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

Part 1. Standard Exercise Method —With Special Reference to Work Load and Volume Injected—

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IT IS always important to measure muscle blood flow of the lower extremities for either diagnosis or prognosis of the patients suffering from peripheral vascular diseases.

The local isotope clearance technique was first introduced by Kety.¹ Lassen *et al*.² used the radioactive inert gas Xe-133 instead of Na-24 as the radioactive tracer. His demonstrations of this tracer revealed many advantages over radioactive sodium.

In the Xe-133 clearance method there are three different techniques: 1. ischemic work method,^{2,3} 2. walking test method,^{4,5} and 3. non-ischemic work method^{6,7} — we call it standard exercise method. Each has its own advantages.

Muscle blood flow has been measured in the anterior tibial muscle of patients with peripheral vascular diseases by Xe-133 clearance method, using the standard exercise method, at the Branch Hospital of the Nagoya University in Japan since 1968.

From previous results, diagnostic significance of this method has been considered to be limited⁴ because of considerable overlapping between normal subjects and patients. The present study includes, therefore, a reconsideration of the clearance method. Special reference was given to the relationship of the work

intensity or the total volume injected to the clearance curve.

MATERIAL AND METHOD

All experimental studies were performed on healthy subjects. The 40 healthy volunteers included young students and staff members of our clinic with no history of claudication and all peripheral pulses present. They were all male and their ages ranged between 18 and 40 years, with a mean of 24.

The subjects were examined in the recumbent position. Sterile isotonic solution of radioactive Xe-133 was injected into the anterior tibial muscle. Reproducibility of repeated studies was assured by locating the injection site 10 cm distal to the inferior border of the patella and 2 cm lateral to the tibial crest. The disappearance rate of the tracer was measured with thallium-activated NaI crystal coupled to a ratemeter. A wide collimeter was used which covered an area with a diameter of 8 cm. The time constant of a ratemeter was 3 seconds. The volunteer subjects were instructed to exercise their feet. The foot exercise performed was maximal dorsal flexion without ischemia of the thigh — that is the standard exercise method.

The work intensity and the volume injected were varied in each experiment. Usually each subject underwent the studies three or four times successively on the same day.

From the clearance curves four parameters were calculated (Fig. 1).

1. MBF_E : maximal blood flow during the exercise

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Fig. 1. From the clearance curves four parameters were calculated.

2. MBF_H : maximal blood flow after the exercise

Blood flow can be calculated using the formula of Lassen.² This formula states $Flow = 161 \times D$ ml/100g/min where D is the decrease in one minute of a tangent drawn to the logarithmic plot of the clearance curve.

3. T-time: the duration of post-exercise hyperemic reaction measured in minutes. It goes from the cessation of the exercise until the curve reaches its pre-exercise value.

4. R-index: an index of the remaining part of the hyperemia that occurs one minute after the cessation of the exercise.

This remaining hyperemia is calculated from the equation:

$$R = \frac{\Delta_3}{\Delta_1 + \Delta_2} \cdot 100 (\%)$$

This equation defines R as that percentage of the total decrease of the clearance curve during and after exercise which occurs after one minute of rest. Δ_1 is the cumulative fall of the clearance curve during the first one and a half minute of the exercise. Δ_2 is the cumulative fall of the clearance curve between the cessation of the exercise and T . Δ_3 is the cumulative fall of the

Work Intensity and Xe-133 Clearance Curve

Fig. 2. There was no association between the number of contractions and MBF_E . However, the degree of post-exercise hyperemia was roughly proportional to the work load.

clearance curve between one and T minutes after the cessation of the exercise.

RESULTS

1. Work intensity and Xe-133 clearance curve (Fig. 2)

The experiment was studied to clarify the relation of the work intensity to Xe-133 clearance curve. Eighteen normal subjects were instructed to make maximal dorsal flexion of their ankles for 2 minutes using various contractions: 10, 20, 35, 50 times per min and finally the maximal number possible. The mean contractions of maximal work were 102 ± 15 times per min. The working speed was controlled by metronome. The injected volume of Xe-133 solution was the same amount in all cases.

There was no association between the number of contractions and MBF_E . However, the more numerous contractions; the values were higher of MBF_H , R-index and T-time. So we can see that the degree of post-exercise hyperemia is roughly proportional to the work load.

2. Duration of the exercise and MBF_E (Fig. 3)

In 14 normal subjects the exercise was continued for 3 minutes. In all except one MBF_E increased when the work was continued throughout 3 minutes. This difference between 2 min- and 3 min-exercise was small, but still had statistically significant difference ($p < 0.01$).

3. The volume injected and Xe-133 clearance

Fig.3. In all cases except one MBF_E increased when the work was continued throughout 3 minutes. This difference between 2 min- and 3 min-exercise was small, but still had statistically significant difference.

curve

The experiment was undertaken to determine the relation of the volume injected of Xe-133 solution to the muscle blood flow. In 17 normal subjects Xe-133 solution was injected at various amounts from 0.05 to 0.45 ml. Each contained the same radioactivity of Xe-133, about 50 μ Ci.

There was no significant difference in the mean values of MBF_E from the various amounts of the solution injected.

In each individual the coefficient of variation of MBF_E from the different volume injected was examined (Fig. 4): that is A (the coefficient of variation between 0.15 and 0.05 ml), B (that between 0.15 and 0.25 ml), C (that between 0.15 and 0.35 ml) and D (that between 0.15 and 0.45 ml).

Significant differences were found between B and both C and D ($p < 0.05$). Between B and A there was no significant difference.

The coefficient of variation of reproducibility of minute-to-minute variation was $6.2 \pm 5.4\%$. In comparison of this coefficient of variation with A, B, C and D, there were significant differences

Fig.4. In each individual the coefficient of variation of MBF_E from the different volume injected was examined. Significant differences were found between B and both C and D ($p < 0.05$). Between B and A there was no significant difference. In comparison of the coefficient of variation of minute-to-minute variation with A, B, C and D, there were significant differences between this value and both C and D ($p < 0.05$).

between this value and both C and D ($p < 0.05$).

From the results above, it is clear that at a volume of 0.05 to 0.25 ml constant clearance curves are registered.

DISCUSSION

Larsen and co-workers⁸ have used the Xe-133 walking test method and ischemic work method for measuring the muscle blood flow of the legs as routine examinations. Walking test method has a reliable diagnostic value for obliterative arterial diseases and the muscle blood flow during the most physiological exercise can be estimated. However, severely affected patients cannot readily take this type of test and special instruments, such as specially constructed scintillation probe or treadmill, are needed. Ischemic work method is, also, a fairly reliable indicator for obliterative arterial diseases. However, it causes severe pain during exercise and the muscle blood flow during

the exercise cannot be estimated. To measure the muscle blood flow during the exercise is much important in order to disclose the arterial insufficiency of the legs from the pathophysiological aspects. Standard exercise method is easily used in any laboratory provided with usual scintillation counter.

Tønnesen⁹ said that on normal subjects where the blood flow was measured during two exercise periods from the same depot on the same day, a lower blood flow was found at the same exercise intensity in the second exercise period. In our examination of reproducibility his observation was not found. It is necessary before the next determination to confirm the isotope removed perfectly.

The degree of post-exercise hyperemia increased roughly proportionally to the work load. This findings indicate that the oxygen uptake increases in response to increased work load up to maximal work.^{10,11} And many metabolites stimulate MBF_H to increase when the work load is intensified.

Lindbjerg¹² reported that the maximal post-exercise blood flow did not differ significantly after 50% and 100% of the maximal work intensity using the ischemic work method. The values averaged 67.2 ml/100g/min in 50% and 70.8 ml/100g/min in 100% of the maximal work intensity in his report; 53.5 ml/100g/min in 50% and 74.0 ml/100g/min in 100% in our results.

During the ischemic exercise the muscle blood flow stops perfectly and the transmural pressure is reduced in the calf.¹³ Many metabolites stimulate blood flow to increase after the exercise. In general under the same work load the higher MBF_H is gained in the ischemic exercise than in the non-ischemic exercise. However, there is an upper-limit of inflow capacity — it might be about 70 ml/100g/min. Therefore, in ischemic work method the same MBF_H will be obtained both after 50% and 100% of the maximal work intensity.

There was no association between the number of contractions and MBF_E , and the work level at which the maximal MBF_E was obtained varied in each individual. Six normal subjects reached the maximal MBF_E at a work level of about 20% of the maximal work intensity. Their blood flow decreased as the work load was more intensified. It was general in our results that after reaching the maximal MBF_E their blood flow decreased as the work was further increased. However, the value of the maximal MBF_E was approximately

constant — about 50 ml/100g/min.

The pressure developed in the muscle during contraction is an important factor in the regulation of the blood flow during the exercise. And each individual has different muscle strength. Therefore their blood flow differs on the same work intensity. Due to this mechanical compression on the blood vessels, MBF_E is less than his maximal inflow capacity^{6,11,14}

In our cases the work level at which maximal MBF_E was obtained was generally under 50% of the maximal work intensity. Clausen and Lassen¹⁴ reported that maximal blood flow during the exercise was attained at a work level consisting on average of 70% of the maximal work intensity during rhythmic exercise on a bicycle ergometer.

The reason for this discrepancy appears to be due to the difficulty in estimating what the maximal work intensity is. Their maximal work intensity was that the subjects could sustain on a bicycle ergometer for just 5 minutes. They also used the supramaximal loads that the subjects could not sustain for 3 minutes. The muscle blood flow during the supramaximal loads was less than that during the maximal work intensity. Our maximal work intensity might approximately equal their supramaximal loads.

As it is generally accepted that post-exercise hyperemia has more reliable value for diagnosis because of less overlapping between normals and patients,^{5,7,9} the work intensity should be constant on Xe-133 standard exercise method. The large variations in the flow during the exercise will be inevitably estimated.

From the relation of the volume injected to the muscle blood flow, at a volume of 0.05 to 0.25 ml reliable clearance curves are registered. Little is known about the relationship between the volume injected and the blood flow. When the volume of Xe-133 solution is more than 0.25 ml this might mechanically compress the adjacent capillaries or damage some degree of tissue or capillaries.¹⁵ Minimal volume as possible is desirable.

From the results obtained here, to get constant clearance curve, it is concluded that the work load should be kept constant and the total volume injected must be 0.05 to 0.25 ml. We believe that the work load should be continued 20 contractions per min for 2 minutes. The reason for that is as follows:

1. All patients with intermittent claudication can perform this test without severe pain.

2. In this work load the minimal overlapping is seen between normal subjects and patients. We had two cases with R-value over 50% at the work load of 35 contractions per min.
3. The work load of 10 contractions per min is not enough to distinguish the patients from the normal subjects.
4. The difference between 2 min- and 3 min-exercise is small, but still has statistically significant difference. Therefore it is better to keep the duration of the exercise constant.

CONCLUSION

Muscle blood flow of 70 limbs of 40 normal subjects was measured in the anterior tibial muscle by the Xe-133 clearance method, using the standard exercise method.

The relationship of the work load or the volume injected to the clearance curve was discussed.

To get constant clearance curve in Xe-133 standard exercise method, the work load should be kept constant and be continued 20 contractions per min for 2 minutes, and the volume injected must be 0.05 to 0.25 ml.

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