JCI The Journal of Clinical Investigation

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J Clin Invest. 1964;43(9):1805-1812. https://doi.org/10.1172/JCI105054.

Research Article

Journal of Clinical Investigation
Vol. 43, No. 9, 1964

Muscle Blood Flow in Normal Man and in Patients with Intermittent Claudication Evaluated by Simultaneous Xe^{133} and Na^{24} Clearances *

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Intramuscular injection of a small amount of radioactive sodium (Na^{24}) was used by Kety as an index of local blood flow in skeletal muscle (1, 2). The hydrophilic sodium ions are known to exchange fairly slowly over many biological membranes, in contrast to the lipophilic inert gases to which such membranes offer no diffusion barriers (3). Hence a radioactive inert gas such as xenon^{133} is probably a better indicator of blood flow than Na^{24}. Recent clinical studies with intramuscular injection of Xe^{133} dissolved in saline have tended to support this conclusion (4, 5). However, the possible superiority of employing Xe^{133} instead of Na^{24} is best evaluated by using the two tracers simultaneously. Forty such simultaneous observations in ten normal subjects and in ten patients with intermittent claudication are reported in the present study.

Materials and Methods

Ten normal subjects, ages 41 to 73 years (average, 54 years), were studied as the control group. These normal subjects had no symptoms suggestive of intermittent claudication, and all peripheral pulses were normal. None had clinically manifest heart or lung disease. Six of these control cases were hospitalized for minor disorders not affecting the cardiovascular system, and four were healthy hospital employees.

Ten patients with intermittent claudication, ages 43 to 73 years (average, 56 years), were studied as the pathological group. These patients all had typical symptoms after walking a distance of 3 to 600 feet at normal speed and had, in addition, markedly subnormal oscillometric pulsation and absence of peripheral pulse. Three of the patients (Cases 3, 6, and 9 of this group) were hospitalized and confined to bed because of ischemic ulcerations of the skin of the foot. The other seven patients were all in good general condition and were able to manage some degree of work despite the handicap presented by the claudication. Of the ten patients, three (Cases 1, 3, and 5 of this group) had only symptoms and signs of unilateral arterial insufficiency; in all the others bilateral disease was manifest.

One-tenth ml of normal saline containing 50 μc of Xe^{133} in solution and 20 μc of Na^{24} were injected into the thickest part of the tibialis anterior muscle. A sharp needle with an o.d. of 0.4 mm was inserted 1.5 cm at an angle of about 45° with the surface (i.e., the tip of the needle was about 1 cm below the skin). The injection lasted about 15 seconds; the needle was first withdrawn 30 seconds after the injection to reduce possible backflow of the injected material along the needle track.

The local clearances of Xe^{133} and Na^{24} were followed with one scintillation detector coupled via two spectrometers to two rate meters. The scintillation detector had a NaI (Th) crystal 5 cm in diameter and about 5 cm thick. A tubular heavy lead collimator 5 cm in diameter (wall thickness, about 2.5 cm; length, 5 cm) was used with the aperture about 2 to 3 cm above the injection site. Both rate meters had a time constant of 3 seconds, and their output was recorded on linear writing potentiometers.

During the study one spectrometer was set so that the corresponding rate meter received impulses from only the strong primary gamma radiation from Na^{24}. The other spectrometer was set to record only the peak intensity of the low energy primary gamma radiation (81 kev) of Xe^{133}. For both rate meters the initial counting rate was about 1,000 cps. Approximately a 15% correction for the Na^{24} Compton scatter, of energy similar to the Xe^{133} primary radiation, was applied by using an artificial Na^{24} source and noting the deflection on both potentiometers. This artificial source was a solution of NaCl containing Na^{24} in a glass vial giving about the same amount of scatter in the 81 kev region as Na^{24} injected intramuscularly at a depth of 1 cm. A semilogarithmic plot of each isotope was made after also correcting for background radioactivity (Figure 1).

The subjects were studied after about 15 minutes of rest at a room temperature of approximately 20° C. After the injection of the mixture of the two isotopes, their clearance was followed in the resting muscle for about 5 minutes. Then a cuff placed just above the knee was suddenly inflated to a pressure of 250 to 300 mm Hg, and the subject was asked to move the ankle joint by doing at full force dorsiflexion and plantarflexion movements. After about 60 to 100 such movements, muscle fatigue

* Submitted for publication March 16, 1964; accepted May 15, 1964.

and some degree of ischemic pain developed; further movements could not be carried out. At this point the cuff pressure was released, and the isotope clearance during the reactive hyperemia was followed for 10 to 15 minutes.

The extra radiation dose involved in adding Xe^{133} to the conventional Na^{24} clearance method is exceedingly small, since Xe^{133} is rapidly cleared through the lung. The two intramuscular injections of 50 μc Xe^{133} have been calculated to result in a gonadal exposure of only 0.03 millirads (6).

Calculations. For both Na^{24} and Xe^{133} the rate of decrease of the concentration per gram of tissue, $dC/dt = C'$, can be expressed by applying the Fick principle to 100 g of muscle tissue:

$$100 \cdot C' = -fCv, \qquad [1]$$

where f is the blood flow in milliliters per 100 g per minute in the injected area. In the current studies f was not constant. Cv is the concentration of the venous blood leaving the area. Equation 1 does not on its right-hand side contain a term for the rate of supply of tracer by arterial blood ($f \cdot Ca$), since recirculation is negligible ($Ca = 0$) due to the dilution (and exhalation in the case of Xe^{133}).

The clearance rate of an indicator, Cl, in milliliters per 100 g per minute, can as suggested by Renkin (7), be defined in analogy with the clearance concept in kidney physiology: Cl is that imaginary volume of blood in milliliters per 100 g per minute that would have contained the amount of tracer actually leaving 100 g tissue ($f \cdot Cv$) if complete diffusion equilibrium had occurred. At equilibrium $Cv_{equil} = C/\lambda$, where λ is the tissue-blood partition coefficient defined as $(C/Cv)_{equil}$. According to these definitions,

$$f \cdot Cv = Cl \cdot Cv_{equil} = Cl \cdot C/\lambda. \qquad [2]$$

Inserting Equation 2 in 1, one obtains

$$Cl \text{ (ml/100 g/minute)} = 100 \cdot \lambda \cdot (-C'/C). \qquad [3]$$

λ_{Na} is the ratio of the tissue sodium concentration (including sodium in its contained blood) to the whole blood sodium concentration. These two concentrations may be estimated at about 40 μEq per g (8) and 80 μEq per ml, respectively (sodium in red blood cells and in muscle cells has not been taken into account because of the known slowness of Na exchange in and out of cells). Thus,

$$\lambda_{Na} \simeq \frac{40}{80} = 0.5 \text{ ml/g}. \qquad [4]$$

TABLE I

Clearance rates in skeletal muscle for Na^{24} and Xe^{133} in ten normal subjects

Case no.	Age	Leg	At rest			During hyperemia		
			Cl_{Na}	Cl_{Xe}	Cl_{Na}/Cl_{Xe}	Cl_{Na}	Cl_{Xe}	Cl_{Na}/Cl_{Xe}
			ml/100 g/minute			*ml/100 g/minute*		
1	41	Left	4.8	2.8	1.71	12.6	41.8	0.30
		Right	5.8	3.9	1.49	16.8	49.0	0.34
2	45	Left	3.5	6.1	0.57	12.6	70.4	0.18
		Right	0.8	1.3	0.62	8.1	53.4	0.15
3	47	Left	1.4	1.5	0.93	11.4	47.5	0.24
		Right	2.1	2.7	0.78	7.8	66.5	0.12
4	51	Left	2.4	3.1	0.77	12.9	61.4	0.21
		Right	2.6	2.9	0.90	12.5	50.6	0.25
5	53	Left	1.0	0.7	1.43	9.3	35.9	0.26
		Right	2.0	2.0	1.00	7.1	50.6	0.14
6	53	Left	1.6	1.7	0.94	14.3	79.5	0.18
		Right	2.6	2.5	1.04	13.5	71.4	0.19
7	54	Left	3.8	4.8	0.79	11.3	53.9	0.21
		Right	4.3	5.2	0.83	12.1	55.2	0.22
8	61	Left	2.3	2.1	1.10	11.2	63.0	0.18
		Right	1.4	1.8	0.78	11.0	55.2	0.20
9	63	Left	1.6	2.0	0.80	17.5	49.5	0.35
		Right	2.0	2.1	0.95	16.4	49.0	0.33
10	73	Left	3.9	5.5	0.71	19.4	53.9	0.36
		Right	1.4	2.1	0.67	20.7	58.4	0.35
Mean	54		2.6	2.8	0.94	12.9	55.8	0.24
SD	9		1.4	1.5	0.30	3.7	10.4	0.08

TABLE II

Clearance rates in skeletal muscle for Na^{24} and Xe^{133} in ten patients with intermittent claudication

Case no.	Age	Leg	At rest			During hyperemia		
			Cl_{Na}	Cl_{Xe}	Cl_{Na}/Cl_{Xe}	Cl_{Na}	Cl_{Xe}	Cl_{Na}/Cl_{Xe}
			ml/100 g/minute			*ml/100 g/minute*		
11	43	Left	1.6	2.2	0.73	9.8	13.0	0.75
		Right*	(2.6)	(3.9)	(0.67)	(11.9)	(38.5)	(0.31)
12	44	Left	1.0	0.8	1.25	13.8	23.9	0.58
		Right	1.3	1.0	1.30	12.7	26.7	0.48
13	49	Left	3.2	5.3	0.60	8.9	21.3	0.42
		Right*	(2.2)	(3.1)	(0.71)	(10.7)	(54.5)	(0.20)
14	55	Left	2.4	3.2	0.75	7.6	20.6	0.37
		Right	1.2	1.9	0.63	5.3	21.3	0.21
15	56	Left*	(1.3)	(1.1)	(1.18)	(14.1)	(53.9)	(0.26)
		Right	1.5	1.2	1.25	6.0	13.5	0.44
16	59	Left	2.0	1.1	1.82	7.5	7.2	1.04
		Right	2.0	2.6	1.70	9.5	13.5	0.70
17	63	Left	1.7	1.9	0.89	11.2	24.4	0.46
		Right	1.6	2.0	0.80	9.8	17.8	0.55
18	64	Left	1.1	1.5	0.73	12.3	23.2	0.53
		Right	0.7	0.9	0.77	10.1	31.0	0.33
19	68	Left	3.4	2.3	1.48	14.2	21.1	0.33
		Right	4.2	2.9	1.45	9.5	10.7	0.89
20	73	Left	2.2	2.7	0.81	8.4	15.9	0.52
		Right	2.6	2.9	0.90	8.9	18.4	0.48
Mean	57		2.0	2.1	1.05	9.7†	17.4‡	0.52‡
SD	10		0.9	1.1	0.39	2.5	6.4	0.20

* Values for three asymptomatic legs with normal peripheral pulsations are set in parentheses and are not included in the mean values given below the columns.

† Significantly different from mean value in the normal group ($p < 0.01$).

‡ Highly significantly different from mean value in the normal group ($p < 0.001$).

λ_{Xe} has been determined experimentally (9). It varies slightly with the hematocrit of the blood, but this variation has been neglected, since all subjects studied had a normal hematocrit value. The *in vivo* value of λ_{Xe} corrected for the specific gravity of blood to obtain it in the units employed here was, for blood with 15 g hemoglobin per 100 ml, 0.73/1.05, i.e.,

$$\lambda_{Xe} \simeq 0.7 \text{ ml/g}. \quad [5]$$

$-C'/C$ is the relative rate of decrease of tissue concentration. It can be obtained from the observed curve at any time. This curve gives the tissue concentration multiplied by a factor related to counting efficiency and geometry. But, as this factor affects both numerator and denominator, it cancels out. $-C'/C$ is equal to $d \ln C/dt$, which is the slope of the tangent of $\ln C$. By conventional semilogarithmic plotting, the slope of the tangent is 0.693 per $t_{\frac{1}{2}}$, $t_{\frac{1}{2}}$ being the half-time in minutes of the tangent.

Relation of clearance rates to blood flow. The relation of clearance rates to blood flow is given by Equation 2. If diffusion equilibrium is maintained, then $Cv = Cv_{equil}$, i.e., Cl equals f, and the Cl_{Na}/Cl_{Xe} ratio is unity. If equilibrium is not maintained, then $Cv < Cv_{equil}$, and $Cl < f$. In this situation the Cl_{Na}/Cl_{Xe} ratio is not likely to remain equal to unity, as an equal degree of disequilibrium is rather improbable. A Cl_{Na}/Cl_{Xe} ratio below unity shows predominant exchange limitation for Na, whereas a ratio above unity shows predominant exchange limitation for Xe.

Results

During rest the clearance rates were low in normal as well as diseased legs, and there were no significant differences between the two groups (Tables I and II). The average values for all 40 legs were as follows: $Cl_{Na} = 2.3$ ml per 100 g per minute (SD 1.2), and $Cl_{Xe} = 2.5$ ml per 100 g per minute (SD 1.4). The average Cl_{Na}/Cl_{Xe} was 0.98 (SD of mean 0.05), a value suggesting that diffusion equilibrium is essentially reached for both tracers in the resting muscle, i.e., that

the clearance values equal resting capillary blood flow in the anterior tibial muscle.

After the release of the tourniquet the two clearance rates increased (Figures 1 and 2). The initial hyperemic response was similar for both clearances until about 5 to 10 ml per 100 g had been cleared [the cumulative amount of blood cleared, $\int_{t_1}^{t_2} Cl(t)dt$, equals $100 \cdot \lambda(\ln C[t_1] - \ln C[t_2])$, and it can consequently be obtained directly from the semilogarithmic plot of the observed radioactivity curves]. This initial phase where $Cl_{Na}/Cl_{Xe} \simeq 1$ lasted a fraction of a minute in normal legs and somewhat longer in diseased legs. It would seem to represent mainly the washout of blood having reached diffusion equilibrium before the release of the cuff.

After this brief initial phase the two clearances did not follow the same course. Cl_{Xe} rose to a maximal hyperemic value (Figures 1 and 2). In all cases an extended period (0.5 to several minutes) of maximal Cl_{Xe} was apparent by an almost straight line of steepest slope on the semilogarithmic plot of the observed curves. In the 20

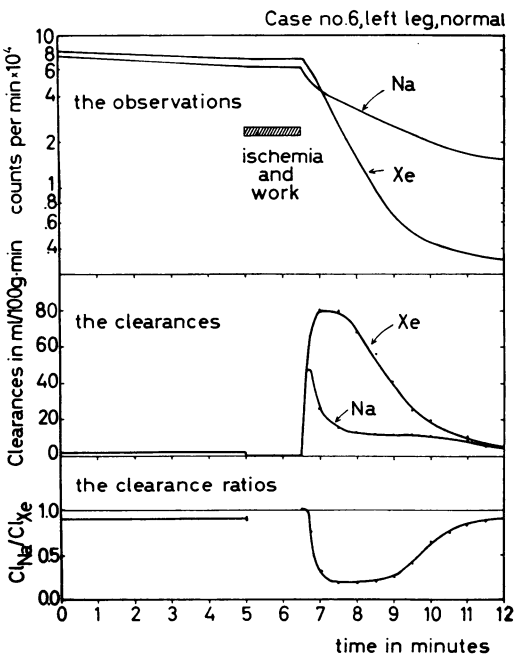

FIG. 1. THE WASHOUT CURVES OF Na^{24} AND Xe^{133}, THEIR CLEARANCES [Cl (ml/100 g/minute) $= \lambda \cdot 100 \cdot$ dln concentration (C)/dt] AND CLEARANCE RATIOS IN A NORMAL LEG. The evaluation of Cl depends on assessing the slope of the washout curve; hence it is subject to some error when this slope changes rapidly.

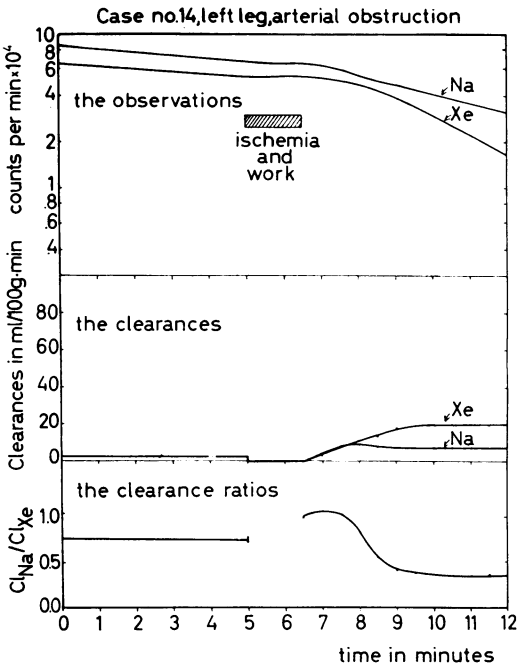

FIG. 2. THE WASHOUT CURVES OF Na^{24} AND Xe^{133}, THEIR CLEARANCES, AND CLEARANCE RATIOS IN A LEG WITH OBSTRUCTIVE ARTERIAL DISEASE. See legend to Figure 1.

normal legs maximal Cl_{Xe} averaged 56 ml per 100 g per minute (SD 10), and in 17 legs with intermittent claudication maximal Cl_{Xe} averaged 17 ml per 100 g per minute (SD 6). This difference is statistically highly significant ($p < 0.001$), and there was no overlapping between the two groups. In most of the legs with claudication the maximal Cl_{Xe} first came over 1 minute after release of the tourniquet (cf. Figure 2).

Cl_{Na}, in contrast, typically decreased again after having reached its maximal value at a time before Cl_{Xe} had become maximal (Figures 1 and 2). This maximal Cl_{Na} was reached in a single point of the curve and was difficult to evaluate accurately. After its maximum, Cl_{Na} found a stable lower level. These values of Cl_{Na}, obtained from the curves in the same interval of time as that in which Cl_{Xe} was at its maximal level, are listed in Tables I and II. This hyperemic value of Cl_{Na} averaged 12.9 ml per 100 g per minute (SD 3.7) in 20 normal legs and 9.7 ml per 100 g per minute (SD 2.5) in the 17 legs with claudication. The difference was statistically significant ($p < 0.001$), but there was considerable overlapping between the two groups.

Corresponding to the above variations of the individual clearances, the ratio Cl_{Na}/Cl_{Xe} decreased to values much below unity during hyperemia (Figures 1 and 2). With the values corresponding to the period of maximal Cl_{Xe}, this ratio averaged 0.24 (SD 0.08) in the 20 normal legs and 0.52 (SD 0.20) in the 17 diseased legs. This difference is highly significant ($p < 0.001$), a relation also apparent from Figure 3, where Cl_{Na} has been plotted against Cl_{Xe}. The figure shows that Cl_{Na} does not rise over a level of about 12 ml per 100 g per minute irrespective of the Cl_{Xe}. Only in a single case, the diseased leg with the lowest Cl_{Xe}, was $(Cl_{Na}/Cl_{Xe}) \simeq 1$ during maximal Cl_{Xe}.

According to the theoretical consideration given above, this result indicates that Na^{24} does not diffuse freely from the tissue to the capillary blood during maximal hyperemia. For the Xe^{133} maintenance, diffusion equilibrium during hyperemia cannot be evaluated from the present studies per se. If it is essentially maintained, then Cl_{Xe} is a measure of capillary muscle blood flow even during maximal hyperemia.

Regardless of whether this is so or not, the present series demonstrated clearly that Xe^{133} gave a more clearcut separation between normal and diseased legs than Na^{24} (cf. Figure 3).

Discussion

The Na^{24} clearance and muscle blood flow. The transport of electrolytes from blood to tissue in isolated skeletal muscles has been investigated in a series of studies by Renkin (7, 10–12). Infusing K^{42} and Rb^{86} at a constant concentration via the arterial supply, he found that only at very low blood flow levels of about 2.0 ml per 100 g per minute did the initial extraction ratio $(C_{artery} - C_{vein})/C_{artery}$ approach the value close to unity theoretically expected for complete equilibrium. At higher flow rates a progressive decrease of this extraction ratio was found, values about 0.5 being reached at a flow level of about 10 ml per 100 g per minute. These findings could be accounted for by shunting of arterial blood past the capillaries. However, to postulate gross shunting reaching 50% at so moderate a flow level as 10 ml per 100 g per minute was on general grounds considered most unreasonable, as such shunted blood would serve no nutritive purpose. Therefore, Renkin believed that incomplete transcapillary exchange of electrolytes was causing the drop in extraction ratio with increasing flow.

This conclusion is confirmed by the present findings. Both Na^{24} and Xe^{133} are cleared locally via the capillaries and are thus unable to measure shunt flow, i.e., the sharp decrease of the Cl_{Na}/Cl_{Xe} ratio during hyperemia points to increasing exchange limitation (lack of equilibrium) at the capillary level for Na with increasing flow.

At high flow rates Cl_{Na} is probably a measure of the capillary diffusion capacity. This capacity or "permeability-surface area product" is defined as the limiting clearance value (in milliliters per 100 g per minute) obtained when blood flow is so rapid (at unchanged capillary permeability and surface area) that the capillary tracer concentration remains very low in the capillary blood (7). Thus it is a measure of the unidirectional Na flux from tissue to capillary blood.

It follows from Renkin's studies and from the data obtained in the present study that for muscle blood flows between a low level of about 2 ml and a high level of 15 to 20 ml per 100 g per minute, Cl_{Na} cannot readily be interpreted. In this range of blood flow, Prentice, Stahl, Dial, and Ponterio studied the total flow and the Na^{24} clearance in the isolated biceps muscle of the dog (13). Only a fairly gross correlation of the two parameters was found, which may be considered as a corollary of the complexity of the factors determining Cl_{Na} in this flow range.

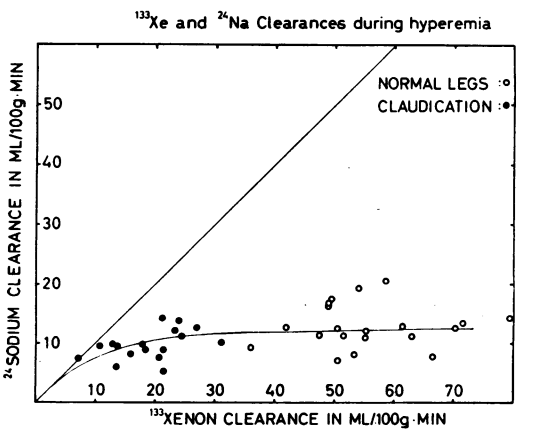

FIG. 3. SIMULTANEOUS Cl_{Na} AND Cl_{Xe} VALUES IN THE INTERVAL WHEN THE LATTER HAD REACHED ITS MAXIMAL LEVEL DURING REACTIVE HYPEREMIA.

As a consequence of the above analysis, it would appear difficult to employ clearance data for Na^{24} or other ions to prove or disprove the existence of a dual circulation (shunt) in skeletal muscle.

The Xe^{133} clearance and muscle blood flow. If Cl_{Xe} is to be a measure of local blood flow, then this tracer must remain essentially in diffusion equilibrium regardless of the flow. Due to its lipoid structure the total capillary membrane surface is presumably available for inert gas transfer. In contrast, the exchange of ions in the capillaries of the extremities appears to be limited to pores in the wall occupying only about 1/1,000 of the surface area (14). Disregarding membrane resistance, the diffusibility of the inert gases in the tissues is high. It can be calculated that the inert gas concentration in capillary blood leaving a tissue is likely to be within a few per cents of the equilibrium value [Copperman as quoted by Kety (3)].

Experimental evidence supports this conclusion. In the myocardium both heavy water and I^{131}-antipyrine have been shown to remain in diffusion equilibrium even under rapidly varying blood concentrations and at high blood flow levels (15, 16). Presumably the lipophilic inert gases diffuse even better in muscle tissue than these two more hydrophilic tracers.

If a shunt exists, then Cl_{Xe} measures only capillary or nutritive flow, but even a less drastic inhomogeneity of flow would have the effect of a shunt. A progressive fall in Cl_{Xe} would result in this situation even if muscle blood flow were absolutely stable. I have on several occasions seen a moderate decrease of Cl_{Xe} in the resting muscle studied over 30 minutes. Probably, however, this reflects an unsteady state of decreasing blood flow. It has not been found in patients studied after prolonged (for hours), complete immobilization of the limb when injecting, as described, at a slow rate through a thin needle only 0.1 ml Xe^{133}-saline containing no additives, e.g., no added bacteriostatic agent.

To critically evaluate Cl_{Xe} as a measure of local capillary blood flow in the muscle, this method should, ideally, be compared to a reliable independent method. Such a method does not exist. The best approach would therefore seem to be to compare Cl_{Xe} to total venous outflow from an isolated muscle in the experimental animal. In man a comparison to the result of venous occlusion plethysmography of the calf is of interest, bearing in mind that the latter method also measures blood flow in bone and skin. Only the results obtained in normal subjects will be compared here, since differences of patient groups are likely to exist.

Plethysmographic studies of calf perfusion are usually expressed in milliliters per 100 ml calf per minute, but since the specific gravity of the calf is close to 1, I have without correction changed the unit to milliliters per 100 g calf per minute. The resting calf perfusion averaged 1.9 and 3.6 ml per 100 g per minute in the two series of normal subjects of all age groups (17, 18). The corresponding resting value averaged 2.8 ml per 100 g per minute in the present series (20 legs). The maximal calf perfusion after ischemic work averaged 44 ml per 100 g per minute in a series of normal subjects of all age groups (19). The corresponding maximal Cl_{Xe} value averaged 56 ml per 100 g per minute.

Since the maximal flow rate in the muscles alone can be expected to exceed that of the calf as a whole, the observed agreement is considered satisfactory and tends to validate the Xe^{133} method.

Cl_{Na} and Cl_{Xe} during reactive hyperemia as a practical test for diagnosing arterial obstruction. The marked difference in the clearance of two tracers during the main part of the hyperemic response has been commented on. Only initially (Figures 1 and 2) was the Cl_{Na} fairly consistently subnormal in the patients with arterial obstruction, and, as mentioned, reliable quantitation of this early difference of Cl_{Na} proved difficult, since it had its maximal value at only a single point (time) after release of the cuff. Apparently Xe^{133} was superior to Na^{24} with respect to separating the two clinical groups.

In addition, Xe^{133} has several other advantages over Na^{24}. The half-life of Xe^{133} is longer (5.3 days) than for Na^{24} (14 hours). The softness of the gamma radiation from Xe^{133} (81 kev) renders this isotope considerably easier to handle in the laboratory than Na^{24} (1,370 and 2,760 kev), and being a gas, Xe^{133} does not contaminate counting equipment and laboratory space. The low radiation energy and especially the very rapid elimination from the body via the lungs render

the Xe^{133} radiation doses more than 1,000 times smaller than with the same amount of Na^{24} (6).

The only clinically useful measure of muscle blood flow in patients with intermittent claudication has so far been obtained by venous occlusion plethysmography. The classical studies of Shepherd (20) established that resting blood flow is normal in such patients. A subnormal and delayed flow response after ischemic work was found in some patients with intermittent claudication (type B of Shepherd). He also found a group of patients with intermittent claudication who had only subnormal hyperemic flow but no delayed onset of maximal blood flow after release of the cuff (type A of Shepherd). We have found both types in the present study: of 17 legs with claudication, 12 had a delay of the onset of maximal Cl_{Xe} of more than 1.0 minute after release of the tourniquet, this delay representing the upper limit in the normal series. (A more detailed discussion of these clinical aspects of the Xe^{133} clearance method has been published elsewhere [5].)

Summary

Muscle blood flow was evaluated by simultaneously injecting Na^{24} and Xe^{133} into the anterior tibial muscle in ten normal subjects (20 normal legs) and ten patients with intermittent claudication (17 symptomatic legs). Studies were made at rest and during maximal reactive hyperemia after ischemic work.

Comparison of the clearances of the two isotopes indicated marked diffusion limitation of Na^{24} at high blood flow levels and demonstrated that Xe^{133} allowed a much clearer separation between normal and pathological cases than Na^{24}. Calculated on the basis of the Xe^{133} clearance studies, the blood flow averaged 2.5 ml per 100 g per minute in resting muscle, there being no significant difference between normal subjects and patients with intermittent claudication. During maximal hyperemia the maximal blood flow averaged 56 ml per 100 g per minute in normal legs as compared to 17 ml per 100 g per minute in the diseased legs, this difference being highly significant statistically ($p < 0.001$). These data are in good agreement with the results of venous occlusion plethysmography of the calf reported in the literature, an agreement tending to validate Xe^{133} clearance as a method for measuring quantitatively the capillary blood flow in skeletal muscles.

The results obtained with Na^{24} relative to Xe^{133} would seem to invalidate clearance data for Na^{24} as a measure of capillary flow except at very low flow levels. During hyperemia the capillary diffusion capacity for Na is rate limiting to an increasing extent. These findings also invalidate attempts to employ Na^{24} or I^{131} clearance measurements of a dual circulation in skeletal muscle.

Acknowledgments

The author wishes to express his gratitude for a very fruitful discussion with Drs. E. M. Renkin and D. C. Tosteson of the data presented in this study.

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