Effects of arterial perfusion pressure on force production in working human hand muscles

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1. The effects of hydrostatic changes in perfusion pressure on performance of working fatigue-resistant muscle fibres in the hand were studied in six normal subjects.

2. Supramaximal stimuli were delivered in trains of 200 ms duration, at 1 train s^{-1}, to the ulnar nerve proximal to the wrist to produce isometric contractions of adductor pollicis. The force of contraction was measured and, after a level contraction force was achieved, the arm was passively raised or lowered.

3. Lifting the hand 45 cm above the heart produced a decline in force output from the muscle within several seconds which, after 4 min, fell by 22% below the steady-state level. Lowering the hand 45 cm below heart level produced an 8% increase in force output. Greater changes in force output occur at higher workloads.

4. It is concluded that in human subjects, muscle performance is sensitive to changes in perfusion pressure that occur across the physiological range. At moderate work levels, force output of the working muscles in the hand can vary by up to 30% over the physiological range of blood pressure. This dependence of muscular force on blood perfusion is of potential importance to motor control during normal activities.

Perfusion pressure in a muscle depends not only on central arterial pressure but also on how far the muscle is above or below the heart. This is particularly relevant in the limbs (Nielsen, 1983): as the arm is raised, perfusion pressure in the hand falls. In isolated cat soleus, a reduction in mean blood pressure within the physiological range of 75–125 mmHg, has been shown to cause a reduction in blood flow and a decrease in force production (Hobbs & McCloskey, 1987). When muscle perfusion is restricted in human subjects by application of positive pressures of up to 50 mmHg to the lower limbs, there is a reduction in muscle performance (Eiken, 1987; Sundberg & Kaisjer, 1992).

In human subjects making regular intermittent contractions of the calf muscles at constant submaximal force, integrated electromyographic activity (EMG) increased when the legs were elevated (Hobbs & McCloskey, 1987). This is consistent with recruitment of additional motor units to compensate for a perfusion-dependent loss of contractile performance. However, it was not clear in this uncontrolled study whether the EMG change truly represented increased recruitment or firing frequency of motor units, or whether a perfusion-induced change in EMG properties might have accounted for the effect. Nevertheless, these results suggest the possibility that in human subjects, physiological changes in perfusion pressure may affect force output. The extent to which auto-regulatory mechanisms may serve to maintain blood flow to muscle when perfusion pressure changes, and so minimize any consequent changes in muscle force, remains unclear.

In the present study, perfusion pressure in the hand was altered by raising and lowering the arm, and the effects on force production in an intrinsic hand muscle were determined. The intrinsic hand muscle, adductor pollicis, was stimulated through the ulnar nerve using intermittent trains of stimuli at 25 Hz in a stimulus protocol chosen specifically to preserve contractile responses in 'fatigue-resistant' muscle fibres. Thus, the effects we describe are of arterial pressure on working, but not fatigued, muscle.

METHODS

Subjects were six normal adults aged between 34 and 53 years. The Institute's Human Ethics Committee approved the experiments and subjects gave their informed consent.

Experimental set-up

Subjects sat in a chair with the right arm extended and resting on a stable support arranged so that it could be rotated about the axis of the shoulder. The arm was secured to the support with double-sided adhesive tape and this permitted the hand to be raised or lowered without voluntary activation of the arm or hand muscles (Fig. 1*A*). Movement of the right arm was recorded using a goniometer, and the height of the hand relative to the manubrium was recorded.

An isometric strain gauge was used to measure the force of adduction of the thumb in a plane perpendicular to the hand (Fig. 1*B*). A tightly fitting metal ring was secured around the interphalangeal joint of the thumb and attached to the strain gauge. The thumb was abducted to approximately 45 deg from the palm and internally rotated. In this position, the flexors of the thumb

cannot assist adduction (Merton, 1954); consequently, adductor pollicis provides almost all of the adduction force.

Intermittent contractions of adductor pollicis were produced by bipolar stimulation of the ulnar nerve using an isolated stimulator (model SD9; Grass Instruments, Qunicy, MA, USA). No other muscles operating on the thumb are supplied by the ulnar nerve. Surface electrodes, separated by 1–2 cm, were placed longitudinally over the ulnar nerve approximately 2 cm proximal to the wrist, with the cathode distal. Electromyographic activity from adductor pollicis was recorded using surface electrodes attached over the belly of the muscle on the palm and over the first metacarpophalangeal joint. A circumferential ground reference was placed around the wrist between the stimulating and recording electrodes.

Systolic and diastolic arterial blood pressures were measured at approximately 45 s intervals throughout the experiments using a servo pulse plethysmograph (Ohmega Finapress) on the middle finger of the left hand (the non-stimulated hand) which the subject rested comfortably on the knee. The height of the finger relative to the manubrium was measured to allow estimation of central arterial pressure: the hydrostatic pressure due to a column of blood between the manubrium and the hand was subtracted from the measured pressure. It was not possible to record from the stimulated hand because the contraction interfered with blood pressure measurements.

Experimental protocol

Trains of five supramaximal pulses of 1 ms duration at 25 Hz (40 ms intervals) were delivered to the ulnar nerve to produce brief unfused tetanic contractions in adductor pollicis. Pulses of supramaximal intensity (70–120 V) were established by identifying the stimulus that produced a maximal compound muscle action potential, and then increasing the stimulus by a further 20%. The tetanic contractions were repeated at 1 s intervals for the duration of the trial, giving a duty cycle for the contractions of 1/5. This frequency and repetition rate of stimulus trains was selected to be well within the range known to preserve indefinitely contractile responses in fatigue-resistant muscle fibres: groups I and II A (Burke, Levine, Tsairis & Zajac, 1973). A single stimulus was

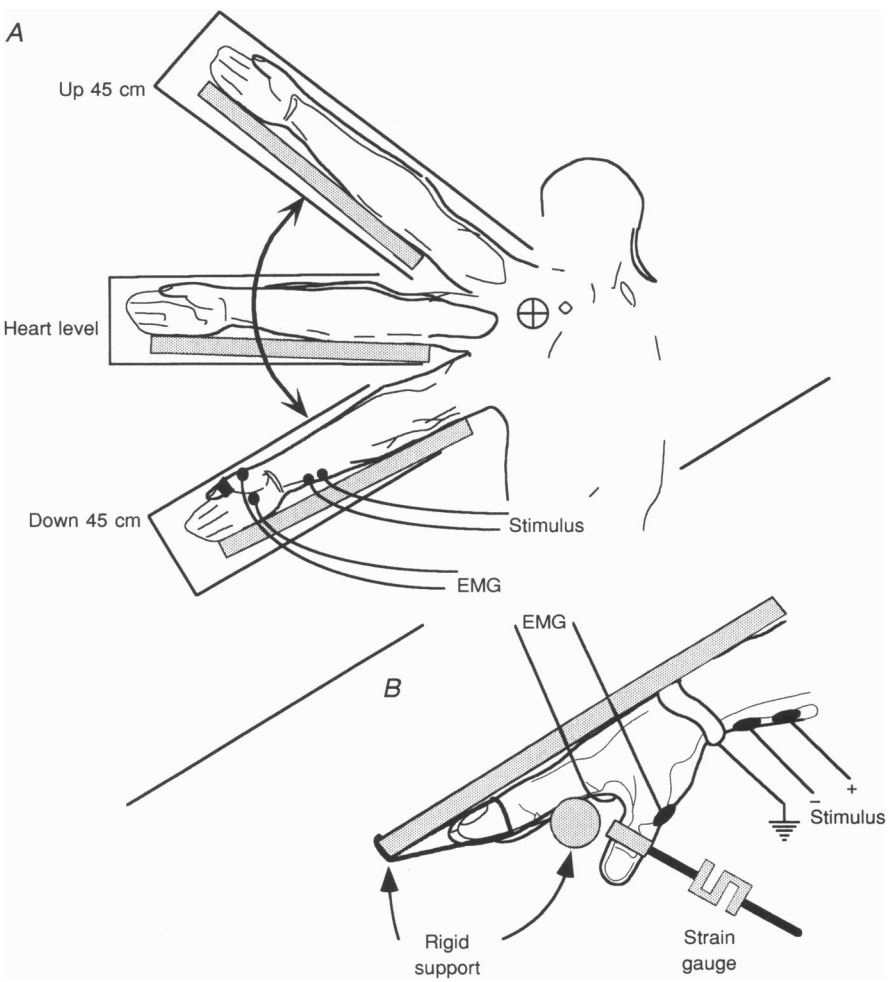

Figure 1. Experimental set-up

A, the right arm was fixed to a support and moved passively about the shoulder to raise the hand to 45 cm above the control position (Heart level) or to lower the hand by 45 cm. *B*, the hand was firmly fixed to the support with the fingers held extended and a rod across the palm securing the metacarpals. A force transducer (Strain gauge) carried on the support measured thumb adduction force. Ulnar nerve stimulation (Stimulus) and recording of adductor pollicis EMG were carried out through surface electrodes.

delivered to produce a twitch following every ten tetanic contractions. EMG was used as a measure of muscle activation. Throughout the trials, subjects were provided with audio feedback of their EMG so that any voluntary contraction, identifiable as noise between the stimulus trains, could be suppressed.

In each trial, the stimulated hand was held at heart level for 6 min after the stimulated contractions began. The hand was then quickly raised 45 cm, or lowered 45 cm, by the experimenter over a period of 2–3 s. Subjects were instructed to relax the arm muscles during these movements. The arm was held in this test position for 4 min while the stimulated contractions continued, then the arm was returned to the starting heart-level position for a further 4 min. Thus, each trial lasted 14 min. After a rest of approximately 10 min, a further trial was performed in which the subject's arm was moved in the other direction: the up–down order was randomized between subjects. To estimate the relative force of these contractions, subjects performed a brief (< 2 s) maximal voluntary contraction before the first trial and after the final trial.

Measurement and analysis

All data were recorded on computer through an A/D interface (CED 1401; Cambridge Electronic Designs, Cambridge, UK). Muscle force was sampled at 100 Hz. Small shifts occurred in the baseline force between contractions because the weight of the thumb on the force transducer altered with arm position. Consequently, the net muscle force developed during each contraction was calculated as the difference between the force before the stimuli began and the maximal force developed during the contraction. EMG was filtered (100 Hz–10 kHz) and sampled at 5 kHz. The potentials evoked by the stimuli were rectified and integrated by computer. Data obtained from the six subjects were averaged by first normalizing each subject's data to their force of contraction at the time the arm was raised or lowered.

In one subject, arterial systolic and diastolic pressure was measured in the middle finger of the right hand while the arm was passively raised and lowered in the absence of any stimulation to determine the effects of raising and lowering the arm on perfusion pressure in the hand. Simultaneously, venous pressure was recorded from the cephalic vein at the wrist using a short Teflon catheter connected to a pressure transducer (P23XL; Statham). The net perfusion pressure across the hand was calculated as the difference between the arterial and venous blood pressures.

To determine the effects of different muscle work loads, single twitches, and tetani of three, five, seven or nine stimuli at 25 Hz delivered every second were tested in three subjects. The arm was lifted, as described above, in five successive trials that were separated by 15 min rest periods.

Values are given as means ± S.E.M. and N indicates the number of subjects.

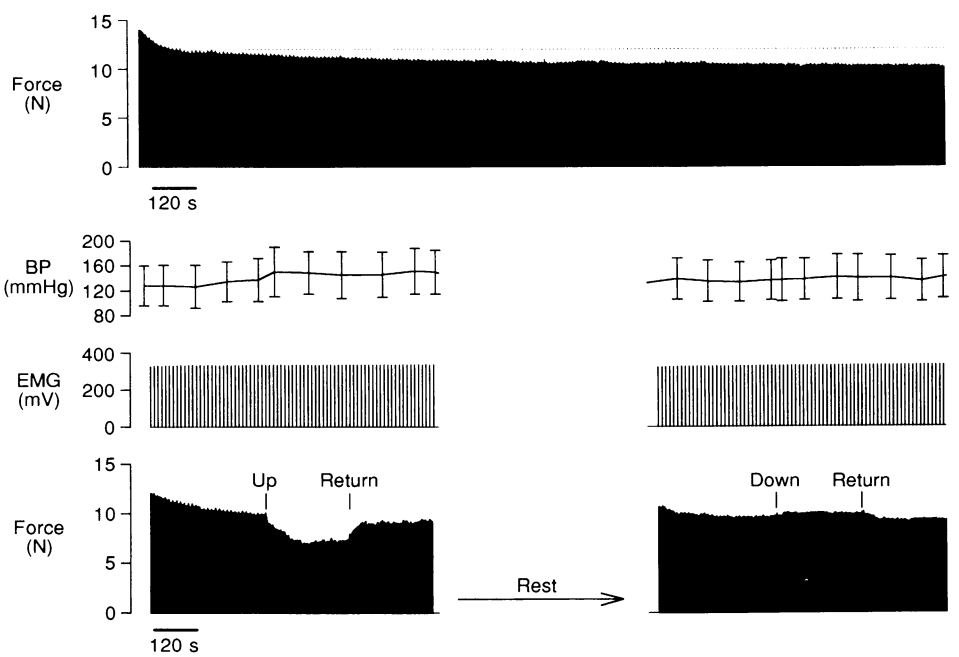

Figure 2. Thumb adduction forces in single subjects with and without changes in arm position

The top trace shows thumb adduction force produced by trains of five supramaximal 25 Hz stimuli to the ulnar nerve delivered each second in one subject for 40 min. The force of each tetanus is represented by a vertical line. There is an initial rapid decline in force followed by a much slower decline. The dotted line represents a constant force. The lower panels show data from a different subject stimulated in the same way but over two 14 min intervals during which the hand was raised 45 cm above heart level (left panel) or lowered 45 cm (right panel). The bottom traces represent thumb adduction force. Vertical lines (Up, Return, Down, Return) mark when the arm was moved. Force drops when the hand is raised (Up) and increases when the hand is lowered (Down). The middle traces show for every tenth contraction the sum of the areas of the EMG potentials evoked by the five stimuli. These were unchanged by arm movements. Systolic (upper limits), diastolic (lower limits) and mean central arterial (main curve) blood pressures (BP) are shown in the upper traces. The small rise in blood pressure when the arm was raised is typical.

RESULTS

The trains of five supramaximal stimuli used in this study produced tetani with approximately 40% of the force of subjects' maximal voluntary contractions. The top trace of Fig. 2 shows muscle force in a typical subject when the muscle was stimulated for approximately 40 min while it was kept at heart level. With repeated contractions of adductor pollicis at 1 Hz, there was a relatively rapid decline of the developed muscle force during the first 2 min (mean decrease, 11·6%), followed by a prolonged period of slower decline (>1 h). Time constants for these decays (τ_1 and τ_2) were estimated by fitting the double-exponential function:

$$\text{Force} = C_1\exp(-t/\tau_1) - C_2\exp(-t/\tau_2),$$

where t is time and C_1 and C_2 are constants: to the first 6 min of data from each subject. This gave τ_1 and τ_2 values of 53 ± 6 s and $4{\cdot}0 \pm 1{\cdot}5$ h ($N = 6$), respectively. Thus, after 14 min of stimulation without intervention the predicted decrease in force was 19·3%; a mean drop of 19·9% was observed following intervention and recovery during the trials (Fig. 4).

In all subjects, force production from adductor pollicis decreased when the arm was raised and increased when the arm was lowered. Raising the arm had a greater effect than lowering the arm; representative responses for one subject are shown in the bottom traces of Fig. 2. On raising the arm, the decrease in muscle force became apparent during the first ten contractions. To exclude the possibility that the stimulus characteristics might have changed during the movement and thereby contributed to the changes in muscle force, single twitches were interpolated within the trials every 10 s. The EMG of the single twitches and the tetanic contractions remained steady throughout the trials, and did not show a change in muscle activation that could explain the changes in muscle force (Figs 2 and 3). The interpolated single twitches showed changes in tension equivalent to those of the tetani, yet the compound muscle action potentials were unaffected by raising and lowering the arm (Fig. 3).

For the six subjects, the mean normalized changes in muscle tension associated with raising and lowering the arm are shown in Fig. 4. Raising the arm by 45 cm produced a $10{\cdot}0 \pm 3{\cdot}7$% decrease in tension at 20 s, and a $21{\cdot}8 \pm 6{\cdot}3$% decrease at 240 s relative to the values predicted by extrapolation of initial data with the exponential decay functions (compare filled circles with dashed line). Lowering the hand by 45 cm resulted in a $8{\cdot}3 \pm 1{\cdot}9$% increase in tension at 240 s (compare open circles with dashed line). On returning the hand to the resting position, there was a relatively rapid return of force towards the slowly declining baseline (Fig. 4). The force developed by the single interpolated twitches paralleled the changes in force produced by the tetani. Central arterial pressure was

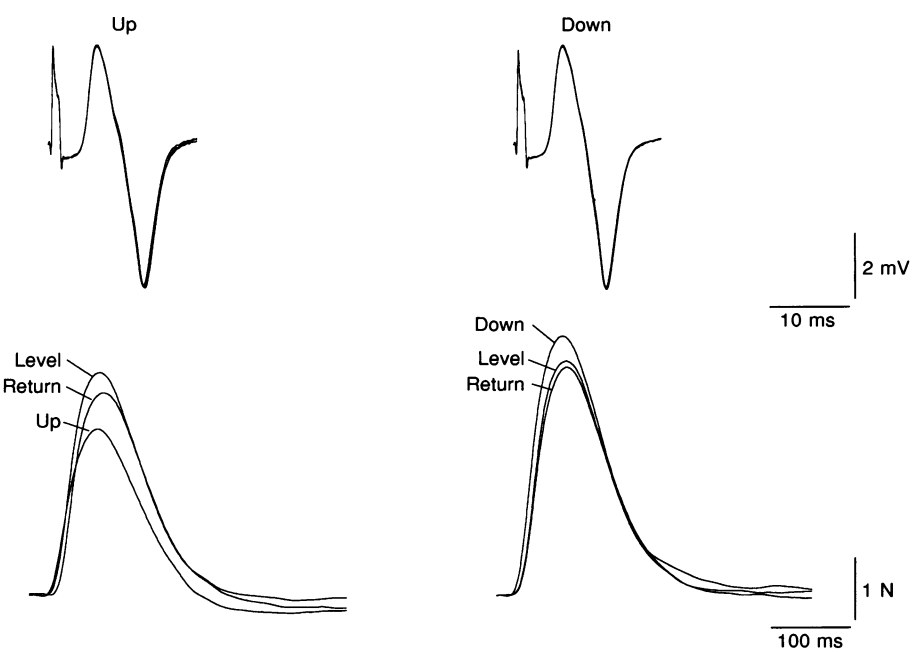

Figure 3. EMG potentials and twitches evoked by single supramaximal stimuli in one subject

During experiments in which trains of five stimuli were usually delivered each second, single stimuli were sometimes given. The upper panels show compound muscle action potentials evoked in adductor pollicis. For each panel, three traces are overlaid. These are potentials recorded immediately before the arm was moved, immediately before it was returned to heart level and just before the end of the 14 min trial. The corresponding changes in thumb adduction force are shown beneath. On the left, from the control size when the arm is at heart level (Level), twitch force decreases when the arm is raised (Up) and increases again when the arm is returned (Return). However, the muscle action potential is unchanged. Similarly on the right, twitch force increases when the arm is lowered (Down) but the EMG potential is unaltered.

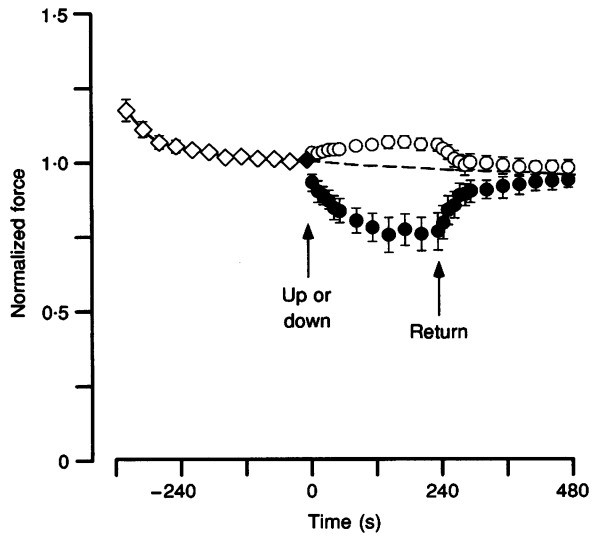

Figure 4. Changes in thumb adduction force with changes in arm position in six subjects

Forces of tetani (normalized units) produced by trains of five stimuli each second with the arm level (◇), raised (●) or lowered (○) and then returned to level are shown. The arrows indicate when the arm was moved. For each subject, force throughout the trial was normalized to give a value of 1·0 at a time just before the arm was moved (time 0). Means ± S.E.M. of the normalized forces are shown.

relatively constant throughout the trials, although there was a small but significant increase in mean arterial pressure when the arm was raised (10 ± 3 mmHg, $P < 0{\cdot}05$, Student's paired t test). Arterial perfusion pressure of adductor pollicis could be expected to decrease by 35 mmHg (hydrostatic pressure of a 45 cm column of blood) when the hand was raised, and increase by 35 mmHg when the hand was lowered (see Discussion).

To determine the effects of raising the arm on muscle performance at different muscle work loads, in three subjects the arm was raised in five successive trials with contractions of different strength and duration (single twitches, and tetani of three, five, seven or nine stimuli at 25 Hz delivered every second). The dependence of force output on perfusion pressure increased with increasing workloads (Fig. 5). Raising the arm had a negligible effect (< 5%) on force production for single-twitch contractions, but at higher workloads, the relative decline in muscle force increased as the number of stimuli increased (17, 22, 32 and 36% for three, five, seven and nine stimuli, respectively, at 240 s).

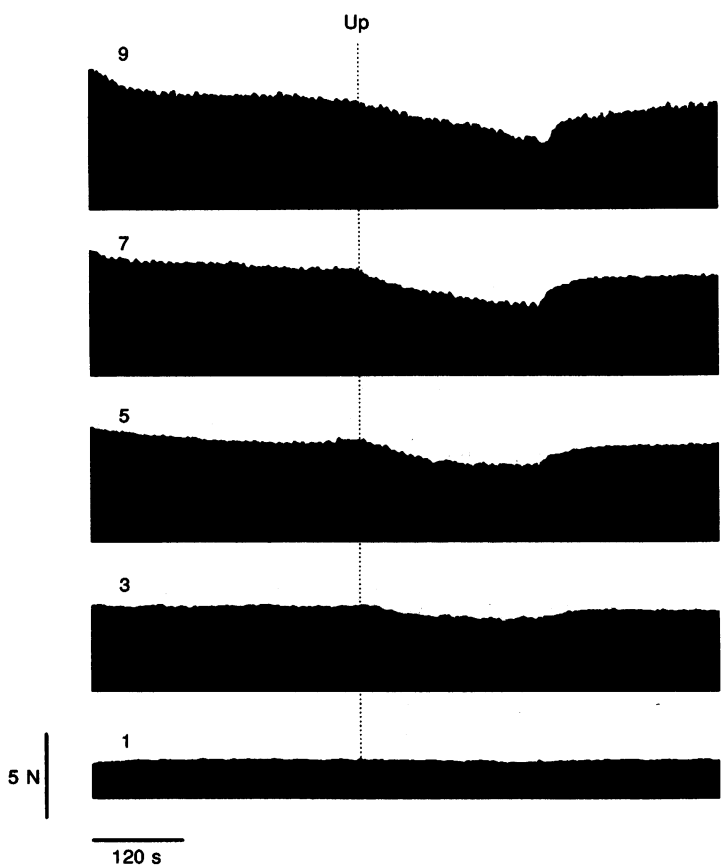

Figure 5. Elevating the hand decreases thumb adduction force more when work rates are higher

Thumb adduction forces produced by one stimulus or trains of three, five, seven or nine stimuli (25 Hz) delivered each second when the arm was held level, raised and then returned to level are shown for one subject. Each trace is labelled with the number of stimuli used. The vertical dotted line indicates when the arm was raised.

DISCUSSION

This study shows that performance of working fatigue-resistant muscle fibres in human subjects is highly sensitive to the physiological changes in arterial pressure that occur during normal movement, particularly when the muscle is raised above heart level. Previous studies on isolated muscles in anaesthetized cats have demonstrated a dependence of muscle performance on blood flow with near-maximal workloads (Hirvonen & Sonnenschein, 1962; Hobbs & McCloskey, 1987). The present study shows that human muscles are sensitive to perfusion pressure at smaller workloads and that this sensitivity increases as the workload increases. An important finding in the present study is that no systematic changes in EMG occurred with changes in perfusion pressure. This finding resolves a difficulty of the earlier study by Hobbs & McCloskey (1978; see Introduction).

As the central arterial pressure remained relatively constant throughout the trials, perfusion pressure in the hand should have changed by the hydrostatic pressure of a column of blood between the heart and the hand. This was verified by measuring arterial pressure in the hand while the arm was raised and lowered in the absence of stimulation. We presume that the modest increase in central arterial pressure accompanying arm elevation during stimulated contractions was attributable to local metabolic factors activating sensory nerve endings and the well-known muscle reflex (McCloskey & Mitchell, 1972). The changes in systolic, diastolic and mean arterial pressures are well predicted by the calculated hydrostatic pressure of a column of blood (specific gravity = 1·05) between the heart and the hand (Fig. 6, compare the slope of the mean arterial pressure, open squares, with dashed line).

Muscle force fell by 22% when the hand was raised but increased by only 8% when the hand was lowered, yet in each situation arterial pressure changed by 35 mmHg (33%). A likely explanation for this non-linearity in the response is that venous pressure was approximately zero when the hand was at heart level, rose by an amount predicted by the hydrostatic pressure when the hand was lowered, but did not fall when it was raised, presumably because the veins collapse in this situation. Figure 6 shows measurements made during this study of both arterial and venous pressures confirming these changes in pressure. The net perfusion pressure (arterial minus venous pressures) across the muscle vasculature fell by 32% when the arm was raised, but only rose by only 8% when the arm was lowered (Fig. 6).

Type I and type II A mammalian muscle fibres that contain high levels of oxidative enzymes fatigue slowly, and type II B fibres that contain low levels of oxidative enzymes fatigue rapidly (Burke *et al.* 1973; Burke, Levine, Salcman & Tsairis, 1974; Essen, Jansson, Henriksson, Taylor & Saltin, 1975). In the cat soleus muscle that contains type I fibres exclusively, the force developed by repeated tetanic contractions depended on muscle perfusion pressure, but in caudofemoralis muscle, comprising predominantly (91%) type II B fibres, perfusion pressure did not affect muscle force (Hobbs & McCloskey, 1987). Human muscles contain a mixture of all three fibre types, although adductor pollicis has a relatively high proportion (80·4 ± 9·1%) of type I, fatigue-resistant fibres (Johnson, Polgar, Weightman & Appleton, 1973). The results reported here show two phases of decline in muscle force with repeated contractions. There is an early period of rapid decline followed by a prolonged period of slower decline in muscle force. This is consistent with there being two populations of muscle fibres (fast and slow fatiguing). Burke *et al.* (1973) reported that type II B fibres in the cat fatigued rapidly to produce less than 10% of their initial force after 1 min of repeated contractions, and this is consistent with the estimated time constant of 53 s for the rapid decline in muscle force in the present study. Thus, at the time the arm was raised or lowered after the initial 6 min of contractions with the arm level (i.e. approximately 6 time constants), it is likely that fast-

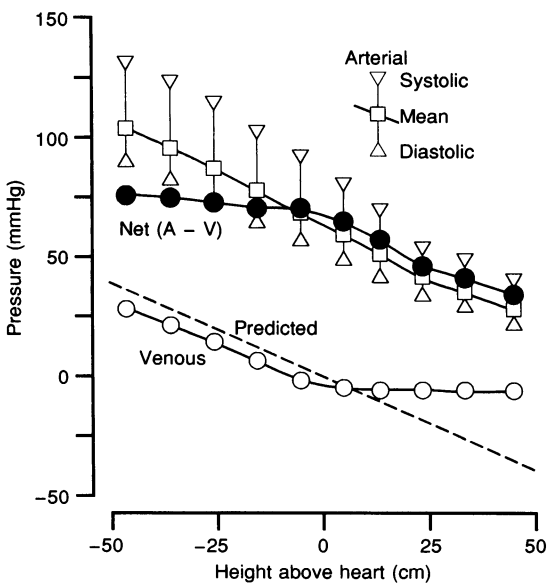

Figure 6. Blood pressure in the hand when located at different heights relative to heart level

Measured arterial (□) and venous (○) pressures with the hand at positions between 45 cm below and 45 cm above heart level are shown for one subject. The net pressure (●) across the tissues is the difference between mean arterial pressure (A) and venous pressure (V) at each height. The dashed line indicates the change in blood pressure that can be predicted from purely hydrostatic effects.

fatiguing muscle fibres made only a small contribution to muscle force. This implies that the effects seen in this study are due to changes in the performance of fatigue-resistant muscle fibres (types I and II A). However, although muscle fibres are classified according to their oxidative capacity, there is nothing in this study that indicates whether oxygen delivery to the contracting muscle or other flow-related factors such as removal of metabolic byproducts (Barclay, 1986) are responsible for the changes in muscle performance.

During strong muscle contractions, intramuscular blood flow can be halted. In the present study, where the contractions were approximately 40% of maximum voluntary contraction, it is likely that muscle perfusion is mainly or wholly confined to the relaxation phase between successive trains of stimuli. This is the circumstance in which Burke *et al.* (1973) defined the behaviour of working fatigue-resistant muscles, and this aspect of our study introduced no novel element. What is novel here is that raising or lowering perfusion pressure strongly influences the contractile performance of the working muscle. If this effect is caused by changes in muscle blood flow, as we presume it is, then any autoregulation of flow was insufficient to offset it. Hobbs & McCloskey (1987) found no autoregulation of flow in working, fatigue-resistant muscle in cats.

Because of the behaviour that we have described, it follows that human subjects must increase muscle activation in order to maintain a constant force output when perfusion pressure to contracting muscles falls across the physiological range. In normal conditions, there is an orderly recruitment of type I muscle fibres first followed by type II A and type II B (Milner-Brown, Stein & Yemm, 1973). As Type I fibres appear to be most sensitive to changes in perfusion pressure, the effects of elevating the arm are likely to affect muscle force for most normal contractions. The rapid fall off in muscle force on elevating the hand suggests that such regulation should operate at relatively short duration. To increase muscle activation, centrally generated motor commands would have to increase. Such command signals have sensory consequences (e.g. Gandevia & McCloskey, 1977) and are implicated also in the cardiovascular and respiratory responses to muscular exercise (Hobbs & McCloskey, 1987).

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