Effects of muscle perfusion pressure on fatigue and systemic arterial pressure in human subjects

Wright, Julie R., D. I. McCloskey, and Richard C. Fitzpatrick. Effects of muscle perfusion pressure on fatigue and systemic arterial pressure in human subjects. J. Appl. Physiol. 86(3): 845–851, 1999.—The effects of changes in arterial perfusion across the physiological range on the fatigue of a working human hand muscle were studied in seven normal subjects. With the hand above heart level, subjects made repeated isometric contractions of the adductor pollicis muscle at 50% of maximal voluntary contraction in a 6-s on, 4-s off cycle. To assess fatigue, a maximal isometric twitch was elicited in each “off” period by electrical stimulation of the ulnar nerve. The experiment was repeated at least 2 days later with the hand at heart level. Five subjects showed faster fatigue with the arm elevated, and two subjects showed little difference in fatigue for the two conditions. Central blood pressure rose in proportion to fatigue for the subjects overall and returned quickly to its initial level afterwards. We conclude that human muscle fatigue can be increased by physiological reductions in perfusion pressure. Central blood pressure increases as the muscle fatigues, a response that may partially offset declining muscle performance.

Muscle fatigue; blood pressure

Variations in the perfusion pressure to a muscle can affect the force output of the muscle. Hobbs and McCloskey (8) showed that, as muscle perfusion pressure to the cat soleus is varied across the physiological range (75–125 mmHg) by partially occluding aortic blood flow, the tetanic force output changes. Regulation of muscle vasodilatation to compensate for the drop in perfusion pressure was not complete because blood flow through the muscle varied with the perfusion pressure. The cat soleus muscle is largely composed of type I and IIA slow-fatiguing oxidative fibers (1). Thus the likely explanation for the changes in force output is that the oxidative metabolism of the muscle requires a continuous supply of O2 and nutrients, and this is compromised by decreased blood flow. In contrast, in the same experiment, changes in muscle perfusion pressure did not affect the force output of the caudofemoralis muscle, which is largely (91%) composed of type IIB fast-fatiguing glycolytic fibers (1). Presumably, this occurred because glycolytic metabolism does not require the same continuous supply of nutrients.

In human subjects, the tetanic force output of adductor pollicis, a muscle composed largely of slow-fatiguing oxidative fibers (10), also shows a dependence on muscle perfusion pressure across the physiological range (5). Muscle force output falls as the hand is elevated above heart level to lower perfusion pressure by 35 mmHg but returns quickly to normal when the hand is lowered again. This occurs at very low work levels, i.e., as few as three action potentials per second. However, with steady perfusion, mammalian slow-fatiguing oxidative type I fibers will produce a constant force output for at least 1 h when stimulated at work levels of 13 action potentials per second (3). Thus these observations in the cat and in humans show that the force output of working fatigue-resistant muscle is sensitive to changes in perfusion pressure at low workloads that produce only minimal fatigue at normal perfusion pressure.

At high workloads, muscle fatigue will occur. It could be predicted, although it has never been shown, that the changing performance of fatigue-resistant fibers under different physiological perfusion pressures will alter fatigue rates. Therefore, the present study was undertaken to investigate the effects of changes in perfusion pressure within the physiological range on the rate of fatigue of human adductor pollicis, a muscle composed, on average, of 80% fatigue-resistant type I fibers (10). Subjects performed repeated voluntary contractions at a workload known to induce muscle fatigue (2). Type I fatigue-resistant muscle fibers tend to be recruited first as voluntary muscle activation increases (15), and so these fibers are engaged in fatiguing contractions of the kind studied here. To assess muscle fatigue, a supramaximal twitch was elicited by stimulating the ulnar nerve during each off period. The rate and extent of muscle fatigue were compared with the hand at heart level and above heart level.

Methods

The subjects were seven normal adults (2 women and 5 men) between 27 and 55 yr of age. The Institutional Human Ethics Committee approved the experiments, and subjects gave their informed consent. Muscle fatigue was measured in two situations: the first with the hand elevated above heart level and the second with the hand at heart level. These trials were performed on different days.

Experimental Setup

Subjects sat with their right arm extended and resting on a stable support that could rotate around the axis of the shoulder (Fig. 1). A cord around the palm held the hand against the support, and strings held the fingers extended (Fig. 1). In this way, the experimenter could raise and lower the hand relative to the heart without voluntary muscle activity by the subject. The hand was elevated 39 cm above the level of the jugular notch for the first trial and was level with the jugular notch for the second trial. To measure adduction force of the thumb, a metal ring was secured around the interphalangeal joint of the thumb and attached to an isometric strain gauge oriented in the plane perpendicular to the hand (Fig. 1). The thumb was abducted ~45° from the palm and internally rotated, and this corresponds to ~60% of the range of movement for thumb abduction. In this position, the flexors of the thumb cannot assist adduction (14); consequently, the adductor pollicis provides almost all of
the adduction force. Single twitches of the adductor pollicis were elicited by monopolar supramaximal stimulation via surface electrodes over the ulnar nerve proximal to the wrist (SD9 stimulator, Grass Instruments, Quincy, MA). The ulnar nerve supplies no other muscles operating on the thumb. An adductor pollicis electromyogram (EMG) was recorded from surface electrodes over the belly of the muscle and adjacent to the first metacarpophalangeal joint, with a reference electrode on the head of the radius.

Arterial blood pressure was not measured in the test hand because the contractions interfered with measurements. Instead, blood pressure in the middle finger of the left hand, which rested on the knee, was measured with a servo-pulse plethysmograph (Ohmeda Finapres 2300). Central arterial pressure was calculated from the blood pressure measured in the left hand by subtracting the hydrostatic pressure of a column of blood between the jugular notch and the hand.

Experimental Protocol

For each subject, the stimulus level that produced a maximal compound action potential in the adductor pollicis (60–100 V at 2 ms) was determined. This voltage level was then increased by 20% to provide a safety margin that ensured maximal twitches. With the hand at heart level, the forces produced by three brief maximal voluntary contractions (MVC) of the adductor pollicis 1 min apart were recorded, and the largest force was selected as the subject’s maximum. After this, the subject remained relaxed for 5 min before the fatiguing contractions commenced. A protocol of repeated 6-s contractions at 50% of the subject’s maximum with 4-s rest periods was chosen because it produces substantial fatigue after 4–5 min (2). The subject viewed an oscilloscope screen that had one horizontal trace indicating the adduction force from the strain gauge and another trace indicating the target force for contractions (i.e., 50% of the subject’s maximal force). In response to an auditory “on” signal, the subject raised the force trace to the target trace and held it there for 6 s until an off signal sounded. To assist the subject in avoiding any muscle activation during the 4-s rest periods, auditory feedback of EMG was provided. At approximately the midpoint of the rest period when no EMG noise was heard, the experimenter delivered a single-twitch stimulus. This protocol is illustrated in Fig. 2, which shows results for one subject. The trial continued for ~10 min but ceased earlier if the subject could no longer attain the target force. In this situation, the subject’s MVC was now ≤50% of the initial MVC. During a 5-min recovery period in which no contractions were made, single-twitch stimuli continued every 10 s.

After a break of at least 48 h, a second trial was performed with the hand at heart level. The subject’s hand was carefully placed in the same position as that used during the first trial.

The maximal contraction force and initial twitch force were measured to ensure that they approximated (± 12%) those of the initial experiment. The experiments were undertaken in this order to prevent any possible residual fatigue from a prior trial contributing to an accelerated fatigue profile when the hand was elevated, even though this was thought to be unlikely. The duration of the trial with the hand at heart level was at least as long as that with the elevated hand so that responses could be compared on a time basis. Subjects usually did not reach the point at which they could no longer sustain the 50% MVC for 6 s in this condition.

Measurement and Analysis

Data were sampled and recorded on computer (National Instruments AT-MIO-16XE-50 DAQ card and Labview 4.0 software). Muscle force and arterial blood pressure were sampled at 10 and 50 Hz, respectively. EMG was band-pass filtered (160 Hz–1 kHz). For each test twitch, EMG and force were sampled at 5 kHz for 400 ms. The net twitch force was calculated as the difference between the prestimulus force and the maximal twitch force.
RESULTS

Before the hand-elevated trial, subjects exerted maximal voluntary forces in the range of 96–192 N. Before the hand-level trial, performed at least 2 days later, the maximal force varied from the first value by $10\%$ for all subjects, and the twitch force varied by $12\%$. In both trials, forces elicited by single twitches before the fatiguing contractions started were between 7 and 15\% of the maximal voluntary force.

Fatigue

For all subjects, the first few contractions after starting each fatiguing trial resulted in an increase, or potentiation, of the twitch force (Figs. 2 and 3). After peaking, twitch force fell steadily for the remainder of the trial. The rate of decline of twitch force was most often greater when the hand was elevated, with differences seen after two contraction cycles. Two minutes after the peak, average twitch force had fallen by $19 \pm 3$ (SE) \% with the hand at heart level and $36 \pm 4$\% with the hand elevated ($P < 0.01$, paired t-test). Four minutes after the peak, force had fallen by $29 \pm 4$ and $50 \pm 5\%$, respectively (Fig. 4). Two subjects (subjects JW and AC) showed little or no difference in twitch force decline between conditions, but in others (subjects RF and MM), force declined more than twice as fast.
with the hand elevated (Fig. 3). The amplitudes of the compound action potentials remained relatively constant throughout each trial and are shown for one subject in Fig. 2.

Recovery

Recovery was monitored for 5 min after cessation of contractions. In most trials, there was some increase in twitch force, but the amount of increase varied greatly (Figs. 3 and 4). After 5 min of recovery, twitch force reached its initial maximum level in only one trial in one subject.

For two subjects in whom recovery was monitored for a much longer period with the hand elevated, neither the longer 20-min period of passive recovery nor lowering the hand induced a faster increase in twitch force. However, with the hand still elevated, a brief voluntary contraction produced a large and immediate increase in twitch force followed by a steady decay until twitch force settled at a level slightly higher than that following the initial contractions.

Blood Pressure

Overall, the trend was for central arterial blood pressure to rise continuously throughout the period of contractions despite ongoing fluctuations (Figs. 3 and 4). The mean increase in blood pressure was greater with the hand elevated than with the hand at heart level (24 vs. 14 mmHg, \( P < 0.05 \), paired t-test comparing the linear regression slopes of the rise in blood pressure with time for individual subjects). However, there was considerable variation in this response, with subject JW showing a greater rise with the hand at heart level and subject RG showing little difference between the two conditions (Fig. 3). After cessation of contractions, arterial blood pressure returned very quickly to its initial level in every trial and remained at or below this level for the remainder of the recording period.

Throughout the period of fatiguing contractions, the percent increase in mean blood pressure showed a linear relationship with the percent decrease in twitch force (Fig. 5). Although twitch force fell more and blood pressure rose more with the hand elevated, the linear relationship between twitch force and blood pressure was very similar regardless of whether the hand was elevated or at heart level (means for all the subjects are shown in the bottom right plot of Fig. 5). In the data from individual subjects, there was considerable scatter, but the similarity of regression slopes is still evident in all but one subject. In the data from subject RG, there was a significant difference in regression slopes demonstrable at the 95% confidence level (t-test with Bonferroni post hoc correction, \( P < 0.001 \)).

DISCUSSION

Fatigue

Constant muscle activation at a low work output produces decreased force output when muscle perfusion pressure is reduced in the physiological range (5).
This effect occurs over a short time period and is quickly reversible when perfusion pressure is restored. In the present study examining muscle fatigue at higher workloads, subjects made repeated voluntary contractions at a force output sufficient to fatigue the muscle. With this protocol, the reduction of muscle perfusion pressure produced by elevating the hand increased the rate of muscle fatigue. Because muscle force output falls as perfusion pressure decreases, subjects must recruit additional muscle fibers to maintain the constant force. This additional recruitment of motor units increases the scope for gradual fatigue because more muscle fibers are engaged and so become subject to fatigue (8). The rate of fatigue is likely to decline as the supply of recruitable fibers becomes depleted as the voluntary force approaches MVC. Increased muscle metabolism can be presumed to have caused local vasodilatation in the muscle and, working with the elevated hand, increased central blood pressure, with both factors increasing the transfer of nutrients and metabolites to and from the blood. However, these factors were not sufficient to offset the faster muscle fatigue when perfusion pressure had fallen by only 29 mmHg. It should be noted that the failure of flow regulation demonstrated here applies for this high-workload situation in which there is vasodilatation in the muscle such that the limit for recruitment of vascular conductance may be approached. The same failure cannot be assumed for the resting muscle or low-workload situation when perfusion pressure is changed, because there is likely to be adequate scope for vasodilatation.

Central fatigue and motivational factors cannot explain the fatigue seen here because electrical nerve stimulation was used to elicit twitches. However, it should be noted that the subjects’ efforts in making maximal contractions might have varied. Any subject who underperformed during the maximal contraction would then work at less than the true 50% level, whereas any who might have overperformed by virtue of having engaged additional muscles in the maximal contraction would work at more than the true 50% level. For all subjects, however, the fatiguing workload was constant in the control and arm-elevated conditions. Failure of neuromuscular transmission was not responsible for the decline in output force because the compound action potentials showed only minor changes throughout the fatiguing contractions. In a study using MVC to assess fatigue of the adductor pollicis, Bigland-Ritchie et al. (2) also found no evidence for failure of neuromuscular transmission. By exclusion, the decline in twitch force must originate from changes in either excitation-contraction coupling or the contractile process.

Muscle blood flow was not measured directly here. However, local arterial pressure in an elevated limb is less than central arterial pressure by an amount equal to the hydrostatic column of blood above the heart (15); in the present study, this represents a reduction of 29 mmHg. Lowering mean perfusion pressure to an isolated working muscle by this amount reduces muscle blood flow in the cat (8). This could lead to reduced O2 delivery to the muscle and to the accumulation of metabolites. Furthermore, it has been established in human subjects that, when the perfusion pressure to the forearm is reduced by elevation above heart level, the rate of increase in muscle blood flow at the onset of low-workload, intermittent forearm exercise is reduced, and this leads to a reduced rate of increase of muscle O2 uptake (9). O2 supply is the product of perfusion and arterial O2 concentration, and the protocol of contracting a small hand muscle, as in the present study, will not affect arterial O2 or metabolite concentrations. Therefore, it is likely that the rate of fatigue in the elevated hand was greater because the lower perfusion pressure reduced blood flow.

In most trials, twitch force showed some recovery after the cessation of contractions, but in only one trial did it recover to its prefatigue level within 5 min. Potentiation decreases as the time from the last contraction increases (6). During the voluntary contraction series tested here, twitches were elicited at a fixed time after each preceding voluntary contraction to exclude this time-dependent potentiation factor. However, during the recovery period the time from the last contraction increases. Consequently, twitch-force potentiation decreases after the contractions cease. This was observed in the present study when a brief voluntary contraction during the recovery period produced a large and immediate increase in twitch force. Therefore, twitch force does not provide a reliable estimate of muscle fatigue during the recovery period.

Factors Affecting Muscle Force

Factors other than muscle perfusion pressure that might influence force output and thereby affect these results are now considered. Because this study used the same technique to test and retest individual subjects for two conditions of perfusion pressure, most of these factors are controlled within each subject.

Residual fatigue and training. The hand-elevated trial was always first, and consequently performance during the hand-level trial might have been affected by the earlier trial. The effects of fatigue from a protocol of sustained contractions can be observed for up to 24 h (4). For this reason, a period of at least 2 days was allowed for recovery. However, if some residual fatigue had worsened performance in the second trial, the effect of perfusion pressure on fatigue would be underestimated, a finding directly opposite to what we have reported. Conversely, if the first period of work had a training effect, this would have improved performance in the second trial, and the effect of perfusion pressure on fatigue would be overestimated. This would also apply to any fatiguing work that subjects undertook outside the experiment.

Muscle length. Muscle length affects muscle force. In this experimental setup, the thumb was abducted by ~45°, which is ~60% of the total range of movement. It is, therefore, likely that the muscle was performing toward the middle of its length-tension curve. To minimize length-tension effects, for each subject, contrac-
Fatigue of human hand muscles respectively). A greater decline in force when measured with low-voluntary contractions shows a disproportionately fatiguing protocol also fell by approximately one-half (Fig. 3, fatiguing protocol). For the subjects in these trials whose fall in twitch should more accurately indicate the fatigue in these fibers recruited voluntarily. Later, as fatigue recruit smaller motor units, yet the test twitch predomniately: the smaller fatigue-resistant units before larger fatigable units. As the smaller fatigue-resistant units activated at the start of the contractions fatigue and produce less force, additional units will be recruited. Therefore, the temporal profile of force output will reflect the processes of both fatigue and recruitment. As newly recruited units will provide an increasing proportion of fast-fatiguing fibers with larger force production, there will be a shift toward faster reduction of force output as the contraction proceeds. When subjects contracted quadriceps muscle with the same fatigue protocol as used here, Bigland-Ritchie et al. (2) showed that twitch force falls by 63% in ~240 s. This faster fatigue, compared with average falls of 29% (hand level) and 50% (hand elevated) in 240 s (see Fig. 4) for adductor pollicis in the present study, may reflect the smaller proportion of fatigue-resistant fibers (5% type I (10) in the quadriceps.

Subject differences. The sensitivity of fatigue to changes in perfusion pressure varied among subjects, with two subjects showing little change and two subjects more than doubling their fatigue rate with the hand elevated (Fig. 3). Several causes for this variation are considered. First, muscles vary in their capacity to exchange O2 and metabolites with blood. In a muscle that could extract more nutrients per unit of blood flow, the need to increase perfusion might not be as great, and, consequently, the rate of muscle fatigue might be less dependent on perfusion pressure. This is particularly relevant with subjects who have had previous muscle training (16) and could introduce significant differences among subject responses. Second, because muscle perfusion greatly affects both the performance of slow oxidative fibers (9), the muscle performance of subjects with a high proportion of fast glycolytic fibers is likely to be less sensitive to changes in arterial pressure. This might suggest that subjects with the least fatigue when the hand was level would have the least increase in fatigue when the hand was elevated, but this was not observed here (Fig. 3). Third, the extent to which the subjects’ central arterial pressure increased during the contractions would affect fatigue. Motor command and muscle afferents are only two factors of many that determine the final blood pressure (7, 12), and natural variation in blood pressure control is likely to affect fatigue. Finally, muscle architecture

Stimulation frequency. Excitation-contraction coupling is frequency dependent. Muscle fatigue produced by voluntary contractions shows a disproportionately greater decline in force when measured with low-frequency (<20 Hz) rather than high-frequency (>50 Hz) stimulation (4). Thus different test stimuli will produce different estimates of fatigue. Here, a single twitch was chosen to measure fatigue because it is not fatiguing in itself. As the same single twitch was used in situations of different perfusion pressure, they provide a reliable relative measure of muscle fatigue. We would have expected qualitatively similar results had a brief tetanus been used to measure muscle performance. It should be noted that muscle twitch force may not be an exact indicator of muscle fatigue. In the early part of the fatiguing protocol, subjects voluntarily recruit smaller motor units, yet the test twitch predominately represents the force of the larger motor units. Thus twitch force might be an underestimate of fatigue in these fibers recruited voluntarily. Later, as fatigue develops and larger motor units are recruited, the twitch should more accurately indicate the fatigue process. For the subjects in these trials whose fall in MVC approached 50%, the twitch force during the fatiguing protocol also fell by approximately one-half (Fig. 3, subjects RF, AC, IM, and MM).

Potentiation. Fatigue and twitch potentiation are separate but concurrent processes within muscle fibers, and both affect force output. Twitch potentiation increases as the level and duration of recent muscle activation increase but decreases with time when the muscle is not active and is attributed to free calcium and myosin phosphorylation arising from recent activation (6). At the beginning of a trial, potentiation outweighs the fatigue and so explains the increasing twitch force observed after the first few contractions of each trial (Fig. 3). Later in the trial, the rate of potentiation decreases while the rate of fatigue increases, and so fatigue dominates the effect on twitch force (6). Consequently, twitch force can provide a useful measure of muscle fatigue if the twitches are timed appropriately relative to the fatiguing contraction (6). In the present experiment, twitch force was used to measure muscle performance. To minimize changes in twitch potentiation within and between trials, contractions of equal force and duration were made at regular intervals, and twitches were interspersed with an approximately constant time delay after each contraction.

The greater activation required to produce the same force as a muscle fatigues will increase potentiation. Therefore, greater potentiation would be expected with the hand elevated. These results show that any additional potentiation did not overcome the increased fatigue and indicate that using single twitches to measure fatigue is likely to underestimate the effect of decreased perfusion pressure on muscle fatigue.

Muscle fiber type. Adductor pollicis is, on average, composed of 80% type I fibers, but there is significant individual variation (10). When adductor pollicis is electrically stimulated to produce repeated tetanic contractions, there is an initial, rapid decline in force output followed by a longer, slower decline (5). Voluntary contraction of the muscle recruits motor units sequentially: the smaller fatigue-resistant units before larger fatigable units. As the smaller fatigue-resistant units activated at the start of the contractions fatigue and produce less force, additional units will be recruited. Therefore, the temporal profile of force output will reflect the processes of both fatigue and recruitment. As newly recruited units will provide an increasing proportion of fast-fatiguing fibers with larger force production, there will be a shift toward faster reduction of force output as the contraction proceeds. When subjects contracted quadriceps muscle with the same fatiguing protocol as used here, Bigland-Ritchie et al. (2) showed that twitch force falls by 63% in ~240 s. This faster fatigue, compared with average falls of 29% (hand level) and 50% (hand elevated) in 240 s (see Fig. 4) for adductor pollicis in the present study, may reflect the smaller proportion of fatigue-resistant fibers (~45% type I (10) in the quadriceps.
influences the effect of muscle contraction on the blood flow response in isometric contractions (18). There is substantial variation among subjects in the muscle attachments and fiber compositions and distributions of the adductor pollicis (17).

Blood Pressure

Central arterial blood pressure tended to rise at the start of the contractions and then rise progressively as the contractions proceeded. All subjects showed a fast fall of central blood pressure back to initial levels after cessation of contractions, and most stayed at or below this level until the end of the monitored recovery period. As the muscle fatigued, a progressively larger central motor drive maintained the force output of the muscle, and the increase in motor drive per unit time was greater when the hand was elevated. The percent fall in twitch force output was linearly associated with the percent rise in central blood pressure and showed the same proportional increase regardless of whether the hand was level or elevated (Fig. 5). The cardiovascular response to the increased motor drive (7), therefore, increased central blood pressure more quickly with the hand elevated. Muscle reflexes could also have contributed to the increased cardiovascular drive. However, the cardiovascular response to exercise is thought to be driven mainly by the size of the central motor command, whereas muscle reflexes contribute a smaller fraction, perhaps acting as a fine-tuning mechanism (11). The component of the response associated with the central command is related to the percentage of MVC used, whereas the reflex response is reported to depend on the mass of the activated muscle (13). Adductor pollicis is a small muscle and is unlikely to produce a large reflex response to exercise. Thus, in these experiments, the rise in blood pressure produced by the central command is likely to have been far more important than the effect of the muscle reflex.

Elevating the hand 39 cm reduces muscle perfusion pressure by 29 mmHg. Arterial blood pressure rose on average by 14 mmHg for the level hand and by 24 mmHg for the elevated hand (Fig. 4), giving a difference of ~10 mmHg, or approximately one-third (10/29) the drop in perfusion pressure responsible for the additional fatigue. This suggests that the fatigue-induced increase in blood pressure achieved a partial compensation for the hydrostatic effect.

In summary, these results show that a reduction in muscle perfusion pressure increases the rate of fatigue of adductor pollicis during intermittent voluntary isometric contractions. Central arterial pressure increases in proportion to muscle fatigue and increases muscle perfusion pressure because a greater central motor command is required. This suggests that motor performance provides information concerning the adequacy of the rise in blood pressure, ensuring that the regulation of blood pressure is not entirely "open loop" (7).

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