Diagnostic Use of Radioactive Xenon
Clearance and a Standardized Walking Test
in Obliterative Arterial Disease of the Legs

By J. ALPERT, M.D., H. GARCIA DEL RÍO, M.D., AND N. A. LASSEN, M.D.

Intermittent claudication is a characteristic symptom in obliterative arterial disease of the legs. It is generally agreed that this symptom is caused by inadequate blood flow in the muscles of the legs during walking. In 1951, Walder used the 24Na clearance method of Kety for studying the blood flow of the gastrocnemius muscle during static rhythmic leg exercise. His observations demonstrated the circulatory insufficiency in the patients with arterial disease. This was also clearly evident in the studies of Lassen and Kampp who utilized a more "physiological" type of leg exercise, namely walking. These authors employed 133Xe as an indicator of muscle blood flow as 133Xe has theoretic and practical advantages over 24Na.

The present study extends Lassen and Kampp’s observations by utilizing the 133Xe clearance method in three different calf muscles and by standardizing the walking test. The aim has been to develop a test of diagnostic value in obliterative arterial disease.

Method

The Blood Flow

To study blood flow by the 133Xenon clearance technique, two specially constructed scintillation probes were used. The probes which weighted only 80 g were attached laterally and anteriorly to the leg by adhesive tape. In the patients with intermittent claudication, special care was taken not to tighten the tape so that it would interfere with circulation in the muscles. Moreover, the adhesive tape was always attached to the leg below the region studied. A coaxial cable, several meters long, was attached between the probe and a charge-sensitive amplifier. This allowed the subject considerable freedom of movement.

133Xe† dissolved in isotonic NaCl solution (approximately 1.0 mc per milliliter) was injected with a thin needle (0.4-mm outer diameter) into the thickest part of the lateral head of the gastrocnemius muscle, into the lateral part of the soleus muscle, and into the thickest part of the anterior tibial muscle. Usually only one puncture was made to inject at a slow rate two volumes of 0.1 ml each at approximately 1.5 and 3 cm below the surface of the skin. The scintillation detector crystals were fixed as closely as possible to the surface of the skin overlying the intramuscular depots. Each detector was coupled to a scaler with a time constant of 5 seconds and to a logarithmic potentiometer writer. The maximum counting rate was about 3,000 cps.

The Walking Test

The walking test on the treadmill was varied considerably in the methodological observations (see below). In the clinical studies, on the other hand, a standardized test was used: the speed of the treadmill was 4.6 km/hr and the angle was +9° (= 16% elevation). The subject was studied after 30 minutes of rest. Following injection of isotope the subject stood motionless on the treadmill for 2 to 3 minutes; then the patients with intermittent claudication were required to walk until fatigue and pain in the legs stopped them, usually after about 2 minutes of walking; the control subjects walked for 4 minutes or until approximately 70% of the 133Xe was washed out, whichever came first. Each subject was wearing ordinary low-heeled walking shoes and was required to walk as normally as possible. After the walking test, all subjects stood motionless until a slow and fairly constant clearance rate approximating the pre-exercise resting value had become established. Usually three or four successive studies were made on the same subject on the same day (for example, both anterior tibial muscles were studied first, then both gastrocnemius muscles, then both soleus muscles, and finally both anterior tibial muscles again). Usually some or all measurements were repeated on a second day. All subjects cooperated well on this test, the rationale of which was easy to explain to them.

†Radiochemical Center, Amersham, England.

From the Department of Clinical Physiology, Bispebjerg Hospital, Copenhagen, Denmark.
*Dansk Impulfsyisk, Holte, Denmark.
**Group Studied**

Twelve young normal persons were studied to explore the methodological aspects of the procedure. Clinical observations were made on 11 persons with intermittent claudication and on the 12 normal control subjects.

The 11 patients all had been studied angiographically. In 20 of the 22 legs of these patients occlusion of the femoral artery was found whereas two legs had only stenosing lesions. All 20 legs with vascular occlusion responded abnormally to the \(^{133}\)Xe test performed in the recumbent position as carried out routinely in this laboratory, whereas the two legs having stenosing lesions only showed normal values on this test. Of the 20 legs with vascular occlusion, 18 manifested intermittent claudication during the walking test; that is, in four of 11 patients the pains were unilateral, in seven bilateral. The average age of the patients was 55 years (sd 9).

The 12 control subjects were selected from healthy hospital personnel and from patients admitted for complaints not related to the circulatory system. All had normal peripheral pulsations in the legs, and none had complaints suggestive of intermittent claudication. The average age was 49 years (sd 8).

**Calculations**

Assuming that diffusion equilibrium between muscle tissue and venous capillary blood is reached for \(^{133}\)Xe, it can be shown that muscle blood flow (MBF) in milliliters/100 g·minute is given by:

\[
MBF = 100 \cdot \lambda \cdot \ln(10) \cdot D \text{ ml/100 g·min}
\]

where 100 is the factor introduced since the unit of tissue is 100 g, \(\lambda\) is the muscle-to-blood partition-coefficient taken to be 0.7 ml/g for all three muscles studied, and \(\ln(10)\) is the factor converting the observed decimal logarithms on the logarithmically recorded clearance curve to natural logarithms, and D is the (negative) slope of the tangent of the curve, that is, it is that fraction of a decade that the tangent decreases in 1 minute (fig. 1). Since \(100 \cdot \lambda \cdot \ln(10) \approx 161\), this factor is used in practice, that is, MBF = 161• D ml/100 g·min.

When evaluating the \(^{133}\)Xe clearance curves obtained during and after walking the standardized walking test in normal man and in patients with intermittent claudication, five parameters were utilized (figs. 1 and 2) as follows: 1. Maximal MBF during walking (MBF\(_w\)):

\[
MBF_w = 161 \cdot D_w \text{ ml/100 g·min}
\]

where \(D_w\) is the maximal slope of the tangent to the logarithmic clearance curve during walking (that is, the steepest slope).

2. Duration of the post-exercise hyperemic reaction (T) measured in minutes: T is the time interval from the cessation of walking and until the MBF (as indicated by the slope of the curve) returns to a low and fairly stable level.

- **Figure 1**

\(^{133}\)Xe clearance curve from the right anterior tibial muscle in a normal person. The figure illustrates how the various parameters are calculated from the curve.

- **Figure 2**

\(^{133}\)Xe clearance curve from the left gastrocnemius muscle of a patient with occluded femoral artery and intermittent claudication in that leg. The figure illustrates how the various parameters are calculated from the curve. It also shows a typical artifact due to changing geometry at beginning and cessation of walking.
constant value considered as the post-exercise resting value.

3. The index (R) of the remaining part of the hyperemic reaction to exercise 1.0 minute following cessation of walking:

\[ R = 100 \cdot \frac{\Delta_3}{\Delta_1 + \Delta_2} \%
\]

This equation defines R as that percentage of the total decrease of the clearance curve during and after walking which occurs after 1.0 minute of rest. It differs slightly from the index of delayed hyperemia of Lassen and Kampp\(^2\) as the resting clearance rate was not subtracted:

\( \Delta_3 \) is the (cumulative) decrease of the clearance curve between 1.0 and T minutes after walking measured in fractions of a decade.

\( \Delta_1 + \Delta_2 \) is the decrease of the clearance curve from the beginning of the walking test until resting flow is again observed (in the same unit as \( \Delta_3 \)). Since small variations in the duration of the walking periods occurred, it is defined to include only the first 1.5 minutes of walking, that is, \( \Delta_1 \) is the decrease between 0 and 1.5 minutes of walking and \( \Delta_2 \) is the decrease between 0 and T minutes after walking (figs. 1 and 2).

A few of the patients with intermittent claudication could not walk for 1.5 minutes. In these cases \( \Delta_1 \) was obtained by extrapolation.

4. Maximal MBF during the hyperemia after walking (MBF\(_H\)):

\[ \text{MBF}_H = 161 \cdot D_H \text{ ml/100 g\cdot min} \]

when \( D_H \) is the steepest slope of the curve after walking.

5. Time when MBF\(_H\) is first observed (T\(_H\)):

\( T_H \), measured in minutes, is the time interval between the cessation of walking and until the steepest slope after cessation of walking is first recorded.

**Methodological Observations**

These studies were made in order better to understand the response of the \(^{133}\text{Xe}\) clearance curve to a standardized walking test.

Repeated \(^{133}\text{Xe}\) clearance studies (a total of 27 determinations) were made from the anterior tibial muscles of four normal subjects who were so highly trained in walking on the treadmill (speed 4.6 km/hr, elevation 16\%) that they could maintain a fairly even degree of muscular effort from study and throughout an individual study. The results of some of these clearance observations that were extended over many minutes are depicted in figure 3. Each subject tended to have his own characteristic MBF value during the initial part of the clearance. From the observed variations from study to study, a coefficient of variation of between 15 and 20\% was calculated for MBF.

In almost all the studies of prolonged steady-state exercise, a decreasing MBF was seen after about 90\% of the radioactivity had been washed out. This "tail effect" varied considerably from one study to another in the same muscle. On this basis it was concluded that this phenomenon was due to details of the injection which could not be controlled, for example, a variable amount of \(^{133}\text{Xe}\) refluxing.

![Figure 3](image-url)

(A) Five curves from the anterior tibial muscle obtained on different days from the same normal person. The subjects were highly trained in walking on the treadmill (4.6 km/hr, elevation 16\%) and continued steady-state walking throughout the clearance study. Monoexponential curves were obtained until about 90\% of the \(^{133}\text{Xe}\) had been cleared. (B) Same as A but from another normal person having a different MBF\(_{w^*}\).
out of the muscle or variable $^{133}$Xe deposition near the fascial septa or other tissues (adipose tissue) inside the muscle that have a slow $^{133}$Xe clearance rate. The variability of the phenomenon was rendered less attractive by having to consider the possibility of a "two-compartment system" in the muscle tissue proper as one then would have to explain how the "slow" compartment could at times be marked and at other times (for example, 10 minutes later) appear to disappear completely in the same muscle injected at about the same place and exposed to the same degree of exercise.

Due to the observed "tail effect," conclusions in the clinical material were only based on MBF values observed during the initial clearance of about 80% of the depot.

The effect of training on the treadmill was studied in a small series of normal young subjects. Only moderate reduction of MBF was found on repeated tests. This small effect was disregarded in the clinical studies reported below, that is, the results obtained in the three muscles were compared directly regardless of the order in which they had been studied.

The effect on MBF of the type of walking performed was pronounced. Walking on the heels and thus only allowing isometric calf muscle contraction gave low MBF values. Maximal MBF values resulted when the subject was asked during each step to lift his entire body weight to his toe tip before taking a new step. In view thereof care was taken to have each subject in the clinical studies walk as "economically" as possible using his ordinary shoes.

As might be expected, the slope and speed of the walking also influenced the MBF response. To obtain clear-cut results in the clinical studies, the fairly strenuous exercise test described was useful.

Clinical Studies

Control Subjects

The maximal MBF during walking averaged in the 24 legs 42.2 (SD 15.6), 33.4 (SD 16.1), 36.7 (SD 15.1) ml/100 g·min for the anterior tibial muscle, the soleus muscle, and the lateral head of the gastrocnemius muscle, respectively. Only one of the 123 curves had a maximal MBF of less than 10 ml/100 g·min (the value found being 9 ml/100 g·min).

The duration of the hyperemic reaction after cessation of walking ($T_H$) was about the same in the three muscles, averaging 1.4 min (SD 0.7 min) in the 123 curves (fig. 2). Values of $T_H$ above 3.0 min may be considered abnormal with a probability of 98%.

The remaining hyperemia after 1.0 min of rest (R) also had almost the same value in all three muscles. The average for R was 5% and values above 20% could be considered pathological with a probability of 98%. In agreement with this statistical analysis is the overall numerical result of the 123 normal curves as only two gave R-values above 20% in both of which $R = 21\%$.

The MBF$_H$ (maximal hyperemic flow) did not exceed MBF$_w$ in any of the normal subjects, and MBF$_H$ was in all cases recorded immediately after cessation of walking (that is, $T_H = 0$).

Patients with Obstructive Arterial Disease

In the 11 patients with obstructive arterial disease, the 138 studies made revealed a spectrum of abnormal responses ranging from slightly prolonged hyperemic reaction to extremely extended hyperemia of slow onset and lasting 10 minutes or more (fig. 4).

MBF$_w$ ranged from 0 to 40 ml/100 g·min (average, 6.4 ml/100 g·min) in the 18 legs with arterial obstruction and intermittent claudication. A considerable overlapping with normal values was apparent as in eight of the 52 muscles studied in these 18 legs MBF$_w$ was 10 ml/100 g·min or more. On the other hand in all 18 legs the MBF$_w$ was less than 10 ml/100 g·min in at least one muscle. In the four asymptomatic legs the MBF$_w$ was within the normal range in all three muscles studied.

$T$ was abnormally prolonged (more than 3.0 min) in 51 of the 52 muscles studied in the 18 symptomatic legs and it was 3.0 min in the remaining muscle (average, $T = 10.4$ min, range 3 to 21 min).

$R$ was abnormally increased (above 20%) in all 18 symptomatic legs (range, 34 to 100%,
A schematic drawing shows the different $^{133}\text{Xe}$ clearance curves observed during studies of patients with peripheral vascular diseases. 1, normal subjects; 2 to 5, patients with claudication.

and average, 79.5%, in the 52 muscles studied) (fig. 5). In the four asymptomatic legs $R$ was normal in all three muscles of two legs (in one of these legs complete occlusion of the femoral artery with many collaterals was seen angiographically; in the other leg only uneven caliber of the vessels was found); in the other two legs $R$ was abnormally elevated in two muscles of each leg.

The shape of the post-exercise hyperemic curve differed somewhat in the 52 muscles studied in the 18 symptomatic legs. In 43 muscles $\text{MBF}_H$ exceeded $\text{MBF}_w$ (average $\text{MBF}_H = 11.7 \, \text{ml/100 g min}$). $T_H$ (the time after cessation of walking and until $\text{MBF}_H$) exceeded 0.5 min in 34 muscles. Neither of these signs was found in the normal group.

A clear correlation was not found between the localization of the pain of claudication in the three calf muscles as indicated by the patient and the results of the $^{133}\text{Xe}$ clearance studies. In this context it should be reemphasized that all the patients suffered from occlusion of the arteries above the knee.

Technical Problems and Experimental Accuracy

The test was easy to perform and caused minimal discomfort to the subject and often 10 or more examinations have been made in the same patients.

Technical problems of three types were encountered:

1. Failure of the patient to rest the muscles after the walking period was a problem in one normal subject who had an $R$-value of 38% and a $T$ of 5.0 min in one muscle (left soleus). As completely normal values ($R = 6\%$, $T = 1.3 \text{ min}$) were found in the same muscle on repetition of the test a few minutes later, the first observation was discarded as being caused by continued muscle work after the exercise. No other measurement was excluded for this reason.

2. Artifacts due to changes of the geometry of the counting probe at the beginning and stopping of walking were seen in most curves as evidenced by sudden jumps in the counting rate. This problem is easily corrected when $\Delta_1$, $\Delta_2$, and $\Delta_3$ are read from the curve. It is minimized by proper fixation of the probe and by an appropriate injection technique. No measurement was discarded because of artifacts.

3. Erroneous injection of the isotope into nonmuscular tissue was felt to be responsible for the occasional finding of a very small $^{133}\text{Xe}$ wash-out response, a response not found in previous or subsequent studies of the same muscle. It was recognized by the low amplitude of cumulative clearance from onset of walking until complete rest could be presumed to be regained. Seven curves of a total of 268 were discarded on the basis of such a "small," irreproducible result.

The relation between $T$ (the duration of the post-exercise hyperemia) and $R$ (the percentage of hyperemia after 1 minute of rest). In all 18 symptomatic legs (52 muscles) with claudication both parameters were significantly abnormal.
The experimental accuracy in the clinical studies was calculated from 36 pairs of repeated observations in the control group and from 52 pairs in the group of patients with intermittent claudication. The standard deviations (sd) were as follows: for MBF<sub>n</sub>, 13.3 ml/100 g·min for the normals and 6.3 ml/100 g·min for the patients; for T, 0.6 min for the normals and 2.1 min for the patients; for R, 4.6% for the normals and 9.8% for the patients; for MBF<sub>H</sub>, 5.9 ml/100 g·min for patients in whom MBF<sub>H</sub> exceeded MBF<sub>n</sub>; and for T<sub>H</sub> 1.5 min for the same group of patients.

**Discussion**

Circulatory insufficiency is not synonymous with obliterator arterial disease per se. Insufficiency is produced in subjects without arterial disease by the strain of lifting the body weight on the toe tips using only one leg and performing the movement at a rapid speed. Conversely, adequate blood flow may be found in the calf muscles of patients with complete obliteration of the femoral artery during fairly strenuous walking. This occurred in one of the two asymptomatic legs with obliteration reported in the present study.

The clinically important aspect of the leg circulation is clearly not the patency of this or that artery, but the adequacy of the overall supply via all channels during the maximal functional state to which the muscle is normally exposed. This is the rationale of the present test which was designed with the aim of separating symptomatic from asymptomatic (normals in this context) cases of arterial disease. The principal finding was that this 133Xe test demonstrated ischemia of the calf muscles in all 18 legs in which claudication occurred.

The clinical usefulness of the present test has been suggested by the results obtained in several atypical cases studied. Two of these cases will be reported briefly to illustrate the type of problems encountered.

**Report of Cases**

**Case 1: Intermittent Claudication Without Arterial Disease**

This subject was a 45-year-old man who had muscle pain in the legs during walking. Despite normal peripheral arterial pulses he was considered to have vascular disease and was treated with various vasoactive drugs for 3 years. The 133Xe walking test was normal and led to a revision of the diagnosis. Electromyography and muscle biopsy showed polyneuropathy as the underlying cause of the muscle pains.

**Case 2: Intermittent Claudication due to Aortic Disease**

The subject, a 45-year-old woman, was applying for economic support due to pain in the legs during walking. Peripheral pulses were palpable and considered normal. Femoral arteriography revealed normal conditions. Standard 133Xe test made with the patient recumbent and calf muscle exercise<sup>3</sup> was also normal. Patient was dismissed with a diagnosis of muscle pain of "rheumatic" origin with possible malingering. Four months later a 133Xe walking test showed unequivocal circulatory insufficiency. Translumbar aortography was tried without success but aortography from the brachial artery showed complete obstruction with many collateral vessels. The patient was cured by aortic endarterectomy.

The test described herein may be compared to other means of assessing the adequacy of the circulation of the legs. Registration of pulsations by oscillometry or by various plethysmographic methods can be dismissed in this context. They may help in the diagnosis of the patency of the normal arterial tree but seem ill suited to assess collateral circulatory capacity. Blood flow cannot be measured with venous occlusion plethysmography during muscle exercise. Thus, whereas it undoubtedly is a useful aid in diagnosing arterial disease, using the circulatory response to ischemia or ischemia + exercise, it appears to have a less direct approach than the present method has. This comment also applies for the 133Xe standard test as developed in this laboratory where the subject is studied in the supine position after ischemic exercise of the calf muscles alone.<sup>3</sup> Case 2 shows that in a case of a proximal obstruction with many collaterals these auxiliary channels may suffice to supply the calf normally during this test but may be inadequate for supplying the calf muscles when the entire musculature of the legs is exercised during walking.

On the basis of this brief discussion it is concluded the walking test appears to be the
most "physiological" test for disclosing the pathophysiological mechanism of patients with intermittent claudication of vascular origin. Since it demands fairly strenuous exercise, it is designed for the study of borderline cases. It does not, in our opinion, supplant other methods, but can be used as a supplement in the differential diagnosis in difficult cases. The test offers possibility of simultaneously measuring the walking distance of the subject. This is done routinely in our laboratory but has not been commented on in this presentation as it is considered outside its immediate scope.

Summary

The 133Xe clearance method was used for studying the muscle blood flow (MBF) and the time course of the hyperemic reaction in the calf muscles during walking.

Methodological observations showed that the type of walking markedly influenced the hyperemic reaction. However, even during steady-state walking in trained subjects a variability of 15 to 20% in the muscle blood flow was noted in repeated tests.

Clinical studies were made in 11 patients with occlusive arterial disease of the femoral artery and intermittent claudication. Twelve control subjects were also studied. On use of a standardized and fairly strenuous walking test on a treadmill, all 18 legs with intermittent claudication showed abnormal 133Xe clearance curves from the anterior tibial, the soleus, and the gastrocnemius muscles. All the curves disclosed subnormal MBF during walking and prolonged post-exercise hyperemia.

It is concluded that this 133Xe clearance test constitutes a very direct and diagnostically valuable method for disclosing the basic pathophysiological mechanism underlying intermittent claudication.

References

Diagnostic Use of Radioactive Xenon Clearance and a Standardized Walking Test in Obliterative Arterial Disease of the Legs
J. ALPERT, H. GARCIA DEL RIOÓ and N. A. LASSEN

Circulation. 1966;34:849-855
doi: 10.1161/01.CIR.34.5.849

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1966 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/34/5/849

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/