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A Study of Pain and Fatigue in Working Ischemic Muscle of the Human Forearm

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A STUDY OF PAIN AND FATIGUE IN WORKING ISCHEMIC MUSCLE OF THE HUMAN FOREARM

by

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LIFE

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TABLE OF CONTENTS

INTRODUCTION AND LITERATURE REVIEW

The purpose of this paper is to study pain and fatigue in contracting ischemic muscle. Early investigators of this subject explored the causes of muscular pain with little attention devoted to its frequency of development. This present study not only deals with the rate of occurrence of pain in working ischemic muscle but also notes its absence of development.

It has long been known to clinicians that when a limb is exercised while its blood supply is arrested, the limb becomes painful. Bouley (1831) described this phenomena while exercising a ligated limb. Charcot (1859) after studying cases of Intermittent Claudication in man concluded that pain was the predominant symptom.

The first theory to account for this phenomena was postulated by Charcot (1859) who felt that arresting the blood supply to a muscle caused it to become cramped, and, therefore, regarded the pain of ischemic muscle to be likened to cadaveric rigidity. Marinesco (1896) held the view that during rest the blood supply to a limb was adequate, but when exercised, it was not, thereby producing cramps in the exercised muscles. It was not until Zak (1921) began his experiments that a second view was introduced. After rendering forearm muscles ischemic by a tourniquet, he found that repeated contractions caused pain to appear in the working muscles. This pain he likened to Intermittent Claudication and attributed the causes of both to arterial spasms.

MacWilliam and Webster (1923) in further experiments on pain in ischemic muscle noted "that the pain...arises from the exercise of... muscle tissue...in the presence of an acute lack of blood supply, involving urgent want of oxygen (anoxemia) and its consequences with excessive accumulation of metabolic products, acids, and other bodies." They also felt that the pain produced in Intermittent Claudication had the same mechanism of production as did that of Angina Pectoris.

Lewis, Pickering, and Rothschild (1931) working along these same lines demonstrated that pain characterizing Intermittent Claudication could be reproduced in a healthy limb by exercising it after its circulation had been arrested, and that this pain was not caused by the obstructed vessels entering into a state of spasm or by anoxemia, but by a physical-chemical stimulus developed in the muscle mass itself during its exercise. Lewis termed this stimulus the "P Factor" which he felt was stable in resting muscle and only increased during muscular contractions. They also felt that since the "P Factor" is determined by the amount of exercise performed by the muscle, it was also largely dependent upon the state of the circulation to the muscle. Through their experimentation they concluded that the "P Factor" accumulates in the tissue spaces surrounding the working muscles, and that the level necessary to excite pain can only be reached when the circulation is partly or completely arrested.

In relating pain to the amount of exercise performed, it was found that if the rhythm of muscular contraction remained constant, but the load increased, pain developed sooner. Secondly, if the tension was kept constant but the rhythm of contraction doubled, the time for the onset of pain was reduced by one-half. Recovery from pain was stated to be complete in seven to ten minutes. Preliminary periods of ischemia of ten minutes had no effect on the amount of work necessary to produce pain.

Pickering and Wayne (1933) in working with severely anaemic patients concluded that the occurrence of muscular pain during exercise is not due to an inadequate bloodflow, but to an inadequate oxygen supply to the working muscles. And, therefore, the "P Factor" as postulated by Lewis, must normally be removed by an oxidative process. When nine anaemic patients with free circulation were tested, pain was produced. The disappearance of the pain was slower in the anaemic patients than in those that were not. After the anaemia had been cured similar exercise produced no, or only slight, pain. The observations made by Pickering and Wayne support the view that Intermittent Claudication and Angina Pectoris are due to similar mechanisms operating in the heart and skeletal muscle, namely, a diminished oxygen supply.

A similar view was postulated by Kissen (1934), when he showed that normal patients breathing air deficient in oxygen complained of pain in exercised skeletal muscle. The severity and the rapidity of the onset of the pain varied with the degree of anoxemia and the rate at which the exercised skeletal muscle worked. Therefore, he also concluded that the pain must be due to an accumulation of muscle metabolites that require oxygen for their disposal.

Perlow, Markle, and Katz (1934) were the only men to study the effects of ischemic muscle in the human leg. Their investigation validates the previously found results of Lewis and other workers. By showing that a previous ischemic exercise will substantially shorten the time necessary to produce pain in a second ischemic exercise, they felt that pain of ischemic muscle was not produced by a single mechanism but that muscular activity, circulatory stasis, and most importantly, anoxemia, contribute to its production. A preliminary period of ischemia of five or ten minutes shortened the duration of exercise necessary to produce pain.

LaPlace and Crane (1934) made some interesting observations on the development of pain and fatigue in contracting ischemic muscle. Experimenting with sixteen subjects, thirteen instances occurred in which fatigue and not pain caused the cessation of work. If the subject performed the same exercise with a lighter load, pain became the predominant cause of cessation of work. Therefore, they suggested that the amount of work performed by the muscle had a definite effect on the degree of pain obtained. Comparison of right and left arm showed no consistency in the amount of work performed or the cause of cessation of exercise. They also concluded that the intensity of the pain does not appear to be affected by constitutional differences in nervous sensitivity among different subjects tested. It was also felt that pain and fatigue are independent phenomena occurring under similar conditions though they may both be associated with the accumulation of some metabolic product or products.

Maison and Broeker (1941) discovered that when an ischemic muscle was routinely, daily exercised, the time of onset of pain was delayed only slightly, but that the intensity of the pain was markedly reduced. But, an interim of daily work with free circulation reintensified the pain on later trials when the blood supply was again occluded.

McArdle and Verel (1956) in the most comprehensive study to date, dealt with observations on the local effects of exercise on ischemic forearm muscles. Measurements were made on: 1) varied loads and rates of contraction to effect the time of onset of pain, 2) rate of recovery from fatigue, and 3) bloodflow responses to different amounts of work performed with different loads. Their results showed that as the load and rate of contraction was increased the time of onset of pain decreased. Bloodflow increased proportionally after ischemic exercise depending on the amount of prior metabolism. Recovery from fatigue was said to be complete in fifteen minutes.

Horisberger and Rodbard (1961) present results which support the concepts of Lewis that a "P Factor" produced in contracting muscle diffuses into the extra-cellular spaces where it stimulates pain fibers. Recovery from fatigue is said to be complete in ten minutes.

Park and Rodbard (1962) studied the effects of load and duration of tension in pain induced by ischemic muscular contraction. Their findings indicate that the development of pain was fairly uniform for each subject tested regardless of the loads and durations. This result differs from that of McArdle and Verel who reported that the rate of development of pain was directly proportional to the product of the number of contractions and the load. Their experiments also showed that after pain had been produced in one arm and the bloodflow released to permit relief of the pain, inflating the cuff on the other arm did not cause an increase in the number of contractions necessary to produce intolerable pain in the second arm tested. Ischemia produced in the forearm for periods up to fifteen minutes had no effect on quickening the onset of pain and simultaneous exercise of the contralateral arm had no effect on the rate of pain development.

MATERIAL AND METHODS

During the course of this investigation one hundred healthy male Freshman medical and graduate students were used as experimental subjects. This number assured variance in physical and psychic types.

The investigation consisted essentially in a study of pain and fatigue arising in the human forearm during repeated muscular contractions in the normal as compared to the ischemic condition.

The exercise chosen was that of a simple gripping movement exerted on a hand ergometer at a rate of one contraction per second. An audio signal was used to establish this frequency. All muscular work was recorded by means of a Grass Polygraph to which the audio signal and ergometer were connected. Ischemia was produced by inflation of an air sphygmomanometer applied to the arm above the cubital fossa, to a pressure exceeding 240 mm. Hg.; the subject was seated in front of the polygraph with the arm to be tested placed on a table at his side. Work would cease when either complete fatigue developed or pain reached intolerable levels. Fatigue was determined by the subject not being able to squeeze the ergometer to make the writing pen reach a line 2 cm. above thebase line. The polygraph was balanced so that this level remained constant for each subject tested.

Pain, being subjective in nature, cannot be mechanically recorded, but each subject was instructed to squeeze the ergometer until the pain was so severe that he was no longer willing to continue.

Experimental Procedures:

1. Normal exercise with free circulation -- work continued until fatigue was recorded. Right and left arms tested.

2. Immediate occlusion -- work began immediately after occlusion and continued until complete fatigue or intolerable pain. Right and left arms tested.

3. Occlusion for seven minutes prior to the onset of exercise -- work continued until complete fatigue or intolerable pain. Right and left arms tested.

4. Latent pain -- left arm tested.

   a) Fifty subjects tested -- occlusion and work started immediately until the first recording of fatigue.

   b) Fifty subjects tested -- work was started and an occlusion was not produced until the first sign of fatigue was recorded. Work was then stopped.

5. Time for recovery from fatigue -- Experimental Procedure No. 1 was repeated after ten minutes rest for the first fifty subjects tested and fifteen minutes rest for the second fifty subjects tested.

RESULTS

Fatigue is used here to indicate the inability of a subject to exert enough force to displace the ink writer two centimeters above the base line. As fatigue became apparent, increasing amounts of effort were exerted by the subjects to compensate for the increasing muscular weakness. Complete fatigue is an inability to continue contractile movements.

<u>Muscular Exercise with Free Circulation:</u>

The tabulated results of the onset of fatigue during muscular exercise with free circulation in both the right and left human forearms are shown in Table No. 1. The fatigue range for right arm exercise was from 18 to 410 contractions and for the left arm, 22 to 620 contractions. The mean number of contractions necessary to produce fatigue was 118.4 for the right arm and 112.0 for the left arm.

Graph I shows that during exercise of the right arm 76 percent of the tested population fell within a fatigue range of 40 to 160 contractions, and similarly for the left arm, 74 percent of the tested population fell within this same range.

As exercise continued and fatigue became progressively more pronounced, the tested subjects complained of a feeling of tiredness and deep muscular ache in the flexor region of the forearm and hand. No subject reported pain either during exercise or after its completion.

<u>Fatigue of Ischemic Muscle -- Right Arms:</u>

Tabulated results, Table No. 1, of fatigue in muscle with the circulation arrested shows a range of 10 to 85 contractions following immediate right arm occlusion, and 8 to 83 contractions when occlusion of the right arm was affected seven minutes prior to the onset of exercise. The mean number of contractions necessary to produce fatigue was 40.6 when circulation was arrested immediately and 37.4 when a prior occlusion of seven minutes was affected.

Graph II shows that 89 percent of the total tested population developed fatigue in the range of 20 to 64 contractions whether the tests were started immediately or seven minutes after occlusion of the circulation.

<u>Fatigue of Ischemic Muscle -- Left Arms:</u>

Tabulated results, Table No. 1, of fatigue in muscle with the circulation arrested shows a range of 7 to 100 contractions following immediate left arm occlusion, and 8 to 83 contractions when occlusion of the left arm was affected seven minutes prior to the onset of exercise. The mean number of contractions necessary to produce fatigue was 39.6 when the circulation was arrested immediately and 41.5 when a prior occlusion of seven minutes was affected.

Graph III shows that between the range of 20 to 64 contractions, 88 percent of the tested population developed fatigue when an immediate occlusion was affected and 86 percent when the test was started seven minutes after occlusion of the circulation.

Fatigue of ischemic muscle, as shown from the data, occurs at a rate approximately three times faster than fatigue when the muscle has free circulation. Tiredness and muscular ache in the flexor region of the forearm and hand was more pronounced during exercise of the ischemic muscle. Some subjects also reported an inability to extend their fingers or open their hands with a generalized stiffness occurring. No subject reported any feeling of pain before fatigue was recorded.

<u>Pain of Ischemic Muscle:</u>

Arrest of the circulation to the human forearm produces sensations of numbness and tingling but pain does not develop. If continuous muscular effort follows however, pain soon appears and may increase to an extreme degree of intensity.

The moment of onset of pain was not always easily ascertained, as it usually began with a vague sense of discomfort which gradually increased in intensity. It was decided to continue each exercise to the point at which the subject would not proceed further.

The pain was felt over the flexor region of the forearm and was most intense in the central part of the forearm; it was especially marked from the wrist to the elbow along the flexor digitorum sublimis. It seemed to be centered in the belly of the working muscle with a good deal of spreading, but there was usually no pain in more distant parts of the extremity. In some subjects there was pain in the palm of the hand. The pain increased progressively while contractile activity continued, and was relieved in two to three seconds when the circulation was reestablished.

Ischemia for periods up to seven minutes caused sensations of numbness, tingling, and coldness and a certain amount of discomfort, but no pain.

Pain of Ischemic Muscle -- Right Arms:

The data for this group of experiments, Table No. 1, shows the number of contractions which produced intolerable pain and caused the cessation of exercise. Following immediate right arm occlusion, intolerable pain occurred between the range of 30 to 150 contractions. When a prior occlusion of seven minutes was affected, intolerable pain occurred between the range of 34 to 103 contractions. The mean number of contractions that caused cessation of exercise because of intolerable pain was 58.47 when the circulation was arrested immediately and 54.11 when a prior occlusion of seven minutes was affected.

Graph IV shows that 81 percent ceased exercise because of intolerable pain between the range of 30 to 69 contractions. Nine subjects witnessed no pain and ceased exercise because of complete muscular fatigue. When a prior occlusion of seven minutes was affected 89 percent ceased exercise due to intolerable pain between the same range of contractions.

Eleven subjects developed no pain, and ceased exercise because of complete muscular fatigue.

Pain of Ischemic Muscle -- Left Arms:

Tabulated results for this group of experiments, Table No. 1, shows that cessation of exercise due to intolerable pain occurred within a range of 35 to 123 contractions following immediate left arm occlusion, and 14 to 121 contractions when occlusion of the left arm was affected seven minutes prior to the onset of exercise. The mean number of contractions necessary to produce cessation was 59.26 and 62.22 respectively.

Graph V shows that following immediate left arm occlusion 84 percent ceased exercise because of intolerable pain between the range of 30 to 69 contractions. Eleven subjects witnessed no pain and ceased exercise because of complete muscular fatigue. When a prior occlusion of seven minutes was affected, 67 percent ceased work due to intolerable pain between the same range of contractions. Ten subjects developed no pain and ceased exercise because of complete muscular fatigue.

Latent Pain:

I. Occlusion and exercise started immediately until the first recording of fatigue.

At no time during the course of testing, did an individual report muscular pain before fatigue. But, if muscular exercise was stopped at the first sign of fatigue and the subject allowed to rest with the cuff still inflated, pain developed after a latency of ten to twenty seconds.

Of the fifty subjects tested in this manner, nine individuals reported no latent pain. Seven of these individuals reported no pain during prior testing. Two subjects had reported pain in all other previous experiments.

II. Exercise started and an occlusion was produced when the first sign of fatigue was recorded.

When the bloodflow was arrested at the instant exercise ceased, no pain was reported, but pain developed after a latency of twenty to thirty seconds.

Of the fifty subjects tested in the above manner, five reported no latent pain. Two of these subjects reported no pain during prior testing. Three subjects had reported pain in all other previous experiments.

The intensity of the pain varied from subject to subject. In some cases the pain was not only distinct but severe, being relieved only when circulation was reestablished.

<u>Recovery from Fatigue:</u>

The rate at which a muscle recovers from fatigue was measured in the right forearm. Half the subjects tested were allowed ten minutes rest and the other half fifteen minutes rest. The data is represented in percent recovery assuming that the first test, muscular exercise with free circulation was each subject's maximal amount of work before the onset of fatigue (Table No. 3).

Percent recovery from fatigue after ten minutes rest showed a range of 34.3 percent to 221.2 percent. The mean percent recovery was 83.4 percent for the fifty subjects tested.

Graph VI shows that thirty-nine subjects had less than 100 percent recovery, and fourteen subjects, or 28 percent, showed complete recovery after ten minutes rest.

Percent recovery from fatigue after fifteen minutes rest showed a range of 41.7 percent to 236.8 percent. The mean percent recovery was 112.5 percent for the fifty subjects tested.

Graph VI shows that seventeen subjects had less than 100 percent recovery, and thirty-three subjects, or 66 percent, showed complete recovery after fifteen minutes rest.

DISCUSSION AND CONCLUSION

Fatigue:

The time of onset of fatigue following muscular exercise with free circulation in both the right and left forearms showed broad ranges of 18 to 410 and 22 to 620 contractions respectively. The mean number of contractions necessary to produce fatigue was 118.4 for the right arm and 112.0 for the left arm. Fatigue occurred earlier in ischemic muscle. Following immediate right arm occlusion the fatigue range and the mean number of contractions necessary to produce fatigue decreased to 10 to 85 and 40.6 respectively. Following a prior occlusion of seven minutes the fatigue range and the mean number of contractions necessary to produce fatigue again decreased to 8 to 83 and 37.4.

A similar decrease occurs on the left side. Immediate left arm occlusion shows a fatigue range of 7 to 100 contractions and an occlusion seven minutes prior to the onset of exercise shows a decrease of 8 to 83 contractions. However, the mean number of contractions necessary to produce fatigue are 39.6 following an immediate arrest of the circulation and 41.5 when a prior occlusion of seven minutes was affected. This observation is just the opposite of that found in the right arm where a preliminary period of ischemia shortened the time necessary to produce fatigue.

In an effort to try and explain these contrary results, it must be remembered that a previous exercise of ischemic muscle will substantially shorten the time necessary to produce pain and fatigue in a second exercise of ischemic muscle unless the muscle is given adequate time for recovery. Perlow, Markle and Katz (1934) and Lewis (1931) claimed that recovery from ischemic muscular work was complete in seven to ten minutes. McArdle and Verel (1956) stated that recovery was complete in fifteen minutes and Horisberger and Rodbard (1961) claimed that ten minutes was sufficient time for complete recovery. All of our subjects received a minimum of ten minutes rest with free circulation before they were permitted to go on to the next test. However, ten or even fifteen minutes rest does not appear to be adequate enough time for complete recovery from fatigue as the above observers had stated.

Our results of recovery from fatigue show that after ten minutes rest only 28 percent of the subjects tested showed complete recovery and after fifteen minutes rest still only 66 percent were able to demonstrate complete recovery. It, therefore, appears that a minimum of twenty minutes rest with free circulation is required before one can safely say that complete recovery from ischemic muscular work has occurred. The fact that recovery may occur faster in some individuals than in others is not in question here.

In seeking an answer to our original problem of why a preliminary period of seven minutes ischemia shortened the time necessary to produce fatigue in the right arm and lengthened it in the left arm, it must be remembered that the right arm was allowed ten minutes rest before the preliminary ischemia of seven minutes was produced and that the left arm rested seventeen minutes during free circulation and an additional seven minutes rest during the period of prior ischemia. Therefore, the results obtained from left arm experiments following a preliminary period of seven minutes ischemia, would appear to be more accurate since the left arm would show almost complete recovery. Our results show that preliminary periods of ischemia does not seem to shorten the time necessary to produce fatigue. More will be discussed on this subject when pain in ischemic muscle is reviewed.

Pain:

The results of pain in ischemic muscle following an immediate occlusion or after an occlusion affected seven minutes prior to the onset of exercise closely resembles the results found when fatigue in ischemic muscle was examined. When the right arm was tested following immediate occlusion, intolerable pain occurred between the range of 30 to 150 contractions. The mean number of contractions necessary to produce intolerable pain was 58.47. With a prior occlusion of seven minutes, intolerable pain occurred between the range of 34 to 103 contractions with a mean number of 54.11. Similar results from the left arms showed a contraction range of 35 to 123 and a mean number of contractions of 59.26 following immediate occlusion. With a prior occlusion of seven minutes, intolerable pain occurred between the range of 14 to 121 contractions with a mean number of contractions of 62.22.

Again, like fatigue of ischemic muscle, we find that following a preliminary occlusion of seven minutes, the mean number of contractions necessary to produce intolerable pain in the right arm was less than in the left arm. This, too, can be explained in a like manner, namely, increased muscular rest, resulting in a more complete recovery.

Lack of oxygen, such as developed following a preliminary ischemia of seven minutes, does not appear to have a direct effect on the onset of either fatigue or intolerable pain. During muscular exercise oxygen will be used much more rapidly than during circulatory arrest, but if lack of oxygen were a direct cause of pain and fatigue a preliminary ischemia of seven minutes should appreciably diminish the time taken for pain or fatigue to appear in the succeeding exercise. Actually, as we have seen, it does not. Our results, therefore, are in agreement with the findings of Lewis (1931), and Park and Rodbard (1962), and contrary to those of Perlow, Markle and Katz (1934) who claimed that preliminary periods of ischemia of five or ten minutes shortened the amount of exercise necessary to produce pain or fatigue. On the basis of these observations, the process leading to the development of pain and fatigue does not occur to any appreciable extent during simple circulatory arrest and excludes the possibility that a prior deficiency of oxygen promotes or hastens the process that leads to the development of pain or fatigue. Recovery from both pain and fatigue may be dependent upon oxygen since only after the circulation is reestablished does the muscle begin its process of recovery. How this is actually accomplished is unknown, but it is thought that the substance or substances which caused both the pain and fatigue are removed by an oxidative process. Pickering and Wayne (1933), Kissen (1934).

More noteworthy of mention than the fact that pain was elicited in the majority of subjects tested is its complete absence of development in nine of the subjects tested. LaPlace and Crane (1934) noted that if a subject performed exercise with a heavy load, fatigue became the predominant cause of cessation of exercise and no pain was elicited, but if the same individuals worked with lightened loads pain again became the predominant cause of cessation of work. Park and Rodbard's (1962) findings indicate that the development of pain was fairly uniform for each subject tested regardless of the loads and durations. This result differs from that of McArdle and Verel (1956) who reported that the rate of development of pain was directly proportional to the product of the number of contractions and the load. Differences in loads and rates of contractions were not used in our experiments and therefore could not have influenced the outcome of our results when no pain was produced. However, the load and rate of contractions used in this experiment was adequate to elicit pain in 91 percent of the subjects tested. Differences in the muscular strength of the nine subjects seemed to have no bearing on whether pain occurred or not. Table No. 1 shows that subjects 10, 11, 18 and 30 were able to do considerably more muscular work with free circulation than subjects 19, 35, 46, 77 and 85.

Three individuals showed bizarre results when the circulation was arrested. Subject 15 witnessed right arm pain in ischemic muscle following both an immediate and prior occlusion, but no pain in the left arm following an immediate occlusion or an occlusion seven minutes prior to the onset of exercise. Subject 47 reported pain in the right arm after exercise following immediate arrest of the circulation, but not in the left arm. However, pain was felt in the left arm after exercise following a prior occlusion of seven minutes, but none was reported in the right arm. Subject 60 reported pain in all the tests where the blood supply was arrested except in the right arm after exercise following a prior occlusion of seven minutes.

In instances where pain was not reported, the cessation of exercise was the result of fatigue.

When muscular exercise with an arrested circulation was stopped at the first sign of fatigue and the subject allowed to rest with the cuff still inflated, pain developed after a latency of 10 to 20 seconds. When the bloodflow was arrested at the instant exercise ceased, no pain was reported but developed after a latency of 20 to 30 seconds. It, therefore, appears that the latency of the development of pain accounts for the time necessary for "P Factor" to build up within the tissue spaces to a level high enough to elicit pain.

The fact that some individuals do not experience pain might be accounted for by the fact that the "P Factor" is not produced in high enough levels to elicit pain or that there are individual differences in constitutional nervous sensitivity to the "P Factor".

It was previously mentioned that recovery from fatigue is complete after approximately twenty minutes of rest with free circulation. It, therefore, does not seem unlikely that recovery from pain takes the same amount of time to recover as fatigue. Lewis (1931) states that recovery from pain is complete in seven to ten minutes.

The ideas expressed in this paper can also be applied to clinical problems of pain production in Intermittent Claudication and Angina Pectoris.

Intermittent Claudication appears to be produced by the same mechanisms that produce pain in exercising ischemic muscle. But, because the circulation is not completely arrested, the time necessary for the development of pain may be longer and its recovery shorter.

Ischemia of cardiac muscle is thought to be the cause of Angina Pectoris. When the energy expenditure of the heart increases to an extent that the available blood supply is not sufficient to meet the heart's demands, pain results. As long as the demands of the myocardium are met, no pain appears. Another question also bears answering: why does anginal pain not occur in many cases of advanced coronary disease? Assuming that the mechanism of the production of anginal pain is similar to the pain occurring in ischemic skeletal muscle, it may be that myocardial fatigue may so diminish the energy expenditure of the heart that the pain producing substances never reach a high enough level to elicit pain.

SUMMARY

1. The relationship between the development of pain and fatigue was studied in the rhythmically contracting ischemic muscles of the forearm of man.
2. When the circulation was arrested fatigue occurred three times sooner than fatigue when the muscle had free circulation. Pain occurred following the first recording of fatigue and was not elicited unless the circulation was arrested.
3. Previous exercise of ischemic muscle substantially shortened the time necessary to produce fatigue and pain in a second exercise of ischemic muscle unless the muscle was given adequate time for recovery.
4. Recovery from ischemic muscular work is probably complete in about twenty minutes.
5. Obstruction of the bloodflow to the arm for seven minutes prior to exercise had no effect on the time required to produce fatigue or pain.
6. Pain, characteristic of ischemic muscular exercise, did not occur in nine of the subjects tested. Three subjects showed bizarre pain reactions.

7. Our results support the concept of Lewis that a "P Factor" produced in contracting ischemic muscle diffuses into the extracellular spaces where it stimulates pain fibers.

8. Pain characteristic of Intermittent Claudication and Angina Pectoris may be due to a similar mechanism of production.

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TABLE NO. 1

Data shown in this table represents number of contractions or seconds (1 contraction/second) until:

Subject Number	Fatigue -- Free Circulation During Exercise: Right Arm	Fatigue -- Free Circulation During Exercise: Left Arm	Fatigue -- Circulation Occluded Immediately Before Exercise: Right Arm	Fatigue -- Circulation Occluded Immediately Before Exercise: Left Arm	Fatigue -- Circulation Occluded 7 Minutes Prior to Exercise: Right Arm	Fatigue -- Circulation Occluded 7 Minutes Prior to Exercise: Left Arm
1	105	175	55	56	60	80
2	85	100	30	25	27	40
3	410	110	50	30	40	27
4	40	90	30	30	27	55
5	90	85	30	25	10	25
6	113	65	31	35	30	37
7	135	128	44	34	34	40
8	45	35	45	30	43	44
9	180	195	65	50	45	42
10	245	240	85	90	55	50
11	133	165	76	75	72	72
12	313	175	58	58	45	50
13	85	80	50	50	50	60
14	97	60	29	30	30	42
15	155	112	45	55	43	52
16	71	75	22	40	25	39
17	110	71	47	40	34	36
18	235	200	50	45	68	38
19	38	77	25	31	18	62
20	295	95	60	45	40	55
21	227	190	42	40	37	40
22	105	160	55	48	25	55
23	235	333	65	67	37	52
24	74	65	25	29	38	38
25	65	175	20	43	43	55
26	140	185	55	43	45	54
27	385	620	70	70	70	70
28	110	105	35	34	35	45
29	163	131	64	56	65	60
30	242	173	53	43	45	55
31	140	90	48	35	27	36
32	117	106	47	53	46	66
33	355	460	80	100	83	85
34	110	128	50	45	50	53
35	134	90	54	43	56	34
36	60	68	26	21	26	20

Subject Number	Fatigue -- Free Circulation During Exercise		Fatigue -- Circulation Occluded Immediately Before Exercise		Fatigue -- Circulation Occluded 7 Minutes Prior to Exercise	
	Right Arm	Left Arm	Right Arm	Left Arm	Right Arm	Left Arm
37	60	65	40	35	25	35
38	195	170	46	35	35	41
39	215	196	74	45	41	45
40	167	124	52	45	45	35
41	60	67	23	29	28	45
42	90	68	48	54	48	51
43	55	48	14	27	8	34
44	35	55	37	37	37	44
45	46	66	26	33	44	35
46	60	39	37	33	39	35
47	72	65	34	20	23	15
48	80	70	20	25	25	26
49	137	115	35	35	25	39
50	60	50	42	25	33	27
51	84	66	56	39	48	35
52	87	134	55	40	24	35
53	175	145	41	58	36	49
54	118	285	70	68	45	64
55	145	145	38	38	25	44
56	75	51	22	23	20	30
57	74	56	27	29	32	20
58	86	103	26	26	51	46
59	48	72	21	30	30	50
60	53	60	58	72	57	40
61	148	110	30	28	20	36
62	52	61	40	42	39	46
63	185	210	55	68	63	70
64	120	68	30	36	35	23
65	154	170	42	48	45	65
66	52	60	25	31	20	19
67	83	50	27	37	30	24
68	78	91	34	22	40	32
69	202	140	57	45	45	60
70	75	70	55	38	36	50
71	52	42	31	29	30	32
72	96	91	35	40	42	48
73	62	36	31	38	31	11
74	68	63	38	45	38	48
75	96	67	33	35	25	41
76	249	177	60	45	55	52
77	99	127	42	49	42	28
78	142	332	47	47	42	62

Subject Number	Fatigue -- Free Circulation During Exercise Right Arm	Left Arm	Fatigue -- Circulation Occluded Immediately Before Exercise Right Arm	Left Arm	Fatigue -- Circulation Occluded 7 Minutes Prior to Exercise Right Arm	Left Arm
79	36	26	10	7	9	12
80	75	47	22	12	35	18
81	45	43	24	19	15	14
82	125	51	36	40	31	30
83	50	65	24	34	38	37
84	18	22	17	12	16	12
85	69	90	23	30	45	33
86	114	62	31	33	30	35
87	86	81	51	51	51	61
88	111	72	48	41	34	37
89	71	71	26	28	39	37
90	111	106	36	35	36	46
91	89	84	29	24	29	24
92	89	67	47	53	47	50
93	47	67	27	34	45	36
94	81	71	20	26	24	28
95	85	67	57	40	49	36
96	76	52	23	24	21	31
97	149	111	31	29	21	37
98	119	67	29	35	34	22
99	84	51	28	38	31	25
100	169	139	56	44	44	59
Ranges	410/18	620/22	85/10	100/7	83/8	85/11
Total	11,839 / 100	11,204 / 100	4,062 / 100	3,962 / 100	3,736 / 100	4,149 / 100
Mean	118.4	112.0	40.6	39.6	37.4	41.5

TABLE NO. 1 (Continued)

Data shown in this table represents number of contractions or seconds (1 contraction/second) until:

Subject Number	Intolerable Pain -- Circulation Occluded Immediately Before Exercise		Intolerable Pain -- Circulation Occluded 7 Minutes Prior to Exercise	
	Right Arm	Left Arm	Right Arm	Left Arm
1	63	75	76	104
2	50	50	55	70
3	70	50	60	55
4	55	55	50	75
5	60	60	54	55
6	60	65	57	65
7	48	46	40	49
8	45	35	43	44
9	102	75	63	75
10				
11				
12	67	65	67	70
13	62	62	62	73
14	50	50	42	46
15	52		43	
16	38	55	37	50
17	55	47	35	41
18				
19				
20	80	67	65	68
21	68	63	46	65
22	80	57	45	65
23	105	102	69	76
24	51	49	55	56
25	67	95	103	100
26	67	65	65	67
27	71	104	75	73
28	82	67	58	67
29	73	61	68	63
30				
31	61	57	42	58
32	55	58	50	77
33	90	111	89	106
34	66	53	56	63
35				
36	55	48	45	50

Subject Number	Intolerable Pain -- Circulation Occluded Immediately Before Exercise: Right Arm	Intolerable Pain -- Circulation Occluded Immediately Before Exercise: Left Arm	Intolerable Pain -- Circulation Occluded 7 Minutes Prior to Exercise: Right Arm	Intolerable Pain -- Circulation Occluded 7 Minutes Prior to Exercise: Left Arm
37	67	54	48	62
38	50	41	36	48
39	88	67	50	58
40	61	50	65	60
41	34	35	34	50
42	38	49	48	51
43	43	46	36	53
44	50	63	55	50
45	43	55	39	59
46				
47	45			73
48	40	45	40	43
49	90	80	75	91
50	63	57	57	67
51	79	71	71	75
52	63	64	83	65
53	37	53	64	80
54	98	98	80	98
55	49	42	36	49
56	48	60	45	48
57	45	45	44	44
58	46	39	67	63
59	63	71	55	61
60	90	123		121
61	59	57	51	65
62	64	48	47	57
63	75	79	78	89
64	39	65	60	60
65	65	64	60	92
66	45	51	48	61
67	47	50	42	25
68	52	52	61	71
69	67	59	62	76
70	59	41	39	69
71	49	50	49	49
72	44	51	53	67
73	33	40	34	14
74	47	58	60	80
75	38	39	35	44
76	60	54	64	60
77				
78	55	50	51	70

Subject Number	Intolerable Pain -- Circulation Occluded Immediately Before Exercise		Intolerable Pain -- Circulation Occluded 7 Minutes Prior to Exercise	
	Right Arm	Left Arm	Right Arm	Left Arm
79	64	57	62	72
80	50	45	55	40
81	50	56	34	56
82	55	70	49	49
83	50	58	55	57
84	46	63	37	33
85				
86	60	65	58	63
87	63	63	63	74
88	56	48	36	42
89	53	48	56	55
90	83	68	59	67
91	59	59	53	54
92	37	48	47	50
93	44	56	40	60
94	41	46	41	44
95	80	72	73	76
96	49	61	46	49
97	60	58	52	66
98	30	64	59	59
99	48	51	43	26
100	66	58	61	75
Ranges	105/30	123/35	103/34	121/14
Total	5,321 / 91	5,274 / 89	4,816 / 89	5,600 / 90
Mean	58.47	59.26	54.11	62.22

TABLE NO. 2

Latent Pain

A. Left Arm -- Occlusion and work started immediately until the first recording of fatigue.

Subject Number	Intensity of Pain	Pain Elicited in Previous Tests
1	Strong	Yes
2	Moderate	Yes
3	Moderate	Yes
4	Moderate	Yes
5	Mild	Yes
6	Mild	Yes
7	Mild	Yes
8	Moderate	Yes
9	Mild	Yes
10	No pain	No
11	No pain	No
12	Mild	Yes
13	Moderate	Yes
14	Moderate	Yes
15	Mild	Yes
16	Strong	Yes
17	Strong	Yes
18	No pain	No
19	No pain	No
20	Mild	Yes
21	Moderate	Yes
22	Strong	Yes
23	Strong	Yes
24	Strong	Yes
25	Mild	Yes
26	Moderate	Yes
27	Strong	Yes
28	Moderate	Yes
29	Moderate	Yes
30	No pain	Yes
31	Moderate	Yes
32	No pain	Yes
33	Moderate	Yes
34	Moderate	Yes
35	No pain	No
36	Strong	Yes

Subject Number	Intensity of Pain	Pain Elicited in Previous Tests
37	No pain	Yes
38	Strong	Yes
39	Strong	Yes
40	Mild	Yes
41	Strong	Yes
42	Mild	Yes
43	Strong	Yes
44	Strong	Yes
45	Strong	Yes
46	No pain	No
47	No pain	Yes
48	Moderate	Yes
49	Moderate	Yes
50	Moderate	Yes

B. Left Arm -- Work was started and an occlusion was not produced until the first sign of fatigue was recorded. Work was then stopped.

51	No pain	Yes
52	Mild	Yes
53	Mild	Yes
54	No pain	Yes
55	Moderate	Yes
56	Mild	Yes
57	Moderate	Yes
58	Mild	Yes
59	Mild	Yes
60	Moderate	Yes
61	Strong	Yes
62	Strong	Yes
63	Mild	Yes
64	Mild	Yes
65	Moderate	Yes
66	Mild	Yes
67	Moderate	Yes
68	Moderate	Yes
69	Mild	Yes
70	Strong	Yes
71	Mild	Yes
72	Moderate	Yes
73	No pain	Yes
74	Moderate	Yes

Subject Number	Intensity of Pain	Pain Elicited in Previous Tests
75	Mild	Yes
76	Strong	Yes
77	No pain	No
78	Strong	Yes
79	Strong	Yes
80	Mild	Yes
81	Moderate	Yes
82	Mild	Yes
83	Mild	Yes
84	Mild	Yes
85	No pain	No
86	Mild	Yes
87	Moderate	Yes
88	Mild	Yes
89	Moderate	Yes
90	Moderate	Yes
91	Mild	Yes
92	Mild	Yes
93	Strong	Yes
94	Moderate	Yes
95	Moderate	Yes
96	Mild	Yes
97	Strong	Yes
98	Mild	Yes
99	Mild	Yes
100	Moderate	Yes

TABLE NO. 3

Recovery from fatigue after ten minutes rest with free circulation:

Subject Number	Number of Contractions until Fatigue -- Free Circulation -- Right Arm	Number of Contractions Possible after Recovery from Fatigue -- Right Arm	Percent Recovery -- Right Arm
1	105	69	65.7
2	85	75	88.2
3	410	320	78.0
4	40	53	132.5
5	90	85	94.4
6	113	80	70.8
7	135	90	66.6
8	45	35	77.7
10	245	240	97.9
15	155	95	61.3
18	235	190	80.9
20	295	130	44.1
21	227	110	48.5
22	105	55	52.4
23	235	140	59.6
25	65	45	69.2
26	140	95	67.9
27	385	180	46.8
31	140	48	34.3
33	355	260	73.2
38	195	92	47.2
48	80	38	47.5
49	157	63	40.1
54	118	217	183.9
55	145	86	59.3
56	75	42	56.0
57	74	42	56.8
58	86	130	151.2
59	48	65	135.4
60	53	100	188.7
61	148	75	50.7
62	52	115	221.2
66	52	27	51.9
67	83	125	150.6

Subject Number	Number of Contractions until Fatigue -- Free Circulation -- Right Arm	Number of Contractions Possible after Recovery from Fatigue -- Right Arm	Percent Recovery -- Right Arm
68	78	39	50.0
69	202	225	111.4
70	75	58	77.3
71	52	45	86.5
72	96	51	53.1
73	62	43	69.4
75	96	38	39.6
76	249	125	50.2
77	99	92	92.9
78	142	130	91.5
79	36	30	83.3
81	45	30	66.6
82	125	103	82.4
83	50	51	102.0
84	18	27	150.0
85	69	77	111.6
Total			4168.3 / 50
Mean			83.4
Range			34.3/221.2

Recovery from fatigue after fifteen minutes rest with free circulation:

9	180	182	101.1
11	133	170	127.8
12	313	273	87.2
13	85	163	191.7
14	97	95	97.9
16	71	51	71.8
17	110	116	105.4
19	38	60	157.9
24	70	69	98.5
28	110	128	116.4
29	163	68	41.7
30	242	220	90.0
32	117	125	106.8
34	110	200	181.8
35	126	92	73.2
36	50	60	120.0
37	60	75	125.0

Subject Number	Number of Contractions until Fatigue -- Free Circulation -- Right Arm	Number of Contractions Possible after Recovery from Fatigue -- Right Arm	Percent Recovery -- Right Arm
39	215	235	109.3
40	167	145	86.8
41	60	44	73.3
42	90	120	133.3
43	55	55	100.0
44	35	50	142.8
45	46	53	115.2
46	60	67	111.6
47	72	90	125.0
50	60	57	95.0
51	84	125	148.8
52	87	120	137.9
53	175	363	207.4
63	185	130	70.3
64	120	68	56.7
65	154	160	103.9
74	68	161	236.8
80	75	89	118.7
86	114	114	100.0
87	86	90	104.7
88	111	123	110.8
89	71	65	91.5
90	111	117	105.4
91	89	94	105.6
92	89	97	109.0
93	47	63	134.0
94	81	88	108.6
95	85	101	118.8
96	76	72	94.7
97	149	133	89.3
98	119	140	117.6
99	84	75	89.3
100	169	146	86.4
Total			5627.4 / 50
Mean			112.5
Range			41.7/236.8

FIGURE 1

This figure shows the apparatus used for our experimentation and the manner in which the subject was tested. The investigator is seated to the subject's left.

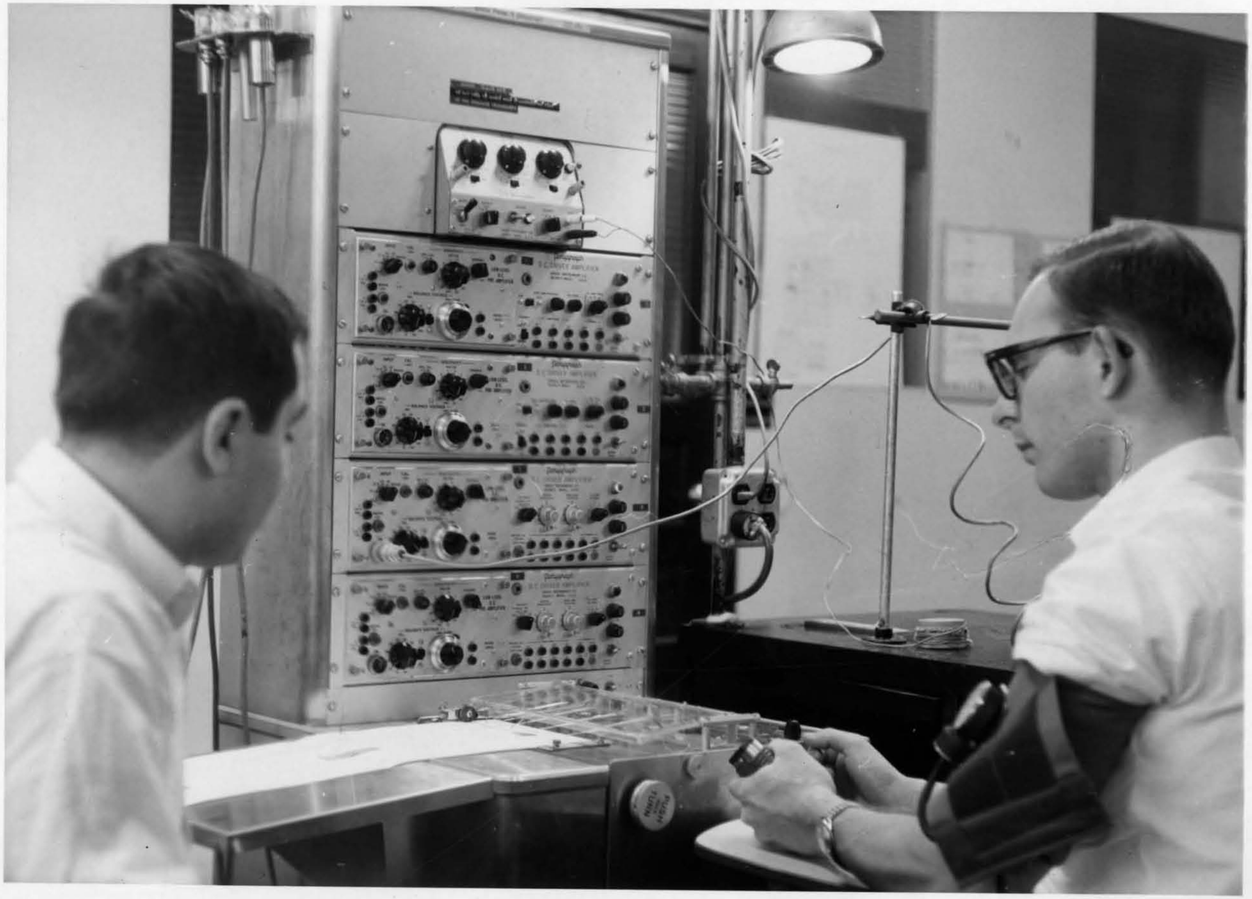


FIGURE 1

FIGURE 2

Subject #24: This figure illustrates the number of contractions achieved until fatigue with free circulation. 1 - 1 = Right Arm; 1 - 2 = Left Arm.

FIGURE 3

Subject #24: This figure shows the number of contractions achieved until fatigue and intolerable pain following an immediate arrest of the circulation. 2 - 1 = Right Arm; 2 - 2 = Left Arm.

FIGURE 2

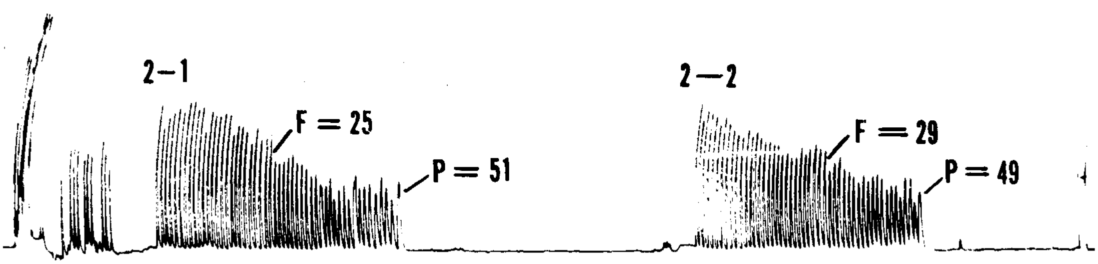


FIGURE 3

FIGURE 4

Subject #24: This figure shows the number of contractions performed until fatigue and intolerable pain after a prior occlusion of seven minutes had been affected. 3 - 1 = Right Arm; 3 - 2 = Left Arm.

FIGURE 5

Subject #24: 4 - 1, (Latent Pain, Left Arm), shows the number of contractions achieved until the first sign of fatigue. The circulation was arrested immediately before the exercise started.

Subject #24: 5 - 1, (Recovery from Fatigue, Right Arm), shows the number of contractions possible after fifteen minutes rest with free circulation.

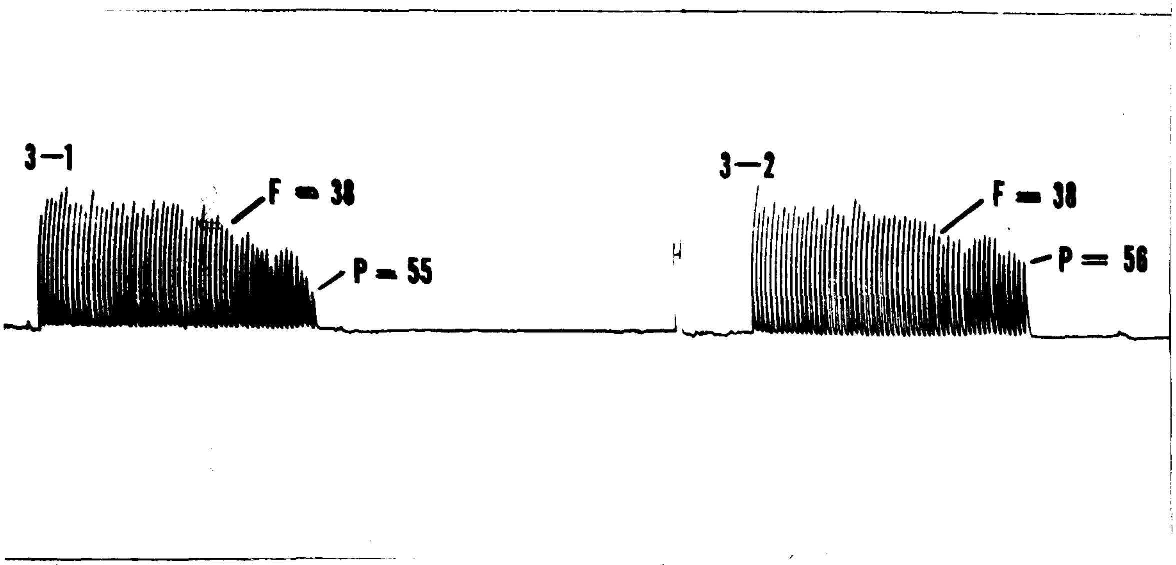


FIGURE 4

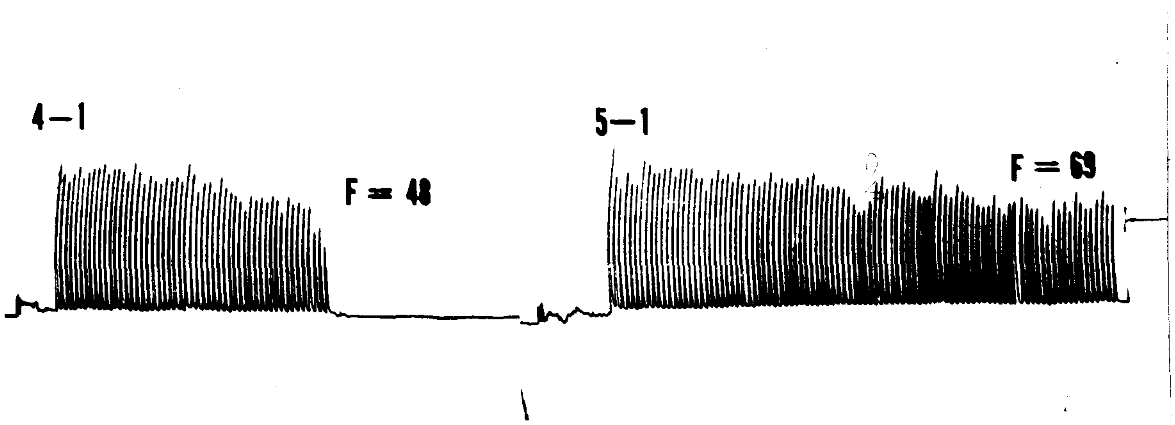


FIGURE 5

FIGURE 6

Subject #35: This figure illustrates the number of contractions performed until fatigue with free circulation. 1 - 1 = Right Arm; 1 - 2 = Left Arm.

FIGURE 7

Subject #35: This figure shows the number of contractions achieved until fatigue following an immediate arrest of the circulation. Subject #35 reported no pain. 2 - 1 = Right Arm; 2 - 2 = Left Arm.

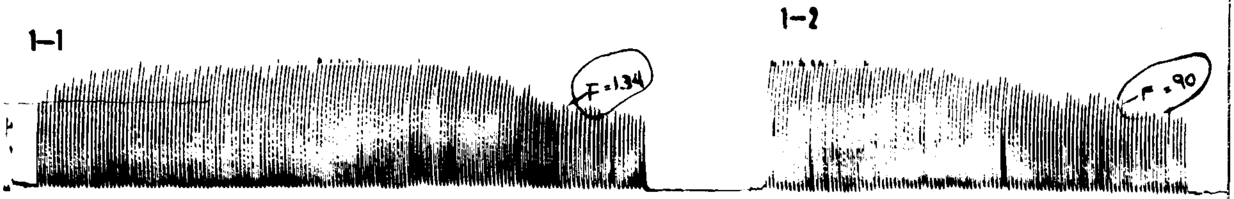


FIGURE 6

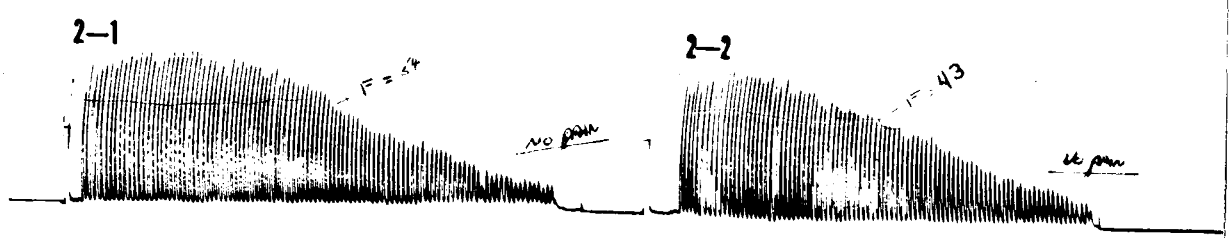


FIGURE 7

FIGURE 8

Subject #35: This figure shows the number of contractions performed until fatigue after a prior occlusion of seven minutes had been affected. Subject #35 reported no pain. 3 - 1 = Right Arm; 3 - 2 = Left Arm.

FIGURE 9

Subject #35: 5 - 1, (Recovery from Fatigue), shows the number of contractions achieved after fifteen minutes rest with free circulation.

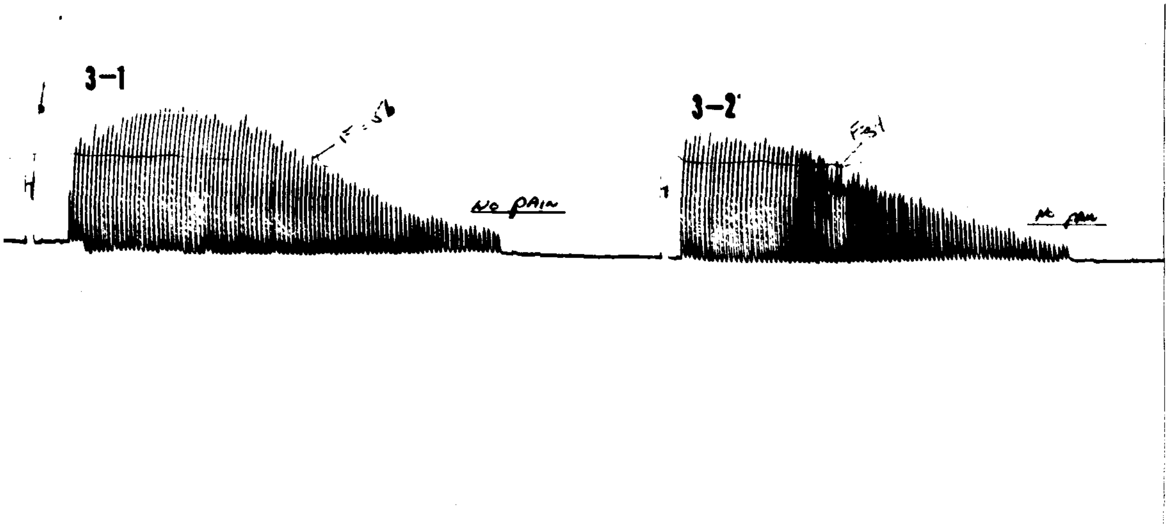


FIGURE 8

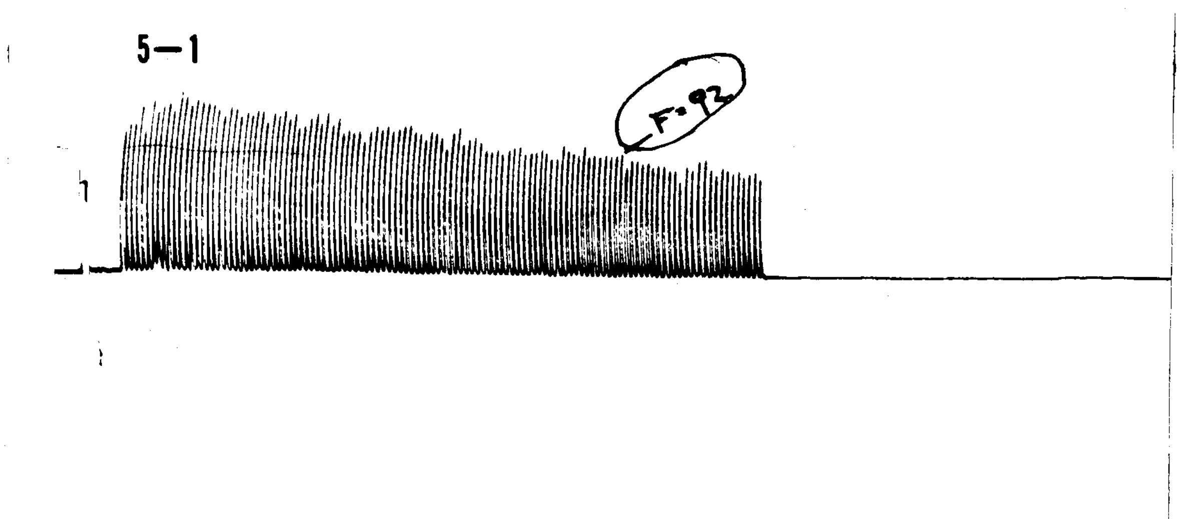
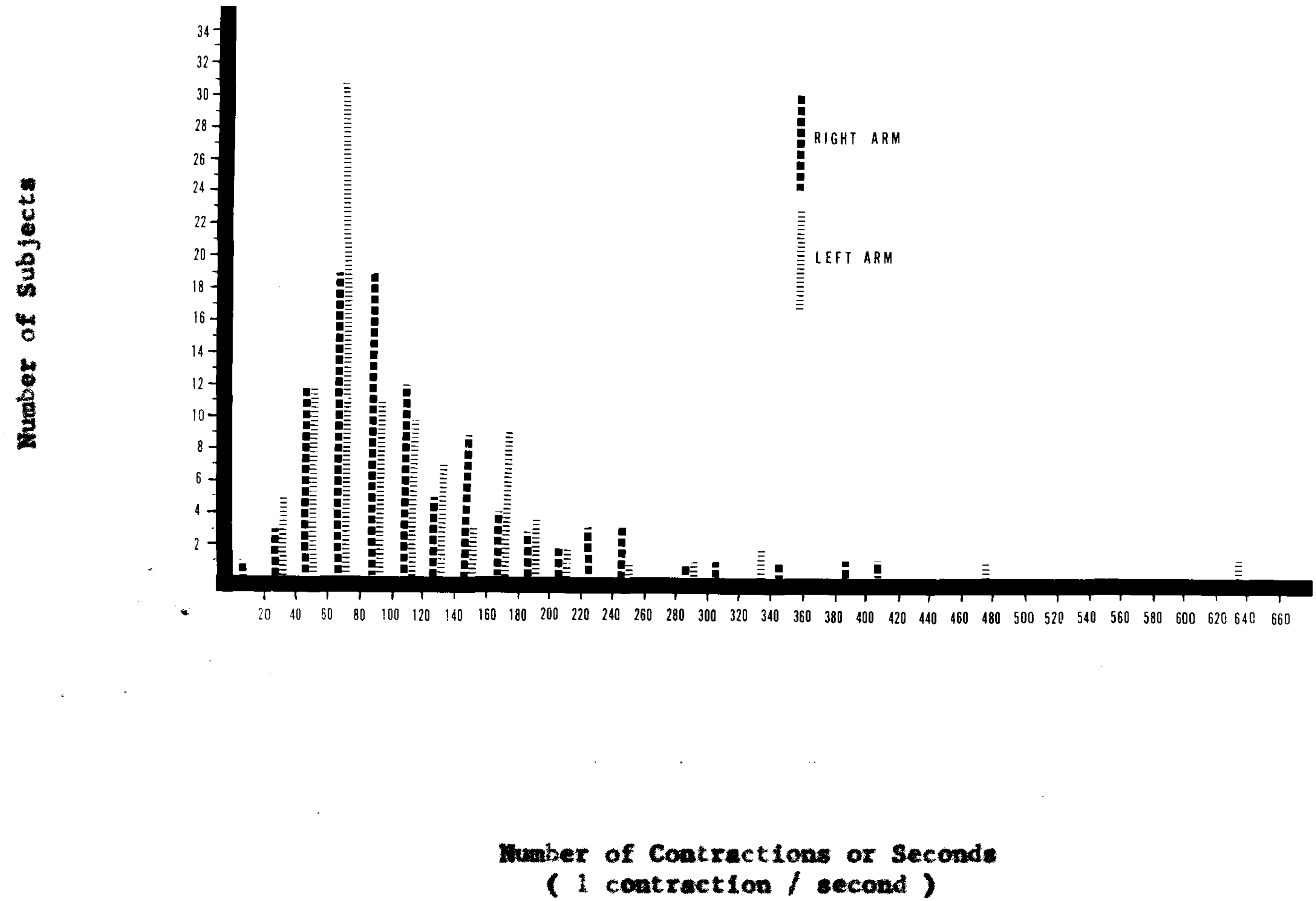


FIGURE 9

GRAPH I Onset of Fatigue with Free Circulation. Wide band tape - right arm; narrow band tape - left arm.

Frequency Distribution:

Number of Contractions until Fatigue	Number of Subjects	
	Right Arm	Left Arm
0 - 19	1	0
20 - 39	3	5
40 - 59	12	12
60 - 79	19	31
80 - 99	19	11
100 - 119	12	10
120 - 139	5	7
140 - 159	9	3
160 - 179	4	9
180 - 199	3	4
200 - 219	2	2
220 - 239	3	0
240 - 259	3	1
260 - 279	0	0
280 - 299	1	1
300 - 319	1	0
320 - 339	0	2
340 - 359	1	0
360 - 379	0	0
380 - 399	1	0
400 - 419	1	0
460 - 479	0	1
620 - 639	0	1

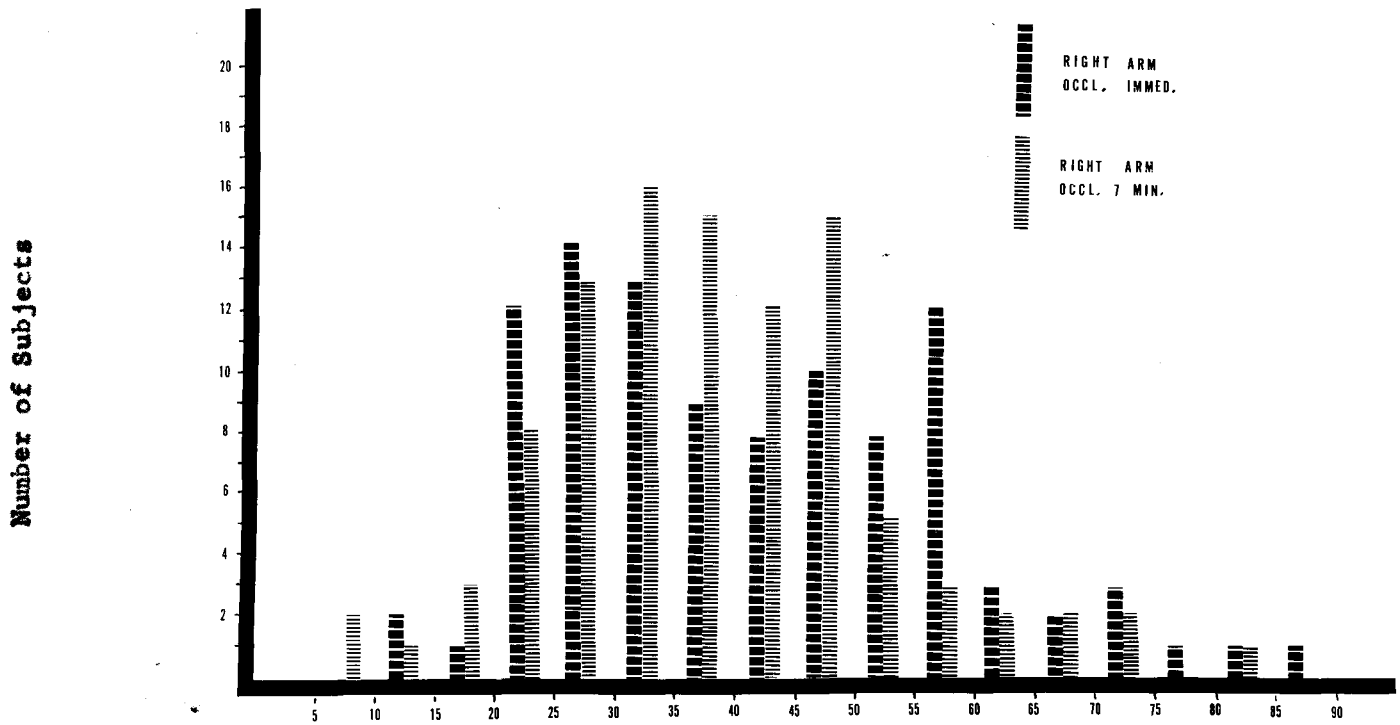

Number of Subjects
34
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
RIGHT ARM
LEFT ARM
20 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500 520 540 560 580 600 620 640 660
Number of Contractions or Seconds
(1 contraction / second)

GRAPH 1

GRAPH II Onset of Fatigue after an Immediate Occlusion and after an Occlusion affected seven minutes prior to Exercise. Right arms.

Frequency Distribution:

Number of Contractions until Fatigue	Number of Subjects: Immed. Occl.	Number of Subjects: 7 min. prior
0 - 4	0	0
5 - 9	0	2
10 - 14	2	1
15 - 19	1	3
20 - 24	12	8
25 - 29	14	13
30 - 34	13	16
35 - 39	9	15
40 - 44	8	12
45 - 49	10	15
50 - 54	8	5
55 - 59	12	3
60 - 64	3	2
65 - 69	2	2
70 - 74	3	2
75 - 79	1	0
80 - 84	1	1
85 - 90	1	0



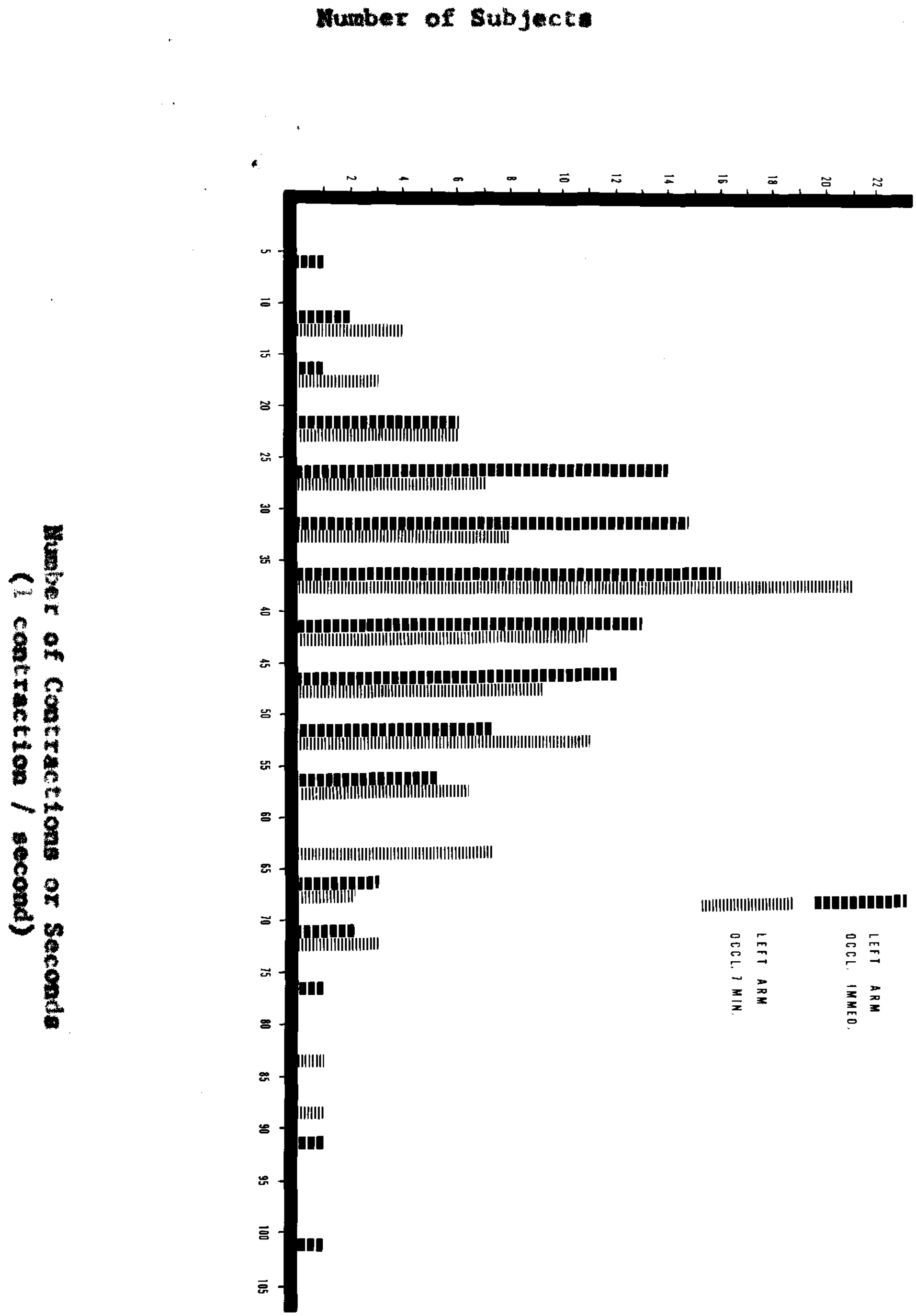
Number of Contractions or Seconds
(1 contraction / second)

GRAPH II

GRAPH III Onset of Fatigue after an Immediate Occlusion and after an Occlusion affected seven minutes prior to Exercise. Left arms.

Frequency Distribution:

Number of Contractions until Fatigue	Number of Subjects	
	Immed. Occl.	7 min. prior
0 - 4	0	0
5 - 9	1	0
10 - 14	2	4
15 - 19	1	3
20 - 24	6	6
25 - 29	14	7
30 - 34	15	8
35 - 39	16	21
40 - 44	13	11
45 - 49	12	9
50 - 54	7	11
55 - 59	5	6
60 - 64	0	7
65 - 69	3	2
70 - 74	2	3
75 - 79	1	0
80 - 84	0	1
85 - 89	0	1
90 - 94	1	0
95 - 99	0	0
100 - 104	1	0



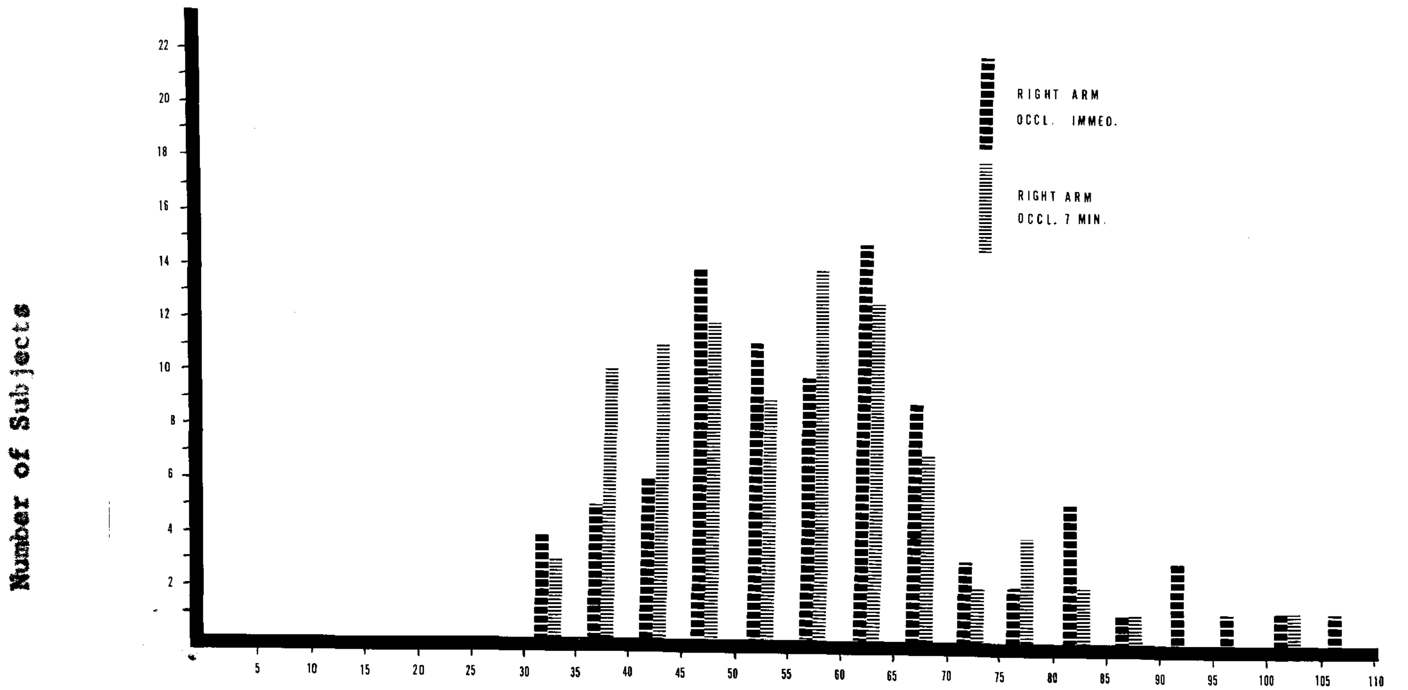
Number of Subjects
2
4
6
8
10
12
14
16
18
20
22
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
LEFT ARM
OCCL. IMMED.
LEFT ARM
OCCL. 7 MIN.
Number of Contractions or Seconds
(1 contraction / second)

GRAPH III

GRAPH IV **Cessation of Work due to Intolerable Pain after an Immediate Occlusion and after an Occlusion affected seven minutes prior to Exercise. Right Arms.**

Frequency Distribution:

Number of Contractions until Intolerable Pain	Number of Subjects	
	Occl. Immed.	7 min. prior
25 - 29	0	0
30 - 34	4	3
35 - 39	5	10
40 - 44	6	11
45 - 49	14	12
50 - 54	11	9
55 - 59	10	14
60 - 64	15	13
65 - 69	9	7
70 - 74	3	2
75 - 79	2	4
80 - 84	5	2
85 - 89	1	1
90 - 94	3	0
95 - 99	1	0
100 - 104	1	1
105 - 109	1	0
110 - 114	0	0



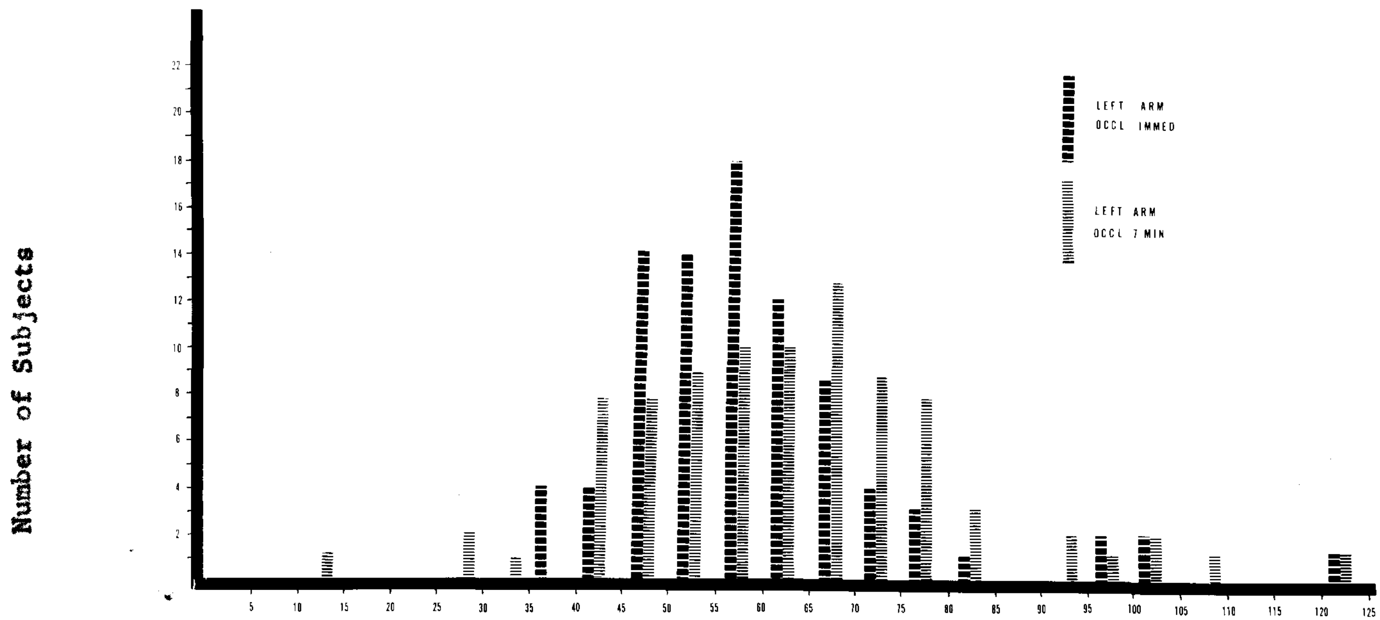
Number of Contractions or Seconds
(1 contraction / second)

GRAPH IV

GRAPH V Cessation of Work due to Intolerable Pain after an Immediate Occlusion and after an Occlusion affected seven minutes prior to Exercise. Left arms.

Frequency Distribution:

Number of Contractions until Intolerable Pain	Number of Subjects	
	Occl. Immed.	7 min. prior
5 - 9	0	0
10 - 14	0	1
15 - 19	0	0
20 - 24	0	0
25 - 29	0	2
30 - 34	0	1
35 - 39	4	0
40 - 44	4	8
45 - 49	14	8
50 - 54	14	9
55 - 59	18	10
60 - 64	11	11
65 - 69	9	13
70 - 74	4	9
75 - 79	3	8
80 - 84	1	3
85 - 89	0	0
90 - 94	0	2
95 - 99	2	1
100 - 104	2	2
105 - 109	0	1
110 - 114	1	0
115 - 119	0	0
120 - 124	1	1



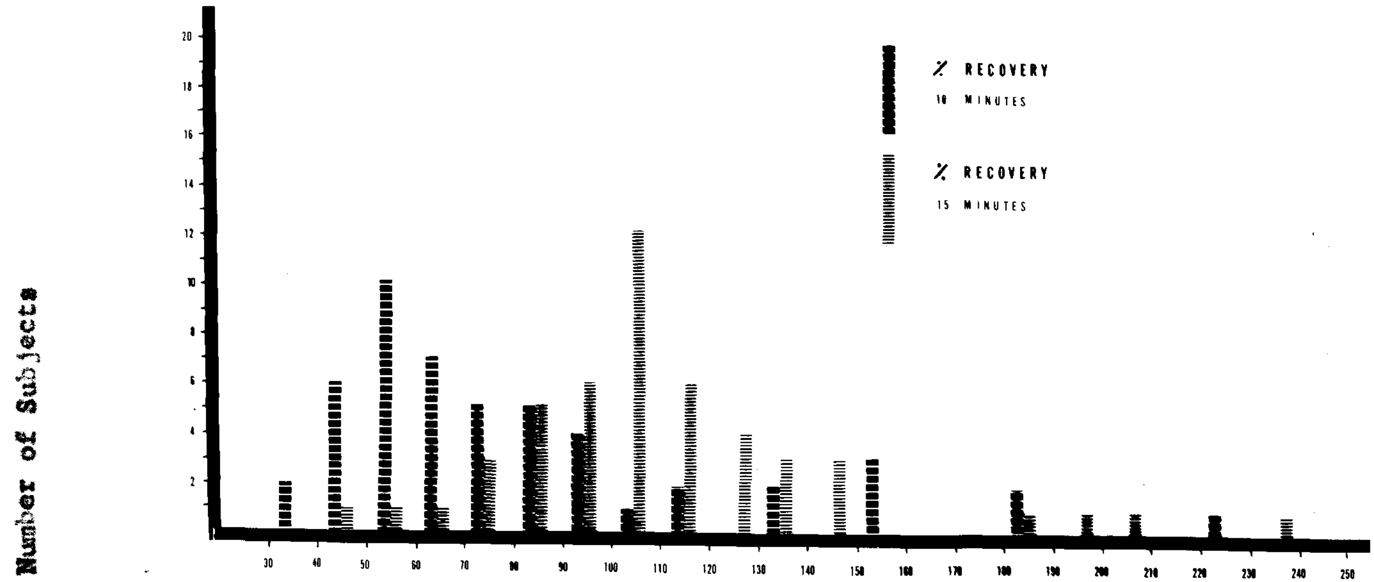
Number of Contractions or Seconds
(1 contraction / second)

GRAPH V

GRAPH VI Percent Recovery from Fatigue after ten minutes rest and fifteen minutes rest. Right arm.

Frequency Distribution:

Number of Contractions until Fatigue	Number of Subjects	
	10 min. rest	15 min. rest
20 - 29	0	0
30 - 39	2	0
40 - 49	6	1
50 - 59	10	1
60 - 69	7	1
70 - 79	5	3
80 - 89	5	5
90 - 99	4	6
100 - 109	1	13
110 - 119	2	6
120 - 129	0	4
130 - 139	2	3
140 - 149	0	3
150 - 159	4	0
160 - 169	0	0
170 - 179	0	0
180 - 189	2	1
190 - 199	0	1
200 - 209	0	1
210 - 219	0	0
220 - 229	1	0
230 - 239	0	1
240 - 249	0	0



Percent Recovery from Fatigue

GRAPH VI

APPROVAL SHEET

The thesis submitted by Jerome Michael Colletti has been read and approved by three members of the faculty of the Graduate School.

The final copies have been examined by the director of the thesis and the signature which appears below verifies the fact that any necessary changes have been incorporated, and that the thesis is now given final approval with reference to content, form, and mechanical accuracy.

The thesis is therefore accepted in partial fulfillment of the requirements for the Degree of Master of Science.

[illegible]-21-66

Date

David S. Jones

Signature of Advisor