Exercise and Intermittent Claudication

Blood Flow in the Calf Muscle During Walking Studied by the Xenon-133 Clearance Method

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SUMMARY

Nineteen patients with obliterative arteriosclerotic disease of the legs and suffering from intermittent claudication were studied before and during a 6 months' training program. The maximal walking distance and the calf muscle blood flow during walking (xenon-133 clearance technique) was recorded at monthly intervals.

A significant correlation was established between improvement in maximal walking distance and a change on exercise toward more normal (that is, more adequate) blood flow in the calf. In particular, it was found that calf muscle blood flow during walking was increased by physical training. The data suggest that functional factors (for example, better coordination of the working muscles or a decrease of in-between-step intramuscular pressure) as well as anatomic factors (increase in number or diameter of collateral vessels, or both) are involved in increasing collateral efficiency.

Additional Indexing Words:
Treatment of obliterative arterial disease
Collateral circulation

Peripheral vascular disease

Daily leg exercise in the form of brisk walking is now widely recognized as an effective form of conservative treatment of intermittent claudication. In those patients who adhere to the exercise program, walking tolerance is typically increased severalfold. Often symptoms are reduced to a level at which they are not provoked by the patient's ordinary daily activity; that is, the patient becomes asymptomatic. The mechanism of this therapeutic effect of physical exercise on intermittent claudication, is, however, not clear. Earlier reports on the benefits of training contained no observations elucidating the possible mechanism of these improvements in performance.1–3 Animal studies have pointed to increased development of collateral vessels.4 But, it is not clear to what degree observations on the effect of exercise after acute total arterial occlusions in healthy young animals are relevant to the situation in man.

Recently, two clinical studies have been published on the measurement of peripheral circulation in patients with intermittent claudication treated by physical exercise.5 6 These studies yielded conflicting results, which will be commented on in detail in the discussion, and they did not include observations of the blood flow in the ischemic calf muscles during walking. For this reason the present study, using the 133Xe clearance technique during and after a standardized walking test7 was undertaken.

Methods

Nineteen patients were studied; they had an average age of 59 years and a clinical picture of arteriosclerosis obliterans with intermittent claudication as their only major complaint. Essentially, claudication was unilateral in 12 patients and bilateral in seven. In the seven patients with roughly symmetrical symptoms the muscle blood flow data given below are the average of both legs.
All the patients were in a clinically steady state at the onset of training and most of them had been studied monthly as outpatients for the preceding many months. Angiograms were available in most cases and in all patients so studied, occlusive arterial lesions of the femoral or the iliac arteries of the claudicating limbs, or both were present. In all the 26 symptomatic legs, the $^{133}$Xe clearance curves from the gastrocnemius muscle showed the subnormal and delayed response pathognomonic of arterial insufficiency.7

Walking Distance

This was recorded by using a treadmill with a speed of 4.6 km/hr at an elevation of 8% or 16%; the steepest slope the patient could walk on for about 2.0 min being employed. The time to the initial pains and the maximal walking time were noted.

The first walking test often gives somewhat lower values than subsequent tests even though no therapy has been given, and no subjective improvement is noted by the patient. Apparently in such cases the patient learns how to walk in an efficient and properly relaxed manner on the treadmill. For this reason all patients were familiarized with the walking test before the two control studies initiating exercise treatment were made. Apart from this initial effect, the walking test was fairly reproducible with a coefficient of variation of only 8% in repeated testing in patients with maximal walking distances for

Figure 1

$^{133}$Xe clearance curve obtained during and after the standardized walking test in a leg with femoral arterial occlusion. The curve shows moderate blood flow during walking and higher blood flow ($MBF_H$) after the end of walking. (In normal man, $MBF_W > 10$ ml/100 g/min and $MBF_H$ never exceeds the value obtained for $MBF_W$.) The time from the cessation of walking to the commencement of $MBF_H$ ($T_H$) on this curve is 1.8 min and the total duration of post-walking hyperemia is 5.7 min. (In normal man $T_H$ is 0 min and the upper limit of normality for $T$ is 3 min.) The remaining hyperemia ($R$) after 1 min of rest is 80% (in normal man it is < 25%).

$$R = 100 \left( \frac{\Delta_3}{\Delta_1 + \Delta_2 + \Delta_3} \right) \times \frac{0.41}{0.04+0.06+0.41} = 80\%$$
about 2.0 min (for longer walking distances and durations the percentage of error increases).

Calf Muscle Blood Flow During Walking

$^{133}$Xe dissolved in saline was injected into that part of the gastrocnemius muscle where the pain occurred during walking. The clearance was followed by means of a light-weight scintillator detector strapped on the leg and coupled to a rate meter and a logarithmic potentiometer writer. After about 5 min of resting clearance had been recorded, the patient was asked to walk on the treadmill until he was stopped by muscle pains and muscle fatigue. Thereafter the patient was required to stand motionless until the $^{133}$Xe clearance had returned to its slow pre-exercise resting level. In all patients this time to resting flow was abnormally long, that is, longer than 3 min, and therefore reflected an abnormal degree of muscle hypoxia during walking (fig. 1).

The muscle blood flow (MBF) was calculated in ml/100 g/min as 161 × D where D is the slope of the logarithmically recorded clearance curve, this slope being measured as a fraction of a decade per minute. The same five parameters, described previously, were evaluated: (1) maximal blood flow during walking; (2) maximal blood flow after walking; (3) time in minutes to maximal blood flow after walking; (4) total duration of post-walking hyperemia; and (5) hyperemia remaining after 1.0 min of rest.

The definition and evaluation of these parameters is readily seen from figure 1.

Daily Walking Exercise

All 19 patients were instructed to walk 1 hour daily during the 6 months of the trial. The patients were instructed to walk briskly until stopped by pains, to rest a few minutes, and then to resume brisk walking. Because of various factors such as concomitant diseases notably those of a cardiopulmonary or psychic nature (lack of motivation), it was clear to us that the degree of adherence to the training program varied within the group. Indeed, in some cases we had reason to believe that practically no exercise was performed. Other patients evidently kept to the training program meticulously, clearly being stimulated by their marked improvement in walking ability.

We did not exclude any patient because of suspected poor training but continued to follow the walking distance and muscle blood flow (MBF) values by monthly tests. Our intention was to compare the different patients within the wide spectrum of therapeutic effect. For this reason we did not exclude two patients, cases 1 and 2, who apparently did not exercise at all and in whom the clinical picture and the walking tests suggested progression of the vascular lesions. Indeed, we suspect that in all 19 patients the atheromatous occlusive arterial disease per se tended to progress slowly.

Results

Two control studies before the exercise treatment and six studies during it were available for analysis. To facilitate the analysis, we averaged the two pretreatment values and compared them to the average of the fifth and sixth months' results. It should be mentioned that an analysis of the first plus the second and the third plus the fourth

![Figure 2](http://circ.ahajournals.org/)

The figure presents the relation between the clinical effect of training in walking and the results of the $^{133}$Xe test. The five curves (A to E) represent the difference between control and the average of the 5 to 6 months' treatment values. On the abscissa is seen the percentage increase in walking distance measured on a treadmill. On each ordinate is seen one of the five muscle blood flow parameters investigated (see text).
months' data did not alter the results materially and these values will therefore not be reported here.

Apart from the two patients (cases 1 and 2) already mentioned, all the other patients showed a moderate to marked improvement in walking distance (table 1). The results of the 133Xe studies are given in table 1 and in figure 2, presenting the relation between clinical results (walking test) and the blood flow data. For the five parameters investigated the following relations were found for the difference between control and five plus six months' treatment values:

1. Increase in maximal blood flow during walking (MBFw) was positively and significantly correlated to an increase in walking distance \((r = +0.65, P < 0.0025)\). As seen in figure 2A there was a tendency to a decrease in MBFw in the patients with the smallest clinical effect while an increase of 3 to 4 ml/100 g/min accompanied the most pronounced clinical improvements.

2. Changes in maximal blood flow after walking showed much the same pattern as noted for MBFw (fig. 2B). Also here a positive and statistically significant correlation to changes in walking distance was noted \((r = +0.65, P < 0.0025)\).

3. Changes in the time to maximal blood flow after walking were also noted: An increase of this time tended to be associated with a poor clinical result while a decrease in this time was seen in patients with a good clinical result (fig. 2C, \(r = -0.45, P < 0.025\)).

4. Changes in time to resting blood flow showed practically the same pattern (fig. 2D, \(r = -0.58, P < 0.005\)) as time to maximal blood flow after walking.

5. The remaining hyperemia decreased in magnitude as the therapeutic effect increased (fig. 2E, \(r = -0.77, P < 0.0005\)).

The above presented pattern of change of calf muscle blood flow yields a coherent picture: patients with a good clinical result showed flow changes which with respect to all five parameters analyzed changed in the direction of normalization; patients with no or only moderate clinical improvement.

### Table 1

Changes in Walking Distance (Given as the Time to Onset of Claudication Pain and the Maximal Walking Time) and the Maximal Blood Flow during Walking (Measured in the Gastrocnemius Muscles by the 133Xe Clearance Technique) before and after Six Months of Daily Training in Walking

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Elevation of treadmill (m)</th>
<th>Time to onset of claudication pain (min)</th>
<th>Maximal walking time (min)</th>
<th>Maximal muscle blood flow during walking (ml/100 g/min)</th>
<th>Maximal muscle blood flow during walking (ml/100 g/min)</th>
<th>Difference</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>60</td>
<td>8</td>
<td>2.2 Before 1.3 After</td>
<td>2.7 Before 1.9 After</td>
<td>11.0 Before 5.8 After</td>
<td>-5.2</td>
<td></td>
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<tr>
<td>2</td>
<td>M</td>
<td>64</td>
<td>8</td>
<td>1.8 Before 1.6 After</td>
<td>3.1 Before 2.8 After</td>
<td>5.0 Before 2.0 After</td>
<td>-3.0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>60</td>
<td>16</td>
<td>0.7 Before 0.8 After</td>
<td>1.8 Before 1.9 After</td>
<td>8.0 Before 5.1 After</td>
<td>-2.9</td>
<td></td>
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<tr>
<td>4</td>
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<td>61</td>
<td>16</td>
<td>1.3 Before 1.6 After</td>
<td>1.9 Before 2.1 After</td>
<td>0.5 Before 2.3 After</td>
<td>+1.8</td>
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</tr>
<tr>
<td>5</td>
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<td>65</td>
<td>8</td>
<td>1.2 Before 1.6 After</td>
<td>3.0 Before 3.4 After</td>
<td>3.0 Before 2.0 After</td>
<td>-1.0</td>
<td></td>
</tr>
<tr>
<td>6</td>
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<td>66</td>
<td>16</td>
<td>1.2 Before 2.0 After</td>
<td>2.0 Before 2.4 After</td>
<td>15.0 Before 5.9 After</td>
<td>-9.1</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>58</td>
<td>8</td>
<td>1.6 Before 3.3 After</td>
<td>3.6 Before 4.8 After</td>
<td>4.5 Before 2.8 After</td>
<td>-1.7</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>52</td>
<td>16</td>
<td>1.5 Before 6.0 After</td>
<td>5.8 Before 8.7 After</td>
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<td>+4.0</td>
<td></td>
</tr>
<tr>
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<td>61</td>
<td>8</td>
<td>0.9 Before 2.2 After</td>
<td>1.7 Before 2.6 After</td>
<td>1.7 Before 2.4 After</td>
<td>+0.7</td>
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<tr>
<td>10</td>
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<td>16</td>
<td>3.4 Before 4.4 After</td>
<td>4.5 Before 6.9 After</td>
<td>7.0 Before 7.1 After</td>
<td>+0.1</td>
<td></td>
</tr>
<tr>
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<td>M</td>
<td>58</td>
<td>16</td>
<td>1.3 Before 2.6 After</td>
<td>2.0 Before 3.1 After</td>
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<td>+1.2</td>
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<td>M</td>
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<td>8</td>
<td>1.3 Before 2.4 After</td>
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<td>8</td>
<td>0.7 Before 2.2 After</td>
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<td>-1.0</td>
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</tr>
<tr>
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<td>M</td>
<td>67</td>
<td>16</td>
<td>1.5 Before 2.6 After</td>
<td>2.5 Before 5.2 After</td>
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<td>+2.8</td>
<td></td>
</tr>
<tr>
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<td>M</td>
<td>67</td>
<td>8</td>
<td>1.5 Before 4.1 After</td>
<td>2.6 Before 5.6 After</td>
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<td>M</td>
<td>42</td>
<td>16</td>
<td>0.9 Before 1.5 After</td>
<td>2.3 Before 5.7 After</td>
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<td></td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>54</td>
<td>8</td>
<td>0.9 Before 1.4 After</td>
<td>2.4 Before 7.2 After</td>
<td>11.0 Before 15.0 After</td>
<td>+4.0</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>58</td>
<td>8</td>
<td>1.6 Before 3.1 After</td>
<td>2.2 Before 7.6 After</td>
<td>11.5 Before 16.5 After</td>
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</tr>
<tr>
<td>19</td>
<td>M</td>
<td>56</td>
<td>16</td>
<td>2.1 Before &gt;10.0 After</td>
<td>3.3 Before &gt;10.0 After</td>
<td>7.5 Before 10.0 After</td>
<td>+2.5</td>
<td></td>
</tr>
</tbody>
</table>
tended, on the other hand, to show more pathological blood flow curves.

Discussion

The effect of training on blood flow during walking in the calf muscles in normals is not known. Indeed, the hemodynamic response to training is not known for any muscle group. Available evidence shows, however, that training tends to decrease cardiac output and to increase total body arteriovenous oxygen difference during a standard exercise test.\textsuperscript{8-10} Elsner and Carlson\textsuperscript{11} observed that athletes had less post-exercise and post-ischemic hyperemia than untrained subjects. These findings suggest that training may cause adaptive changes in the muscles enabling them to perform the same work with less demand for hyperemia. An essential point is probably that training reduces the local production of vasodilator metabolites which are thought to elicit the exercise hyperemia.

In patients with intermittent claudication one must in principle expect the same adaptive changes to occur. But, before discussing this problem further, it is appropriate to summarize the available evidence regarding the effect of training on the peripheral circulation in this disorder.

Larsen and Lassen\textsuperscript{5} studied patients with intermittent claudication during training; they used the $^{133}$Xe clearance technique to measure the maximal blood flow in the anterior tibial muscle in the recumbent position after ischemia combined with exhaustive muscle exercise. This maximal hyperemia increased only 8% ($P > 0.40$) in the seven effectively trained patients (threefold increase in walking ability) compared to the pretreatment values or to the values of the seven placebo-tablet treated controls (no change in walking ability). With the reservation that only one muscle was tested, it must be concluded that no massive development of new collateral vessels could be demonstrated as the subnormal and delayed hyperemic responses were essentially unaltered. In an unpublished study by Ericsson, Haeger, and Lindell (personal communication from Lindell, S.-E., Dept. Clin. Physiol., University Hospital, Malmö, Sweden), the daily exercise was carried out in the laboratory. In this study the maximal hyperemia after 5 min of leg ischemia as measured by a venous occlusion plethysmograph increased significantly.

Skinner and Strandness\textsuperscript{6} employed a plethysmographic technique to measure distal blood pressure at the ankle in five patients, all of whom increased their walking ability quite markedly during intensive training in the laboratory. Their main finding was that the distal blood pressure returned more rapidly to its resting level after the training period. This indicates that the post-exercise hyperemia was of shorter duration than the pretreatment hyperemia, and hence suggests more adequate muscle perfusion during walking.

In the present study a reduction of the duration of the post-exercise hyperemic period was also found in those patients who exhibited the most marked therapeutic effect. In addition, we found in the same patients direct evidence of better circulation in the claudicating muscles, namely, increased blood flow during and after walking. Since our exercise program was not carried out in the laboratory but at the patient's own initiative, the fairly poor clinical result in some cases came as no surprise. That muscle blood flow in these cases tended toward a more insufficient calf muscle perfusion may reflect the spontaneous course of the disease.

With these data at hand we shall attempt to describe the mechanism of the beneficial action.

Psychic Effects

The confidence of the patients increases often quite appreciably. Usually prior to the therapy the patients have been accustomed to avoid walking, to consider slow progression of symptoms unavoidable, and to fear gangrene. But the improved calf muscle circulation during walking, evident from Skinner and Strandness' study and from the present observations, render it unlikely that
psychic effects play a major role in increasing the walking ability.

**Adaptive Changes in the Calf Muscles**

The normal adaptive response to exercise could perhaps lessen the demand for muscle hyperemia in the calf. This cannot, however, explain the effect observed: we should then have expected to find an unchanged MBF work whereas an increased value was actually found in effectively trained subjects. Thus, while training might well cause such adaptive changes in our patients, these changes cannot be the sole cause of the therapeutic effect.

**Increased Number or Diameter of Collateral Vessels or Both**

Since such changes have been found in animals, they must also be supposed to take place in man although probably to a much lesser degree: Our patients are biologically old in comparison to the animals studied and they had arterial disease; furthermore the exercise was quite moderate. The data on maximal hyperemia in the calf muscles summarized above support the concept of development of new, or larger collaterals, or both. Nevertheless, this is not likely to be the only factor involved, since we have repeatedly observed systematic relapse with reduction of walking distance after 1 to 2 weeks of inactivity (as may be caused by intercurrent disease). It is not considered likely that collaterals would disappear so rapidly.

**Improved Collateral Circulation Due to Functional Factors**

This factor appears to us to be the main mechanism of the therapeutic effect of exercise in intermittent claudication. Daily training may reduce the amount of muscle mass involved in walking by improving muscle coordination. Training via adaptive processes may also reduce blood flow demands in proximal muscles and thus reduce the proximal steal effect which is of prime importance in the calf muscle's circulatory insufficiency. This would cause a blood flow redistribution in favor of the critical muscle areas by a different version of flow. Finally, purely local mechanical factors in the calf muscles could be involved, namely, a lowering of the intramuscular pressure especially in the noncontracted state (cf., for example, Nilsson and Ingvar, 1967), or a more marked increase in the systemic blood pressure during exercise, or both of these factors.

That such functional factors can improve collateral circulation to the calf muscles is also suggested by the second-wind phenomenon often noted in patients with intermittent claudication on walking at a speed and on a slope that just elicits light symptoms. Under such conditions, pains may disappear with continued walking. A small rise in systemic blood pressure transmitted to the pathologically low distal blood pressure region would appear to be the simplest explanation for this apparent improvement in calf circulation.

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Exercise and Intermittent Claudication: Blood Flow in the Calf Muscle During Walking Studied by the Xenon-133 Clearance Method

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