The Investigation of Metabolic and Cardiovascular Responses to Fatiguing Static Effort.

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**Air Force Office of Scientific Research (AFOSR) 76-3084**

**Report Date:**
August 1981

**Number of Pages:**
19

**DISTRIBUTION STATEMENT:**
Approved for public release, distribution unlimited

**KEY WORDS:**
- Muscular fatigue
- Electromyography
- Vasodilation
- Forearm blood flow
- ENG amplitude
- Vasoconstriction
- Isometric exercise
- ENG frequency
- Static effort
- Blood pressure

**ABSTRACT:**
In the animal experiments a new method of stimulating muscles was developed in the laboratory to mimic voluntary contractions. Cat muscles were stimulated to fatigue at various constant tensions. The soleus muscle (slow twitch) did not fatigue unless the tension exceeded 30% of maximal strength whereas the plantaris muscle (fast-twitch) fatigued at all tensions above 3% of maximal strength. Fatigue was not attributable to failure of the neuromuscular junction. Fatiguing contractions of the soleus muscle did not elicit an increase in blood pressure whereas fast-twitch muscles did so, just...
as in voluntary contractions in man.

In human studies, women held given fractions of maximal strength longer than men. But because men are stronger than women, transposing the same data into absolute tension shows that the men have a longer isometric endurance for any given tension examined. Electromyographic studies show that the integrated amplitude increases as contractions are held to fatigue by about the same amount, irrespective of the tension held. The frequency of the electromyogram fell by an absolute amount at all tensions. This kind of analysis may be used as a tool to detect fatigue. Extensive studies of the control of muscle blood flow showed that during intermittent isometric exercise, local metabolites were responsible for dilating the vessels but that that effect could be opposed, in part, by neural vasoconstriction.
ANIMAL USE STATEMENT

The experiments reported herein were conducted according to the principles described in "The Guide for the Care and Use of Laboratory Animals" prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council, DHEW Publication No. (NIH) 78-23, Revised 1978.

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FINAL REPORT

AFOSR-76-3084

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The work going on in this laboratory deals largely, though not exclusively, with problems associated with isometric muscular function. It has been known for a long time that isometric contractions readily induce muscular fatigue, and that recovery from that fatigue is slow. It has been our contention that much of the muscular fatigue in the everyday working situation may well be due to "pure" isometric contractions or to the "isometric component" of tasks in which dynamic and static effort are mixed. It is important, therefore, to characterize the fatigue generated by static effort, to understand the factors that affect its development and, ultimately, to specify the cause(s). Given such an understanding, then appropriate steps can be taken to prevent it or avoid the development of fatigue or, less probably, at least in the foreseeable future, to reverse it once it has occurred. Although the serious study of isometric exercise is relatively recent, dating back only some 3 decades, the understanding of its underlying physiology is now quite extensive and knowledge concerning the factors that affect and control the fatigue, along with associated physiological responses, are probably better understood than they are for dynamic exercise, which has received much more attention in the laboratory. The work done in this laboratory has contributed heavily to our present knowledge.

The work described in the present report deals with several approaches, each from a different angle. Much of the work deals with fundamental physiological problems. But there are also ventures into purely practical studies, sometimes to test the validity of our conclusions from fundamental studies, sometimes because a practical question is baffling and requires to
be answered. Practical and fundamental studies go hand-in-hand, each providing feedback to the other. Customarily the applied problem can be properly answered only when the underlying fundamental controls are understood.

Much of the work done involves experimentation on humans. But a significant proportion deals with studies on animals, involving the use of a unique method of stimulating muscles (developed in this laboratory) to mimic voluntary exercise. Using this procedure, several studies have been devoted to characterize the properties of muscles, to study the generation of isometric fatigue, its relationship to 1) the order of recruitment and rate coding of motor units, 2) the type of muscle fiber activated, 3) muscle temperature and 4) the pressor response to isometric exercise. The studies on humans fall broadly into three categories, a) the comparison of isometric strength and endurance of female and male subjects, and examination of the reasons for differences in their physiological responses b) examination of electromyographic responses and study of the various factors (mechanical, neural and metabolic) that control the blood supply to exercising muscle and c) practical studies such as the investigation of hand-grip size on the strength and endurance of men and women, the influence of oral contraceptives on strength and endurance of women, etc.

There is a good deal of interaction in the thinking underlying these various and apparently very different parts of the program. For example, the temperature of muscles, which can vary quite widely in everyday life, profoundly affects isometric endurance and in many of these studies its influence has been either investigated or controlled. In fact, from the animal studies, it is clear that the dependence of endurance on muscle temperature is high in slow-twitch motor units and is low or absent in fast-twitch motor units. Such information may provide a useful tool to assess
the proportions of different types of fiber, or the origin of fatigue in one or the other type of fiber in man; studies to explore those possibilities are under consideration.

c. STATUS OF RESEARCH

1. Animal Experiments

The development in this laboratory, of a novel method by which to stimulate the motor nerves of animal muscles to mimic voluntary muscular function has been a major component of this period of experimental work.

The method depends on dividing the motor nerves into 3 or more bundles and applying a stimulus in rotation to each bundle. Recruitment of motor units is controlled by varying the amplitude of the stimulus. However, this results in the largest motor units being recruited first and the smallest units being recruited last, the reverse of the events in voluntary contractions. To overcome this difficulty it is necessary to apply an anodal block to all the motor nerves, releasing the block, as required, to recruit motor units in the correct order. At the outset of any prolonged isometric contraction, the tension is developed by recruitment of motor units at low frequencies. Once fatigue becomes detectable, more units are recruited at first. Once all the units are recruited, fatigue is offset by increasing the frequency of stimulation. This follows the general plan of recruitment of motor units and their rate coding (frequency of stimulation) found in voluntary contractions. The method thereby avoids the pitfalls experienced in previous animal studies, using synchronous stimuli to all motor units at high voltages and with rate coding commonly above the physiological range; such procedures do not allow control of the tension generated and inevitably result in rapid fatigue. Our new method was virtually complete in 1976,
since when we have completed a number of investigations. The procedure which is given in summary above was published in detail.

Another feature of this preparation is of great importance. In the cat hind limb, for example, there are found muscles which comprise only slow-twitch muscle fibers (m. soleus), only fast-twitch fibers (m. plantaris), and muscles with a mixture of slow- and fast-twitch fibers (m. gastrocnemius). In man, no muscles have been demonstrated to comprise only slow- or fast-twitch motor units. Obviously, exploration of the various muscles in the cat hind-limb offers the chance of relating physiological responses to exercise by specific types of motor unit. Several of our experiments have exploited this feature of the new experimental model.

In the first study of muscular function using this preparation we showed that smooth contractions could be obtained when muscles were stimulated at low frequencies. This is a necessary adjunct to voluntary contractions where smooth muscular contractions occur at frequencies much lower than those required to tetanize a motor unit. The non-tetanic function of a number of motor units presents itself as a smooth contraction of the whole muscle. This function was more readily demonstrated in slow-twitch muscles than fast-twitch muscles. Furthermore, the maximal tetanic contractions were generated with lower frequencies in the slow twitch muscles than in the fast-twitch muscles. We believe that the primary benefit of this kind of asynchronous stimulation over synchronous stimulation is that the tendon is continuously engaged, thereby permitting motor units to exert their tension without having to overcome a major portion of the elastic resistance and damping. After we established these fundamental properties of the muscle to asynchronous stimulation we then applied the logical sequence of varying the recruitment and rate coding to generate specific tensions and to hold them until fatigue occurred. The first series
of experiments was designed to determine how long, with serial contractions held to fatigue, each muscle required for recovery. Recovery of both strength and endurance was fastest for the slow-twitch muscle (soleus) and became progressively longer the faster the muscle was. The plantaris muscle, comprised solely or mainly of fast-twitch fibers was slowest to recover, taking up to 4 hours as opposed to about 10 minutes for soleus.

Major differences in endurance times were also found to be related to the muscle fiber type. The plantaris muscle fatigued at all tensions examined, as low as 3% of its maximum strength, whereas the soleus could maintain a tension of 30% of its maximal strength without evidence of fatigue (for periods of up to 4 hours, which is as long as the muscle has been stimulated in these experiments). Part of these differences could be attributed to the blood flow through the muscles because arterial occlusion markedly reduced the endurance of the soleus muscle but had only a small influence on the endurance time of the plantaris muscle. The origin of the fatigue in these experiments appeared to lie in biochemical events in the muscles because there was no evidence of failure of the neuromuscular junction at any tension. In all the experiments, the gastrocnemius muscle which has a mixed population of fiber types yielded results which were intermediate between the soleus and plantaris muscles.

Several experiments have been conducted on the pressor response to sustained isometric contractions in animals. The first of these yielded the dramatic finding that on stimulation of the motor nerve of the soleus muscle, there was no increase in blood pressure. In contrast, sustained isometric contractions of muscles with a population of fast-twitch fibers resulted in a large, linear increase in blood pressure, just as is found in voluntary contractions in man. In addition, in the gastrocnemius, "selective" blockade of the function of slow- or fast-twitch fibers by curare or
Decamethonium resulted in changes in the rise of blood pressure which supported the idea that slow-twitch fibers do not contribute to the pressor response. This was followed by a study in which the flexibility of the method of stimulation was used to generate tensions by recruiting either a) from fast-twitch to slow-twitch motor units or b) from slow-twitch to fast-twitch motor units, and where, in both conditions muscle temperature was controlled at 28°C or 38°C. When the recruitment followed the pattern known to occur in voluntary contractions (i.e., slow-twitch motor units first) there was a lower blood pressure response in the early part of the contraction, emphasizing the importance of muscle fiber type in determining the pressor response. In these experiments, there was no difference in the dimension of the pressor response due to the muscles' temperature. But the endurance times were substantially lower when the recruitment order was reversed from the "voluntary" pattern.

Muscle temperature is well known to have a profound influence on the endurance time of isometric contractions in man. In another series of experiments the change in endurance of the various cat muscles was examined when the temperature was controlled within the range of 20 to 40°C. From these experiments, it was shown that the fast-twitch motor units are more susceptible to fatigue when they are cooled from 38 to 28°C than are the slow-twitch motor units. This greater influence of temperature on the susceptibility to fatigue in fast-twitch fibers was further supported by the demonstration that the change in endurance of contractions at relatively low tensions was proportionally much greater than it was at high isometric tensions.
Comparison of the abilities of men and women to perform isometric exercise

In earlier studies we had shown in a large number of subjects that while women were much less strong (about 65%) than men, the endurance time of a sustained contraction at 40% MVC was 20% longer in women than in men. In addition, both men and women lost strength as they aged. The subjects who yielded those responses were not trained to perform isometric exercise and were examined only once. In a later experiment we have examined about 20 women and 20 men, all of whom were trained, measuring their hand-grip strength and their endurance times to sustained contractions at tensions from 25% MVC, to 70% MVC. At all tensions, from 25 to 70% MVC, the endurance times were significantly longer (by up to 30%) for women than for men. But the strength of the women was again only 65% of that of the men, so that when the data were plotted to show endurance times for absolute tensions generated, the men's endurance was significantly and substantially longer than that of the women; for example, when the tension held was 15kg (33 lb) the endurance time for the men was 340 sec while that for the women was only 185 sec, or just over half of the men's endurance. Because given tasks in everyday work are commonly set in absolute terms, without regard to relative strength due to sex, women are obviously at a disadvantage where there is a high static component in the work being done.

Stabilization of muscle temperature at 37°C by immersing the arms of a small number of men and women in water tended to reduce the differences in relative endurance times and performing the exercise with the circulation to the arm arrested also reduced the difference. It was concluded that differences in both muscle temperatures and the local blood flow played some part in the longer endurance time of women at specified relative tensions.
However, about half the difference remaining is due to sex; the nature of the difference is not presently known. The electromyogram was measured in these subjects. Analysis of the components of the surface electromyogram showed no difference in either the integrated amplitude or the center frequency when the men and women were compared.

In another study the forearm blood flow of 4 women was measured throughout the menstrual cycle. Two of the women were taking oral contraceptives and their blood flow did not vary throughout the menstrual cycle. The other two subjects were not taking oral contraceptives and showed cyclical variation in their blood flows throughout the menstrual cycle, in the same fashion as we have previously demonstrated that endurance time changes.

Isometric Fatigue in Man and the Surface Electromyogram

In an extensive series of experiments, we have examined the changes in the surface EMG during brief and sustained isometric contractions. This systematic study was intended to examine the characteristics of the EMG during fatiguing contractions in the hope that the procedure would not only shed light on the causal fundamental mechanisms but also would generate a tool by which to assess fatigue. Methods were devised to analyze the surface EMG by providing a continuous measurement of the integrated amplitude of the EMG. In addition, we measured the power spectrum of frequencies recorded from the surface electrodes. This procedure involved sampling the EMG over 6 "windows" each of 250 msec duration, permitting an average assessment of the power spectrum over any given period of 1.5 sec selected at will from a continuous tape recording of the EMG.

We showed that for brief 3 sec contractions at various proportions of
the maximal voluntary contraction (MVC) there was a direct, linear relationship with the integrated amplitude of the EMG. When sub-maximum tensions were held to fatigue, there was a consistent and approximately linear increase in the integrated amplitude of the EMG. The increase was about 30% of the total amplitude, so that when a contraction was held at 25% MVC, the amplitude of the EMG increased from 25% to about 55% of the maximal value. The experimental procedure was then altered so that at given times during a sustained contraction at sub-maximum tensions, brief maximal efforts were exerted, while the EMG was still recorded. It was surprising to find that at all the tensions examined, from low (25% MVC) to high (70% MVC) the strength developed by the intermittent brief maximal efforts showed a linear reduction throughout the sustained contractions. During that sustained contraction, the integrated amplitude of the EMG steadily increased as before. But during the brief contractions of maximal effort, the integrated amplitude behaved differently, depending on the tension of the sustained contraction. Thus, at the highest tension examined, 70% MVC, the integrated amplitude of the EMG always reached 100% of the maximal value in those brief maximal efforts, despite the fact that the tension fell linearly, indicating that muscular fatigue was present. The interpretation of those data, in conventional terms, is that during a sustained contraction at 70% MVC, there is no loss of electrical activity and thereby the fatigue is not related to transmission failure over the neuromuscular junction or along the muscle membrane and must thereby be related to biochemical contractile phenomena. During the sustained contraction at 25% MVC the integrated amplitude of the EMG increased linearly as found before. But during the brief maximal efforts it fell linearly, not parallel with the loss of strength, but only at about half that rate. In conventional terms, this must be interpreted that about half the fatigue is attributable to failure of neuromuscular
transmission and half to biochemical contractile events. In our publication we point out that this interpretation does not fit expectations from generally accepted physiological precepts. Either those precepts are not accurate or the conventional interpretation of the electromyogram is not accurate.

Several studies have been undertaken to explore this difficulty, to extend the use of the surface EMG to different kinds of muscular activity and to assess factors, such as muscle temperature, which might affect the behavior of both the amplitude and frequency analysis of the EMG. These studies have led increasingly to the view that, at least in some specific conditions, the analysis of the EMG can be used to assess the generation of fatigue.

Factors Controlling the Blood Supply to Exercising Muscle

The metabolites released by active muscle provide one or more powerful vasodilators to reduce the local vascular resistance and, thereby, an increased blood flow. Such "autoregulation" invests an important role to the muscle to control its own blood flow during exercise. The only other hemodynamic factor that can increase the local blood flow is an increase in the perfusion pressure (reflected by the mean blood pressure). The demonstration of neural vasodilator control of vessels in skeletal muscle, by cholinergic sympathetic nerves, has convincingly been shown to play no part in exercise but responds only to emotion of an unspecific nature. That control is doubtless responsible for the syncope associated with severe emotional stress. It may be that cholinergic nervous control is implicated in the commonly experienced increase in blood flow through a limb following preparatory instructions to a subject in laboratory experiments. Indeed,
the time course of such changes make it possible that such preparatory events play an important part of the "fight or flight" reaction which is attributed to release into the circulation of catecholamines from the adrenal gland.

There are 3 factors that can, or are suspected to oppose the increased blood flow to active muscle. First, when a skeletal muscle contracts (whether or not it also becomes shorter) it increases its intramuscular hydrostatic pressure. That increased pressure hinders the flow of blood through the local vessels or, alternatively and more likely, it creates shearing forces across the walls of local vessels which can and do diminish or abolish the local blood flow. In rhythmic exercise, where contractions are interspaced with periods of relaxation when the blood flow can be high, this interference with the blood flow is of smaller consequence than in isometric contractions where the compression of local vessels is unremitting in nature. The second possible factor to oppose the increased blood flow due to an increased perfusion pressure is the myogenic reflex. This response has been demonstrated in some animal arterial vessels and in the human umbilical artery (which has no neural control). It results in a myogenic constriction when the perfusion pressure increases. As a result, the myogenic response has been considered as another form of "autoregulation". Finally, the vessels in skeletal muscles are served by sympathetic adrenergic nerve fibers. An increase in adrenergic traffic results in vasoconstriction and a decrease permits release of that constriction. This powerful control has been shown to generate a widespread vasoconstriction in inactive tissues, such as in the gut, the skin and in inactive muscles when other muscles become active. Clearly this process is the agent responsible for controlling regional blood flow. An important question that arises is whether the constriction is also applied to the blood vessels in active
muscles (and then is inhibited in some way) or whether the constrictor tone of the vessels in the active muscles is selectively released from the generalized increase in sympathetic neural traffic.

When we consider the changes in blood flow through muscles which sustain isometric contractions we know that the blood flow can increase, which is doubtless due, in part at least, to metabolic vasodilators. But the large increase in perfusion pressure that occurs in sustained isometric contractions may also have a part to play, depending on the influence of the myogenic reflex. Certainly, the compression of local vessels opposes the increased blood flow.

With those facts in mind, the investigation was planned to measure the blood flow immediately (2 sec) after an isometric contraction. The argument was that if the contractions were quite brief there would be little or no change of blood pressure and, by measuring the flow after release of the tension, there would be no compression of the local vessels by the skeletal muscle. The hypothesis to be tested was that if metabolites were the sole contributor to the change in local blood flow, there ought to be a direct and linear relationship between the tension exerted and the resultant vasodilation. In the early experiments this proved to be true, but only for tensions up to about 60% of the maximal voluntary contraction (MVC). Further increases in tension yielded no further increase in the blood flow. Those findings suggested that at high tensions some constrictor influence might be opposing the effect of metabolic dilators. Because at tensions of about 60% MVC the local flow is occluded by mechanical compression, the myogenic reflex became an obvious suspect as the controlling mechanism. The suspicion was heightened when a series of intermittent isometric contractions of 4 sec duration with intervals of 8 sec between resulted in fatigue associated with a large increase in blood pressure but with a constant local
blood flow which, even in the presence of the steadily increasing blood pressure only reached about half the maximal flow possible. Consequently, several experiments were undertaken to test that possibility. Digital compression of the brachial artery for short periods, either with the arm at rest or concomitant with isometric contraction, resulted in no change in blood flow. Nor was there a change in flow following compression of all the tissues in the forearm above and below the plethysmograph by inflating pneumatic cuffs; the pressures in the cuffs ranged up to 200 mm Hg. Finally, to test the possibility that the rapidity of stretch of the smooth muscles might be the responsible myogenic agent, a series of experiments was carried out where tensions were exerted and released rapidly (square-wave) or gradually and linearly, with a rapid release (ramp-up) or quickly with a gradual and linear decrease (ramp-down). All contractions took the same time to perform. The blood flow following square-wave contractions was always the highest for the maximum tension reached, and the blood flow following ramp-up and ramp-down contractions were similar. The data indicated that the dominant relationship was the product of tension and time, supporting the view that the metabolic control was dominant. Those findings, taken together, make it clear that in the intact human forearm the myogenic reflex has no detectable influence on the local blood flow. As a result, the only known possibility that remains to explain the data described above is that in these experimental circumstances there must be a neural sympathetic vasoconstriction which prevents the development of maximal blood flow through exercising muscles, at a time when there is a marked increase in mean arterial blood pressure. The postulation is that there was a metabolically-induced maximal dilatation of resistance vessels within the active muscles but that there was a neurally controlled vasoconstriction upstream, in relatively large arterial vessels which are beyond the
influence of the interstitial metabolic dilators. That pursuit of that concept is the subject of current A.F. research support. For the first time since Gaskell described the basic events that control the circulation in exercising muscle, evidence is now available which seriously infers that the widespread sympathetic vasoconstriction induced by exercise also affects the active muscles and can, at least in some circumstances, limit the blood flow to those muscles.
LIST OF PUBLICATIONS


ABSTRACTS


e. PROFESSIONAL PERSONNEL

A. R. Lind (Principal Investigator)
J. S. Petrofsky
C. A. Williams
T. E. Dahms
G. Kamen
f. **INTERACTIONS**

(1) Frequent oral communications have been given to the Physiological Society and the American Physiological Society and at the International Congress of Physiology, 1980; some of these are given under "Abstracts" in the list of publications.

In addition, oral communications have been presented at the Fall Meetings of the AFOSR Life Sciences Directorate in 1976, 1977, and 1978.

(2) While no specific consultations or advice has been sought, shared research activities and discussion continue with Dr. J. S. Petrofsky, who is now at Wright State University. Dr. Petrofsky provided advice to Dr. Veghte of AMRL, Wright-Patterson, before he left St. Louis University, and since joining Wright State University is an active consultant to AMRL.

g. **NEW DISCOVERIES**

Not applicable.

h. **ANY OTHER STATEMENTS**

Not applicable.