THE EFFECT OF A SUPERVISED WALKING PROGRAM ON PATIENTS WITH INTERMITTENT CLAUDICATION

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A thesis submitted to the Faculty of Graduate Studies of the University of Manitoba in partial fulfillment of the requirements of the degree of

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INTRODUCTION

Intermittent claudication is a symptom of chronic arterial occlusive disease (AOD). The arteries in the lower limbs are often obstructed by the atherosclerotic process. This restriction may take the form of a narrowing or a complete occlusion, and collaterals may develop around it. At rest, flows are often adequate, but when the patient starts to exercise, the demand for oxygen in the muscle is increased. Since blood flow cannot increase maximally because of the restriction, oxygen debt occurs, and metabolites accumulate. After a certain distance, pain develops, and the patient is forced to stop walking. This pain is known as intermittent claudication, and the symptoms may interfere with the patient's ability to earn a livelihood, or other needs.

Prescribed treatments have included vasodilator drugs, sympathectomy, and arterial reconstruction. The two former alternatives have not proven of value (1). Arterial reconstruction is of value because it may restore normal hemodynmamics, but, it is not feasible in all patients because of risks and/or the extent of the disease. Also, reocclusion occurs in a significant proportion of cases over a variable period of time (1).

Because of the above reasons, and because the natural history of the disease is such that only a small proportion (less than ten percent) (1) of patients actually develop more severe manifestations such as skin breakdown and/or loss of limb, surgery in patients with claudication is usually reserved for those whose livelihood or other important activities are affected (2).

If there were a treatment not associated with the risks, which improved the quality of life, it would be a valuable addition to the available options. Exercise has been shown to be of value as several studies have indicated an improvement in walking ability after training programs (3-11). However, the studies have not established whether a change in hemodynamics accompanies the increase in functional ability, or how site and severity of disease affect the degree of benefit. This study was undertaken to try and answer these questions.

PART I

THE EFFECT OF A SUPERVISED WALKING PROGRAM ON PATIENTS WITH INTERMITTENT CLAUDICATION

Review of the Literature

CIRCULATION IN THE LOWER LIMB

I - The Normal Limb

A) Relationship of pressure and flow

The peripheral vasculature is a branching, tapering network of distensible tubes. The blood ejected from the heart during systole is received by the aorta and large arteries, which constitute the reservoir portion of the arterial system. During diastole, the recoil of the elastic walls of the vessels provides pressure energy for a continued supply of oxygenated blood to the periphery. The division of the abdominal aorta into the two common iliac arteries is the beginning of the arterial system of the lower limbs.

Repetitive branching increases the number of vessels in parallel and in series. Larger arteries do not contribute much resistance to the flow of blood. It is the small vessels (small arteries, arterioles, precapillary sphincters, capillaries and venules) that constitute the major sites of resistance in the vascular system. Of these, the arterioles are the most important, and, most of the pressure drop occurs in this segment. The relationship of pressure, flow and resistance can be expressed as follows:

$$\text{Resistance} = \frac{\text{arterial - venous pressure}}{\text{flow}}$$

Variations in muscle flow are mainly due to changes in the diameter and therefore the resistance in the arterioles.

Central arterial and central venous pressures do not change much, even during walking. However, as metabolic demands rise, arterioles dilate. In addition, more precapillary sphincters open, and a large number of capillaries are perfused. Resistance decreases and flow increases.

The muscle vascular bed shows a tremendous range of blood flow that varies according to need. In resting muscle, the average flow in man is 2-5 ml/100g/minute (12). Studies in man and experimental animals reveal that their maximal flow capacity is 40-60 ml/100g/minute (12). During maximal exercise, when mean arterial pressure increases 10-20%, the maximal blood flow through the musculature of the lower limbs in man is 12-16 litres per minute, and 30% higher in athletes (12).

The "muscle pump" action plays an important role in the blood flow of the lower limb. Even during quiet standing pressure is exerted intermittently on the walls and contents of the veins. Because the venous system is equipped with a one-way valve system, this pressure forces blood towards the heart. When in an upright position, this lowers the venous pressure by breaking up the hydrostatic column of blood between the heart and the lower limb. With lowered venous pressure, the difference in pressure between the arteries and veins of the limb is

greater, and flow is augmented further through the muscle. During exercise, such as walking, this "muscle pump" effect is even more pronounced. The muscle contraction actually interferes with flow by squeezing the intramuscular arteries. But, this is compensated for by the lowering of venous pressure as explained previously and by the squeezing of blood from the muscle into the veins (13).

B) Measurement of Pressure and Flow

1. Flow

There are several techniques which allow measurement of blood flow in the human limb. Plethysmography is a commonly used technique in which venous outflow from a limb is briefly arrested by means of a pneumatic cuff, while allowing arterial inflow to continue. Under these conditions, the initial rate of volume change during venous occlusion is assumed to be equal to arterial inflow.

Three types of plethysmographs are used most commonly:

i) water-filled plethysmographs

ii) air-filled plethysmographs

iii) mercury in silastic strain guage plethysmographs

The first two types measure volume changes directly as they completely enclose the limb to be measured. The rate of water or air displacement reflects the rate of arterial inflow. This method is fairly accurate when compared to direct intraarterial flow measurements (14). Its major advantage is that it is noninvasive, and can be used for repeated

measurements. However, the apparatus is bulky and must be applied with care. Consequently the subject needs to be still. This factor makes measurements during some types of exercise difficult.

The mercury in silastic strain guage method is less cumbersome to handle in that it eliminates the water or air filled enclosure to be adjusted.

In patients with arterial occlusive disease, and the resulting lower arterial systolic pressures, cuff pressures required to occlude venous flow may impede arterial inflow as well. This presents a problem when flow measurements are necessary in patients subject to this situation.

The indicator dilution methods used to measure blood flows are based on the Fick principle that states that:

$$\text{Blood Flow (l/min)} = \frac{\text{units of indicator/minute}}{\text{(indicator) entering-(indicator) leaving}}$$

An indicator, for example dye, is injected into an artery leading to the vascular bed being studied. Venous blood leaving the segment is sampled. The changing concentration of the indicator is detected and used to calculate the rate of flow.

The thermodilution technique is an application of the indicator-dilution principle in which a known change in heat content of blood is induced at one point in the circulation, and the resulting

change in blood temperature is monitored at a point downstream from the injection site.

This indicator dilution method cannot be easily adapted for repeated determinations because of several limitations:

1) frequent blood sampling required
2) calibration procedures
3) indicator accumulation
4) the need for arterial puncture

However, the technique has provided reproducible results and has been used to measure extremity flow (15).

The local clearance method involves the washout or clearance of a truly diffusable, radioactive tracer from the tissue. Essentially, after its injection, the concentration of radioactivity is counted over time to calculate the washout of the isotope by blood flow. The rate at which the isotope is washed away depends upon its concentration in the tissue, and the rate of capillary blood flow. Xenon^{133} has been used extensively by Lassen, Tonneson and others, especially for measuring flows during exercise, where previous methods had made it difficult (16-18). Other radioisotopes that have been used include iodine^{125} and technetium^{99}. The validity of this method depends upon several factors: the isotope should be truly diffusable, it must not interfere with the steady state of the system, and there must be uniform tissue labelling. The major advantage of this method is that the clearance can

be followed from a depot of isotope in saline during rest and exercise in a muscle. There is still some controversy over the validity of this method for blood flow measurement in varying tissue beds (19). However, its use for measuring flows in patients with arterial occlusive disease was outlined by Tonneson (18) who found that the use of exercise blood flows determined by the $Xenon^{133}$ clearance technique gave better discrimination between normals and patients than does plethysmography because the latter cannot be used during exercise.

2. Pressure

Blood pressures can be measured intra-arterially, but this method is invasive. There are good indirect methods that allow measurement of arterial pressure; usually a pneumatic cuff and stethoscope being the sole equipment required. The cuff is wrapped around the limb in question, and Korotkoff sounds, heard by the stethoscope placed over an artery distal to the cuff is commonly used for clinical pressure determinations. This auscultatory method utilizes the appearance of the first sound during cuff deflation to signify systolic pressure, and the onset of "muffling" of the sound as diastolic pressure.

When arterial pressures are low, as in arteries distal to sites of obstruction, the Korotkoff sounds are often impossible to hear through a stethoscope. The transcutaneous Doppler ultrasonic flowmeter is an example of equipment that can be employed to pick up even small flows in

an artery where pressures are very low. This is done by directing high frequency sound towards the vessel in question. The frequency is not changed when it is back scattered by non-moving surfaces. But, when it is reflected from moving particles, such as cells within the bloodstream, sound waves are shifted in frequency by an amount proportional to flow velocity (20). As the cuff is gradually deflated, the detector, placed over a distal artery, emits responses as soon as the falling cuff pressure allows the flow of blood into the limb segment. This signifies systolic pressure. This method of systolic pressure measurement has proven easy to perform and the results reproducible (21).

Another way to measure limb systolic pressures utilizes the pulse pick-up method. This involves placement of capacitance or other pulse pick-ups over the artery. Mechanical displacement by a pulsating artery of the sensitive pick up, signals when cuff pressure falls just below systolic pressure. One drawback of this method is that the tension needed to apply and hold the pick up in position is sometimes too severe for limbs with low pressures, rest pain or gangrene.

The spectroscopic method requires that the foot be elevated to decrease blood contained in the superficial vessels. A pneumatic cuff is inflated prior to returning the limb to a horizontal position. A hand spectroscope is an instrument used to detect the return of oxyhemoglobin in the skin distal to the cuff during gradual deflation.

The visual "flush" method duplicates the previous process, but utilizes the naked eye to observe when the return of a pink flush to the skin of the foot or digit, denotes onset of flow. Tests of both these methods agree well with the results of pulse pick up measurements (22).

C) Control of Circulation in Vascular Smooth Muscle

1. Basal Tone

Smooth muscle vessels exhibit a basal tone. Inherent myogenic activity of the smooth muscle in the arterioles and precapillary sphincters is responsible for a basal vascular tone which keeps these vessels in a state of partial constriction. This basic activity of smooth muscle is manifest even in the absence of extrinsic nervous influences, or of blood borne agents such as adrenaline, noradrenaline, angiotensin or vasopressin (23).

2. Central Control

The adrenergic vasoconstrictor influences arise principally from the rostral region of the medulla oblongata where tonically active neurons located in the lateral reticular formation cause generalized vasoconstriction in most vascular beds. This medullary region is known as the vasomotor center, and it exerts its control on the cardiovascular system via sympathetic adrenergic pathways which are tonically active. They have an inherent tendency to transmit nerve impulses all the time, thereby maintaining even normally a slow rate of firing in essentially

all vasoconstrictor nerve fibers of the body at a rate of about one-half to two impulses per second (24). This continual firing pattern is known as sympathetic vasoconstrictor tone, and the partial state of contraction it produces in the blood vessels is called vasomotor tone.

The primary influence on the vasomotor center is exerted by the stretch receptors, or baroreceptors. These mechano receptors are located at strategic high pressure sites of the cardiovascular system; namely the carotid sinus, the aortic arch, the thyrocarotid junction and cardiopulmonary area (25).

The medullary cardiovascular center also collaborates intimately with higher centers in the cortex by means of descending excitatory and inhibitory pathways. This higher center may modulate or even dominate control of the tonically active vasomotor center.

The vasomotor center, then, integrates information from the periphery and higher autonomic control system and is capable of regulating blood pressure, the cardiac output, and flow distribution.

3) Neural Control

Primarily, the sympathetic adrenergic vasoconstrictor nerves act by releasing noradrenaline (NA) which combines with alpha receptors in the membranes of the smooth muscle cell and induces tonic contraction of this muscle. The general function of this system is blood pressure control. The activity of these nerves supplying skeletal muscle vessels

modulates blood pressure by reflexly altered afferent impulses from baroreceptors located mainly in the carotid sinus and aortic arch. Blood vessels tend to constrict in response to sympathetic adrenergic discharge to the vessels during exercise. Local metabolic factors in the exercising muscle bed itself actually override any significant effect of this discharge there. However, the generalized constriction response supports the blood pressure rise in the face of vasodilatation in the large exercising muscle areas. Vasodilator fibers, cholinergic sympathetic fibers, have been demonstrated in dog and cat, but their presence cannot be taken for granted in man (26). They release acetycholine to stimulate receptors in the vascular smooth muscle and produce vasodilatation. A barrage of vasodilator impulses to the muscle vascular bed accompanies other sympthatic responses to coordinate the need of the muscles for a high blood supply during a defence reaction - the "fight or flight" response.

4) Hormonal Control

The adrenal medullae secrete both epinephrine and norepinephrine. When the sympathetic nervous system throughout the body is stimulated to cause direct effects on the blood vessels, it also causes the adrenal medullae to secrete these two hormones which reinforces the action of neurogenic control. This is especially true of epinephrine. These hormones then circulate throughout the body and accentuate the neural effects on the vascular system. Two types of receptor sites have been found on the smooth muscle walls of the vasculature supplying

skeletal muscle. These are known as alpha and beta sites, and occur in varying concentrations in different tissue beds (27). Norepinephrine acts primarily on alpha receptors, and has slight effects on beta sites. Epinephrine, on the other hand, excites alpha and beta receptors equally. In the vascular bed of skeletal muscle, the arteriolar smooth muscle contains so many beta receptors that epinephrine secretion causes a resistance decrease.

Various other substances such as vasopressin, angiotensin II, adrenal corticoids, serotonin (5-H-T), prostaglandins and histamine may exert various influences, but their roles are not well understood. Their effects may range from a permissive action, as in the case of corticoids, to the reinforcement of sympathetic vasoconstriction by angiotensin II (28). Again, though, hormonal control is far less influential than its sympathetic neural counterpart.

5) Local Control (Autoregulation)

i) Theories of Control

"The capacity of tissues to regulate their own blood flow is referred to as autoregulation" (29)

All of the details explaining the mechanism responsible for autoregulation are not known, and may vary with different vascular beds. The use of the term is often restricted to mean the ability of some tissues or organs to maintain a relatively constant rate of blood flow

through them despite changes in arterial perfusion pressure over a moderate range of pressure. Autoregulation involves a local alteration in pressure and resistance that is automatically followed by flow changes. Several theories have been proposed in an attempt to explain the phenomenon. These include: the tissue pressure hypothesis, the myogenic hypothesis, and the metabolic hypothesis (30). The tissue pressure hypothesis can be summarized by stating that an increase in perfusion pressure produces an increase in blood volume of the tissue, and a net transfer of fluids from the intravascular to the extravascular compartments. The resulting increase in tissue pressure is believed to compress the thin-walled vessels, and reduce the flow of blood to the tissues. However, this mechanism could only operate in an encapsulated organ, and evidence for this theory is lacking.

Support for a myogenic hypothesis came from several reports (31). These are based solely on negative evidence: that is that an autoregulatory response occurred despite manipulation of variables such as oxygen, altered perfusion pressures, and denervation. From this research evolved the myogenic hypothesis which states that vascular smooth muscle contracts in response to stretch, and relaxes with reduction in stretch. Therefore, the initial flow increment produced by an increase in perfusion pressure which distends the blood vessels would be followed by a return of flow to the previous control level by contraction of the smooth muscles of the resistance vessels and decreasing their diameter (32).

The smooth muscle found in the arterioles and sphincter sections of the resistance vessels is known as visceral or single-unit smooth muscle. Many independent pacemakers exist in the precapillary vessels, resulting in "vasomotion" and rhythmic closure of the precapillary sphincters (33). Stretch of the vessel walls increases the rate of firing of action potentials in precapillary sphincter muscles, causing contraction. Conversely, the reduction of membrane distension decreases the discharge rate, and contraction is relaxed.

The metabolic hypothesis states that vasodilation of vessels in metabollically active tissue is due to relative concentrations of local metabolites. Many substances have been proposed as mediators of metabolic vasodilatation, and they vary with the tissue involved. Some of the earliest proposed substances include lactic acid, CO_2, and hydrogen ions. Another widely investigated candidate is PO_2. Changes in oxygen tension provoke changes in the contractile state of vascular smooth muscle: increases in PO_2 lead to increased contraction which in turn leads to a reduction in PO_2, and this results in the relaxation of smooth muscle. The osmolality of the tissue fluids are also thought to play a major role in influencing local control. Other proposed vasodilators are: potassium ion, inorganic phosphates, adenosine (especially in the coronary vessels), and, more recently, prostaglandins (34).

Currently, it is thought that control of local blood supply in skeletal muscle is achieved by a combination of myogenic and metabolic

factors. The two act to provide blood flow according to tissue needs even when arterial pressure is experimentally altered, and despite the absence of neural and hormonal influences.

ii) Reactive Hyperemia

a) Review

Reactive hyperemia is the local vascular response to temporary arterial inflow occlusion. It occurs when flow is reintroduced, and increases to a point above control resting level. This can be explained by the effects of an accumulation of metabolites, and the low transmural pressure combining to allow large quantities of blood to perfuse the area. Blood flow returns to preocclusion values over varying time periods, depending on the length of ischemia, and the relative health of the arterial channels. This appears to take place independent of any nervous connections (35). Following five minutes of ischemia, the reactive hyperemia blood flow to the calves of a group of twenty normal subjects varied from 14 to 38 cc/100 cc/min. (avg. 23 cc/100 cc/min) (36). Flows were measured by venous occlusion plethysmography during the first 5 seconds of flow after arterial inflow occlusion. This wide range of peak flow is also documented in similar studies (36). In addition, Eichna and Wilkins (37) reported that hyperemic blood flows were augmented with successive trials, five minutes apart during an experimental session. These flows varied from 1 cc to 8 cc/100 cc/min. above previously measured values in the calves of forty-two normal subjects.

Characteristically, second trial flows exceeded the first, and those of the third trial exceeded the second. By the fourth determination, there was no further increase. The average increase between the first and fourth measurement was 4 cc/100 cc/min, or 20-25% of the initial flow. This would seem to indicate a gradual dilatation of peripheral vessels during the time of testing.

Reactive hyperemia blood flow varies directly with arterial pressure (37.,38). Other factors also affect hyperemic flows, and were tested under the following conditions:

1) during full body heating to promote peripheral vasodilatation
2) during local heating of the limb in question to 40°C after five, ten and fifteen minutes of ischemia
3) during mild vasoconstricctor stimuli, eg. i) deep breathing, ii) ice on face and neck, iii) pricking the skin
4) during strong vasoconstrictor stimuli, i.e. cooling
5) following preganglionic sympathectomy
6) during sleep - both natural and narcotically induced.

Eichna and Wilkins (35) found that flows were relatively unaffected by the aforementioned factors. The strong vasoconstrictor stimuli(4) and some vasodilator stimuli (1) altered flows only if there was accompanying changes in arterial pressure.

To study the effect of altering arterial pressure on blood flow, a study of red blood cell velocity in the cat sartorius muscle

circulation was undertaken by Henrich et al (38). The femoral artery and vein supplying the isolated sartorius muscle were cannulated and connected to the central ends of the contralateral femoral vessels by means of a circuit containing a 5 ml reservoir interposed between the vessel and the central artery. A valve arrangement permitted perfusion of the muscle at desired pressures and shift between two perfusion pressures without appreciable delay. They found that the time to peak flow remained constant over the pressure ranges tested even though hyperemia duration varied considerably.

The myogenic theory of autoregulation may explain the results of this study. The higher arterial pressures cause a greater stretch of the resistance vessels. When the arterial occlusion is terminated, a myogenic constrictor response is triggered, and flow is allowed to decrease rapidly. A second explanation for the decreased hyperemic flow duration at higher pressures may be that more rapid washout of metabolites occurs with higher peak flows.

b) Role of Skin and Muscle Vasculature

Excluding bone, the lower limb is made up of two main tissue beds: muscle and skin. When measuring blood flows with the plethysmographic method, the flows of muscle and skin are included in the calculated total flow. From measurements done in rabbits, Folkow and Neil (39) deduce that total skeleton marrow blood supply per minute would

be about 400 to 600 ml per unit weight; or 8 to 12% of resting cardiac output.

Although reactive hyperemia occurs in both skin and in tissues deep to the skin, the greatest contributor to the increased flow values is muscle (40). To investigate this conclusion, Coles and Cooper (40) placed a subject's forearms in plethysmographs with the water at body temperature. Forearm flows were measured before and after a five minute period of circulatory arrest. Then the left forearm was cooled by water at 12^{o}C for 20 minutes within the plethysmograph. Measurements were repeated, and the hyperemia in the left forearm was considerably reduced. It could be concluded that both skin and muscle circulation contributes to hyperemic flows in the warm human forearm. To insure that the post-cooling hyperemia reflected that of intramuscular vasculature, another series of experiments were repeated in which skin flow was halted by adrenalin iontophoresis. Results indicated little absolute difference between the reactive hyperemia in the cold forearm subjected to iontophoresis, and the cold forearm which had not been treated. Therefore, reactive hyperemia flows in warm human forearms reflect flows of both skin and the muscle it surrounds. However, when cooling has taken place, as in the previous experiments, hyperemic flows are attributed to the muscular vasculature alone.

c) Role of Training

The effects of training on reactive hyperemia in the human calf has been studied (41,45). Using strain guage plethysmography, Kroese (41) compared reactive hyperemia flows in trained and untrained subjects with matched ages. He found a significant difference in maximal flows between trained adult groups, and their untrained counterparts (Table I) (41).

Table I

	Age 24		Age 58	
Max. Flows	Trained	Untrained	Trained	Untrained
ml/min/dl)	38.9	26.5	37.5	23

No significant difference was found between the groups in basal flow or recovery time. Mahler et al confirms this (45). This may reflect a trained response of the arterioles which have been dilated repeatedly during recurrent periods of running. Kroese suggests that this training of the arterioles may induce a greater ability of the arterioles to dilate in response to the stimulus of circulatory arrest. He tested this theory by repeating his experiments on subjects who had one leg immobilized in a cast for 6.5 weeks (41). These legs showed a significantly lower post ischemic maximal flow than the limbs which had not been immobilized. In addition, six weeks after the cast was removed, maximal flows increased with resumed use of the afflicted leg. Kroese emphasizes that since arterioles receive few stimuli for dilatation during leg immobilization, there is a reduced ability to dilate in response to circulatory arrest.

iii) Exercise Hyperemia

The vascular response to exercise differs in two ways from reactive hyperemia. Firstly, hyperemia after exercise has been shown to occur solely in the tissues deep to the skin (40). Secondly, exercise hyperemia is primarily evoked by local metabolite accumulation occurring in the exercised limb, and is linearly related to the amount of work performed provided it exceeds a certain minimal quantity (43). It is thought that up to a critical level, blood flow increases with the workload, and-removes the products of metabolism. Beyond this point, at which blood flow can no longer increase, a metabolic debt is established that must be repaid in the post exercise period. The magnitude of this debt determines the excess flow that is called post exercise hyperemia. When reactive and exercise hyperemia flows were compared in healthy subjects, Bartoli et al (44) found that only in the duration of hyperemia (i.e. time to return to basal flows) did a difference in the two reactions exist. The experimenters compared hyperemia flows after five minutes of arterial inflow occlusion with the flow characteristics after 135 seconds of exercise on an electronic foot ergometer at 50 kg. Mahler et al (45) found no significant difference in post exercise reactive hyperemia between controls and marathon runners when measuring flow and pressure components. However, recovery half times (time for mean arterial velocity to return to one half the increase over resting velocity values as measured by Doppler ultrasound) was significantly longer during exercise

hyperemia in control subjects than in marathon runners. Exercise was performed on a foot ergometer for four minutes, and flow velocities measured over the femoral artery immediately after work stoppage. It should be noted that the runners performed significant ly more work in the allotted time (control subjects did 146 kg, and runners completed 179 kg, $p<.02$) (45).

D) Effects of Exercise

1. On Lower Limb Flow

During muscular contractions, blood flow may actually cease through pinched arteries, only to stream through rapidly between contractions. Folkow et al (46) used the $Xenon^{133}$ clearance technique to substantitate this theory by measuring blood flows to the limb during heavy rhythmic exercise. The subject worked while tilted at a 60^{o} angle, and also while supine. The authors investigated the influence of transmural pressure differences as controlled by the subject's position. Maximal flow rate during supine exercise was significantly less than flows measured in subjects exercising at a 60^{o} angle. These observations supported the theory that the pumping action of the muscles on distended veins with competent valves caused a rhythmic emptying of venous segments, and a subsequent lowering of venous pressure. This resulted in a net gain in the pressure head (Pa-Pv) and flow increased accordingly.

Indicator and thermodilution or isotope clearance techniques have been employed by many investigators to measure blood flows during

exercise (17,47,48). Tonneson (17) had his subjects exercising on an ergograph that mimmicked the gastrocnemius contractions of walking. Using $Xenon^{133}$ clearance, he found that blood flow increased gradually with increased workloads up to a maximum of 40 ml/100 gm/min. At approximately one-half the maximum capacity for muscular exertion, no further increase in flow rates occurred. This is probably due to the limiting effect of squeezing the arteries and preventing a further increase in flow during hard muscular contraction. Tonneson and Sjersen (49) later confirmed that the upper limit of muscle flow appears to be reached rapidly in 30-48 seconds after onset of exercise.

Pentecost (47) using indicator dilution technique, measured blood flows in the external iliac vein before, during and after exercise on a bicycle ergometer. His results agreed with other work and showed that the onset of exercise results in a rapid increase in perfusion of the working limb. By monitoring oxygen consumption, he found that it too, increased to a maximum level during exercise of about 231-248 ml/min. in comparison to the 20-24 ml/min. at rest. Hlavova et al (48) also substantiated these results.

Wahren and others (50) compared fit, male subjects aged 25-30 with men aged 52-59 of comparable fitness levels, and found that even with increasing age, blood flows increased linearly with oxygen consumption at submaximal workloads in all subjects.

Artificially induced ischemic exercise in normal subjects can demonstrate a post exercise hyperemia considerably higher than that measured after normal exercise conditions (51). Hillestad (43) compared peak calf flows under exercise conditions similar to those assigned to subjects with tourniquets, and after one minute of ischemic exercise. The post ischemic exercise flows averaged 29.8 $\pm$ 6.0 ml/100 ml/min. These were significantly higher than peak flows following similar levels of free exercise (12.0 ml/100 ml/min). The post exercise hyperemia in the ischemic limbs was prolonged over that measured in the normal subjects. These levels in the normal limb are relatively low because of the low metabolic demand of the minute of exercise. The limb after ischemic exercise may mimic that of a muscle bed distal to an arterial obstruction in a subject with peripheral vascular disease. The abnormally prolonged time of increased muscle blood flow may reflect greater dilatation of intramuscular arteries when subjected to increased demands for nutritive flow during and after ischemic exercise.

2. On Ankle Systolic Pressures

The greatest drops in mean pressures in the resting circulation of man occurs in the arterioles. When systolic pressures are recorded at the level of the ankle, values are usually higher than the brachial (22).

During walking exercise, vasodilatation of the arterioles in the muscle results in decreased peripheral resistance. Flow is augmented

to meet the metabolic needs of the working muscle. Figure 1 in Carters' review (22) illustrates the brachial and ankle systolic pressure response to exercise in healthy subjects. Before exercise, systolic pressures at the ankle are greater than brachial, and the brachial minus ankle pressure difference is negative. After exercise, there is a slight fall in ankle pressures, and some rise in the brachial pressure. However, the brachial pressure remained lower than the ankle throughout the period of post exercise measurements.

Strandness and Bell (52) utilized treadmill walking at 2 mph, 12% incline, to stress their normal control subjects. They found that after five minutes of exercise the ankle pressures remained at 140 mm Hg. No data regarding systemic pressure response was provided.

E) Effect of Training

1. On Lower Limb Blood Flow

Using the $Xenon^{133}$ clearance technique to calculate flows during exercise, several authors have evaluated the effect of training on blood flow to the leg muscles (17,53-55).

Grimby et al (53) compared muscle blood flow at submaximal and maximal exercise levels in both trained and untrained subjects. When flow values were expressed as $\frac{\dot{V}O_2}{\text{Max. } \dot{V}O_2} \times 100$, there was no significant difference between trained and untrained subjects at any given workload. However, when flows were compared at equal VO_2 levels, the untrained

subjects had an average flow rate significantly higher than that of the trained. Muscle blood flows had increased gradually with increasing work loads in both groups. Maximal flows reached values of equal proportions for trained and untrained subjects alike. The authors concluded that an untrained individual will have a higher blood flow per unit muscle tissue at comparable workloads than a well trained counterpart.

2. On Local Enzyme Activity

Studies have shown that a good correlation exists between the increasing ability of a muscle to perform prolonged exercise and an increasing content of respiratory enzymes (55-57).

Varnauskas et al (55) studied blood flow and enzymatic activity in skeletal muscle in seven subjects before and after training. A six-week schedule of 3x/week cycling regimen was assigned. Significant increases in maximal oxygen consumption were measured in all subjects. The vastus-lateralis blood flow, when measured using the $Xenon^{133}$ clearance technique at a workload at 60% Max.$\dot{V}O_2$ decreased after 14 days of training in all but one subject. The most prominent effect of training was the 44% increase in succinate dehydrogenase (SDHG) activity, an enzyme probably present only in the mitochondua and constituting an integral part of the respiratory chain (58). This parameter was sampled by muscle biopsy. Measurements of leg circumference ruled out any relationship between leg size, or change in size, and blood flow changes.

These findings of increased oxygen extraction due to enhanced SDHG activity, suggests that less blood flow is needed in the muscle to secure the required amount of oxygen for the work output.

3. On Capillary Density

Hermansen and Wachtlova (59) compared the capillary density of skeletal muscle in well trained and untrained men. They emphasized that the number of capillaries per square millimeter were approximately the same in the two groups. However, the average size of the muscle cell in well trained muscle was larger than the untrained muscle cell. With the same number of capillaries observed in both trained and untrained muscle sections, yet a smaller number of fibers per section, the number of capillaries per fiber must be higher in the well trained muscle. This would lend itself to improved blood and nutrient supply, and more efficient metabolic waste removal.

4. Conclusions

Training has been shown to improve the muscle's ability to extract oxygen from its blood supply by decreasing the ratio of the number of muscle fiber per capillary, and increasing respiratory enzyme activity. Succinate dehydrogenase, reduced diphosphopyridine nuclietide dehydrogenase, DPNH cytochrome c reductase, succinate oxidase and cytochrome oxidase activities have all been shown to increase approximately twofold in response to training (56).

Exercise muscle blood flow is also affected by training. Untrained individuals achieve maximal flows of the same magnitude as trained subjects, but at any given submaximal workload the untrained have higher flows. This suggests that a higher rate of flow per unit tissue is available to the untrained muscle, whereas, the trained muscle group makes more efficient use of the available nutrients.

Muscle lactate accumulation has been suggested as a source of muscle exhaustion, but Saltin (54) indicates that it may be the pH changes that accompany increased lactate levels that decrease the speed of many biochemical reactions in the muscle cell. This would limit the availability of energy and cause fatigue.

The vascular response to training when tested during reactive hyperemia showed an ability to allow higher peak flows in trained limbs as compared to untrained limbs (41). It has been suggested that repeated dilatation of the arterioles during training sessions augmented the ability to dilate in response to circulatory requirements. When exercise hyperemia was compared between marathon runners and control subjects, mean arterial velocity recovery was significantly shorter in the trained subjects (45). Again, this may indicate a training response of the vasculature to dilate quickly and wider so that cellular needs are satisfied in the most efficient way.

II - THE ABNORMAL LIMB

A) Arterial Occlusive Disease (AOD)

1. Atherosclerosis: An Overview

The most frequent cause of chronic limb ischemia in an overwhelming majority of patients is atherosclerosis. The available literature on atherosclerotic lesions reveals that the ediology, cause and mechanism of the production of atheromatous lesions and the progression of atherosclerotic disease are not completely understood.

The role of local endothelial injury in atherosclerosis has long been recognized and many factors can potentially contribute to endothelial damage including: hemodynamic factors, metabolites, hormones, toxins and viruses (61). Plasma lipoproteins penetrate into the artery wall. When the endothelial barrier is broken and platelet aggregation occurs, the underlying cells are exposed to very high lipoprotein concentrations. The result is cellular uptake of lipoprotein. Platelets appear to contain and release a very potent factor that is mitogenic for smooth muscle cells, and thus atherosclerotic lesions proliferate.

Elevated fibrous and complicated plaques represent a more advanced stage of the disease. These plaques are the basis for many of the clinical manifestations of atherosclerosis such as a thrombosis leading to abrupt narrowing or occlusion of a vessel. Also, atheromatous or thrombotic fragments may break off and embolize to a more distal portion

of the arterial tree. Weakness of the vessel walls due to degeneration may lead to aneurysmal dilatation.

The progress of atherosclerosis is slow, usually spanning several decades. Lesions tend to progress with age, but both "early" and "late" lesions are found in the same patient. Investigators now know that early changes in the vessel wall can be seen as soon as three years of age, and, in humans, are common by the second decade (62). The process of atherosclerosis is enhanced by the presence of diabetes, hypertension, lipoprotein abnormalities, obesity and smoking (61,63,64).

Atherosclerosis predominantly affects large and medium size arteries. Often it develops at arterial bifurcations, sites of curvature, and near the origins of vessels. When laminar flow is disrupted, eddy currents are set up which may traumitize the intima. Segmental distribution of the disease is demonstrated by the frequent involvement of the distal superficial femoral in Hunter's canal. Commonly affected bifurcations include those of the abdominal aorta, common iliac, and common carotid arteries.

2. Peripheral Vascular Disease

Peripheral vascular disease is the term used to refer to the obstruction of the peripheral arterial system by atherosclerosis. The obstruction may consist of one or more stenoses, or one or more occlusions. Sites of high frequency of involvement include the abdominal

aorta, the aorta-iliac branches, the superficial femoral artery, the poplitial and its distal channels. Symptoms may become noticeable as a result of slow progressive obliteration of the arterial lumen, or abruptly, as the result of an acute arterial thrombosis or embolism.

Investigators have sought to quantify the 'critical stenosis' at which flow conditions are affected adversely (65,66). Using short, graded stenoses in the iliac arteries of anesthetized dogs, they found no reduction in flow until the stenosis had encroached on 80% of the cross-sectional area of the artery under examination. Likewise, the pressure drop across the stenotic segment was less than 10% until there was a reduction of cross-sectional area by more than 80% (67).

Intermittent claudication is a symptom of AOD manifested in the leg only during exercise. Patients describe cladication pain in various ways including: pain, ache, cramp, numbness, pulling, or a sense of fatigue in the affected muscles. The disease may start unilaterally, but often affects both limbs. The patient may report that one leg is worse than the other. The disease often does not progress past the stage of claudication. But, in some patients, rest pain, gangrene and skin necrosis occurs in more advanced stages of arterial obstruction.

When describing their walking ability, a subject will use the distance at which pain occurs as a reference point. This may including distances of less than 50 feet, to up to several hundred yards. Stopping

for a few seconds to a few minutes, or simply slowing down their pace, will relieve the pain and enable the subject to resume.

B. Intermittent Claudication

The encroachment of the obstructive process on the lumen of the major arteries of the lower limb is responsible for the symptoms of intermittent claudication. Physiologically, these symptoms can be explained by pressure and flow changes that develop due to the luminal encroachment. During exercise, as in walking, muscular contractions increase the demand for nutritive blood flows. Dilatation of the vasculature of the muscle is the automatic response. Normally, this decrease in peripheral resistance would augment blood flow according to the laws governing flow:

$$\text{Flow} = \text{Pressure}/\text{Resistance}$$

However, when a vessel is narrowed by atherosclerotic lesions, local control may decrease peripheral resistance even in the resting condition. This compensation will enable resting flow rates to approach or equal that of normal control subjects (68). When pressures are measured at an artery distal to the obstruction, systolic readings are lower than normal. This is a result of pressure energy in the form of friction being lost as the blood flows past the obstructed portion of the vessel. Also, the combined resistances in series of any collateral vessels present also adds to the pressure loss.

When nutritive flows to the muscle are increased, as during exercise, the capacity for supplying blood is hampered by the obstructed vessel. As demand for nutrients and oxygen rises in the working muscle, maximal peripheral vasodilatation is effected, and the pressure drops even further as additional pressure energy is lost when the blood forces its way through the narrowed segment.

1. Effect on Blood Flow

Several authors have measured blood flows in limbs of patients with intermittent claudication (3,48,69-71). At rest, blood flow does not differ appreciably from flows measured in normal individuals (47,60,72). In a study that compared limbs with varying levels of disease (superficial-femoral and isolated iliac occlusions), resting flows as measured by venous occlusion plethysmography were within normal limits (approx. 4 cc/100 cc/min) (71).

Gaskell (72) found that 'cuff occlusion pressures'; the minimum cuff pressure required to prevent flow of blood into the distal limb segment, was the single most reliable index of arterial occlusion. It was always appreciably reduced in the presence of arterial obstruction. Pentecost (47) measured blood flows in patient before, during and after supine exercise on a bicycle ergometer using the continuous injection indicator dilution technique in the external iliac vein. He found that exercise by patients with AOD resulted in lower peak flows, and a slower return of blood flow to pre-exercise levels than in normal controls. All

subjects exercised at 300 kpm until intermittent claudication was experienced. In those with moderately severe obstruction, flows dropped rapidly from 2450 ml/min during exercise to 1200 ml/min immediately upon cessation. Seven minutes were required for flows to return to the pre-exercise rates of 500 ml/min. More severely affected limbs demonstrated maximum flow rates during exercise of 1450 ml/min, but recovery flows approached resting levels over a period of ten minutes following exercise. Flow patterns for the normal subjects included a maximum flow during exercise of 2100 ml/min which rapidly returned to pre-exercise level about 1.5 minutes after exercise.

Using the $Xenon^{133}$ isotope clearance technique, Lassen and Kamp (73) had patients with claudication walking on a treadmill for two minutes or until onset of pain. Blood flows were measured in the gastrocnemius, and averaged 4.5 ml/100 g/min during maximal exercise.

Tonneson (18) walked his subjects on a treadmill until forced to stop due to pain. In comparing the $Xenon^{133}$ clearance, and the plethysmographic method of measuring flows, he validated Pentecost's results (47) by reporting post exercise maximum flow rate values of 45.2 ml/100 ml/min in the normal limbs, as compared to 11.2 ml/100 ml/min. in the patient group. The flow rates were 35.1 ml/100 g/min. for the controls, and 6.1 ml/100 gm/min for patients with AOD when the same subjects were measured using isotope clearance.

When obstruction occurs at more than one site in a vessel, for example in aorto-iliac region and superficial femoral artery, the time to peak flow is even more prolonged than if there is just one obstruction site (79). This may be accounted for by the "stealing" of blood from the distal muscle mass until the needs of the proximal muscle group are satisfied. This theory was confirmed by Angelides et al (69) who utilized technetium^{99} clearance, and studied calf and thigh flows simultaneously. They found that in all limbs after exercise with superficial femoral occlusions, with or without aorta-iliac lesions, the peak clearance in the calf was reached only when clearance in the thigh decreased to pre-exercise levels.

Thus, it was established that peak flows during exercise in limbs of patients with AOD were significantly lower than flows in the normal limb. In addition, a characteristic post-exercise flow pattern helps to differentiate the diseased limb from the normal. The former takes several minutes longer to recover from the exercise-induced oxygen debt.

2. Effect on Blood Pressure

a) Response of Ankle Systolic Pressure (ASP)

In normal extremities under resting conditions, ASP are equal to, or higher than, brachial systolic pressure (75-77). However, in patient with AOD, ASP's are diminished, and their values can be used as a sensitive index of the occlusive process.

Carter (22) measured ASP in 146 limbs with angiographically documented AOD. He found that ASP was below 82% of the brachial in all limbs with complete occlusions, usually below 50% in those with multiple occlusions, and above 50% in limbs with a single block. ASP was below normal in 19 of 25 limbs with severe, and in 5 of 9 with mild stenosis.

Sumner and Strandness (71) correlated the post exercise changes in ASP with the calf blood flow, and related these changes to the level of occlusive disease and the severity of the patient's symptoms. They found an inverse relationship between post exercise ASP as measured by mercury in silastic strain guage on the digits, and the calf blood flow measured by venous plethysmography. The more extensive the disease process, the greater is the post-exercise depression of ASP, and the slower is the recovery to pre-exercise values.

b) Response of Central Systolic Pressure

The central pressure response to exercise has been investigated in patients with intermittent claudication (78,79). Lorentsen (78) measured systolic pressures by means of a catheter placed in the distal aorta. Pressures were significantly higher when patients with unilateral disease exercised the limb with arterial obstruction on a foot ergometer, than when they exercised the normal limb. The mean difference in systolic pressures between the two exercise sessions was 18.08 mm Hg $\pm$ 4.27 S.E. (<0.001). Thulesius (79) found that the blood pressure rise, as determined by the auscultatory method over the brachial artery, was more

pronounced in cases with arterial insufficiency than in controls. The experimental subjects were patients with peripheral artery disease, 60% of whom also had coronary insufficiency. Blood pressure elevation with exercise at comparable treadmill loads was found to be more marked in patients with coronary or peripheral arterial disease than in a normal control group.

Since the systolic pressure at the ankle depends on the central systolic pressure, it is important to be aware of the gradient between these two anatomic levels both at rest and during exercise. Therefore, any increase in the pressure gradient (Pa-Pv) across a capillary bed would cause an increase in blood flow in proportion to the increase in central pressure. However, one has to be careful when brachial pressure is used as an index of central pressure. Rowell and co-workers (80) have found that peripheral pulse pressures are amplified centrally due to vasoconstriction during exercise. For example, when brachial pressures are measured during walking, they may not reflect central pressure values. This may result in an overestimation of pressures proximal to an obstruction. Therefore, one cannot assume that an increase in brachial pressure is a precise measure of an increase in pressure proximal to a stenosis.

3. Effect on Reactive Hyperemia

The mechanism of reactive hyperemia is not yet fully understood, but in their attempts to elucidate the process several authors

have measured the hyperemic response to arterial inflow occlusion in patients with AOD (43,44,81,82). In comparison to the reactive hyperemia response in normal limbs, the response in limbs with AOD is characterized by lower peak blood flow, a delay in the peak blood flow, a prolonged hyperemic response, and an underpayment of the flow debt. Strandness (83) estimates the usual normal peak reactive hyperemic flow to be two to four times that of the flow in AOD. However, this would depend on the severity of the disease, the degree to which the arterial channels are narrowed, and the functional capacity of the collateral circulation.

The delay in peak flow time is one of the most obvious differences in reactive hyperemic responses in the diseased limb. It may be delayed by about 15 seconds to 2 minutes when there is a proximal arterial occlusion (45). This delay in peak flow is followed by a prolonged hyperemic response.

Ankle systolic pressures measured during reactive hyperemia show a significant difference between normal limbs and those with AOD. The mean maximal percent drop in ankle pressure of normal legs was 17% $\pm$ 11% compared to a 54% $\pm$ 15% drop in the diseased extremeties in a study by Hummel et al (81).

Bartoli and Dorigo (44) found that reactive and exercise hyperemias differed markedly in patients with AOD. This was in contrast to the response of normal control subjects where first and peak flows showed no significant difference between the two hyperemic flows. The

authors found that after exercise, recovery time was more prolonged in the patient group and first and peak flows were significantly higher.

It may be that the control mechanism of reactive and exercise hyperemias are different and this may help explain the difference with AOD. If, after exercise, the diseased limb has a metabolite accumulation higher than that of a normal limb after similar stress, then the exercise hyperemia response in the abnormal limb may more closely resemble that of exercise hyperemia, and would account for the higher peak flows and prolonged recovery time.

C) Exercise and Intermittent Claudication

1. The Effect of Varying Conditions of Exercise

a) Body Weight

Hillestad (84) found that body weight played a role in limiting the claudication distance (distance walked until forced to stop). He walked his subjects on a treadmill at 3 kph while they wore a bag on their shoulders which was filled with loads varying from 10 to 40 percent of their body weight. For example, when 30% of their body weight was added, the subjects walked 50% of their previously determined maximal walking distance.

b) Speed

Increasing the treadmill speed to 4 kph from 2 kph resulted in a 53% decrease in the mean maximal walking distance of patients with intermittent claudication (84). The onset of claudication is much more influenced by speed than by distance walked.

Peterson (85) verified Hillestad's results by examining the relationship between speed and the claudication distance. The subjects walked on a treadmill at 2.4, 3.6, 4.0 and 4.9 kph. The tests were done at 0% grade and then at 5% incline. The results showed that at 2.4 kph the claudication distance was 114 metrers, at 3.6 kph the distance was 110 meters, and 4.9 kph it decreased to 101 meters. The reduction in distances was less marked compared to Hillestad's observations, but Petersen postulates that a partial training effect took place over the second and third days of testing. Therefore, the subjects managed a relatively greater distance on subsequent test days.

2. Effect of Physical Training on Limb Blood Flows and Ankle Systolic Pressures.

Larsen and Lassen (8) used the $Xenon^{133}$ clearance technique in the anterior tibial muscle to study blood flows after exercise in fourteen patients. Seven of the subjects went on a walking program, and seven took placebos for an equivalent time period. Improvement in claudication pain time (CPT) (1.8 mins) and maximal walking time (MWT) (5.3 mins) in the exercise group was measured after six months of training. No corresponding changes occurred in the control group, and blood flows showed no significant changes in either group.

To investigate further the blood flow response to exercise training in patients with intermittent claudication, Alpert et al (3) put nineteen subjects on a regular walking program. This program was un-

supervised, and called for one hour of daily walking for six months. Patients were tested on a treadmill at 4.6 kpm at 8% or 16% grade. All except two patients showed an improvement in walking distance. Maximal blood flow in the gastrocnemius muscle as measured by $Xenon^{133}$ increased after training in twelve of the nineteen, and was positively and significantly correlated to the increase in walking distance ($r = 0.64$ p 0.0025). Collateral development was proposed as the most plausible explanation for the increase in muscle blood flow during exercise.

ASP is a sensitive indicator of the severity of the overall obstruction involving the major arterial channels to the limbs. Skinner and Strandness (86) investigated the effects of repetition and intensity of exercise on ankle systolic pressure. Four men exercised on a treadmill for four consecutive days, five times each day at 60, 75 and 95% of their predetermined maximal walking time (MWT). Despite marked differences in the severity of disease among the patients, ASP fell to a lesser degree with successive walks, 10-15 minutes apart, on any given day. The reduction in fall of ASP immediately after exercise was attributed to the progressive dilatation of collateral channels in the affected limbs. Skinner and Strandness (9) also studied five men who underwent a 3-8 month walking program. They investigated ASP, MWT and CPT and found increases in resting ASP in three subjects, and improved CPT and MWT in all five subjects after training. The post-exercise ankle systolic pressures were increased with training. The authors suggest that a sig

nificant increase in collateral circulation at rest, during or after exercise, improved the blood supply to the obstructed leg.

Carter and Spack (87) conducted a study in which five patients exercised twice a week for six months on a motorized treadmill. The exercise sessions lasted for one hour. They measured ankle systolic pressure and maximal walking ability, and found a remarkable increase in walking ability in four patients after training. Ankle systolic pressure changes, both at rest and after exercise, were less pronounced, but showed a trend towards improvement. Five subjects on placebo treatment showed no consistent changes in ankle systolic pressures or walking ability.

Other authors have found no increase in maximal blood flow despite a significant increase in walking time after a training program (88). One such program consisted of a regimen which included heel raising, stair climbing and unspecified road walking daily for three to four months. Blood flows were measured by the thermodilution technique at rest and during exercise on a bicycle ergometer. No significant change in mean lower leg blood flow was recorded after training. The authors felt that the increase in CPT and exercise capacity could not be attributed to an increased lower limb blood flow.

Since my research was started, Ekroth et al (5) reported on 148 subjects who undertook a four to six month training program consisting of marking time, walking, running, dancing and playing ball. Sessions took

place three times per week for 30 minutes under the guidance of a physiotherapist. Walking ability increased in 88% of the patients with an average of 234% increase as measured on a treadmill (4 kph, 0% grade). Blood flow was measured by strain guage plethysmography at the calf during exercise on a foot ergometer. Mean calf blood flows remained unchanged after training, even though the walking ability more than doubled. When subgroups were compared, those subjects with aorto-iliac and combined obstruction improved their walking ability as much as those with femoro-popliteal obstruction. However, the latter group also showed a significant increase in maximal calf blood flows in response to training. No change in blood flow was measured in the subjects with aorto-iliac or combined obstruction. The change in walking ability was not significantly different between the two groups.

The method used for blood flow measurement during exercise measured flows during calf contractions simulating the walking movement. It may not be valid to compare blood flow changes during supine calf contractions on a foot ergometer, to changes in walking ability after training. Possibly the specificity of training principle may be applicable whereby only those muscle groups being repeatedly taxed during training will show a beneficial response. Testing another muscle group other than those being trained will give false results.

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3) Effect of Training on Metabolic Capacity of Calf Muscle

It is well known that in the normal limb the main circulatory changes in physical training occur in the circulation of the skeletal muscle (55). Several reports support the hypothesis that in patients with claudication, as the only symptom, the metabolic capacity to utilize available substrates for energy, are improved (5,10,89,90). Muscle biopsies of the vastus lateralis muscle revealed that the glycogen content of the muscle tissue influences the maximal walking time of patients with intermittent claudication (89). Holm et al (90) have reported that the rate of glycogen synthesis increased in the leg muscles of patients with intermittent claudication. Moreover, physical training in claudication caused an increase in the metabolic capacity of the muscle tissue - an increase which was correlated well with the improvement of walking ability (4). The Schersten group (5) summarized their six years of training of 148 patients with intermittent claudication by analyzing calf blood flow and walking tolerance. The authors felt that development of collateral circulation does not occur to an extent that can explain the increased walking ability. They propose that their earlier work on adaptation of the calf muscle metabolism to training accounts for the changes. Sorlie and Myhre (10) support the theory of increased local aerobic working capacity which they propose may be partly explained by increased oxygen extraction. Their study showed that following training oxygen uptake in the lower leg at exhaustion was higher than pre-training

levels. This was validated by analysis of local blood lactates (11).

4. Conclusions

Regular exercise training programs have been shown to increase the walking ability of patients with intermittent claudication. Several questions concerning the reasons for the improvement are unanswered.

This research was undertaken to explore just how well patients can walk after a training period; what is the relationship of walking ability to site and severity of disease as determined by ankle systolic pressures; and, whether training is associated with circulatory changes measured by ankle systolic pressures.

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PART II

RESEARCH REPORT

THE EFFECT OF A SUPERVISED WALKING PROGRAM ON PATIENTS WITH INTERMITTENT CLAUDICATION

ABSTRACT

The Effect of a Supervised Walking Program on Patients with Intermittent Claudication

Previous studies show that walking exercise may improve the walking ability of patients with intermittent claudication (IC) in whom pain on exercise due to arterial occlusive disease often results in considerable disability. This report deals with several unresolved questions concerning the effect of exercise training: 1) what level of walking ability can be achieved; 2) can all patients benefit; 3) does site and severity of disease affect the degree of benefit; 4) does a hemodynamic change accompany an improvement in walking ability?

Twenty-three patients with stable IC were evaluated clinically, by blood pressure measurements, and, when indicated, by angiography prior to entry into the program. Brachial and ankle systolic pressures (ASP) were measured at rest, after a 5 minute walk at 3.2 kph on a 7% grade, and during reactive hyperemia induced by 4 minutes of inflow occlusion using a cuff placed just above the knee. The maximal walking ability was tested on a treadmill on an upgrade and on the level. In addition, patients were timed during their training sessions. Retesting was done after 3 and 6 months of supervised training which consisted of three 1-hour periods per week.

The average ASP index at rest in the leg with the more severe occlusive process was 0.66 $\pm$ 0.16 at entry into the program. Five

patients had obstruction in the aorto-iliac region, 13 in the superficial-femoral artery; 4 had lesions both above and below the inguinal ligament, and 1 had distal disease. The disease was bilateral in 16 patients and unilateral in 7.

To date, 15 patients have completed 6 months of training, and 8 at least 3 months. The maximal walking distance (MWD) improved 25% when tested on an upgrade (19 patients showed improvement), and 70% on the level treadmill (20 improved). The results showed no significant correlation between site and severity of disease and the degree of improvement. All but 1 patient could walk at least 1/2 kilometer, and 19 walked 2 to 5-1/2 km during their training sessions without stopping. The average speed was 4.1 $\pm$ 1.0 kph. There was a significant increase both in absolute ASP at rest and after exercise in 11 of 15 patients who completed 6 months of training, and in ASP expressed as a percent of brachial. No significant difference was found in ASP during reactive hyperemia.

The results indicate that patients with IC can improve their walking ability sufficiently to improve their quality of life. The site and severity of disease do not preclude improved walking ability, as long as ASP at rest is 60 mm Hg and/or 45% of the brachial. Also, the initial walking ability does not forecast the likelihood or degree of improvement. Increases in pressure support the idea that collateral circulation improves in response to training to meet the needs of muscles subjected to regular exercise. Further research is needed to assess the reactive

importance of the roles played by collateral development and by metabolic adaptations, including the possible relationship to the intensity of the training stimulus.

Introduction

Pain on exercise due to arterial occlusive disease (intermittent claudication) often results in considerable disability. Treatment by vasodilator drugs or sympathectomy have been shown not to be of value (1). Although arterial reconstruction can restore hemodynamics to normal and eliminate symptoms, a significant percentage of patients develop reocclusion (2). Also, in other patients surgery may not be justified due to risks or not technically feasible due to the extent of the disease.

Several reports published over the last fifteen years indicate that exercise programs improve the walking ability of patients suffering from intermittent claudication and may improve the quality of life (7-14). However, several important questions concerning exercise as a treatment have not been answered satisfactorily. These include the following: what level of walking ability can be achieved, can all patients benefit, does site and severity of disease affect the degree of benefit, and does a change in hemodynamics accompany the changes in walking ability?

Materials and Methods

I - Patients Studied

Twenty-three patients, 8 females and 15 males with occlusive disease and stable intermittent claudication, participated in the study after informed consent was obtained. Patients had an average duration of stable symptoms of 2.0 years $\pm$ S.E. 0.4 prior to starting the program,

and none suffered from gangrene or rest pain. The mean age was 59 years ± S.D. 10. Twelve of the patients had ischemic heart disease.

Physical examination, segmental blood pressure measurements (3,4), and angiographic data when available, were used to assess the site and severity of disease. The ankle systolic pressure expressed as percent of brachial systolic pressure averaged 66 ± S.D. 0.16. Five patients had obstruction in the aorto-iliac region, 13 in the superficial femoral artery; in 4 the disease was present both above and below the inguinal ligament, and in 1 patient the obstruction was distal to the knee. The disease was bilateral in 16 patients, and unilateral in 7.

II - Initial Assessment

i) EKG Stress Test

An EKG stress test was carried out to establish safe limits of heart rate and blood pressure for use in further testing and training, and to detect the possible presence of subclinical ischemic heart disease.

ii) Techniques of Blood Pressure Determination

Brachial and lower limb pressure measurements were carried out with the patient supine, on a hospital bed, comfortably warm, and at least two hours after the last meal.

Brachial systolic pressures were first measured by auscultation in both arms. The right arm was used for subsequent measurement unless the left arm pressure exceeded the right by more than 12 mm Hg.

Brachial and lower limb pressures were measured using inflatable pneumatic cuffs. The dimensions of the inflatable portion of the brachial cuff were 23 x 12.5 cm, and for the cuffs applied just above the ankles 30 x 12.5 cm. All three cuffs were connected to a pressure source, a mercury manometer, and a Statham* pressure transducer. Figure 1 illustrates the arrangement of the apparatus. Systolic pressures were obtained by detecting the onset of pulsations during gradual deflation of the cuffs. For that purpose a pulse pick-up was applied over the brachial artery in the anticubital space, and Doppler ultrasonic flow detectors over a pedal artery. Preliminary measurements had been carried out over both dorsalis pedis and posterior tibial arteries. As a rule, measurements using both vessels agreed well in this and a previous study (5). The vessel with the clearest signal and higher pressure was used for subsequent measurements unless a gross discrepancy was found.

The output of the pick-up, the Doppler probes, and the cuff pressure transducer was recorded on an optical oscillograph using a paper speed of 5 mm/sec. The sensitivity of the pressure system was 1 mm deflection per mm Hg.

* Model PM6TC±5-350, Stham Instruments, Inc., Los Angeles, Calif.

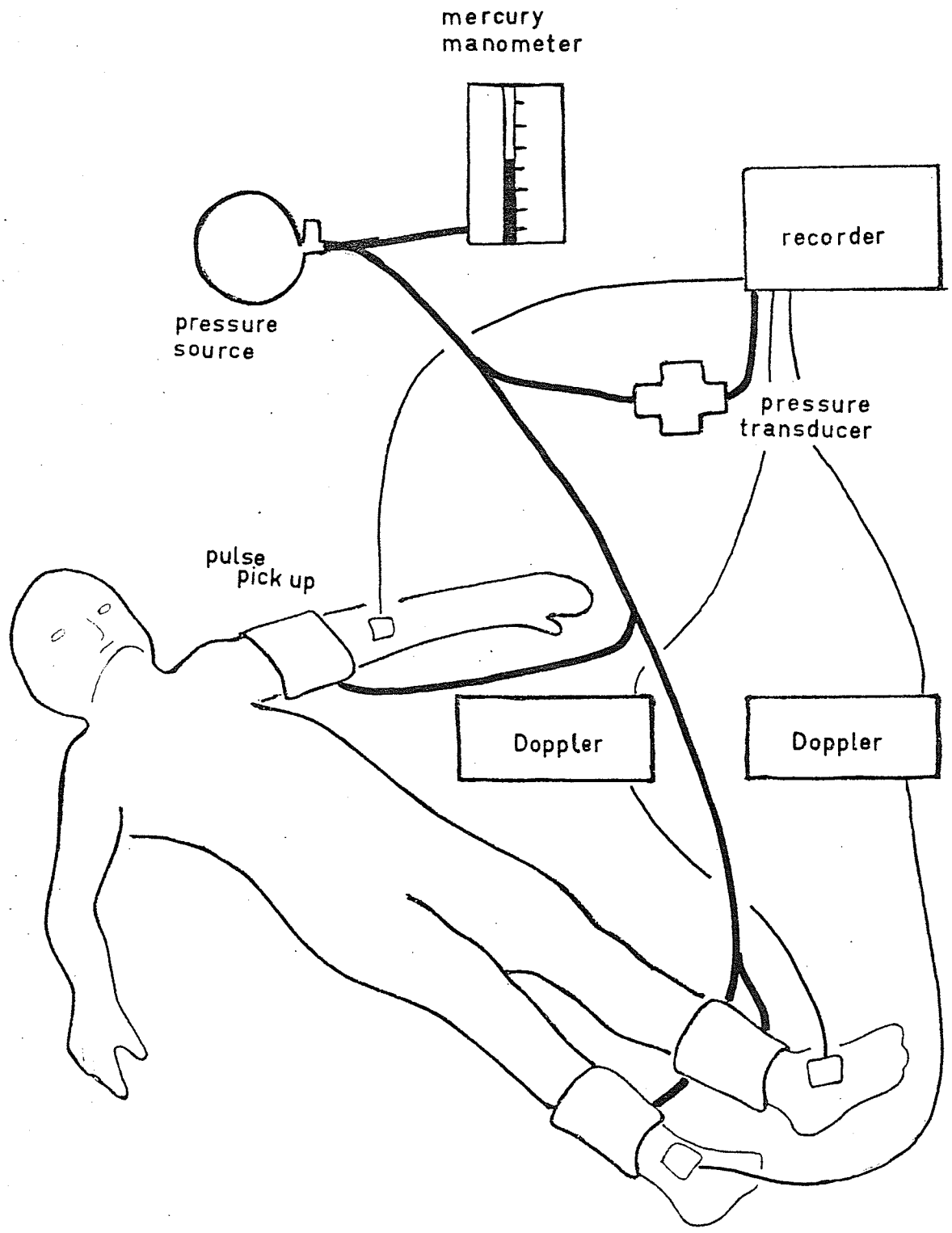

FIGURE 1: Apparatus arrangement used for measuring ankle systolic pressures before and after exercise.

iii) Testing Protocol

Patients were tested on four or more different days within approximately a two week period. At least two days elapsed between test days.

a) Measurement of pressures at rest

On each test day, pressures were determined in triplicate after 60 minutes of rest in the supine position. The average of 3 pressures were used for data analysis.

b) Measurement of pressures during reactive hyperemia

These were carried out on two of the test days after resting pressure measurements. Additional pressure cuffs with inflatable bladders measuring 40 x 15 cm were wrapped around the lower thighs, just above the patellae. Air was rapidly introduced to one cuff at a time using a reservoir bottle and inflated above systolic pressure for four minutes. The cuff was then rapidly deflated, and ankle systolic pressures were measured repeatedly for 5 minutes, by which time they always reached stable levels.

c) Standard walk and measurement of post-exercise pressures

After the measurement of resting pressures, or 30 minutes after measurements during reactive hyperemia, the patient performed a standard walk on a motorized treadmill. The walk consisted of a 2 minute "warm-up" at 0% grade; the first minute at the speed of 2.4 kph, and the second at 3.2 kph. This was followed by 5 minutes at 7% grade, at 3.2

kph. The test was terminated when the subject had walked the 5 minutes, or was forced to stop by claudication pain.

After the walk, the subject resumed the supine position. Doppler probes and pulse pick-up were replaced, and systolic pressures were taken as often as possible for 5 minutes. Thereafter, measurements were taken every 1/2 - 2 minutes until pressures stabilized at or near the resting values. Pressure measurements were started as soon as the apparatus was in place; usually between 2 and 3 minutes after stopping the walk. Also, comparison between pre and post training pressures was carried out only on pressures obtained at the same time after stopping.

d) Maximal walking ability on an inclined treadmill

This was carried out following 60 minutes of rest in a supine position after the standard walk. The 2 minute "warm-up" was repeated as in the standard walk, and then, while the speed remained at 3.2 kph, the grade was increased by 1% every minute until the patient was forced to stop by claudication pain. In rare cases when the patient was stopped because limits of heart rate or blood pressure were reached, or onset of chest pain or several general fatigue set in, the test was not considered in the analysis.

If the patient walked for 10 minutes or more at 3.2 kph after the "warm-up", a speed of 4.3 kph was used on the subsequent test day. If the patient then walked 10 minutes or more at 4.3 kph, further tests were done at 5.4 kph. The 4.3 kph speed was added after the study was begun so that some patients went directly to 5.4 kph from the 3.2 kph speed.

Only the data from the last two tests were used in the analysis because there is a significant difference in the results between the first and subsequent tests, but no significant difference between the second and third tests (8,9).

e) Maximal walking ability on a level treadmill

Walking ability was assessed on a treadmill at 0% grade on another day. The 2 minute "warm-up" was repeated, and then the patient walked until forced to stop, or to a maximum of a further 18 minutes after the "warm-up".

Treadmill speeds were chosen using the highest speed achieved during the maximal inclined walk; i.e. 3.2, 4.3 or 5.4 kph. If a patient walked the 18 minutes, he returned on another day and walked at the next higher speed.

During all walks, brachial systolic pressure was measured approximately every minute using the auscultatory technique over the brachial artery. The heart rate was determined over 15 second periods by maintaining cuff pressure between systolic and diastolic, and counting the Korotkoff sounds. During all walks, the time of onset of claudication pain was noted.

III - Training Sessions

The patients trained 3 times per week for 3 to 6 months. To date, 3 patients dropped out after 3 months, 5 are in the training program between 3 and 6 months, and 15 have completed 6 months of training. Eight of the 23 patients trained on a motorized treadmill at the hospital under the supervision of a physiotherapist, who also kept the training records. The other 15 patients trained at an indoor track, supervised by physical education and medical staff. There, the patients kept their own records, which were regularly reviewed. Patients were assigned to either facility depending upon their convenience or the available time of the physiotherapy department. Participants with varying degrees of severity and sites of obstruction were included in both patient groups.

The patients were instructed to walk at speeds fast enough to elicit some, but not severe leg discomfort. If the discomfort became severe, the patient slowed down or stopped until the pain eased or disappeared. The walking and resting or slowing down sequence was repeated over a one hour period. Heart rates, rest times, walking time and distances were recorded. When the one hour period of walking could be completed without stopping, the patients were asked to increase their speeds gradually.

The differences in training benefits, if any, between the two training programs will be analyzed when more patients have completed the 6 month regimen. At the present time the results show similar trends.

IV - Reassessment and Follow-Up

After 3 and 6 months of training, the patients were retested. Another EKG stress test was carried out to assess any change in the cardiac status. Pressures at rest, during reactive hyperemia and after the standard walk, and, the maximal walking ability on an upgrade and on the flat treadmill were determined once each.

In addition, the patients were timed at their training location during a workout session near the time of their scheduled follow-up tests. This was done to assess objectively their walking ability under conditions more similar to their own usual daily walking needs than the treadmill tests.

Results

Walking Ability

The maximal walking distance on the treadmill increased significantly, both when tested on an upgrade, and on the level (Table I). On the upgrade, the average increase was about 25%, and 19 patients showed an improvement. The increase on the level was 70%, and 20 patients improved their walking distance.

The maximal walking ability showed a significant increase on the upgrade and flat tests already after 3 months of training, but there was a further significant increase between 3 and 6 months.

MAXIMAL WALKING DISTANCE (Km)

	BEFORE TRAINING	AFTER TRAINING	p
UPGRADE	0.50 ± 0.04	0.63 ± 0.05	<0.001
FLAT	0.64 ± 0.06	1.10 ± 0.09	<0.001

Table I - Comparison between mean values of distances achieved before and after training on the graded and flat treadmill tests.

Claudication pain time (time to onset of claudication) also increased significantly after training. The increase amounted to 25% during the standard walk ($p<.05$), 38% during maximal walk on an upgrade ($p<.001$), and 46% for the flat walk ($p<.01$).

Figure 2 shows the maximum distance achieved by individual patients on the flat treadmill test after training, plotted against the initial maximum walking distance. Three patients were able to walk the full 20 minutes at 5.4 kph prior to the beginning of training, and thus showed no change; 4 more patients achieved this distance with training. Varying degrees of improvement are seen in other subjects. Among the patients who entered the program before the intermediate speed of 4.3 kph was introduced, 4 were tested at 5.4 kph which may have been an excessive speed for them. This may explain the relatively small changes when tested on the treadmill, which contrast with good performance during training (see below).

Site and Severity of Disease

Figure 3 shows the distance which the patients walked consistently without stopping during one hour training sessions, plotted against ankle systolic pressure in the worst leg measured prior to training. All but one patient could walk at least 1/2 kilometer, and the majority 2 kilometers or more. These walking distances were achieved at a reasonable speed which averaged 4.1 ± 1.0 kph, with a range of 2.3 to 6.0 ± 1.0.

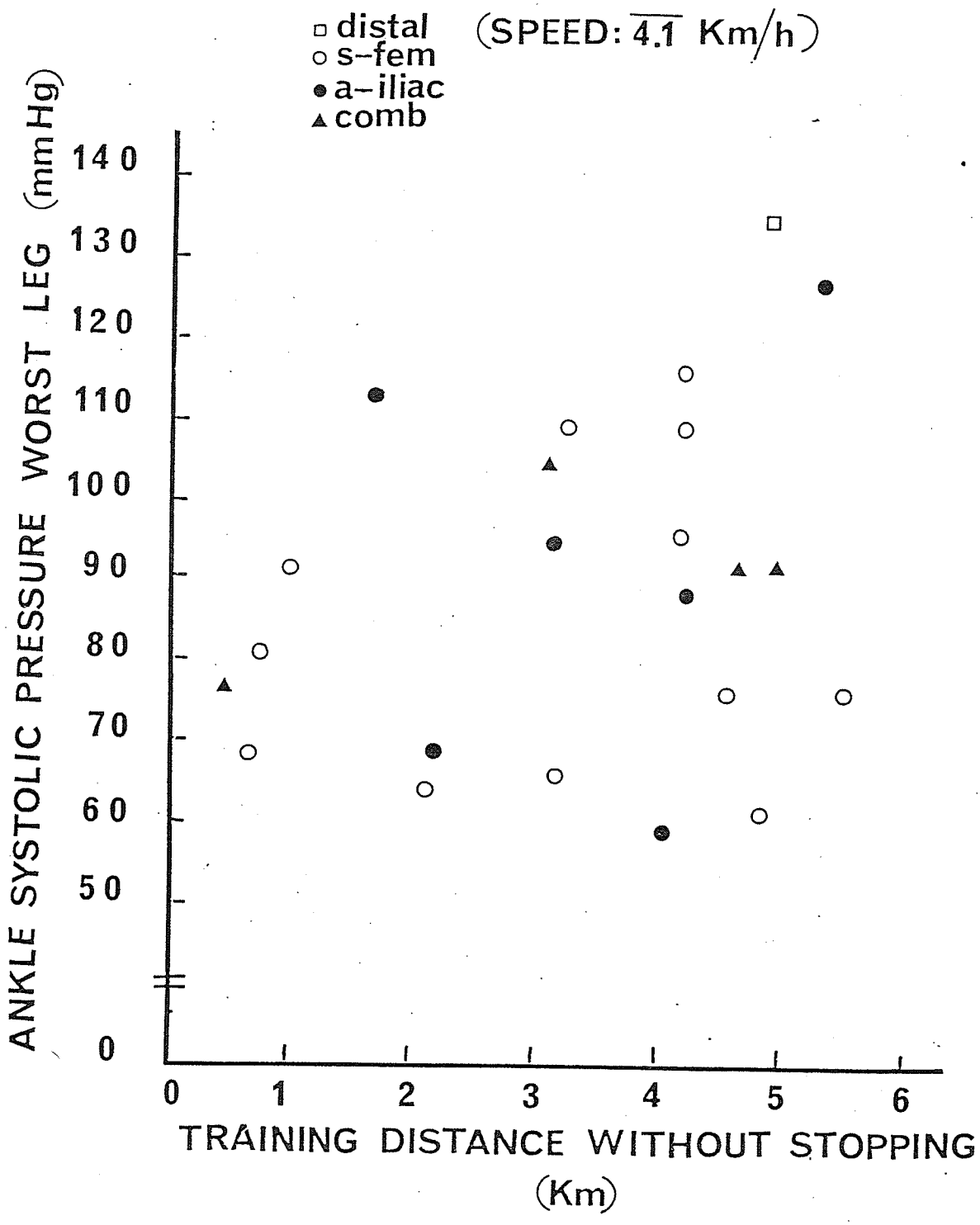

FIGURE 2: Relationship between ASP and distance walked without stopping during the 1 hour training session. The open and closed symbols designate site of obstruction: distal, superficial femoral, aorto-iliac, and when combined above and below the inguinal ligament.

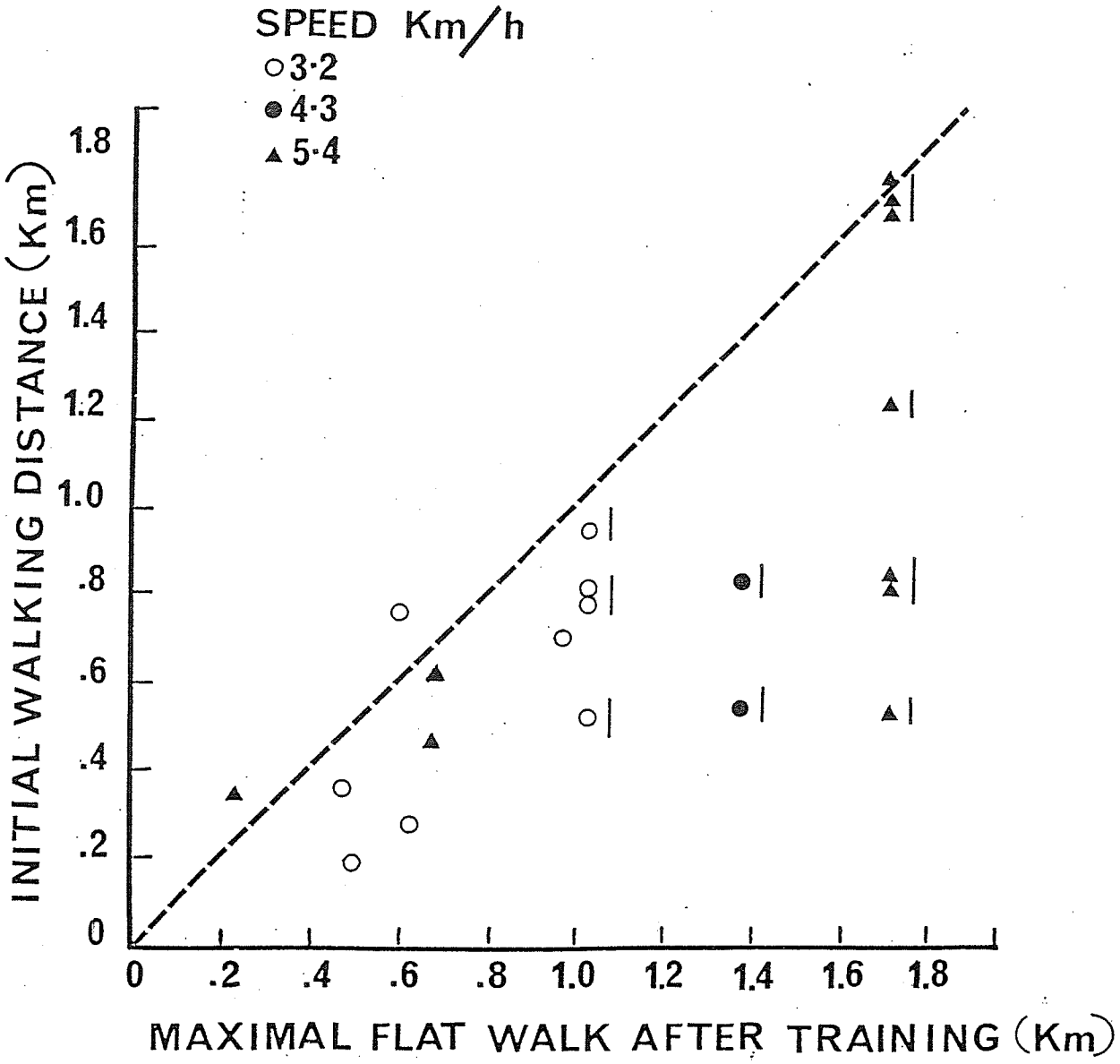

FIGURE 3: Relationship between the initial walking distance of the patients on the flat treadmill test, and the distance achieved on the same test after training. Some of the subjects shown only completed 3 months to date. The solid bars following some of the symbols indicate the maximal distance possible at a given speed during the allotted time period. Three of the subjects achieved the maximal distance in the beginning, and thus could show no improvement.

Only 2 of the 23 patients walked at less than 3 kph. There was no correlation between absolute ASP and the training distance, or between ASP index (ASP/BSP) and the training distance. The pressure index ranged from 0.4 to 0.8 in 20 patients. There were 2 patients with indices of 0.9 and 1.1 respectively that had abnormal pressure response to exercise; one had mild disease above the inguinal ligament, and the other's obstructive process was below the knee.

Long distances during training were achieved by patients with superficial femoral, aorto-iliac or combined disease, whereas some could walk only shorter distances. There was no significant correlation between ankle systolic pressures or location of obstruction and the distance walked during training. For example, some patients with superficial femoral obstruction could walk over 5 kilometers, whereas others with the same site of disease and similar pressures could manage less than 1 kilometer.

Patients' Weight

When the patient weight was compared to the initial walking ability, there was no significant correlation. There was little change in the weight over the training period (0.02 kg $\pm$ 2.2), although one man lost 6 kilograms in the 6 months time. Also, there was no significant correlation between the change in walking ability and the weight.

Pressure Measurements

Table II shows the results of ankle systolic pressure measurements before and after training. These results are based on 15 patients who completed 6 months of training. The others are presently completing their walking regimen, and the trends are similar. Measurements done after 3 months of training showed smaller changes in ankle systolic pressures and most comparisons did not reach the statistically significant level.

Resting Pressures

Mean resting ASP increased by 6 mm Hg, and the brachial minus ankle difference decreased by a similar amount. If ASP is expressed as a percent of the brachial systolic pressure, there is a significant increase in the percentage. There was no significant change in brachial systolic pressure before and after training. Increases in ASP expressed as a percent of brachial were found in 11 of 15 patients.

Pressures after exercise or during reactive hyperemia

The pressures after the standard walk showed comparable increases of 6 mm Hg in the ankle systolic pressures which did not quite reach the significant level. There was, however, a significant decrease in brachial minus ankle pressure difference of 14 mm Hg. No significant difference in ASP was found during reactive hyperemia.

PRESSURE MEASUREMENTS

AT REST	BEFORE TRAINING	AFTER TRAINING	p
ASP mm Hg	98 ± 5	104 ± 6	< 0.05
BR-AK mm Hg	41 ± 6	36 ± 6	< 0.05
ASPI (% BR)	72 ± 4	77 ± 4	< 0.025
AFTER WALK			
ASP mm Hg	68 ± 9	74 ± 9	> 0.05
BR-AK mm Hg	96 ± 8	82 ± 8	< 0.05

Table II - Comparison between mean values of the ASP of 15 patients who completed 6 months of training. Pressure measurements at rest and after the standard walk are given before and after the training regimen.

Discussion

A - Previous Work

It has been shown that training improves the maximal walking ability of patients with intermittent claudication (7-14). However, different conclusions have been drawn concerning the mechanisms for the increase in walking ability. At first, researchers studied lower limb blood flows to see if changes in flow could account for the improved walking. Larsen and Lassen (11) trained 7 subjects by daily walking for a 6 month period. Measured maximal walking distance (MWD) increased significantly in the trained group, but not in the placebo-given controls. Blood flows were not significantly different as measured in the anterior tibial muscle by $Xenon^{133}$ clearance. This contrasted with the results of Alpert et al (7) and Ericsson and co-workers (10) who also measured blood flows in patients after training periods ranging from 6-11 months. These reports showed improved walking ability associated with increases in calf blood flows. Alpert et al (7) found increased maximal blood flows in 12 of 19 patients. The study done by Ericsson and co-workers (10) showed a significant increase in flows during reactive hyperemia, and, the resting blood flow. Both author groups agreed that increased blood flow was a mechanism involved in the therapeutic effects of exercise in intermittent claudication. They proposed a theory suggesting that improved collateral circulation explained the increases in maximal flows.

Skinner and Strandness (13) utilized the measurement of ankle systolic pressures to follow the circulatory changes in subjects after training. The authors placed 5 men on individualized training programs of repeated walks at 75% of their maximal walking time for 45 minutes. The program lasted 3-8 months. Results showed that in this small group there was a trend towards increases in resting ASP (3 of 5 patients), and in all 5 significant increases in MWT and CPT and a significant reduction in the fall of ASP (in mm Hg) after exercise. The authors concluded that a walking program was beneficial for patients with intermittent claudication, and that improved collateral circulation was the most likely reason. Similar trends were found in a pilot study in our own laboratory (6).

Other reports claim that increased blood flow due to development of collaterals is not responsible for improved walking ability after training. The data suggested that blood flow changes did not accompany increased walking ability, and proposals were made to the effect that the metabolic capacity to utilize available substrates for energy were improved (9,14,15,16). Changes in glycogen synthesis (17), increased local aerobic working capacity by improving the rate of oxygen extraction (14), could all contribute to better performance by the working muscle.

Ekroth et al (9), whose study was published since our work was begun, looked at the benefits of training in patients with obstruction at different levels of the arterial tree. They measured blood flows using

plethysmography on the calf after supine foot ergometry. This method may be subject to the criticism that foot ergometry did not correspond to the walking which was used as the yardstick of improvement. Therefore, changes in blood flow which could have developed through the training program may not have been measured with the technique described. This could result in a low flow measurement soon after ergometry, especially in patients with high or combined obstruction who may have higher calf flows later in the post-exercise phase (18). This study, however, showed a significant increase in maximal calf blood flow after training in patients with femoropopliteal stenoses. Also when the average change of maximal calf blood flow of the two legs of all patients was calculated, the patients with increases in maximal flows showed more pronounced increases in walking ability who did not.

B - Present Research

Walking Ability

In the present study, maximal walking ability increased significantly, both when tested on an inclined treadmill, and, on the level. The ability to improve with training confirms the results of others (7,9,10,11,13,14). However, in looking at the walking ability as measured during training sessions, a more practical conclusion can be drawn. All but one patient could walk at least 1/2 kilometer without stopping and without severe discomfort. The majority walked 2-6 km

before having to rest. When these figures are applied to the subjects' daily walking requirements, this should more than allow them to complete average walking tasks such as: going for a walk, shopping, parking and leaving a car at a distance from the destination.

Ability to Improve

Are some patients more likely to benefit from a training program than others?

I - Site and Severity of Disease

There was no correlation between ASP mm Hg, ASP index, or site of obstruction and the maximal walking ability tested on an incline, on a level, and during training sessions. Therefore, the results of this research indicate that site and severity of disease do not preclude improved walking ability, with the proviso that the number of patients in our sample thus far is relatively small, and that the rest ASP is 60 mm Hg or more, and/or the ASP index is 0.45 or greater.

II - Initial Walking Ability

When the initial walking distance is correlated with the maximal distance achieved after training, or the change in distance after training, no significant correlation was found. Therefore, it could not be predicted from the initial walking ability how well a patient would benefit from a training program.

Ankle Systolic Pressures

There is a significant trend towards an increase in resting ASP after training. This agrees with previous studies which found small but significant increases in ASP (13) and blood flows (7,10) after various training programs. The data in the literature is consistent with the idea that an increase in collateral circulation develops to meet the needs of muscles subjected to a regular exercise program. Some of the inconsistencies of the results of the various studies may be due to the variability in training programs, and measurement techniques.

General Remarks

The contribution of other forms of adaptation to training most likely are also important. Just as healthy muscle becomes more efficient at extracting oxygen from the available blood supply (19,20), there is evidence that muscles distal to an obstruction adapt to ischemia similarly (9,14-17). The ischemic limb may experience an even greater stimulus for training-like effect because of lower oxygen supply and a higher metabolic waste concentration due to the reduced flow rates.

The relative importance of the roles played by collateral development and metabolic changes may vary with the training stimulus. The relatively small changes in flows or ASP may be a result of the low intensity training programs usually employed for patients with intermittent claudication. It may be that the stimulus for collateral development has been limited by the low intensity training. It is possible

that with higher intensity programs, greater changes in hemodynamics may occur.

In addition to differences in training techniques, the differences in severity of disease and in motivation among patients likely contribute to the variability of results among and within studies. The personal experience of the author suggests that pain tolerance varies considerably among subjects, and therefore, the intensity of the individual workout sessions varies correspondingly. This might well explain the lack of correlation between the site and severity of the disease, and the walking ability achieved by our group of patients.

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