Physiological Basis of the Radioisotope Renogram

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The renogram, a test of renal function introduced in 1956 by Taplin et al. (1956), is obtained by injecting some substance tagged with radioactivity which accumulates in a relatively selective manner in the kidney. Collimated counters placed over the two kidneys measure the accumulation of radioactivity, and its subsequent decrease. When the counter is connected to automatic recording devices, the curves produced begin at the origin, rise rapidly to a peak, and then fall in an approximately exponential manner. (Fig. 3)

Blaufax, Orvis, and Owen (1963) have done a compartment analysis of Hippuran in dogs and have suggested that characteristics of the radioisotope renogram may be elucidated by compartment analysis. The present paper is based on a similar compartment analysis. A different model, however, is proposed to describe the renogram. Estimates of the parameters are obtained by the method of maximum likelihood rather than by graphical means. In addition, certain implications and possible application of the model, not discussed by Blaufax et al., are developed here.

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Blufax, Orvis, and Owen (1963) have done a compartment analysis of Hippuran in dogs and have suggested that characteristics of the radioisotope renogram may be elucidated by compartment analysis. The present paper is based on a similar compartment analysis. A different model, however, is proposed to describe the renogram. Estimates of the parameters are obtained by the method of maximum likelihood rather than by graphical means. In addition, certain implications and possible application of the model, not discussed by Blaufax et al., are developed here.

The Blood Curve

Assume the injected substance is distributed principally into four compartments during the 20 minute duration of the experiment. These compartments are the blood, kidney, urine, and an extravascular, extrarenal space, and are designated by the subscripts b, k, u, and e, respectively. It is also assumed that:

a) Intravascular mixing takes place very rapidly, compared to exchanges between other compartments.

b) Compartment u exchanges only with k, k only with b and u, and e only with b.

c) The volumes of compartments b, k, and u are each constant.

We may write:

\[ v_i \dot{Y}_i = -C_{bi}Y_i + C_{ei}(Y_e - Y_i), \]  

(1)

\[ v_e \dot{Y}_e = C_{be}(Y_b - Y_e), \]  

(2)

where:

- \( v_i \) = volume of compartment \( i \),
- \( C_{ij} \) = the volume of compartment \( j \) cleared per unit time with transfer to compartment \( i \). No assumptions are made concerning mechanisms of clearance except that \( C_{be} = C_{eb} \); that is, there is no asymmetry of mechanism between compartments \( e \) and \( b \).

\( Y_i \) = concentration of the injected substance in compartment \( i \).

\( \dot{Y}_b \) and \( \dot{Y}_e \) are time derivatives of \( Y_b \) and \( Y_e \), respectively. Equations (1) and (2) are satisfied by

\[ Y_b = B_{bb} \exp (\gamma_1 t) + B_{be} \exp (\gamma_2 t), \]  

(3)

where \( t \) is time, and \( B_{bb} \) and \( B_{be} \) are constants chosen to satisfy the initial conditions. \( \gamma_1 \) and \( \gamma_2 \) are the roots of a quadratic equation,

\[ x^2 + ((C_{bb}/V_b) + (C_{be}/V_b))x + (C_{be}/V_e) = 0 \]  

(4)

\[ + (C_{be}C_{bb})/(V_eV_b) = 0 \]
The choice of a two-compartment system to describe the blood curve is based on the suggestion of previous workers (Sapirstein et al., 1955) but is here merely illustrative. More general systems might be used instead, and appropriate modifications made in the development which follows.

The Renogram

We consider the total kidney count exclusive of contribution from other tissues over one kidney, \( y_t \), to be given by:

\[
y_t = C_{kb}' \int_0^t Y_b(s) ds
\]

where \( s \) is a time variable of integration, \( C_{kb}' \) is the unilateral clearance, assumed to be constant.

\[
\tau = \begin{cases} 
0 & \text{for } 0 \leq t < a \\ 
t - a & \text{for } a \leq t 
\end{cases}
\]

\( a \) is the appearance time of orthoiodohippuran in the kidney.

The choice of limits of integration in (5) means that we imagine \( y \) to be simply accumulating within the kidney until \( t - a \). At that time, \( y \) begins leaving the kidney and appears in the urine. If there is little or no longitudinal mixing of urine within the tubules, the successively excreted quantities of \( y \) in the urine will be just those quantities filtered \( t - a \) minutes ago. Imagine an infinitely long train of microscopic box cars, each filled with an amount of \( y \) proportional to \( y_b \) as it enters the kidney. It takes each box car "\( a \)" minutes to leave the kidney. Thus if we want to measure \( y \) at some \( t \geq a \), we sum up all the \( y \) which has entered, and subtract all that came in box cars which entered at some time, \( t - a \), and has now left the kidney. That is,

\[
y_R = C_{kb}' \left( \int_0^t y_b - \int_0^{t-a} y_b \right) \cdot ds, \ t \geq a,
\]

or

\[
y_R = C_{kb}' \int_{t-a}^t y_b ds, \ t \geq a.
\]

If we substitute (3) into (5), and integrate, we obtain for \( t \geq a,

\[
y_R = A_{1R} \exp(\gamma_1 t) + A_{2R} \exp(\gamma_2 t)
\]

\( A_{1R} \) and \( A_{2R} \) are constants determined by \( C_{kb}' , \gamma_1 , \gamma_2 , B_{1b} , \) and \( B_{2b} \). Since, in fact, we may count over tissue and blood as well as over kidney, the counting device will record,

\[
Y_R = \alpha_1 y_b + \alpha_2 y_e + \alpha_3 y_R + \alpha_4 y_u
\]

where \( \alpha_1 \) are constants determined by the positioning of the detector, and the proportion of each compartment will appear in the counting field. \( Y_R \), however, is still a linear combination of the same exponential terms. So we may rewrite (9) as

\[
Y_R = B_{1R} \exp(\gamma_1 t) + B_{2R} \exp(\gamma_2 t)
\]

\( B_{1R} \) and \( B_{2R} \) are constants.

The Urine Curve

Since the ortho-iodohippuran removed from the blood appears a short time later in the urine, we write

\[
(C_{uk} y_u)_t = (C_{kb}' y_b)_t - a,
\]

where \( C_{uk} \) is the urine flow rate. Sodium ortho-iodohippurate excretion (mg per minute) at time \( t \) is simply equal to the sodium ortho-iodohippurate cleared by the kidney (mg per minute) at \( t - a \). The blood curve is evaluated at \( t - a \) to predict the urine curve at \( t \).

\[
C_{uk} y_u = C_{kb}' \left[ B_{1b} \exp(\gamma_1 (t - a)) + B_{2b} \exp(\gamma_2 (t - a)) \right],
\]

For convenience we rewrite (12) as

\[
Y_u = C_{uk} y_u = B_{1u} \exp(\gamma_1 t) + B_{2u} \exp(\gamma_2 t)
\]

Experimental Methods

Experiments were performed on dogs anesthetized with intravenous sodium pentobarbital (30 mgm per kg body weight). Additional doses of anesthetic were given during the experiment as needed. Respiration was maintained with a motor-driven pump following intratracheal intubation. During the preparatory period and throughout the experiment, the animals received a constant intravenous infusion of isotonic saline, or a mixture of equal volumes of isotonic saline and 5% dextrose in water.

Renograms were obtained with a pair of matched scintillation counters (1 x 1 inch thallium-activated sodium iodide crystals), connected to pulse-height discriminators, ratemeters, and a dual linear recorder. A time constant of 10 seconds, and a full-scale setting of 10,000 counts per minute, were employed. All records were obtained with a paper speed of 12 inches per hour. The tracings were allowed to run for 15–20 minutes.

The radioactive material used was \(^{131}\)I-labeled sodium ortho-iodohippurate (Hipppuran\(^{131}\)), obtained from Abbott Laboratories. All renograms were obtained by injecting within 5 seconds 1.5 mc of radioisotope per kg body weight into the vein of a forelimb.

The experimental procedure was as follows: The animal was placed in the supine position and the peritoneal cavity was entered through a midline incision. The ureters were identified, divided at their upper part and their proximal, and cannulated with polyethylene tubing. To minimize dead space, the length of ureteral catheters was kept short and their tips were introduced into or very near to the renal pelvis. Then the right renal artery was dissected free and a Crutchfield clamp was placed around it without constricting the vessel. When urine flow became constant, the probes were placed immediately overlying the exposed kidneys, and control renograms were obtained. The position of the probes remained the same throughout the experiment.

Aortic blood was sampled through a catheter placed into the lower aorta, at 15 second intervals for the first 3 minutes following the injection of iodohippurate, and at 30 second intervals, subsequently. All urine excreted during the inscription of the renogram was collected. Collection periods lasted 15 seconds for the first 3 minutes following the administration of the radioisotope, and 30 seconds, subsequently.

Blood and urine specimens were counted in a scintillation-well counter, for periods long enough to give standard deviations not exceeding 1%. Background and blank counts were subtracted from each count rate.

The urine count rate per second of each specimen was divided by the duration of the period of collection in minutes to obtain the rate of excretion of radioisotope per minute. The data from
one such experiment is used in this analysis.

**Estimation Procedures**

The data obtained for estimating the blood curve (equation 6) consists of $N_b$ points $(1, 2, \ldots, j, \ldots, N_b)$ recorded in counts per ml at successive time points $(t_1, t_2, \ldots, t_j, \ldots, t_{N_b})$.

\[
Y_{bj} = B_{ub} \exp \left( \gamma(t_j) \right) + B_{sb} \exp \left( \gamma_d(t_j) \right) + \epsilon_{ub}\phi(u(t_j)),
\]

\[
Y_{bj} = \text{counts/ml at time } t_j \text{, and}\]

\[
\epsilon_{ub}\phi(u(t_j)) \text{ is the error, while } \epsilon_{ub} \text{ is taken to be independently distributed with mean zero and constant variance (for the blood curve) } \sigma_u^2.
\]

For the points on the descending portion of the renogram curve we have

\[
Y_{Ri} = B_{ur} \exp \left( \gamma(t_i) \right) + B_{sr} \exp \left( \gamma_d(t_i) \right) + \epsilon_{ur}\phi(r(t_i)),
\]

\[
\epsilon_{ur}\phi(r(t_i)) \text{ is as before the error; the } \epsilon_{ur} \text{ are also taken to be normally and independently distributed with mean zero and constant variance } \sigma_r^2. \text{ Because of the 10 second response time of the recorder, and the extremely rapid rise of the renogram curve in its initial phase, it was decided that this portion of the curve was unsuitable for analysis, and only the portion after the peak was used.}
\]

The urine data is in counts/min per minute of urine flow. Each datum has the dimensions of $(C_{ur}y_{ui})$.

\[
y_u = \text{concentration of counts in the urine}
\]

\[
Y_{uj} = (C_{ur}y_{ui}) + \epsilon_{uj}\phi(u(t_j)),
\]

\[
\epsilon_{uj}\phi(u(t_j)) \text{ is the error and } \epsilon_{uj} \text{ has variance } \sigma_u^2, \text{ but otherwise like } \epsilon_{ub} \text{ and } \epsilon_{ur}.
\]

Equations (14), (15), (16) may be summarized as follows:

\[
Y_{ij} = B_{i1} \exp \left( \gamma_1(t_i) \right) + B_{i2} \exp \left( \gamma_2(t_i) \right) + \epsilon_i\phi_i(t_i);
\]

\[
i = b, R, u;
\]

\[
j = 1, 2, \ldots, N_i;
\]

\[
\phi_i(t_i) = \hat{\gamma}_i,
\]

We will estimate the parameters by the method of maximum likelihood (5).

The likelihood function is proportional to

\[
e^L = \prod_{i=b}^{u} \prod_{j=1}^{N_i} \left( 2\pi\phi_i\sigma^2 \right)^{-1/2} \exp \left( -\left( \epsilon_i\phi_i(t_i) \right)^2 / 2\phi_i\sigma^2 \right).
\]

\[
\hat{Y}_{ij} \text{ is the estimated value of } Y \text{ at } t_i \text{ using the maximum likelihood estimates of the parameters appearing in equation (17). Taking the log of (18), and substituting into it } \epsilon_i \text{ from (17), we obtain}
\]

\[
L = \sum_{i=b}^{u} \sum_{j=1}^{N_i} \left( -\frac{1}{2} \log \left( 2\pi\phi_i\sigma^2 \right) \right)
\]

\[
- \left( Y_{ij} - B_{i1} \exp \left( \gamma_1(t_i) \right) - B_{i2} \exp \left( \gamma_2(t_i) \right) \right)^2 / 2\phi_i\sigma^2.
\]

In order to find those estimates of the parameters which maximize $L$ we take

\[
0 = \partial L / \partial \gamma_1 = \partial L / \partial \gamma_2,
\]

\[
= \partial L / \partial B_{i1} = \partial L / \partial B_{i2}.
\]

Papers on fitting equations of compartment analysis have been published by Berman, Shahn, and Weiss (1962), and Berman. A more general approach, of which this problem is a special case, has been made by Turner, Monroe, and Homer (1963). Because equation (14) is non-linear in $\gamma_1$ and $\gamma_2$, these parameters must be estimated by an iterative procedure. The procedure used in the illustration presented here was as follows:

a) Use trial values of $\phi_{ij}$, $\hat{\gamma}_1$, $\hat{\gamma}_2$.

b) Estimate $\hat{B}_{i1}$ and $\hat{B}_{i2}$.

c) Obtain new estimate of $\hat{\phi}_{ij} = \hat{\gamma}_{ij}$

d) Obtain new trial values of $\hat{\gamma}_1$ and $\hat{\gamma}_2$.

e) Repeat the previous steps until one finds a $\hat{\gamma}_1$ and $\hat{\gamma}_2$ for which the sum of the squared errors given by

\[
\sum_{j=1}^{N_i} \left( \epsilon_i\phi_i(t_i) \right)^2 = SSE_i
\]

is lower than for other values of $\gamma_1$ and $\gamma_2$ in the neighborhood of $\hat{\gamma}_1$ and $\hat{\gamma}_2$.

The best values of $\hat{\gamma}_1$ and $\hat{\gamma}_2$ are found by this procedure for the blood, renogram, and urine, separately. When estimating one curve at a time, no value need be assigned to $\sigma^2$. After the best values of the parameters $B_{i1}$, $B_{i2}$, $\gamma_{1i}$, $\gamma_{2i}$ have been obtained, $SSE$ may


be computed, and an estimate of $\sigma^2$ is given by

$$\sigma^2 = \frac{SSE_i}{(N_i - 4)} \quad (21)$$

Using the combined data to find the values of $\gamma_1$ and $\gamma_2$ which give the best fit for all three sets of data at once requires a slightly different procedure. First of all, as can be seen from equation (19), $\sigma^2$ is required. An alternative is to use estimates of $\sigma^2$ given by (21). This alternative introduces a substantial simplification into the numerical procedure at a cost of some information. $\phi_{ij}$ is kept constant instead of being re-estimated after each iteration as is done when analyzing the data separately. The values chosen are those used in the last iteration on each separate curve. This restriction is necessary in order to be able to compare $SSE_i$ obtained using the combined estimates of $\gamma_1$ and $\gamma_2$. Finally a new criterion of fit must be chosen. The best pair of $\gamma$'s for the combined data was that pair which minimized the weighted least squares criterion $S$, given by

$$S = \sum_{i=1}^{n} SSE_i / \hat{\sigma}_{i}^2 = SSE_i / (Ni - 4);$$

$SSE_i$ is the sum of the squared errors for $i$ set of data using the best separate values of $\hat{\gamma}_1$ and $\hat{\gamma}_2$, and $SSE'_i$ is the sum of the squared errors for $i$ set of data using the best values of $\hat{\gamma}_1$ and $\hat{\gamma}_2$ from the combined data.

A program was written for the RPC 4000 computer to perform the calculations described, and to print out the estimates of the parameters, $SSE_i$ and $R^2$. $R^2$ may be interpreted as the percentage of variation in $Y_i$, which can be accounted for by the hypothesis calculated by

$$R^2 = 1 - \frac{\sum_{i=1}^{N_i} Y_{ij}^2 / \phi_{ij}^2}{\sum_{i=1}^{N_i} 1 / \phi_{ij}^2}$$ \quad (22)

Results

The data, estimates of parameters and estimates of $Y_{ij}$, are given in tables 1 to 4 and figures 2 to 4.

An approximate $F$ test may be devised to test the hypothesis that $\gamma_{ib} = \gamma_{ib} = \gamma_{ia}$, and at the same time, that $\gamma_{ib} = \gamma_{ib} = \gamma_{ib}$. Using our previous notation, we have

$$F = \left\{ \left( \frac{\sum_{i=1}^{n} SSE_i / \hat{\sigma}_{i}^2}{\sum_{i=1}^{n} SSE_i / \hat{\sigma}_{i}^2} \right) / 4 \right\} / \left( \frac{\sum_{i=1}^{n} SSE_i / \hat{\sigma}_{i}^2}{79} \right) = 9.5$$

with 4 and 79 degrees of freedom. We may reject the hypothesis with greater than 99.9% confidence ($P < .001$), in favor of a hypothesis in which some or all of the $\gamma$'s are different. Attention is called to the high values of $R^2$. While fitting the $\gamma$'s separately gives a significantly better fit, it is not much better from the standpoint of the value of $R^2$. The worst fit found has an $R^2$ of 0.94. Examination of tables 1 to 3 shows that, except for perhaps the first 5 points on the blood curve, the estimates of $Y_i$ obtained with $\gamma$'s from pooled data are very close to those obtained with the separately estimated $\gamma$'s. Although the differences are quite significant, they are rather small. We can be relatively sure that the $\gamma$'s differ but the differences may not be important.

Discussion

Clinical investigators have attempted to characterize the renogram by measuring the height of the maximum, the time of the maximum, and the "half time" of the descending slope (Stewart and Haynie, 1962). Our model predicts that these measurements are not related in any simple fashion to either the bilateral or unilateral renal clearance of ortho-iodohippurate. According to the model, the height of the maximum, disregarding contribution from other tissues, will be given by

$$Y_{R(max)} = C_{bb}'\{ - (B_{ib}/\gamma_1)$$

$$\begin{array}{l}
+ B_{ib} / \gamma_1) + B_{ib} \exp (\gamma_2) / \gamma_1 \\
+ B_{ib} \exp (\gamma_2) / \gamma_1) / \gamma_k,
\end{array}$$

from equations (14) and (15). This maximum will depend on renal blood flow since $C_{bb}'$ should approximate unilateral renal blood flow. $Y_{R(max)}$ will also depend on the appearance time and bilateral renal blood flow. The relationship of the maximum and the appearance time to bilateral and unilateral clearance is not a simple one. For example, $Y_{R(max)}$ might be unchanged in spite of a decrease in unilateral clearance if the appearance time were prolonged. The time required for the renogram to fall from its maximum to one-half the maximum is often referred to as the half-time of the renogram. Since the proposed hypothesis describes the renogram as the sum of two exponential functions, no simple interpretation of the meaning of this half time is possible in terms of the fundamental parameters. Ortho-iodohippurate clearances are considered rather direct measures of renal blood flow. A scheme for analysing
TABLE 2

Observed and estimated counts/sec/ml in the blood at $t_1$ minutes after injection of $^{111}$ ortho-iodohippuran. $Y_{bi}$, $\bar{Y}_{bi}$, and $\bar{Y}_{bi}(H_0)$ are reported in counts/sec $\times 10^{-1}$ for one ml of blood. $Y_{bi}$ are the observed values. $\bar{Y}_{bi} = \bar{B}_{ib} \exp (\gamma_i t_i) + \bar{B}_{ib} \exp (\gamma_2 t_i)$ where $\bar{B}_{ib}$, $\bar{B}_{ib}$, $\gamma_i$, and $\gamma_2$ are taken from the top line of table 1. $Y_{bi}(H_0)$ is computed as $Y_{bi}$ except that $\bar{B}_{ib}$, $\bar{B}_{ib}$, $\gamma_i$, and $\gamma_2$ are taken from the second line of table 1.

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The left member of (22) is always positive so that a decrease in $C_{kb}$ should be reflected in a decrease in $\gamma_1 \gamma_2$. Perhaps persons having decreased total renal blood flow will have unusually low values of $\gamma_1 \gamma_2$. Also from equation (4) we have,

$$\gamma_1 + \gamma_2 = -\left( \frac{C_{kb}}{\nu_b} \right) + \left( \frac{C_{be}/\nu_c + C_{be}/\nu_b}{} \right),$$

(25)

$$\frac{\partial (\gamma_1 + \gamma_2)}{\partial C_{kb}} = -\frac{1}{\nu_b}$$

(26)

As $C_{kb}$ decreases, $\gamma_1 + \gamma_2$ increases (becomes less negative). Thus, in general, persons with low renal blood flows might be expected to have values of $\gamma_1 + \gamma_2$, less negative than persons with higher renal blood flows.

The two parameters $\gamma_1$ and $\gamma_2$ could be determined in "normal" patients, and changes in $\gamma_1 \gamma_2$ and $\gamma_1 + \gamma_2$ might be simply interpreted as changes in clearance. If the blood curve were also determined, it would be possible to obtain numerical estimates of bilateral renal blood flow, compartment volumes, and compartment exchange rates, using

TABLE 3

Observed and estimated (counts/min)/22.2 of renogram $t_1$ minutes after injection of $^{111}$ ortho-iodohippuran. $Y_{Ri}$ are obtained from the renogram in figure 3. $\bar{Y}_{Ri} = \bar{B}_{1R} \exp (\gamma_i t_i) + \bar{B}_{2R} \exp (\gamma_2 t_i)$ where $\bar{B}_{1R}$, $\bar{B}_{2R}$, $\gamma_i$, and $\gamma_2$ are taken from line 3 of table 1. $\bar{Y}_{Ri}(H_0)$ is obtained using the estimates in line 4 of table 1.

<table>
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<th>$Y_{Ri}$</th>
<th>$\bar{Y}_{Ri}$</th>
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that the best fitting $\gamma_i$'s and $\gamma_s$'s are not identical, as the model requires.

There are several possible explanations for this. The rejection is largely due to difficulties with the early part of the blood curve (fig. 2), and thus might be partly explained by difficulties in exact timing, where a very few seconds may make a large difference in the activity of the blood sample in a period. Also to be explored are the possible effects of changing blood flow ($C_{0b}$, $C_{0b}'$ not constant), and changing appearance time. If the model fitted to available data is indeed such a sensitive measure of variations in renal blood flow or urinary appearance time, it may prove to be a valuable tool in studying these variations, and in studying relationships between these two parameters.

Summary and Conclusions

A model elucidating the relationships between blood radioactivity, the renogram curve, and urine radioactivity, as a function of time, is derived. Estimation procedures have been devised which use the data from three curves at once to estimate parameters common to the three curves, and which also estimate parameters unique to the individual curves. A program has been written for the RPC 4000 computer to perform the estimation.

It was found that some model in which six different exponential parameters could be justified instead of the two proposed by the model could provide a significantly better fit of the data ($P < .001$), but that the fit under the hypothesis was still quite good. It is proposed that the model be retained for further evaluation and study for the following reasons:

1. It is based on soundly established principles of physiology, and hence provides a link between the renogram curve and those principles.
2. The model fits the descending part of the curve well.
3. On the basis of the model we are able to suggest several improvements in the analysis of renograms for clinical evaluation of renal function.
4. The model leads to reasonable estimates of the time of the renogram peak.
5. The model provides a framework for further study of the renogram and its relations to physiologic function in general. More specifically, it may prove to be a sensitive instrument in studying rapid variations in urinary appearance time and renal blood flow, and the relations between blood flow and appearance time.

References


