Derivation of knee joint synovial perfusion

Using the Xenon (^{133}Xe) clearance technique

W. CARSON DICK, R. A. St. ONGE,[†] F. C. GILLESPIE, W. WILSON DOWNIE, G. NUKI, I. GORDON, K. WHALEY, J. A. BOYLE*, AND W. WATSON BUCHANAN

From the Centre for Rheumatic Diseases and the University Department of Medicine, Glasgow, and the Department of Clinical Physics and Bioengineering, Glasgow, Scotland

Inert gas clearance techniques involving the use of radioactive xenon (^{133}Xe) have been developed to measure blood flow through many organs (Bain and Harper, 1968; Veall, 1968). In this paper a method is described for deriving the blood flow through the synovial tissue of the human knee joint by measuring the rate of clearance of intra-articularly administered ^{133}Xe from the joint. This method provides a measure of capillary blood flow ('perfusion') as opposed to total arterial inflow or venous outflow.

Material and methods

PATIENTS STUDIED

Synovial perfusion was determined in twelve patients who were suffering from 'classical' rheumatoid arthritis (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959), all of whom had active involvement of the knee joint, and in twelve healthy male volunteers. The patients with rheumatoid arthritis were all post-menopausal females aged between 58 and 64 years (mean 60.3). None was receiving corticosteroid therapy. The age of the normal subjects ranged from 18 to 28 years (mean 24.6).

All patients and control subjects volunteered to participate in this study with full knowledge of its content.

^{133}Xe KNEE JOINT INJECTIONS

Using full aseptic technique a solution of 10 μCi of ^{133}Xe in 1 ml. 0.9 per cent. saline was injected into the knee joint by a lateral infrapatellar approach (Dick, Whaley, St. Onge, Downie, Nuki, Gillespie, and Buchanan, 1970). The joint was aspirated as fully as possible before administration of the isotope. With the patient lying supine the knee joint was then extended and immobilized with sandbags.

The clearance of ^{133}Xe from the knee joint was monitored using a lightly collimated scintillation counter which had a sodium iodide crystal 1½ in. in diameter and 1 in. thick and which was connected to a pulse scaler (ECHO type H 530G). The crystal was positioned 6 in. from the medial aspect of the knee joint using the upper border of the patella as a reference point. The count rate was measured at 2-min. intervals for 30 to 45 min. after the injection, and the results, minus the background, were plotted on semilogarithmic graph paper. The initial

count rate was generally of the order of 10,000 to 20,000 counts per minute and the background between 100 and 500 counts per minute. The biological half life ($T_{\frac{1}{2}}$ min.) was then determined from the slope of the disappearance curve, which was monoexponential from 5 to 45 min. after injection in each case.

To verify that ^{133}Xe was removed from the joint by the venous system, the following experiment was performed. One leg of an anaesthetized adult greyhound dog was disarticulated at the hip and all tissues were severed leaving only the femoral artery and vein connecting the leg with the body (Fig. 1). ^{133}Xe was then injected into the stifle joint and the clearance monitored in the same manner as described for the human subjects. After 30 min., by which time the clearance rate had been established, the femoral vein was clamped. Immediately the clearance of ^{133}Xe ceased. It was then established that no lymphatic channels had remained intact. This was done by excising the inguinal and para-aortic lymph nodes, measuring their contents of ^{133}Xe in a well-type scintillation crystal, and noting that no activity was detectable.

The possibility remained that one route of clearance of intra-articularly administered ^{133}Xe might be through articular cartilage and into the nutrient vessels of bone. To confirm that this was not an important route a further study was performed in five rheumatoid patients. In each case ^{133}Xe clearance was monitored in the usual manner for approximately 10 to 15 min. until the rate of clearance was established. A narrow tourniquet was then placed immediately above the knee joint and inflated to a pressure midway between systolic and diastolic blood pressure of the subject. Immediately the tourniquet was applied the clearance of ^{133}Xe ceased (Fig. 2). After 5 to 10 min. the tourniquet was released and in each case the clearance continued at approximately the initial rate.

Measurement of partition coefficient

The value of the partition coefficient of ^{133}Xe between synovial tissue and blood (that is the ratio, at equilibrium, *in vitro* of the concentration of ^{133}Xe ($\mu\text{Ci}/\text{ml.}$) in tissue to the concentration in blood ($\mu\text{Ci}/\text{ml.}$) is required to translate the $T_{\frac{1}{2}}$ values into blood flow (Conn, 1961).

Partition coefficients of ^{133}Xe between synovial

[†] Now at Yale University School of Medicine, New Haven, Connecticut, USA. This investigation was conducted in partial fulfilment of the requirements for the M.D. candidate's thesis of Yale University School of Medicine.

* Harkness Travelling Fellow, Department of Medicine, Basic Sciences Building, University of California, La Jolla, California, 92037, USA.

tissue and saline were measured in seven specimens of tissue obtained from normal knee joints at autopsy and in eight samples of rheumatoid synovial tissue were obtained at synovectomy of the knee. 1 to 2 mm. tissue were carefully dissected from the surface of the specimen which had been bordering on the joint cavity. This was added to a solution of ^{133}Xe in saline in a glass test-tube. Each test-tube was sealed, having checked that all air was excluded, and left for 24 hrs at 37° C. to allow the ^{133}Xe to equilibrate.

The relative activities in paired samples of synovial tissue and saline were then determined and the relative concentrations of activity were calculated using both these results and the measured weights of the samples. The final results gave values for the partition co-efficients of ^{133}Xe between the respective tissues and saline. From these, and from published data (Conn, 1961) on the partition coefficient of ^{133}Xe between saline and blood, the partition co-efficients between the various tissues and blood at a haematocrit of 40 per cent. were calculated.

Results

In all cases the clearance of ^{133}Xe from the knee joint from 5 to 45 min. after injection could be described by a single exponential function. Consequently $T_{\frac{1}{2}}$ values could readily be obtained from semi-log plots of the results. In normal subject and in seven patients with rheumatoid arthritis, repeat determinations of the ^{133}Xe clearance rates were made at an interval of 24 hrs (Dick, Whaley, St. Onge, Downie, Nuki, Gillespie, and Buchanan, 1969). In general there was good agreement between

Table Synovial perfusion (ml./100 ml./min.) and respective $T_{\frac{1}{2}}$ values (min.) obtained in twelve normal and twelve rheumatoid subjects

Perfusion (ml./100 ml./min.)		$T_{\frac{1}{2}}$ values (min.)	
Normal	Rheumatoid	Normal	Rheumatoid
0.49	1.22	140	57
0.36	0.81	190	85
0.15	1.69	460	41
0.11	2.10	600	33
0.58	2.31	120	30
0.11	2.77	630	25
0.26	4.08	264	17
0.46	1.92	150	36
1.05	1.51	66	46
0.58	2.04	120	34
0.40	1.39	175	50
1.00	1.82	71	38
Mean 0.46	1.97	248.8	41.0
SE $\pm$ 0.09	0.24	57.95	5.08

$P = <0.01 > 0.001$

$P = <0.01 > 0.001$

corresponding pairs of results, the standard error of the difference being 1.9 min.

The $T_{\frac{1}{2}}$ values obtained in normal and rheumatoid subjects (Table) show that the values for rheumatoid patients (mean $41.0 \pm \text{SEM } 5.08$ min.) were much lower than those for normal subjects (mean 248.8 ± 57.9 min.).

The result obtained (Fig. 1) when the clearance of ^{133}Xe from the isolated stifle joint of the anaesthetized dog was interrupted by the application of a clamp on the femoral vein shows clearly that the count rate over the joint remained constant after venous drainage was interrupted, and that no further clearance occurred.

FIG. 1 Experiment to determine role of disappearance of ^{133}Xe from stifle joint of an anaesthetized dog (see text).

Graph shows semilog plot of clearance of ^{133}Xe from stifle joint. Point '↓' indicates the time that the femoral vein was clamped. It can be seen that the clearance of ^{133}Xe ceased abruptly at that point.

The results (Fig. 2, opposite) in five rheumatoid patients indicate that, in every case, immediately the tourniquet was inflated the clearance of ^{133}Xe ceased, and that immediately it was released clearance recommenced at the initial rate. The standard error of the difference between $T_{\frac{1}{2}}$ values calculated for the periods before and after the application of the tourniquet was 0.18 min.

The partition coefficients (λ) of ^{133}Xe , determined for both normal and rheumatoid synovial tissue, ranged from 0.87 to 1.1 (mean 1).

For calculation of synovial perfusion a value of 1 was employed for the partition coefficient of ^{133}Xe for rheumatoid and normal synovial tissue with respect to blood. Since in all cases the disappearance of ^{133}Xe could be represented by a monoexponential function, synovial perfusion (SP) is given by:

$$\text{SP} = \frac{69.3}{T_{\frac{1}{2}}} \cdot \lambda \text{ ml./100 ml. synovial tissue/min.},$$

where $T_{\frac{1}{2}}$ min. is the halving time of the dis-

FIG. 2 Semi-log plots of results obtained when ^{133}Xe clearance was interrupted by application of tourniquet. The narrow tourniquet was placed immediately proximal to the knee joint.

appearance curve and λ is the partition coefficient of ^{133}Xe between synovial tissue and blood.

The results are shown in the Table. The values for rheumatoid patients (mean $1.97 \pm \text{SEM } 0.24$ ml./100 ml./min.) are significantly higher ($P < 0.01 > 0.001$) than the values obtained in normal subjects (mean $0.46 \pm \text{SEM } 0.09$ ml./100 ml./min.).

Discussion

^{133}Xe is an ideal isotope for the measurement of tissue perfusion. It is biologically inert and its low solubility in blood results in over 90 per cent. of the isotope presented to the pulmonary circulation being exhaled in the expired air. Recirculation into the area under study is therefore negligible and in addition the half life of the isotope in the body is short, thus reducing radiation exposure. Because it is lipid-soluble, diffusion across cell membranes is unrestricted, and accordingly ^{133}Xe is likely to reflect tissue perfusion more closely than do lipid-insoluble tracers such as radioactive sodium (Gosselin 1966). Diffusion is unlikely to limit the clearance of ^{133}Xe (Kety, 1951; Pappenheimer, 1953; Perl, 1962) and it can be shown that 50 per cent. of the injected isotope will diffuse into the synovial membrane in 10 to 20 sec.

No other technique is presently applicable for the measurement of synovial perfusion. Temperature

measurements cannot be transposed into blood flow without knowledge of the temperature of the blood entering or leaving the tissue (Greenfield, Shepherd, and Whelan, 1951). Plethysmography cannot separate intercompartmental blood flow (Bonney, Hughes, and Janus, 1952), and the use of the electromagnetic flowmeter is complicated by the complexity of the synovial blood supply. Thus the inert gas clearance technique seemed to be worthy of study from this point of view.

That intra-articularly administered ^{133}Xe is cleared by tissue closely related to the site of injection is demonstrated by the fact that clearance is established within 1 min. The diffusion rate of ^{133}Xe in tissue (1.0×10^{-5} cm.²sec.⁻¹ at 37° C.: Unsworth, 1969) underlines the fact that the isotope cannot be clearing from tissue which is more than a few millimetres from the site of injection. The possible alternatives are therefore cartilage or synovium. Clearance through cartilage is rendered unlikely by the fact that cartilage is avascular. In the experiments using a narrow tourniquet placed immediately above the knee, and therefore distal to the site of emergence of the femoral nutrient vessels, no clearance was demonstrable through blood vessels in bone. It would seem reasonable to suggest that clearance was occurring through synovial tissue. Despite the intimacy of the blood supply of synovial tissue and of the epiphysis (Davies and Edwards, 1948), these results would suggest that synovial venous blood does not drain through nutrient venous channels in bone.

Clearance from synovial tissue may occur through lymphatic or venous channels. Lymphatic flow is a small proportion of blood flow and many workers (Stone and Miller, 1949; Walder, 1953; Hollander, Reilly, and Bunov, 1961) have concluded that the removal of small molecular weight substances by lymphatics is negligible. In this study no activity was demonstrable in lymph nodes. On the other hand, both the experiment in the dog and the studies on rheumatoid patients demonstrated that clearance depended on blood flow.

The conclusion suggested by these results is that clearance of ^{133}Xe is mediated by synovial venous channels and may be employed to derive a measure of tissue perfusion. Calculation of perfusion is based on the methods employed by Kety (1949, 1951), Thorburn, Kopald, Hert, and Hollenberg, O'Mochoe, and Barger (1963), and Lassen, Lindbjerg, and Munck (1964). The subject has recently been reviewed by Veall (1968). The results are expressed in terms of perfusion since non-nutritive vascular shunt flow will not be detected. The results which we have obtained, namely that synovial perfusion in rheumatoid joints greatly exceeds perfusion of normal synovium, is in accord with the pathology of rheumatoid arthritis. It is possible that

the determination of synovial perfusion may be of value in assessing drug therapy and synovectomy, and may provide a method for the study of joint patho-physiology.

Summary

A method is presented for the measurement of perfusion in joint tissues in man. By studying the clearance of the inert radioactive gas xenon (^{133}Xe) after intra-articular injection and by measuring the partition of coefficient of ^{133}Xe for synovial tissues with

respect to blood, the results are expressed as millilitres per 100 millilitres of synovial tissue per minute. The synovial perfusion in normal and rheumatoid joints is recorded.

We thank Dr. A. M. Harper, Wellcome Research Laboratories, Glasgow, for helpful advice.

This work would not have been possible without financial support from the Arthritis and Rheumatism Council for Research in Great Britain.

One of us (G.N.) was a CIBA clinical research Fellow. K.W. is an M.R.C. clinical research Fellow.

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RÉSUMÉ

La dérivation de la perfusion synoviale de l'articulation du genou en employant la technique de l'évacuation du Xenon (^{133}Xe)

Une méthode est décrite pour mesurer la perfusion dans les tissus des articulations chez l'homme. En étudiant l'évacuation du gaz radioactif et inerte Xenon (^{133}Xe) après l'injection intra-articulaire, et en mesurant le partage du coefficient de ^{133}Xe pour les tissus synoviaux par rapport au sang, les résultats sont exprimés en millilitres par 100 millilitres de tissu synovial par minute. La perfusion synoviale dans les articulations normales et rhumatoïdes est rapportée.

SUMARIO

Derivación de la perfusión sinovial en articulación de rodilla usando la técnica de eliminación del xenón (Xe^{133})

Se expone un método para medir la perfusión de tejidos de articulación en el hombre. Estudiando la eliminación del gas radioactivo inerte xenón (Xe^{133}) después de la inyección intraarticular, y midiendo la división del coeficiente del Xe^{133} para tejidos sinoviales con respecto a la sangre, los resultados se expresan en mililitros por 100 mililitros de tejido sinovial por minuto. Se anota la perfusión sinovial en articulaciones normales y reumatoideas.