# Estimating the Plasma Time-Activity Curve During Radionuclide Renography

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Quantitative analysis of the radionuclide renogram requires an estimate of the plasma time-activity curve. This estimate is usually obtained from an externally detected blood-pool curve that is calibrated with a single plasma sample. However, external probes detect activity in the extravascular as well as the intravascular space. This may lead to significant errors in estimating the plasma time-activity curve. A method for overcoming this problem by using a continuously varying calibration factor based upon multiple plasma samples was therefore evaluated. Externally detected blood-pool curves were used to estimate the plasma time-activity curves obtained from rabbits during radionuclide renography. Estimates obtained using the externally detected curves calibrated with a constant calibration factor were found to be significantly biased, while estimates obtained using the externally detected curves calibrated with the continuously varying calibration factor were not.

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The renal time-activity curve obtained during radionuclide renography is a function of the time-activity curve of the radionuclide in the plasma as well as the handling of the radionuclide by the kidney. Quantitative analysis of the renogram for such parameters as mean transit time (*1*) and glomerular filtration rate (GFR) (*2*), therefore, requires an estimate of the plasma time-activity curve. This estimate is usually obtained from an externally detected blood-pool curve under the assumption that the plasma curve is proportional to the externally detected curve. If the absolute plasma concentration of the radionuclide must be known, as is the case in the estimation of GFR, the plasma curve is estimated as being equal to the externally detected curve multiplied by a constant calibration factor. This calibration factor is obtained by dividing the radionuclide concentration in a plasma sample taken at a known point in time by the value of the externally detected curve at that time. A plasma sample taken near the end of the renogram has been advocated for this purpose (*2*) because the plasma curve varies less rapidly at this time, thereby reducing the effect of any timing errors.

Unfortunately, estimation of the plasma time-activity curve from an externally detected curve may be confounded by the detection of activity in the extravascular space. Intravenously injected tracers, such as technetium-99m stannous diethylenetriaminepentaacetic acid complex ([$^{99m}$Tc]DTPA), rapidly equilibrate with the intravascular space. There is then a more gradual equilibration with the extravascular space. Thus, the ratio of the intravascular to extravascular radiotracer concentrations varies as a function of time. An external probe detects activity in fixed volumes of the intravascular and extravascular spaces. Since the ratio of the extravascular to intravascular radiotracer concentrations increases over the course of the renogram, the externally detected curve is not truly proportional to the plasma time-activity curve. Rather, the ratio of the externally detected curve to the plasma curve increases as a function of time. Thus, estimation of the plasma time-activity from an externally detected curve is liable to result in significantly biased results.

The purpose of this work was to determine the magnitude of the error introduced by assuming that the plasma curve is proportional to the externally detected curve. We also wished to explore a method for reducing this error by using additional plasma samples acquired throughout the renogram.

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## METHODS

### Technique for Radionuclide Renography

Rabbits weighing between 2 and 4 kg were used for this study. Anesthesia was induced with ketamine (30 mg/kg i.m.)

and acepromazine (2 mg/kg i.m.) and maintained with small supplemental doses of ketamine. Intraarterial lines were then started in the central artery of each ear. One line was used for the injection of radiopharmaceutical and anesthetic agents, and the other line was used for the withdrawal of blood samples. The subject was immobilized in the posterior projection over the face of a gamma camera. The subject was positioned so that his head and thorax were in the center of the gamma camera field. The subject was then given a rapid intraarterial injection of [$^{99m}$Tc]DTPA. Computerized gamma camera image acquisition was started simultaneously with radiopharmaceutical injection. Digital images were recorded at a frame rate of 1 frame every 15 sec for 20 min. Blood samples were taken at 2-min intervals starting at 1 min after radiopharmaceutical injection and ending at 19 min after radiopharmaceutical injection. Plasma was obtained by centrifugation of the blood samples and counted in a well counter.

**Data Analysis**

The images obtained during radionuclide renography were viewed on a computer controlled digital image display system. A region of interest was drawn manually around the subject's heart, and a curve of the activity in this region during each frame of the study was generated. We shall refer to the activity in the 15-sec long frame starting t minutes after radiopharmaceutical injection as E(t). E(t) thus denotes the externally detected curve. The plasma curve was constructed from the activity concentration of the plasma samples. We shall refer to the activity in the plasma sample taken t minutes after radiopharmaceutical injection as P(t). P(t), thus, denotes the plasma curve.

We first investigated the error introduced by the assumption that E(t) was proportional to P(t). Under this assumption, an estimate of P(t), which we shall term $P_c(t)$, may be computed using the formula:

$$P_c(t) = R\ E(t), \quad (1)$$

where R is a constant calibration factor computed using the equation:

$$R = P(t_c)/E(t_c) \quad (2)$$

for some value of $t_c$. In this experiment, a $t_c$ value of 17 min was used. As an index of the error induced by this assumption, we measured the ratios:

$$P_c(t)/P(t) \quad (3)$$

at t = 3, 7, 11, 15, and 19 min.

We then attempted to reduce this error by using additional plasma samples to construct a time-varying calibration factor, R(t), which would account for the decrease in the P(t)/E(t) ratio as a function of time. R(t) was constrained to be an exponential curve of the form:

$$R(t) = ae^{-bt}. \quad (4)$$

The constants a and b were determined by a least squares fit to the ratio P(t)/E(t) for t = 1, 5, 9, 13, and 17 min.

An estimate of P(t), which we shall term $P_v(t)$, was obtained using the equation:

$$P_v(t) = R(t)\ E(t). \quad (5)$$

**TABLE 1**
**$P_c/P$ Ratios**

| Subject | Time from injection (min) 3 | 7 | 11 | 15 | 19 |
|---|---|---|---|---|---|
| 1 | 0.849 | 0.924 | 1.071 | 0.971 | 0.899 |
| 2 | 0.818 | 1.018 | 1.006 | 1.021 | 0.890 |
| 3 | 0.845 | 0.788 | 0.828 | 0.920 | 0.797 |
| 4 | 0.772 | 0.968 | 0.984 | 1.010 | 0.990 |
| 5 | 0.668 | 0.945 | 0.927 | 1.058 | 1.010 |
| Mean | 0.790 | 0.929 | 0.963 | 0.996 | 0.917 |
| s.d. | 0.075 | 0.086 | 0.091 | 0.053 | 0.086 |

Overall mean = 0.919; overall s.d. = 0.102; overall t = 3.971; statistical significance = $p < 0.005$

**TABLE 2**
**$P_v/P$ Ratios**

| Subject | Time from injection (min) 3 | 7 | 11 | 15 | 19 |
|---|---|---|---|---|---|
| 1 | 1.077 | 1.042 | 1.121 | 1.000 | 0.890 |
| 2 | 0.958 | 1.051 | 1.006 | 0.973 | 0.861 |
| 3 | 0.913 | 1.085 | 1.017 | 0.976 | 0.745 |
| 4 | 1.013 | 1.119 | 1.062 | 1.019 | 0.934 |
| 5 | 0.953 | 1.132 | 1.019 | 1.054 | 0.938 |
| Mean | 0.983 | 1.086 | 1.043 | 1.004 | 0.875 |
| s.d. | 0.064 | 0.040 | 0.049 | 0.033 | 0.079 |

Overall mean = 0.998; overall s.d. = 0.089; overall t = 0.112; statistical significance $p > 0.5$.

As an index of the error in estimating P(t) by this method we again measured the ratio:

$$P_v(t)/P(t) \quad (6)$$

evaluated at t = 3, 7, 11, 15, and 19 min.

**Statistical Analysis**

The null hypotheses that the means of the ratios given by Eqs. (4) and (6) were equal to 1 throughout the experiment (i.e., that the estimates of the plasma time-activity curve were unbiased) were tested under the assumption that the ratios were normally distributed with unknown variance. The calculations were done using a two-tailed test on Student's t distribution according to the procedure outlined in (*3*).

## RESULTS

The $P_c(t)/P(t)$ and $P_v(t)/P(t)$ ratios obtained from each subject are shown in Tables 1 and 2, respectively. The mean $P_c(t)/P(t)$ ratio (all times combined) was found to be statistically different from 1 ($p < 0.005$), while the mean $P_v(t)/P(t)$ ratio was not statistically different from 1 ($p > 0.5$). The $P_c/P$ ratio had the largest mean deviation (21%) from 1 at t = 3 min. The remainder of the $P_c/P$ ratios and the $P_v/P$ ratios had means within 10% of 1.

## DISCUSSION

It is common practice in the quantitative analysis of the radionuclide renogram to estimate the plasma curve from an externally detected curve calibrated with a single-plasma sample taken near the end of the study. Our experiments with rabbits show that estimating the plasma curve from an externally detected curve calibrated with a single plasma sample taken near the end of the study may result in significantly biased estimates of the plasma time-activity curve, particularly near the beginning of the study. They also show that this bias can be eliminated by using additional plasma samples taken during the renogram to construct a time-varying calibration factor.

A biased estimate of the plasma time-activity curve will likely result in biased estimates of quantitative renogram parameters. It would be worthwhile, therefore, to evaluate the accuracy of the single and multiple blood sample methods in humans in order to avoid these biases.

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