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^{133}Xenon Clearance in the Diagnosis of Arterial Occlusive Disease

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INTRODUCTION

ARTERIOGRAPHY IS THE MOST RELIABLE METHOD currently available for the diagnosis of obliterative arterial disease of the lower extremity. Nevertheless, a number of significant problems and complications associated with this method make its routine use both impractical and potentially hazardous.

Although plethysmographic flow measurement has been felt by some to be the best noninvasive method available for the diagnosis of arterial occlusive disease, it too has certain drawbacks. The procedure itself is rather cumbersome and requires calibration each time it is used. In addition, it is best suited for the measurement of resting blood flow which cannot always distinguish the normal from the ischemic limb. The measurement of reactive hyperemic blood flow after a period of exercise or ischemia is particularly difficult to accomplish with this method. Plethysmographic pressure measurements, while simple to perform, provide a minimal amount of information and are not very accurate. Thus, it is apparent that there is a need for a simple, noninvasive procedure to measure blood flow in the ischemic limb.

In 1949, Kety [4] first demonstrated that the blood flow to a given tissue could be readily calculated by measuring the rate at which a radioisotope disappeared from that tissue after injection. The rate of removal of such an isotope from a tissue site is directly proportional to the rate of capillary blood flow through that tissue. Using ^{24}Na [4], he was able to measure differences in muscular circulation during both ischemia and exercise.

More recent evidence indicates that ^{133}xenon is better suited for this purpose [5, 6]. Being lipophilic, it readily crosses the cell membrane and more evenly distributes itself than does ^{24}Na which is hydrophilic. In addition, the highly inert character of ^{133}xenon results in a high degree of diffusibility within the tissues themselves. It also is eliminated readily by the lungs and is not recirculated. Consequently, the rate of removal of this isotope from the site of injection more closely coincides with the degree of capillary blood flow than does ^{24}Na.

Because of the unique properties of ^{133}xenon, it seemed appropriate to determine whether the clearance of this isotope from a muscular bed could differentiate the normal from the ischemic limb.

METHODS AND MATERIALS

Muscle blood flow was determined in the anterior tibialis muscle using a modification of the ^{133}xenon clearance technique as originally described by Lassen *et al.* [6]. With the patient in a supine position each leg was studied separately in the following fashion: Using a No. 26-gauge needle (0.4 mm diameter) a volume of 0.25 ml of ^{133}xenon (200–500 μCi) in sterile saline

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solution was injected into the anterior tibialis muscle to a depth of 1–2 cm. With this volume an initial count rate of 40,000–50,000 cpm was generally obtained. Special care was taken during injection so that no air bubbles were introduced into the muscle. In addition, the site of injection was standardized by placing the injection 10 cm below the inferior margin of the patella and 3 cm lateral to the tibial crest (Fig. 1).

A logarithmic potentiometer coupled to a scintillation camera* with a 30% window and a low-energy (250 keV) parallel hole collimator was used. Subsequent to injection the disappearance rate of the isotope was determined. By measuring the slope of the curve recorded on this potentiometer, the clearance of ^{133}xenon from the muscular bed could be determined (Fig. 2). Muscle blood flow could then be calculated by employing the following formula [6]:

Maximum Blood Flow (MBF)
$= 100 \times \lambda \times K$

MBF = Flow in ml/100 g muscle/min

λ = Partition coefficient between muscle and blood which for Xe = 0.7

$$K = \frac{\mathrm{Log}_e 2}{T\frac{1}{2}}$$

$T\frac{1}{2}$ = Time in minutes for the activity to decrease to one-half

Substitution of known values in the above equation:

$$\mathrm{MBF} = \frac{100 \times 0.7 \times 0.693}{T\frac{1}{2}} = \frac{48.51}{T\frac{1}{2}}.$$

After injection, xenon clearance is measured during a 15-min resting phase. Then blood flow to the leg is occluded for a period of 5 min by placing a sphygmomanometer cuff around the thigh and inflating it to a pressure of 230 mm Hg. During this induced ischemia, the patient is asked to exercise his leg by repeated dorsiflexion of his foot for 5 min. While exercise occasionally had to be curtailed because of the resultant severe claudication, at no time was the period of ischemia itself shortened. At the end of this ischemic exercise phase, the cuff was rapidly deflated and the clearance of ^{133}xenon remeasured. This final phase of reactive hyperemia generally lasts for a period of 5–10 min. Using the above formula, the resting and reactive hyperemia flows are calculated.

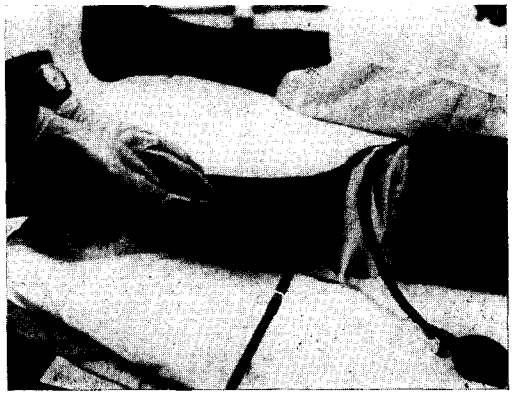

Fig. 1. Photograph of patient undergoing xenon clearance study illustrating site of injection.

Employing this technique, muscle blood flow was determined in 28 normal and 64 abnormal limbs. A normal limb was defined as one free of symptoms with full peripheral pulses and without any evidence of circulatory insufficiency. Arteriography was not performed on the clinically normal limbs.

On the basis of clinical and arteriographic findings, abnormal limbs were separated into three groups. Group I comprised 46 limbs with significant arterial occlusive disease verified by arteriography. Each limb in this group was characterized by one or more of the following: moderate to severe claudication, diminution or absence of pulses, nonhealing ulcers, gangrenous or pregangrenous skin changes, rest pain. Group II consisted of nine limbs with mild intermittent claudication and minimal findings by arteriographic examination. The only physical finding was diminution of peripheral pulses. Group III comprised nine limbs with normal physical findings but with persistent complaints sug-

* Nuclear-Chicago Pho/Gamma III.

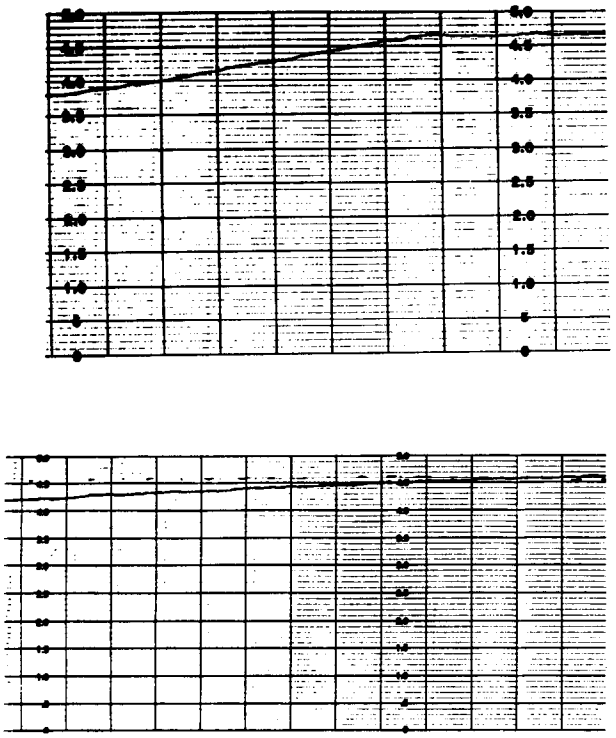

Fig. 2. Xenon clearance curve after injection into normal (upper tracing) and ischemic limb (lower tracing). The slope of the normal tracing is greater than the slope of ischemic limb tracing.

gestive of atypical claudication. Arteriographic findings in this group were either normal or insignificant.

Among the 55 limbs in Groups I and II, 28 have undergone arterial revascularization. Twenty-four of these were Group I and four were Group II limbs. No limbs in Group III were operated upon. Twenty of the 28 reconstructed limbs have been restudied postoperatively using the ^{133}xenon clearance technique.

RESULTS

Resting Blood Flow

There was no statistically significant difference between the resting muscle blood flow in normal and abnormal limbs ($P > 0.9$). In the 24 normal limbs evaluated, resting flow ranged from a low of 0.6 cc/100 g muscle/min to a high of 2.7 cc/100 g muscle/min. The mean was 1.3 cc/100 g muscle/min (SD 0.5). The patients in this group varied in age from 24 to 52 years. The mean age was 32.4 years.

Among the 16 abnormal limbs studied, the resting flow averaged 1.2 cc/100 g muscle/min (SD 0.9). Flows in this group ranged from a high of 3.9 cc/100 g muscle/min to a low of 0.4 cc/100 g muscle/min. The mean age of patients studied was 59.8 years with a range of 42–78 years.

Because of the inability of resting muscle blood flow measurements to differentiate the normal from the abnormal limb, the measurement of this phase of blood flow was deleted from the subsequent portions of the study.

Reactive Hyperemia Blood Flow (Fig. 3)

Twenty-eight normal limbs were studied. Reactive hyperemia muscle blood flow

ranged from 34 to 78 cc/100 g muscle/min with a mean of 54 cc/100 g muscle/min (SD 10.5). The average patient age was 31 years with a range of 23–52 years. In all of these limbs, the maximal flow occurred within the first minute after the release of the thigh cuff.

Among the 46 limbs studied in Group I, the reactive hyperemia flow averaged 14.2 cc/100 g muscle/min (SD 6.1) with a range of 4.1–25.7 cc/100 g muscle/min. Only three limbs demonstrated maximal flow during the first minute after release of the thigh cuff. The majority of limbs demonstrated peak flows at 3–4 min or later. The average age of these patients was 54.5 years with a range of 32–78 years. The difference in mean flow between this group and the normals was highly significant statistically ($P < 0.001$).

The nine limbs in Group II averaged 30.2 cc/100 g muscle/min (SD 1.7) with a range of 28.1–32.6 cc/100 g muscle/min. In comparison to normals the difference in mean flow in this group was also statistically significant ($P < 0.01$). All patients in this group developed peak flows within the first 2 min. The ages ranged from 46 to 63 years with an average of 54.8 years.

Reactive hyperemia flow was normal in the nine patients in Group III and in every instance the peak flow was reached in the first 2 min. The ages of patients in this group ranged from 45 to 50 years with a mean of 47 years.

Postoperative Xenon Flows

Twelve of the 20 limbs undergoing revascularization procedures were felt to have improved significantly after operation. Four limbs had complete correction of their occlusive disease with a return of peripheral pulses and an alleviation of all symptoms. In each instance the reactive hyperemia flow became normal. Eight limbs had improved peripheral pulses postoperatively with either an alleviation or diminution of previous symptoms. In each instance the blood flow improved (Table 1).

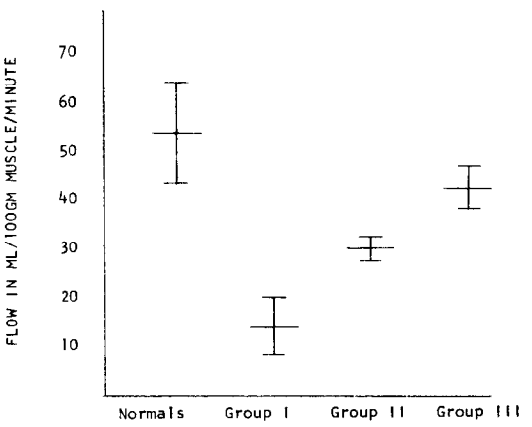

Fig. 3. Reactive hyperemia blood flow in normal and abnormal limbs (mean ± SD).

Eight limbs did not improve postoperatively and the postoperative ^{133}xenon clearance curves were essentially unchanged (Table 2).

DISCUSSION

The measurement of muscle blood flow using the ^{133}xenon clearance technique was first described by Lassen *et al.* [6] in 1964. Studying normal legs and those with occlusive arterial disease, Lassen noted a clear-cut difference between the reactive hyper-

Table 1. Preoperative and Postoperative Reactive Hyperemia Xenon Blood Flow (ml/100 g muscle/min) in Patients with Clinical Relief of Symptoms After Revascularization

Patient	Leg	^{133}Xenon Muscle Blood Flow	
		Preop	Postop
J. S.	R	17.5	61.5
J. K.	R	12.9	75.7
M. B.	R	21.4	30.3
	L	19.0	28.2
R. W.	R	16.2	28.2
E. H.	L	6.9	29.5
G. S.	R	13.6	22.8
W. H.	R	4.4	28.4
J. L.	L	8.0	57.0
R. R.	R	13.5	25.1
	L	17.5	28.1
E. W.	R	30.1	62.4

Table 2. Preoperative and Postoperative Reactive Hyperemia Xenon Blood Flow (ml/100g muscle/min) in Patients Undergoing Revascularization Without Significant Improvement in Symptoms

Patient	Leg	^{133}Xenon Muscle Blood Flow Preop	Postop
A. G.	R	8.2	11.2
	L	9.6	11.5
C. H.	R	16.4	23.0
	L	28.1	30.1
J. S.	L	32.4	28.6
B. S.	R	6.5	6.1
J. L.	R	9.2	13.4
	L	6.0	8.0

emia flows of the two groups of limbs after a period of ischemic exercise. In addition, the flow values they obtained corresponded quite closely to those found using venous occlusion plethysmography. Because of the simplicity of the clearance technique, they recommended its routine use in the evaluation of the ischemic limb.

Other investigators have reported similar findings [1–3]. Simultaneously measuring blood flow in the human brachioradialis and gastrocnemius muscles using venous occlusion plethysmography and ^{133}xenon clearance Barcroft *et al.* [2] noted similar flow values before, during, and after the intravenous injection of adrenalin. Alpert *et al.* [1] used ^{133}xenon clearance to measure blood flow in the calf muscles during walking. They noted a definite difference between the flow rates of normal limbs and those with intermittent claudication. In patients having undergone arterial reconstructive procedures for arterial occlusive disease of the lower extremity, Del Rio *et al.* [3] used ^{133}xenon clearance to measure postoperative blood flows. In all limbs studied they noted a close correlation between the degree of clinical improvement and the ^{133}xenon clearance curves.

The results of the present study confirm these findings. Not a single instance of normal reactive hyperemia flow was obtained in the 46 limbs studied in Group I with significant arteriographic findings. Even the Group II limbs with minimal arteriographic abnormalities uniformly had abnormal flow measurements.

Particularly significant is the close correlation of postoperative ^{133}xenon clearance results with clinical findings. Among the 20 limbs undergoing revascularization, four were felt to have dramatically improved, and were asymptomatic with return of previously absent pulses. Each of these limbs had normal postoperative ^{133}xenon clearances with 4- to 6-fold increases in flow. Eight other limbs with obvious clinical benefit showed substantial increases in ^{133}xenon clearance, even though they still had not become normal. Pre- and postoperative ^{133}xenon clearances were essentially the same in the eight limbs failing to show clinical improvement.

An additional important observation was the ability of ^{133}xenon clearance to distinguish true claudication from leg pain of uncertain etiology. The nine limbs in Group III were all felt to be clinically normal but persistent complaints of nonspecific leg pain resulted in arteriography being performed in each one with essentially normal results. The reactive hyperemia flows in these limbs was also normal and confirmed the adequacy of the peripheral circulation.

Since resting blood flow in normal and abnormal limbs is not statistically different, its measurement is of no clinical value. Therefore, the ^{133}xenon clearance test now consists of a 5-min period of ischemic exercise followed by a 5- to 10-min period of reactive hyperemia flow measurements. Subsequent to injecting the isotope, a 2- to 3-min period of rest is allowed to provide optimal diffusion of the ^{133}xenon within the tissue spaces. Immediately after this, the period of ischemic exercise is commenced.

The abbreviated technique is especially well suited for clinical purposes. Each limb can be completely studied in less than 15 min without the need for large numbers of personnel. After injection of the ^{133}xenon by a physician, the entire test can be performed by one technician. Equally impor-

tant is the lack of need for additional sophisticated equipment such as special detectors, treadmills, exercise bicycles, etc.

Lack of cooperation on the part of the patient during the ischemic exercise phase has not been a problem. When the nature of the test is carefully explained beforehand we have noted excellent cooperation in almost every instance.

We have utilized a 5-min ischemic exercise phase. This differs from the 2-min period originally described by Lassen [6]. We feel that this longer period of time is important in order to distinguish accurately normal and abnormal limbs. In the initial stages of our investigation we noted that a number of clinically normal limbs had low normal xenon flows when only 2 min of ischemic exercise was employed. It would appear that submaximal reactive hyperemia occurred after this shorter ischemic exercise period. By lengthening the time of ischemic exercise, muscle exhaustion could be uniformly obtained. This resulted in maximal reactive hyperemia and more consistent results in all limbs subsequently studied.

SUMMARY

The ^{133}xenon clearance test is an easy, noninvasive method to assess arterial blood flow and can distinguish a normal from an ischemic limb. In addition, the close correlation with clinical findings affords an objective method of evaluating the results of surgical revascularization. On the basis of these findings, we feel that this procedure should be employed in the evaluation of all patients with suspected or proved peripheral vascular insufficiency.

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