Sternal Marrow Circulation by the Radioisotope Clearance Technique

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Information on the physiology of the marrow circulation is fragmentary and incomplete, due, in large measure, to the peculiarity of the architecture of the marrow vasculature and its inaccessibility. Large gaps exist in our knowledge: almost nothing is known of such fundamental events as the arteriovenous differences for gases, metabolic substrates and the products of hematopoiesis. Important questions concerned with the presumably more simple relationships of blood flow and marrow activity still remain unanswered.

The demonstrated feasibility of measuring the regional circulation of a given tissue from the disappearance rate of a locally deposited, diffusible, radioactive tracer substance (1) stimulated some interest in the application of this technique to the study of the blood flow of the marrow (2-4). This rather simple technique has been variously modified by these investigators to yield divergent data which have been interpreted generally as useful measurements of the capillary blood flow of the marrow.

In the light of these reported diverse findings the present study was undertaken to re-evaluate the applicability of the tracer clearance technique to the study of bone marrow blood flow.

MATERIAL AND METHODS

Hospitalized male patients, free from any overt hematological abnormalities, pulmonary, cardiac or renal disease, were selected as subjects for this investigation. The marrow morphology was not studied. In order to minimize injury of the marrow tissue, the aspiration of samples was intentionally omitted.

The technique employed was essentially a modification of the depot radioisotope clearance method described by Kety (1). The tracer substances were injected as isotonic solutions in 0.5 ml volume into the sternum, immediately below the angle of Louis. Doses of the radioisotopes ranged between 5 and 6 µC. Each subject was placed in the supine position and a scintillation probe was positioned against skin directly over the sternal injection site. The probe contained a 1 in. × 1 in. sodium iodide, thallium activated, crystal in a 36° flat field

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collimator, shielded by % in. lead, and was connected to a conventional rate meter and rectilinear recorder as well as a tape deck. The recording was made with a paper speed of 12 in. per minute and rate meter time constant of 2.5 seconds. Attempts to use a lower time constant resulted in erratic fluctuations of the recorded curve. The probe was on a swinging arm which could be moved away from the field and returned to the predetermined site in a fraction of a second. The skin and periosteum of the injection site were anaesthetized with 1.0 ml of 2 per cent procaine, and a sternal needle (Osgood) was introduced into the marrow under aseptic conditions. The test material was injected rapidly into the medullary cavity. The needle was quickly withdrawn, the probe swung into position and locked, and the disappearance rate of the radioisotope recorded. The crystal is recessed 8.0 cm in the lead collimator and the probe remained fixed in position in contact with the skin over the sternum during the entire recording.

Theoretical objections, such as reflux of tracer substance into the needle tract, or bleeding at the puncture site of highly contaminated blood proved in practice to be of no consequence. Despite the fast clearance of the labeled material from the marrow, the described technique is simple and sufficiently rapid to give adequate curves from which the half-time clearance (T%) of the administered radioisotope could be calculated. Calculations were made by plotting the recorded data on semi-logarithmic paper.

Apprehension and anxiety seemed to prolong the clearance time. The procedure was explained to the subject and great care was exercised to allay the patient's fear.

The following aspects of the problem were investigated:
1. normal half-time clearance;
2. relationship of clearance to the molecular size of the labeled material; and
3. comparison of venous versus marrow clearance.

The subjects were divided into the following groups:
1. Sodium$^{22}$ chloride (Na$^{22}$Cl)—43 subjects with a mean age of 54, range 23-75 years.
2. Iodinated $^{131}$ human serum albumin (I$^{131}$ HSA)—25 subjects; mean age—50, range 21-77 years.
3. Sodium orthohippurate $^{131}$ (I$^{131}$ Hippuran)—21 subjects; mean age 48, range 28-68 years.

The percentage of urinary excretion of the administered dose was measured in eleven patients of the last group. Voided urine was collected at 30, 60, 120 and 180 minutes and radioactivity measured. One week later, after all of the previously administered radioisotope had been excreted, the same subjects were given 0.5 ml of I$^{131}$ Hippuran intravenously and urine samples collected in a similar manner. Thus, the rate of clearance of I$^{131}$ Hippuran from marrow and from vein could be compared in the same individual.

RESULTS

The disappearance curves of the injected radioactive substances (Fig. 1) show an initial rapid rise and an immediate fast exponential decline. A second
slow component then follows, most likely the result of intravascular mixing, originating in the heart and the large vessels directly below the probe. The possibility of the marrow itself contributing to this slow component cannot be excluded; further study of this aspect may be indicated. The initial rapid phase of the curve was plotted on semi-logarithmic paper to furnish the Ta data summarized in the accompanying Table.

In a certain number of the subjects a second probe was placed either over the great vessels of the neck, over the lateral aspect of chest, or a more distant site, such as the thigh. The arrival time over these sites lagged only slightly the peak of sternal activity, with overall magnitude appreciably reduced but the general configuration of the curves was essentially similar.

It is apparent that labeled material injected into normal human marrow dis-

**TYPICAL TRACINGS OF RADIOISOTOPE CLEARANCE**

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Fig. 1. Typical plots and tracings. Na\(^{22}\)Cl full scale 30 K, I\(^{131}\) HSA and I\(^{131}\) Hippuran 10 K.
appears very quickly and confirms, in measurement, what clinicians have long
known from experience with intramarrow infusions (5-7). The very rapid clear-
ance of Na\textsuperscript{22} from the marrow is indeed striking, particularly when compared
to the disappearance rates of Na\textsuperscript{24} or I\textsuperscript{131} as iodide from muscle, (8-10) a
highly vascularized tissue, where the T\textsubscript{1/2} is some 60-100 times longer. Since mar-
row contains a large fat component, tracer clearance studies on subcutaneous fat
were conducted. Here, we found the T\textsubscript{1/2} well over 100 times longer than that of
the marrow.

The data also show that there is no significant difference in the clearance
of the locally deposited Na\textsuperscript{22} or of the I\textsuperscript{131} HSA from the marrow despite an
approximate 3,000-fold difference in molecular weight. It is true that the clear-
ance of I\textsuperscript{131} as iodide is as rapid as the clearance of Na\textsuperscript{22} (10). However, one
would have anticipated some difference in clearance of Na\textsuperscript{22} as an ion and I\textsuperscript{131}
in the form of a complex, large molecule, I\textsuperscript{131} HSA, if the clearance were
achieved by capillary blood flow alone.

In Fig. 2 the data for the percent urinary excretion of the administered dose
of I\textsuperscript{131} Hippuran from sternum and vein are presented. No significant difference
exists between the clearance of the radioactive material injected into the normal
marrow or into a peripheral vein.

EXCRETION OF I\textsuperscript{131} HIPPURAN IN URINE

![Graph showing excretion of I\textsuperscript{131} Hippuran in urine]

Fig. 2. Shows the cumulative percent of administered dose excreted per unit time.
DISCUSSION

In 1953, Petrakis et al (2) used I$^{131}$ as the iodide, to determine the local blood flow of the human marrow. These investigators introduced a Turkel needle into the sternum, and then injected the Na$I^{131}$ solution, over a one to two minute period, through a tuberculin syringe with a fine gauge needle which had been inserted into and well beyond the tip of the marrow needle. This slow rate of injection was purposely employed to avoid a sudden increase of intramedullary pressure. The two needle technique was used to avoid contamination of the needle tract and skin by reflux. In their nine control subjects, the calculated T½ ranged between 5.5 and 16.0 minutes. They also studied a group of patients with acute and chronic leukemia and concluded that fundamental differences in the marrow vascular bed exists among the leukemias.

In 1962, Brown-Grant and Cummings (3) studied the clearance of Na I$^{131}$ from the femoral marrow of the rabbit. They introduced a permanently placed bent needle into the marrow to allow simultaneous injection and recording. They observed a very rapid disappearance of the radioactivity from the injection site, a mean T½ of 20-30 sec., surprisingly similar to the half-time clearance found in our human subjects. The rapid appearance of high counting rates over the opposite limb of the animal argued against simple diffusion of the test substance into the marrow away from the probe. Because the I$^{131}$ albumin clearance rate from the marrow was thought to be slower than the radiiodide clearance, the authors concluded that the rapid disappearance of the radiiodide was indeed due to a high effective capillary circulation. The curves shown by Brown-Grant and Cummings, like the curves obtained in the present study, show a rapid initial marrow phase followed by a slow prolonged component, which we believe

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Number of Subjects</th>
<th>$T_{1/2}$</th>
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<tr>
<td></td>
<td></td>
<td>Range</td>
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<tr>
<td></td>
<td></td>
<td>(seconds)</td>
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<tr>
<td>Na$^{22}$Cl</td>
<td>43</td>
<td>8–51</td>
</tr>
<tr>
<td>I$^{131}$ HSA</td>
<td>25</td>
<td>8–43</td>
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<tr>
<td>I$^{131}$ Hippuran</td>
<td>21</td>
<td>11–44</td>
</tr>
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"p" values

Na$^{22}$Cl $\rightarrow$ vs I$^{131}$ HSA 0.5 > p > 0.4
Na$^{22}$Cl $\rightarrow$ vs I$^{131}$ Hippuran 0.1 > p > 0.05
I$^{131}$ HSA $\rightarrow$ vs I$^{131}$ Hippuran 0.3 > p > 0.2
measures the rate of removal of the isotope from the blood. Since $^{1}^{131}$ albumin remains in blood longer than iodide, its clearance rate from the blood should be slower than that of iodide.

Recently, Najean and Clement (4) injected sodium chromate$^{51}$ into the sternal marrow and measured the appearance of radioactivity at the inguinal area. They hoped in this way to avoid the loss of time required to remove the trocar, apply the detector and prevent the theoretical contamination of the needle tract. Two phases were described—a rapid initial phase which appeared to correspond to a direct intravascular injection, and a second which was interpreted as a period of diffusion and equilibration.

Schoen and Doering (12) in their article on polycythemia vera, state that the T% of radioiodide from the sternum is 10 minutes for subjects with polycythemia vera. Details of technique are not given, nor any reference to published material.

It is apparent from the pertinent literature that there has been considerable preoccupation with technique in the attempt to achieve speed in the recording of data, to avoid injury of marrow tissue, gross diffusion of the labeled material into the marrow compartment and contamination of the needle tract. Differences in technique account largely for the differences in the reported results on normal human subjects.

In the present study the problems of technique, we believe, were met successfully. Small volumes of material were injected into the marrow, and contamination of the needle tract was not encountered. The detector could be swung into position rapidly and locked, so that a constant relationship between the detector and the injection site was maintained. Kety (1) pointed out that neither the dose of the labeled material, nor the geometry of the system employed is critical so long as the relations between the injection site and detector are preserved throughout the measurement period.

The present investigation shows clearly that the clearance of labeled material from the marrow is quite rapid and independent of molecular or ion size. The half-time clearance rates from the marrow are indeed striking when compared, as cited previously, with the much slower clearance rates of highly vascularized tissue as muscle. Further, the recovery of $^{1}^{131}$ Hippuran in the urine following marrow injection approaches closely the recovery of the dye after intravenous administration. These findings, high isotope mobilization rates and equal clearance of tagged materials of different molecular or ion size from the marrow, suggest a unique organization where the flow of fluid from the extravascular to the intravascular spaces appears free and uninhibited. Information on the anatomy of the marrow is insufficient to comprehend the structural organization in which these events take place. The role of this flow system in the physiology of the marrow is not clear. Application of the isotope clearance technique to pathological states of the marrow may shed some light.

**SUMMARY**

The clearance rates of Na$^{22}$Cl, $^{1}^{131}$HSA and $^{1}^{131}$Hippuran from marrow have been determined. The disappearance rate of radioisotopes is rapid (T% of 21—24
sec) and independent of molecular or ion size. Mobilization of $^{131}$I Hippuran from marrow lagged slightly behind the clearance of this dye into the bladder following intravenous administration. The marrow appears to possess a unique organization for fluid flow.

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REFERENCES