tremor, not reduce it.

TREMOR AND ISCHAEMIA
Ischaemia causes a substantial decrease in tremor.3 The effects of ischaemia on muscle are complex and depend on the type of fibre of which it is composed. Post mortem studies45 have shown that the human EDC muscle is composed of about 47% type I (slow) fibres. Small motor units, consisting of type I fibres, which are active with the low level contractions that are required to maintain a posture, have a very low anaerobic capacity. It would be expected that a relatively brief period of ischaemia would reduce their ability to contribute to the force that is required and increase the demand on Type II fibres which can function under ischaemic conditions.

Thus under ischaemic conditions, the profile of active motor units is shifted towards ones with faster contraction times.25 Type II fibres produce much more force than Type I fibres and they contract and relax with a greater velocity. The expectation would therefore be that a period of ischaemia would increase the amount of tremor and EMG activity. In practice EMG activity increases, but tremor reduces, progressively.

The similarity of events following occlusion or cooling might suggest a common cause; perhaps the reduction in tremor after application of the cuff is caused by the consequential reduction of temperature in the muscles. Alternatively, there may be mechanical changes in the inactive parts of the muscles. The paradoxical increase in EMG and decrease in tremor is presently under investigation. Adrenaline decreases skin blood flow and increases that to the muscles. The metabolism of muscle is also increased due to an increase in 3', 5' AMP and increased glycogen breakdown. These changes will increase muscle temperature and thus modify muscle properties. This factor may be responsible for the increase of tremor following the injection of adrenaline, or its liberation in
states of anxiety, or with other strong emotions.

Marsden and Meadows\(^2\) showed that infusion of adrenaline caused changes in the mechanical properties of the soleus muscle but not the adductor pollicis muscle. They also showed that during infusion the temperature of the first dorsal interosseous muscle did not increase. It may be that the temperature changes in the muscle that they studied do not adequately reflect changes in other muscles. Perhaps the thermoregemonic effect of adrenaline is related to its metabolic effects on muscle. The thermoregemonic effect of caffeine and thyroid hormones may be exerted in a similar manner. Eccentric exercise often increases tremor a day or two afterwards; at that time there may be some muscle fibre degradation and, as there is inflammation, muscle temperature will be expected to rise. The changes with eccentric exercise are summarised by Jones and Round.\(^26\)

COOLING AS A TREMOLYTIC

The treatment of patients with essential tremor is not simple. Three drugs are commonly used. Ethanol has obvious risks, \(\beta\) blockers, such as propapalol, are contraindicated in some elderly patients and primidone often has unacceptable side effects. Stereotactic surgery may be required in some cases. The present results suggest an alternative method of temporary tremor reduction that is safe, reliable and without side-effects. Several patients have used this technique successfully for signing documents, shaving etc. For others the method may also have its uses. It has been suggested that tremor adversely affects performance in microsurgery.\(^27\) Surgeons and biologists undertaking dissections under the microscope could perhaps use limb cooling as a way of improving performance. Muscle cooling is presently under investigation as a method of improving shooting accuracy.

Conclusion

Temperature appears to be a major determinant of tremor size in humans. Accordingly, when it is desired to make comparative measurements of tremor size it is very important that limb temperature is controlled.

The prolonged reduction of tremor following cooling seems to be due to the absence of a specific mechanism regulating limb temperature. There is homeostatic control of central body temperature, but nothing, apart from a slow drift as environmental heat seeps in and the thermal ‘core’ expands to bring the temperature of a cooled inactive limb back to any particular temperature level. Conversely, after warming, the limb will cool rather rapidly and this probably explains the rapid decline in enhanced tremor size. At the levels of cooling we employed there was no sensory impairment and little discomfort when the temperature was being lowered. The sluggish recovery of temperature causes tremor to be reduced for a prolonged period.

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