MUSCLE BLOOD FLOW MEASURED
BY XE-133 CLEARANCE METHOD
AND PERIPHERAL VASCULAR DISEASES

Part 2. Normals and Patients with Peripheral Vascular Diseases

MASAFUMI HIRAI, M. D.

The work in Part 1 included methodological observation aimed at evaluating the relation between the work load or the volume injected and Xe-133 clearance curve.

The present study was undertaken to compare the blood flow measured by the Xe-133 standard exercise method in normal subjects with that in patients suffering from peripheral vascular diseases. The diagnostic and prognostic value of this test was evaluated by comparing its results with arteriographic and clinical findings.

MATERIAL AND METHOD

Forty normal subjects in Part 1 were used as control. The patient group consisted of 20 with arteriosclerosis obliterans (ASO) and 27 with thromboangiitis obliterans i.e. Buerger's disease (TAO). The mean age was 66.0 years in ASO and 39.4 in TAO. The presence of arterial insufficiency in the legs was further substantiated by absence of arterial pulsations in the lower limbs and occlusion or stenosis of the main artery proximal to the popliteal bifurcation in arteriograms. Fifty-six limbs of 47 patients were examined and 44 limbs of them complained of intermittent claudication in the calf.

The blood flow in the anterior tibial muscle was measured by the Xe-133 standard exercise method as described in Part 1: the work intensity was 20 times per min of dorsal flexion of the ankle for two minutes and the volume injected of Xe-133 solution was 0.05 to 0.25 ml (50 to 100 μCi of Xe-133). The initial counting rate ranged from 2,000 to 4,000 cps.

RESULTS

1. Normal subjects and patients with intermittent claudication

In the curves from 70 limbs of 40 normal subjects, the maximal blood flow during the exercise \( MBF_E \) was \( 34.2 \pm 15.2 \) ml/100g/min. The maximal blood flow after the exercise \( MBF_H \) was \( 30.6 \pm 16.8 \) ml/100g/min. The duration of hyperemia after the exercise (T-time) was \( 1.5 \pm 0.4 \) min. The remaining hyperemia that occurs one minute after the cessation of the exercise (R-index) was \( 6.8 \pm 5.6\% \).

Two ways of reproducibility of \( MBF_E \) were examined. In reference to minute-to-minute variation, the coefficient of variation ranged from 0 to 16.4%, with a mean value of 6.2% (n = 25). As to month-to-month variation, at an interval of two to six months, the coefficient of variation ranged from 0 to 23.9%, with a mean value of 11.6% (n = 21). These figures corresponded well with other authors'.

A total of 44 limbs in 35 patients with intermittent claudication was studied. \( MBF_E \) was \( 9.7 \pm 5.9 \) ml/100g/min, which was significantly lower than that obtained in the normal group, \( p < 0.001 \). T-time was prolonged in the diseased group, the value being \( 6.3 \pm 3.5 \) minutes, \( p < 0.001 \). R-index was \( 70.0 \pm 19.6\% \), which is significantly higher than that obtained in the normal group, \( p < 0.001 \).

In our repeated examinations on normal

Key Words:
Xe-133 clearance method
Muscle blood flow
Peripheral vascular disease
Intermittent claudication

(Received for Publication: August 22, 1973)
Department of Surgery, Nagoya University Branch Hospital, Nagoya, Japan

Japanese Circulation Journal Vol. 38, August 1974 661
subjects, none of 128 curves had MBF_E less than 12.0 ml/100g/min. Values of T-time above 2.6 min and R-index above 22.0% could be considered abnormal with a probability of 99%. In agreement with this statistical analysis are all results of the 128 normal curves.

We consider a normal curve as follows:
1. MBF_E ≥ 12.0 ml/100g/min.
2. T-time ≤ 2.6 min
3. R-index ≤ 22.0%

Using these parameters combined, 2 of 44 limbs with intermittent claudication were found to have borderline values between normal and abnormal clearance curves.

As shown in Fig. 1 one hundred and twenty-eight curves of normal subjects were classified according to the values of MBF_E. The values of MBF_H, T-time and R-index increased as the value of MBF_E increased. So it is clear that low MBF_E produces lower post-exercise hyperemia.

In 40 normal curves with MBF_E under 24 ml/100g/min, all MBF_H, T-time and R-index were significantly, p < 0.001, lower than those of 88 normal curves with MBF_E over 25 ml/100g/min (Fig. 2). In only two of those 40 curves, MBF_H was greater than MBF_E. This discrepancy between MBF_H and MBF_E was under 1.0 ml. As hemodynamically significant arterial abnormalities produce pathological post-exercise hyperemia, the following criterion may be calculated with a probability of 99%:

4. When MBF_E is under 24.0 ml/100g/min, T-time < 1.8 min, R-index < 10.0% and MBF_E ≥ MBF_H

This criterion can be available for diagnosis of the patients with mild intermittent claudication. By using our new criterion (No. 4) in addition to above three criteria (No. 1–3), all the patients with intermittent claudication had abnormal clearance curves.

2. Correlation between arteriograms, clinical data and Xe-133 clearance curves

Observations were made on 56 limbs (TAO:31 and ASO:25) whose clinical status showed no change between at the time of the X-ray examination and Xe-133 clearance test.

The subjects were classified according to their clinical symptoms (Tab. I):

Group 1: legs without intermittent claudication or any complaints in the calf during the Xe-133 standard exercise
TABLE 1  FORTY LIMBS WITH STENOsis OR OCCLUSION PROXIMAL TO THE POPliteAL ARTERY WERE CLASSIFIED
ACCORDING TO THE DEGREES OF INTERMITTENT CLAUDICATION

<table>
<thead>
<tr>
<th>Intermittent Claudication</th>
<th>None</th>
<th>Mild to Moderate Claudication Distance ( \geq 150\text{M} )</th>
<th>Severe Claudication Distance ( \leq 100\text{M} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Cases</td>
<td>TAO</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>ASO</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Localization of Occlusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aorto-Ilio-Femoral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ilio-Femoral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated Iliac</td>
<td></td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Femoro-Popliteal</td>
<td></td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Isolated Femoral</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Isolated Popliteal</td>
<td></td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Stenosis</td>
<td>Iliac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(One Stenosis, Luminal Diameter; 5mm, Length; 8mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral</td>
<td></td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Popliteal</td>
<td></td>
<td>(One to Four Stenosis, Luminal Diameter; 3–5 mm, Sum of this Length: No Greater Than 17mm)</td>
<td>1</td>
</tr>
<tr>
<td>Generalized Atherosclerotic</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Xe-133 Clearance Test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MBFE (mL/100g/min)</td>
<td>28.0 ± 8.3</td>
<td>14.4 ± 4.2</td>
<td>6.0 ± 4.4</td>
</tr>
<tr>
<td>T-time (min)</td>
<td>1.5 ± 0.4</td>
<td>3.6 ± 1.0</td>
<td>8.5 ± 3.2</td>
</tr>
<tr>
<td>R-index (%)</td>
<td>10.2 ± 9.0</td>
<td>52.3 ± 14.1</td>
<td>83.7 ± 9.6</td>
</tr>
</tbody>
</table>
Group 2: legs with mild to moderate intermittent claudication (claudication distance $\geq 150$ m)

Group 3: legs with severe intermittent claudication in the calf (claudication distance $\leq 100$ m)

In three groups arteriographic findings were shown in Table I. In group 1 one patient with popliteal occlusion had excellent collateral vessels in arteriogram and walked without pain as normal. In one patient with femoro-popliteal occlusion, the popliteal pluse was absent, but his pulse of the dorsalis pedis artery was palpable. This finding implied excellent collateral vessels. All the clearance curves in this group were within normal limits. The legs of group 2 produced Xe-133 clearance curve with moderate to poor exercise blood flow and with moderate to large post-exercise hyperemic reactions. Values of 3 parameters were significantly different from those in group 1 (three parameters: $p < 0.001$).

By examining all the clearance curves within each of above 3 groups, we were empirically able to assign boundary values to 3 clearance curve parameters (Tab. II). These three groups of Xe-133 clearance curves correlated very well (a $X^2$ test resulted in a $p < 0.001$) with the groups classified by intermittent claudication (Tab. III). Five legs were borderline cases. Two of 3 cases labelled (a) had the clearance curve group 2 in all parameters, but their values were near the borderline ones between group 1 and 2. As described above, these patients could be divided from normals easily by using our new criterium (No. 4). In the another one, two of three parameters fell in clearance curve group 2, but one in group 3. Two cases labelled (b) had the values of clearance curve group 3 in 2 parameters, but one in group 2. All in three parameters were near the borderline values between group 2 and 3. Two legs do not fall correctly into place and deserve further comments. One with TAO cannot walk more than 200 m due to the calf pain. His values of clearance test fell into group 3 in MBFE and R-index and in group 2 in T-time. The another had a total occlusion of the superficial
femoral artery and markedly abnormal clearance curve. His claudication distance was not accurate because of a big ischemic ulcer in the contralateral foot.

In three cases the changes of their symptoms were observed as follows:

Case 1. A 43-year-old man with TAO had severe pain in the left calf during walking (claudication distance is 100 m). Arteriogram showed the occlusion in the femoral and popliteal arteries. Xe-133 standard exercise test gave markedly abnormal clearance curve belonging to group 3. After 5 months’ medical treatment he could walk about 400 m without pain and Xe-133 clearance test showed moderate abnormal curve belonging to group 2.

Case 2. A 46-year-old man with TAO had intermittent claudication of left leg but no ischemic symptoms in the right leg although pulsations of the popliteal and dorsalis pedis arteries were absent. Xe-133 clearance curve was normal. After 3 months he could not walk more than 100 m due to the muscle pain in the right calf and the pulsation of the posterior tibial artery was not palpable. Arteriogram showed severe femoro-popliteal occlusion and Xe-133 standard exercise test showed markedly abnormal curve belonging to group 3. After 6 months’ medical treatment he could walk about 600 m without pain and had improved clearance curve belonging to group 2.

Case 3. A man with TAO, aged 43, cannot walk more than 100 m due to the calf pain. The arteriogram revealed occlusions of the external iliac and superficial femoral arteries. The Xe-133 clearance test showed remarkably abnormal curve belonging to group 3. After autogenous vein grafting between the external iliac and the popliteal arteries he could walk without pain and Xe-133 clearance curve was within normal limits. After 9 months he complained of intermittent claudication in the same calf at about 400 m. All pulsations distal to the femoral artery were absent, indicating bypass graft was occluded, and Xe-133 clearance test revealed moderate muscle insufficiency belonging to group 2. He underwent prosthetic bypass grafting between the common iliac and the popliteal arteries and could walk without pain again. Xe-133 clearance test revealed improved curve belonging to group 1.

As described above Xe-133 standard exercise method in the anterior tibial muscle can give the quantitative knowledges for the muscle circulatory insufficiency in the cases with occlusion or stenosis proximal to the popliteal bifurcation. However, the anatomical levels of occlusion or stenosis by arteriograms did not so well correlate with muscle insufficiency as could be expected. In 20 cases with femoro-popliteal occlusion, 12 had severe intermittent claudication with remarkably abnormal clearance curves and 8 had mild to moderate intermittent claudication with less abnormal clearance curves.

**DISCUSSION**

The standard exercise method is easily employed in any labatory provided with usual scintillation counter. It has been generally accepted, however, the diagnostic value of this method compared to the walking test method and ischemic work method, has not been established.

As described above, the diagnostic value of this method has been improved by using our technical methods (see Part 1) and criteria. Bell and Short reported that the abnormal response to ischemic exercise is more marked in the group with occlusion distal to the inguinal ligament than in the group with proximal disease. However, Lewis et al. said similar moderate abnormal clearance curves were gained from both occlusion of the isolated iliac and the isolated femoral arteries. They and Alpert et al. reported a relationship of Xe-133 clearance from the calf following moderate exercise correlated well with the anatomical level, with distinctions between single- and multiple-segment diseases; multiple-segment diseases had more markedly abnormal clearance curves than single-segment diseases. Our results in Xe-133 clearance test corresponded better with the degree of intermittent claudication than with the anatomical level of the diseases.

This explains clinical symptoms can be changeable following treatments and/or spontaneously without clear changes of the arteriographic findings. The differences between the clearance curves probably reflect different blood supply through the collateral vessels when the measurement was made even if the degree of main vessel occlusion remained unchanged.

We conclude that in occlusion or stenosis proximal to the popliteal bifurcation, the Xe-133 standard exercise method in the anterior tibial muscle gives objective and quantitative knowledges in the clinical evaluation of arterial insufficiency during the course of the diseases.

As Xe-133 is highly soluble in lipids, the
The disappearance rate of Xe-133 is largely influenced by the fat content of the muscle. Lindbjer et al. reported that the anterior tibial muscle presented advantages over the gastrocnemius muscle in clinical examinations due to its smaller and less variable fat content. We injected Xe-133 solution in the two different sites of the anterior tibial muscle on 10 legs with obstructive arterial diseases by using smaller collimeter (diameter 4 cm). The lower exercise blood flow and post-exercise hyperemia was found in the lower part of the muscle (20 cm distal to the inferior border of the patella) than in the routine injection site (10 cm distal). This observation might indicate the local variation in the fat content of the muscle.

Although we examine the anterior tibial muscle as routine examination in the cases with occlusion or stenosis proximal to the popliteal artery, it is necessary to determine blood flow in the gastrocnemius as well as the anterior tibial muscles in cases with occlusion only in the calf arteries. In our other studies in the patient with complete occlusion of the posterior tibial artery but not of the anterior tibial artery without occlusion or stenosis proximal to the popliteal artery, the clearance curve in the gastrocnemius muscle was moderate abnormal but that in the anterior tibial muscle was completely normal. Therefore, it is not forgotten that the clearance curves of the cases belonging to the intermittent claudication group I must be influenced by the occlusion and/or stenosis in the calf arteries.

SUMMARY AND CONCLUSION

1. The Xe-133 standard exercise method was used to study the muscle blood flow in the 56 limbs of 47 patients suffering from peripheral vascular diseases and the results were compared with clinical manifestations and arteriographic findings.
2. This test has a reliable diagnostic value for the patients with intermittent claudication, by using our technical methods (Part 1) and criteria.
3. In the cases of occlusion or stenosis proximal to the popliteal artery, the clearance curves from the anterior tibial muscle corresponded better with clinical data than with anatomical level of the diseases. In these cases Xe-133 standard exercise method gives the objective and quantitative knowledge in the clinical evaluation of arterial insufficiency during the course of the disease.

Acknowledgements

Great acknowledgement is made to associate Prof. S. Shionoya for his constant interest and guidance in this investigation. Valuable informations were kindly supplied by Dr. T. Nagasaka, physiologist, Dr. M. Kaneko, radiologist, Dr. N. Hayakawa, statistician and Mr. M. Shimo, engineer. Thanks are due to the staff in our clinic for helpful discussions.

REFERENCES