Muscle Blood Flow During Exercise in Intermittent Claudication

Validation of the $^{133}$Xenon Clearance Technique: Clinical Use by Comparison to Plethysmography and Walking Distance

By K. H. Tønnesen, M.D.

SUMMARY

Pathophysiological considerations predict that exercise blood flows at comparable work loads must always be reduced in claudicants in comparison to normal subjects. The present study verified that the exercise blood flow determined by $^{133}$xenon clearance measurements in the gastrocnemius muscle in claudicants and in a control group differed widely.

As expected, a statistically significant correlation was found between the first flow by plethysmography and the maximal exercise blood flow determined by the $^{133}$xenon clearance technique in the patients and for the whole material (but not for the control group alone). The exercise blood flow determined by $^{133}$ xenon clearance in the claudicants was statistically significantly correlated to the walking distance, measured on a treadmill, while the postexercise blood flow as measured by plethysmography was not. This finding establishes the concept, that the $^{133}$xenon clearance technique can be applied in quantitating the degree of arterial insufficiency.

Additional Indexing Words:
One leg calf ergograph  $^{133}$Xenon clearance  Venous occlusion plethysmography
Mercury in rubber strain gauge  Treadmill walking  Arterial insufficiency

BY USING the $^{133}$xenon clearance technique,1, 2 it was possible for the first time to measure the exercise blood flow in human skeletal muscle with a relatively simple technique.3 This method was employed in a study of exercise blood flow in patients suffering from intermittent claudication.4 It was demonstrated in this paper that the sensitivity of the method validated the expectations: exercise blood flow in 13 legs in which angiography had demonstrated occlusions of the iliac, femoral, or popliteal arteries was consistently lower than exercise blood flow in a normal control group.

The results demonstrated, however, coefficients of variation ranging from 18 to 87% with 97 measurements on the 13 legs. The mean value of the coefficient of variation was 33.3% (mean value for the exercise blood flow was 10.1 ml/100 g·min). The mean value of the blood flow determined in repeated experiments on each leg corresponded well with the clinical impression as to the degree of vascular impairment. However, the use of this mean value may seem rather arbitrary in view of the fairly large coefficient of variation.

The present study investigated the validity of this mean value in measuring the degree of vascular derangement in comparison with standard techniques, such as venous occlusion plethysmography and walking distance.

Pathophysiological Considerations

In the normal leg only the resistance in the arterioles is of importance. When arterial occlusion occurs, a resistance in series is added in front of the arterioles.

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In patients suffering from intermittent claudication, the pathologically increased resistance in the arteries will cause a significant drop in the peripheral blood pressure, particularly when the resistance in the arterioles is low, as is the case during hyperemias which follow 5 min of ischemia or occur during periods of exercise.

These two conditions are not quite similar. During reactive hyperemia the muscles are relaxed, and therefore the hydrostatic pressure within the muscle is close to zero. During exercise the intramuscular pressure rises. When the peripheral blood pressure is less than the hydrostatic pressure within the contracting muscle, the blood flow through the muscle stops. In this connection it must be mentioned that the highest exercise blood flow in normal subjects is considerably less than the maximal reactive hyperemia. This indicates that the intramuscular pressure in contracting muscle to some extent slows the flow rate even in normals.

During reactive hyperemia studied by venous occlusion plethysmography in patients suffering from intermittent claudication, an overlapping was reported between the values for maximal reactive hyperemia obtained in patients as compared to those values obtained in normal subjects. This lack of clear separation is not due to deficient technique, since the phenomenon was observed with different kinds of plethysmograms. It can be concluded, therefore, that in some claudicants the increased resistance in the large arteries is compensated for by collateral channels. The amount of blood which flows through these collateral arteries is of such a magnitude that one cannot distinguish patients from normals by the maximal flow rate during reactive hyperemia.

Apparently, the peripheral dilatation of the arterioles during exercise leads to a rapid drop in the distal blood pressure. This combined with increased intramuscular pressure is the physiological basis for intermittent claudication. Thus, if $^{133}\text{Xenon}$ clearance is able to yield a valid measure of the exercise blood flow, a clear separation between normal subjects and claudicants is to be expected at a work rate which is tolerated by normals and which provokes claudication in the patients.

Methods

The material consisted of 35 legs from 26 patients in whom angiography had demonstrated occlusions (lower aorta in one, iliac artery in five, femoral artery in 25, iliac plus femoral arteries in one, and femoral plus popliteal arteries in three). None of the patients had rest pain or trophic lesions. Apart from slight changes in the ECG and one patient with a blood pressure of 210/120 mm Hg, no patients had overt cardiac disease. The group included no diabetics. The mean value of the blood pressure of the patients was 146/97 mm Hg. The age of the patients ranged from 46 to 77 years (mean, 61 years). Four of the patients were females, 22 were males. All patients had been admitted to the hospital.

The control group consisted of 24 legs in 12 subjects (one female). The age ranged from 21 to 52 years (mean, 39). Two were members of the staff, four were students, and six were firemen. By physical examination they were found to be healthy. They had no complaints of cardiac or peripheral vascular disease; none were diabetics.

Exercise Blood Flow Determined by $^{133}\text{Xenon}$ Clearance

The examinations were planned in order to obtain the best experimental conditions with the given method: the $^{133}\text{Xenon}$ clearance measurements were repeated on different days, as only one exercise flow can be measured from each depot and because patients often have relatively high residual activity after the examination. In contrast, plethysmographic examinations were repeated at 10- to 20-min intervals. The walking distance was measured only once in each patient on a treadmill with a speed of 2 km/hr and an uphill inclination of 5°. The patients walked until pain forced them to stop.

The patients were brought to the laboratory in their beds and were kept in bed until the examinations were performed, all of which took place in the morning. The ambulant subjects of the control group rested 15 to 30 min before the examinations.

The exercise blood flow determined by $^{133}\text{Xenon}$ clearance was measured exactly as earlier described, and the reader is referred to this paper for details.

The principle of the examination is that the clearance is followed from a depot of $^{133}\text{Xenon}$ in

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saline (0.1 to 0.2 ml, 0.5 to 1.0 mC/ml)\textsuperscript{*} injected into the lateral belly of the gastrocnemius muscle. The blood flows in ml/100 g \cdot min during rest and exercise were calculated as follows:

\[
\text{Blood flow} = \frac{\ln 2}{T_{1/2}} \cdot 100 \text{ ml/100 g/min}
\]

where the partition coefficient $\lambda = 0.7\textsuperscript{*}$ and $T_{1/2}$ is the half-time of the slope of the clearance curve recorded by the logarithmic potentiometer writer.

The patient reclined in an armchair, mounted on the ergograph, which was constructed so that the calf exercise mimicked that of walking. The foot of the leg to be examined was fixed on the pedal of the ergograph, thus securing a constant geometry for the scintillation probe, which was situated 15 cm lateral to the leg.

The clearance curve was recorded by a 2-decade, logarithmic potentiometer writer (Philips PR 2210) fed by a ratemeter (Philips 4242) with a time constant of 4 sec. By means of an amplifier/analyzer (Philips 4280) only the 81 kev $\gamma$ energy of $^{133}$xenon was counted.

After the injection the clearance rate was followed during 6 min of rest. Exercise was then performed for 6 min. In some cases claudication pains forced the patient to stop after 3 to 4 min. All patients reported claudication pain or pronounced tiredness. Loads from 8 to 18 kg were used. The metronome had a rate of 40 times/min. In the postexercise period the clearance was followed for 15 min. Thereafter the other leg was examined.

Muscles with different physiological cross section will be strained differently in performing the same external exercise. Comparison of the muscle work in different persons was made possible by the following procedure.

The maximal plantar flexion force of each leg was measured on a strain-gauge dynamometer, while the patients were in the same position as on the ergograph. The exercise performed in measuring each exercise blood flow was corrected by multiplying the amount of work performed (in kg-m/min) by the inverse value of the maximal plantar flexion force in the same leg (in ton \cdot cm). This value was called "the corrected work load."

In this way the variations due to differences in physiological cross sections of the gastrocnemius muscle were eliminated and work loads were made directly comparable.\textsuperscript{3}

In both the patient and in the control group the exercise blood flow determined by $^{133}$xenon clearance was measured three times.

\textsuperscript{*}Supplied by the Radiochemical Center, Amersham, England.

The exercise blood flow was always measured at a "corrected work load" which was just above half of the maximal exercise intensity. At this work load maximal values of the exercise blood flow are obtained in normals.\textsuperscript{3}

**Postexercise Blood Flow by Venous Occlusion Plethysmography**

In a few cases a venous or Teflon graft in the femoral artery has been reported to re-thrombose after the application of an arterial occlusion cuff (250 to 300 mm Hg) to the thigh.\textsuperscript{9} Therefore, a short, fatiguing calf exercise was used to provoke maximal vasodilatation instead of the usual 5-min period of ischemia. This was easy to carry out as the patients were already accustomed to the ergograph used in the xenon clearance studies. The subjects lay on the ergograph with the calf at the level of the sternum. The shoulders were supported by a board which prevented the subject from sliding away from the ergograph while working.

A collecting cuff, 12 cm wide, was situated just above the knee, and was supplied with air at a pressure of 50 mm Hg from one 120-L air reservoir; the 6-cm ankle cuff was supplied with air at a pressure of 250 mm Hg from another 20-L reservoir. Both reservoirs were fed by gas flasks. The tubes were as short as possible, and both tubes and three-way stopcocks had an inner diameter of 8 mm.

Whitney's mercury-in-rubber strain-gauge plethysmograph was mounted on the thickest part of the calf. Calibration was done by a micrometer nut with the gauge in situ, as described by Whitney.\textsuperscript{10}

Four technically satisfactory rest tracings were recorded after the ankle cuff had been inflated for 1 min to 250 mm Hg. The loads on the ergograph were generally somewhat greater than in the xenon experiments in order to fatigue the muscles rapidly. The exercise period then lasted only 1 to 3 min. The metronome rate was 40 beats/min. From zero time until 3 min, the post-exercise flow was recorded as often as the base line was reached again after venous occlusions on the thigh of 3- to 15-sec duration while the ankle cuff was kept inflated at 250 mm Hg for 15 sec before interruption of the exercise. The first flow recording was started within 1 to 2 sec of the end of exercise.

**Results**

**Blood Flow During Hyperemia**

The exercise muscle blood flow determined by $^{133}$xenon clearance averaged 35.1, $\pm$ 4.6 ml/100 g \cdot min, in the 24 normal legs (table 1). The corresponding value in the 35 legs

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with arterial occlusion was 6.1, ± 4.6 ml/100 g • min. The difference is highly significant; in fact, there was a large span from the highest flow value in any patient (16.6 ml/100 g • min) to the lowest flow value in any normal (26.6 ml/100 g • min).

The first plethysmographically recorded flow value in the postexercise period averaged 45.2, ± 12.4 ml/100 ml • min, in the normal legs as compared to an average of 11.2, ± 7.2 ml/100 ml • min, in the patient group (table 1). This difference is also highly statistically significant. But, no less than four of the 35 legs with arterial occlusion had plethysmographic first flow values which were larger than the lowest normal value (fig. 1).

Despite the better separation of the cases by the 133Xenon exercise technique, this method had a larger random experimental deviation than the plethysmographic technique (table 2). Even the effect of doing triplicate 133Xenon measurements as compared to only duplicate plethysmographic measurements did not fully equalize this error.

However, part of the deviation associated with the 133Xenon clearance technique may have been due to day-to-day variation in the actual blood flow.

Therefore, in order to evaluate the day-to-day variation on single measurement by plethysmography, both legs of one of the normal subjects were examined on six different days. On the right leg the mean value of the first flow after exercise was 36.2 ml/100 ml • min, ± 8.5; on the left leg, 30.9 ml/100 ml • min, ± 8.0. The coefficients of variations were then 23% and 26%, respectively.

In figure 1 the mean values for blood flow as determined by both methods in the two groups are plotted against each other. A

Table 1
Mean Values of Triple Determinations by 133Xenon and Double Determinations by Venous Occlusion Plethysmography

<table>
<thead>
<tr>
<th></th>
<th>Exercise blood flow by 133Xe clearance (ml/100 g • min)</th>
<th>Postexercise blood flow by plethysmography (ml/100 ml • min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>26.5-43.3</td>
<td>22.8-76.8</td>
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<tr>
<td>Mean value</td>
<td>35.1</td>
<td>45.2</td>
</tr>
<tr>
<td>± of group</td>
<td>4.6</td>
<td>12.4</td>
</tr>
<tr>
<td>No. of legs</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Patients with arterial occlusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0-16.6</td>
<td>0.8-24.7</td>
</tr>
<tr>
<td>Mean value</td>
<td>6.1</td>
<td>11.2</td>
</tr>
<tr>
<td>± of group</td>
<td>4.6</td>
<td>7.2</td>
</tr>
<tr>
<td>No. of legs</td>
<td>35</td>
<td>35</td>
</tr>
</tbody>
</table>

Figure 1
Mean values of three measurements of the exercise muscle blood flow determined by 133Xenon clearance plotted against the mean values of two measurements of the first flow in the postexercise period by venous occlusion in plethysmography. The circles denote the results on patients, in whom occlusion of aorta, iliac, or femoral arteries had been demonstrated by angiography; the crosses, the corresponding values in a normal control group.
Table 2

Results of the Reproducibility of Three Determinations of Exercise Muscle Blood Flow by $^{133}$Xenon Clearance and Two Determinations of First Flow by Venous Occlusion Plethysmography

<table>
<thead>
<tr>
<th></th>
<th>Exercise blood flow by $^{133}$Xe clearance (ml/100 g · min)</th>
<th>First flow in postexercise period by plethysmography (ml/100 ml · min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean value</td>
<td>35.1</td>
<td>45.2</td>
</tr>
<tr>
<td>SD of a single measurement</td>
<td>6.15*</td>
<td>5.90†</td>
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<tr>
<td>Random experimental error</td>
<td>3.50‡</td>
<td>4.17§</td>
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<tr>
<td>Coefficient of variation of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>random error</td>
<td>9.9%</td>
<td>9.2%</td>
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<tr>
<td>No. of examinations</td>
<td>72</td>
<td>48</td>
</tr>
<tr>
<td>No. of legs</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td><strong>Limbs with occlusion of main artery to the leg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean value</td>
<td>6.1</td>
<td>11.2</td>
</tr>
<tr>
<td>SD of a single measurement</td>
<td>3.03*</td>
<td>1.70†</td>
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<tr>
<td>Random experimental error</td>
<td>1.75‡</td>
<td>1.21§</td>
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<tr>
<td>Coefficient of variation of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>random error</td>
<td>28.7%</td>
<td>10.7%</td>
</tr>
<tr>
<td>No. of examinations</td>
<td>150</td>
<td>70</td>
</tr>
<tr>
<td>No. of legs</td>
<td>35</td>
<td>35</td>
</tr>
</tbody>
</table>

*SD was calculated from $\sqrt{\frac{\sum(x_i - \bar{x})^2}{(N - 1)24}}$ where $x_i$ is one of three measurements on one leg, and $\bar{x}$ the respective mean value for this leg; $N$ is the number of single measurements on each leg.

†SD was calculated from $\sqrt{\frac{\sum(x_1 - x_2)}{2N}}$ where $x_1$ and $x_2$ are each of the double determinations, and $N$ is the number of legs.

‡SD of the mean of three xenon measurements (that is, random experimental error) was calculated from $1/\sqrt{3}$ SD of a single measurement.

§SD of the mean of two plethysmographic measurements (that is, random experimental error) was calculated from $1/\sqrt{2}$ SD of a single measurement.

statistically significant correlation is seen between the mean values of the exercise muscle blood flow determined by $^{133}$Xenon clearance and the mean values of the first flow of the calf in the postexercise period as measured by plethysmography: (1) for the diseased legs ($r = 0.79$, $N = 35$, $P < 0.001$), and (2) for both groups pooled ($r = 0.84$, $N = 59$, $P < 0.001$), but not for the control group alone ($r = 0.05$, $N = 24$, $P > 0.1$).

Figure 2 shows the mean value of the exercise muscle blood flow determined by $^{133}$Xenon clearance in the more symptomatic leg of the patients with claudication plotted against the walking distance measured on a treadmill. A linear correlation was obtained when the flow was plotted against the logarithm of the walking distance ($r = 0.65$, $N = 21$, $P < 0.001$). The crosses denote three experiments, in which three young normal subjects walked on the treadmill with arterial occlusion cuffs inflated to 250 mm Hg mounted above the knee.

In figure 3 the corresponding mean values of the first flow after exercise by plethysmography have been plotted against the logarithm of the walking distance. No statistically significant correlation was found ($r = 0.19$, $N = 21$, $P > 0.1$).

Comment on the Plethysmographic Technique

The well-known shape of the plethysmographic flow curve in normal subjects and in
Mean values of three measurements of the muscle blood flow determined by $^{133}$Xenon clearance plotted against the walking distance in logarithmic scale for the claudicants. The walking distance was measured on a treadmill with a speed of 2 km/hr and an uphill inclination of 5°.

 Claudicants in the postexercise period or during reactive hyperemia were first described by Shepherd.11 He found that the first or second flow in normal subjects was the highest recorded value, and resting flows were reached rapidly. In some of the claudicants the first flows were rather low, accelerating during the following minutes and reaching maximal values after 3 to 15 min.

A differentiation between normals and claudicants may be obtained by using the time until the maximal value is reached, that is, the time in minutes from the end of exercise until the highest plethysmographic blood flow is recorded. Normals and claudicants will also differ considerably with respect to the 3-min flow value expressed as a percentage of the maximal value. This is due to the fact that resting flow values are reached much more slowly in patients than in normal subjects.

In the present study, this analysis was done on the plethysmographic material to determine whether the shape of the postexercise flow curve would render the sensitivity of plethysmography as great as that of the $^{133}$Xenon technique.

The results are seen in table 3. Both the time to maximal flow and the 3-min value expressed as a percentage of the maximal flow yielded a fairly good differentiation of patients to normals. However, overlapping was present. By combining the first flow by plethysmography and the parameters in table 3, the overlapping between the patients and the normal control group was reduced to involving only two legs.

Discussion

Validity of Blood Flow Measurement by Plethysmography

The first point to be discussed is the relation between plethysmography and the blood flow.
flow of the calf. Critical reviews on this subject and on the mercury-in-rubber strain-gauge plethysmograph have been published. The reader is referred to these papers for details. However, there is general agreement that venous occlusion plethysmography is the most reliable method of blood flow measurement in normal human limbs. Good agreement was also found between directly measured arterial inflow and plethysmography in cats.

**Validity of the Local 133Xenon Clearance Technique as a Measure of the Muscle Blood Flow**

The local 133xenon clearance technique has not gained general acceptance as a measure of muscle blood flow.

The relation of 133xenon clearance to directly metered blood flow in the isolated gastrocnemius muscle of cats has recently been evaluated during intra-arterial unit input, intra-arterial step input, and intramuscular injection of 133xenon.

The blood flow calculated from the clearance of intra-arterial unit and step function input of 133xenon demonstrated overall agreement with directly metered venous outflow over a wide range of flow values, obtained by stimulation of the somatic motor nerve. Flow calculated from locally, atrumatic gas labeling of the tissue was also representative of the total muscle blood flow. However, flow calculated from clearance curves recorded immediately after injection of 133xenon showed a very large scatter of the results. This is in agreement with the observation of Kjellmer and associates. The difference between the local gas labeling and local injections of 133xenon solution is undoubtedly due to the local trauma of the injection itself.

By injection into a resting muscle and waiting approximately 15 min, it was observed that the clearance rate now increased in step with increasing flow and that the calculated flow now agreed with the directly metered flow.

Thus, by waiting 15 min the trauma of injection is practically eliminated.

In the present study only 6 min elapsed between the injection and the exercise periods. It has been shown (unpublished observation in man) that there is no difference between the magnitude nor the sd of exercise blood flows determined by 133xenon in humans when 6 or 25 min elapse between the injection of the xenon depot and the exercise period.

It is seen in table 2 that the sd found in the present study is in accordance with the values found in the literature. Thus, the sd of the clearance method is greater than that of plethysmography.

This may partly be due to the fact, that the double determination by plethysmography was repeated with a 10-min interval. Repeated single determinations of first flow after exercise by plethysmography on one normal subject gave a coefficient of variation of about 25%.

In spite of the greater sd of the clearance method, the ranges of the groups formed with the results of this method are smaller. This is due to the difference in the experimental procedure: The very high postexercise flows sometimes observed with plethysmography are not seen with the 133xenon clearance technique presumably because intramuscular pressure during exercise causes a decrease in the blood flow.

**Demonstration of the Pathophysiology of Intermittent Claudication by Plethysmography and 133Xenon Clearance Technique**

Snell and associates among others showed that a successful thromboendarterectomy or bypass operation on patients with claudication resulted in a rise in both walking distance and maximal hyperemia, measured by plethysmography. This finding points to the pathophysiological reason for claudication: The exercise muscle blood flow must be lower than in normals.

The maximal blood flow measured by plethysmography or 133xenon clearance after timed ischemia or ischemic exercise, however, revealed overlapping of the results between normals and claudicants. This is not due to inadequacies in the techniques for measuring blood flow, but rather to the fact that reactive hyperemia, as discussed in the
introduction, is different from exercise flow. The postexercise blood flow curve in plethysmography also did not permit separation of the two groups clearly.

Thus, the main result obtained was that use of the exercise blood flow determined by the $^{133}$xenon technique gives a better discrimination between normals and claudication patients than does plethysmography, because the latter cannot readily be carried out during exercise. The highest mean value of the exercise blood flow in limbs with an occluded main artery was 16.6 ml/100 g • min and the lowest value of the control group was 26.5 ml/100 g • min. In the present study overlapping was found between the postexercise values in the two groups with plethysmography.

Relation Between the Blood Flow Measurements and the Degree of Functional Impairment (Walking Distance)

First it should be pointed out that even though the exercise blood flow was zero in two of the patients measured by $^{133}$xenon clearance, they were able to walk about 50 meters on the treadmill. This finding was corroborated by the observation that normal subjects in whom the circulation of both legs was completely interrupted by means of thigh cuffs were able to walk about the same distance (fig. 2). Secondly, the walking distances in the patients were diminished exponentially to percentage decrease in exercise blood flow.

This relation indicates, that the exercise blood flow measured by the $^{133}$xenon clearance technique roughly quantitates the degree of functional arterial insufficiency.

In contrast the first flow after exhausting exercise as measured by plethysmography was not correlated with the walking distance of the patients in the present study. Therefore, it is possible that this value is a more arbitrary index.

The so of the $^{133}$xenon clearance technique was larger than the so of the plethysmographic measurements (table 2). However, when the day-to-day variation of the two methods is considered, the reproducibility is about the same.

From the present study it is thus concluded that the exercise blood flow by the $^{133}$xenon clearance technique is a valid functional parameter of the degree of arterial insufficiency in claudicating patients, it yields a better separation of the blood flow values between normal subjects and patients, and the reproducibility is as good as plethysmography.

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References


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