European Journal of
Nuclear
Medicine

Original article

Estimation of organ input function and plasma clearance from the cardiac curve in dynamic scintigraphy

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Received 15 June and in revised form 17 November 1991

Abstract. A theoretical description of the relationship between the count rate detected in the cardiac region of interest and the arterial organ input function in dynamic scintigraphy is presented. It is shown that, provided the time-activity curve for the heart is corrected for extra-cardiac and unlabelled activity, it is proportional to the arterial organ input over both the first-pass and equilibrium phases of the passage of an intravenously injected radiopharmaceutical. A practical example demonstrating the value and validity of correcting the cardiac curve in dynamic radio colloid scintigraphy is described. Estimates of the colloid clearance rate to reticuloendothelial sites using the cardiac curve without correction were significantly lower (mean 0.085/min) than those derived from the liver uptake curve (mean 0.213/min). However, corrected cardiac curve clearance rates (mean 0.225/min) were not significantly different from the liver ones. Also, the corrected cardiac curve clearance values correlated linearly with liver curve values (correlation coefficient 0.89, standard error of the estimate 0.021/min), whereas the uncorrected values showed no significant correlation. Thus, correction of the cardiac curve gave clearance rate values that were both more accurate and more precise than those obtained without correction.

Key words: Organ input function – Plasma clearance – Cardiac curve – Dynamic scintigraphy

Eur J Nucl Med (1992) 19:248–253

Introduction

In digital dynamic radionuclide scintigraphy, the time-activity curve obtained over the cardiac region of interest provides information on the plasma concentration of the radiopharmaceutical. This is useful in the assessment of plasma clearance and also as a measure of the variation with time of the amount of radiopharmaceutical arriving at organs of interest, their input function. The time variation of the activity of the radiopharmaceutical taken up by an organ will depend not only on the physiological function of the organ but on the shape of the input function to it. If the input function is known, then its influence may be corrected for by mathematical analysis and parameters obtained which reflect only the function of the organ itself. Examples of the application of this principle involve the measurement of blood flow (Peters et al. 1987), organ transit time (Kenny et al. 1975) or, in the case of the kidney, glomerular filtration rate (Rutland 1985). The input function is usually obtained as the time-activity curve for a region of interest (ROI) over the heart. However, the count rate measured from a cardiac ROI may not accurately reflect the organ input or plasma clearance due to four possible factors:

1. Activity in the tissue over and under the heart will contribute to the counts in the cardiac ROI. The variation with time of this activity will in general not be the same as that of the heart, particularly if the radiopharmaceutical distributes into an extravascular space.
2. There may be a contribution to the measured count rate due to the presence in the blood of free radionuclide not associated with the pharmaceutical.
3. If there is any uptake of the radiopharmaceutical in an organ close to the heart, then there will be a contribution to the counts in the cardiac ROI due to scattered radiation from activity in the organ.
4. The vascular activity in the cardiac region may not bear the same relationship to the activity input to an organ over the entire duration of a study covering both the first-pass and subsequent equilibration of the activity in the vascular space.

Techniques have been described for correcting for extra-cardiac activity in the cardiac ROI in renography (Fleming 1977; Bell and Peters 1991). These techniques effectively correct for the extravascular contribution to the counts obtained (factor (1) above). Factors (2) and (3) may also be corrected using background subtraction techniques. This paper covers two aspects of the use of the cardiac curve in dynamic scintigraphy: first, a theoretical description of the relationship between counts

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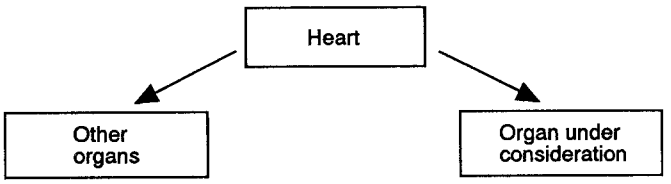

Fig. 1. Compartmental model used in analysing the relationship between counts obtained over the cardiac region of interest and activity arriving at the organ under consideration

measured in the cardiac region and activity input to organs (factor (4)). Then, an experiment is described using liver colloid scintigraphy to study the influence of extra-cardiac contributions on the relationship between counts measured in the cardiac ROI and vascular activity.

Theory

The theory assumes that the count rate in the cardiac region has been corrected for the extravascular contribution to the background activity and that there is no free radionuclide present. It deals with the situation in which the time interval of acquisition of data is a minimum of 10 s so that the first passage of radiopharmaceutical through the heart occurs in one time interval. It assumes that the transit time between the heart and the organ of interest is less than one time interval and can therefore be ignored.

The description of the theory refers to Fig. 1 and investigates the relationship between the counts obtained in the cardiac region in the ith time interval (C_i) and the corresponding activity input to the organ of interest (I_i). The relationship is considered (a) during the first pass of radioactivity following intravenous injection and (b) after equilibration of activity has occurred within the blood.

The factors affecting the counts obtained in the first time interval of acquisition of the cardiac curve are assessed as follows. The interval is assumed to encompass the entire first pass of activity through the heart. During this time, all the injected activity will pass through the cardiac ROI. However, it will only actually be within the region for a period given by the mean transit time through the heart, which has been assumed to be less than the time interval of acquisition. Thus, the counts obtained in the first time interval of the cardiac curve are:

$$C_1 = Q \cdot T \cdot \mathrm{E} \cdot \mathrm{B_C}$$

where Q is the activity injected, T is the mean transit time through the heart, E is the counting efficiency of the gamma-camera in count rate per unit activity and $\mathrm{B_C}$ is the attenuation fraction for cardiac counts due to attenuation by overlying tissue.

The activity arriving at the organ of interest in the first pass will be:

$$I_1 = \mathrm{Q} \cdot P$$

where P is the fraction of the cardiac output to the organ. Thus, the constant of proportionality between $\mathrm{C_1}$ and I_1 is:

$$\mathrm{M_F} = \mathrm{E} \cdot T \cdot \mathrm{B_C}/P \qquad (1)$$

The situation in which equilibrium in the vascular space has already occurred is as follows. The count obtained in the cardiac region of interest during the ith time interval is:

$$C_i = Q_i \cdot V_\mathrm{C} \cdot D \cdot \mathrm{E} \cdot \mathrm{B_R}/\mathrm{V_B}$$

where Q_i is the total activity remaining in the blood at this time, V_C is the vascular volume in the cardiac ROI, D is the time interval of acquisition, $\mathrm{B_R}$ is the mean attenuation fraction for the cardiac region counts and V_B is the blood volume.

The corresponding activity arriving at the organ of interest is:

$$I_i = Q_i \cdot P \cdot C \cdot D/\mathrm{V_B}$$

where C is the cardiac output.

Thus, the constant of proportionality between C_i and I_i in equilibrium is:

$$\mathrm{M_E} = \mathrm{V_C} \cdot \mathrm{E} \cdot \mathrm{B_R}/P \cdot C \qquad (2)$$

In general, Eqs. (1) and (2) will not be equal, meaning that the cardiac curve will not be a true representation of the shape of input to the organ over both first-pass and equilibrium phases. However, if counts were only obtained from the heart itself, avoiding the contribution from the surrounding tissue, then (i) the attenuation factors $\mathrm{B_C}$ and $\mathrm{B_R}$ will be equal, and (ii) $\mathrm{V_C}$ will represent the cardiac volume so that V_C/C will equal T, the cardiac mean transit time. In this situation, the two constants of proportionality in Eqs. (1) and (2) are equal. Therefore, correction of the cardiac curve for the extra-cardiac background will result in a true reflection of organ arterial input covering both first-pass and equilibrium phases.

Validation experiment using liver colloid studies

The validity of the technique was investigated using data from radionuclide studies of the liver effective blood flow by colloid uptake. Analysis of the compartmental model of the dynamics of an intravenously injected colloid shows that the exponential rate constant derived from the liver uptake curve will be equal to that derived from the blood clearance curve (Karran et al. 1979). This has been validated using blood sampling (Miller et al. 1979).

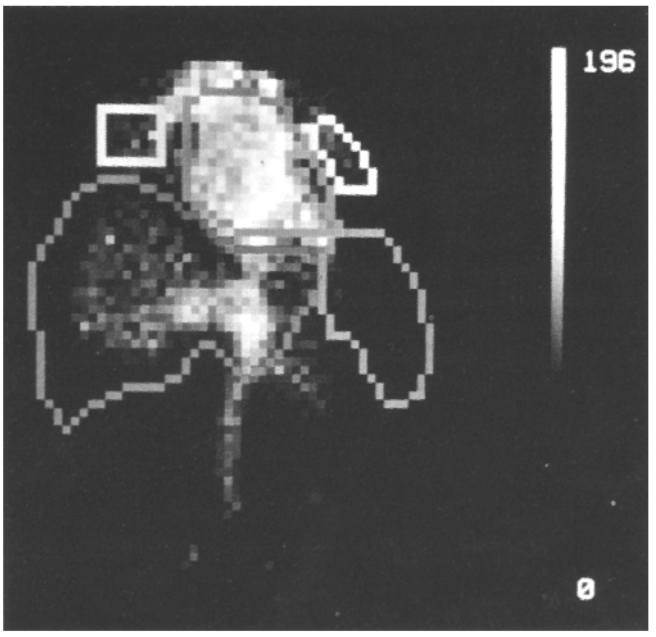

Fig. 2. Image of the first pass of the colloid through the heart with overlay of liver, spleen, heart and cardiac background regions of interest

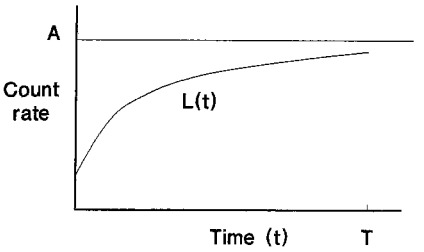

Fig. 3. A schematic plot of a liver uptake curve L(t) illustrating constant A, the plateau count rate value and T, the end of the imaging period (15.75 min)

In this experiment, the rate constants of colloid plasma clearance estimated from the cardiac curve before and after subtraction of the extra-cardiac contribution were compared with that obtained from the liver uptake curve (Miller et al. 1979).

Imaging

The 16 subjects used in the study were undergoing dynamic liver scintigraphy as part of a trial investigating hepatic haemodynamics in patients with suspected liver metastases secondary to cancer of the colon (Hunt et al. 1989). The imaging technique used has been described previously (Fleming et al. 1983). Briefly, the patients were fasted overnight and placed supine under a large field-of-view gamma-camera (International General Electric 400 AT). They were viewed anteriorly to include the liver, spleen and heart in the images. A bolus injection of 160 MBq technetium 99 m sulphur colloid (Technecoll; Mallinckrodt) was given intravenously, and a dynamic study consisting of 63 15-s frames acquired on a Link MAPS 2000 gamma-camera acquisition computer in a 64×64 matrix. The data were then transferred to a DEC VAX 11/730 computer with a Sigmex A7000 data processor running the PICS medical image processing software (Fleming et al. 1987).

Data analysis

From a display of the final frame of the dynamic series a liver ROI was drawn manually. This was then overlaid on an image of the first pass of activity through the heart and a cardiac and two background ROIs created, making sure to avoid any overlap with the liver or spleen (Fig. 2). The background regions were chosen with the aim of containing tissue that was as similar as possible to that over and under the heart, that is, mainly chest wall, ribs and lung. The summed data from two suitable regions on either side of the heart were used to obtain improved counting statistics. The background regions were also situated approximately the same distance from the liver and spleen as the heart. This means that the amount of scattered radiation from activity in the liver and spleen was similar in both background and cardiac regions. Therefore, upon background subtraction, the contribution of scatter to the cardiac counts was corrected for. Count rate versus time curves were created for each of these ROIs.

The curves for the liver region of interest consisted of three components, the actual hepatic uptake of the radiopharmaceutical ($H(t)$), vascular activity ($V(t)$) and unlabelled activity (U), which was considered to be constant after equilibration in the vascular space:

$$L(t) = H(t) + V(t) + U$$

Using compartmental analysis (Karran et al. 1979) this equation can be rewritten:

$$\begin{aligned} L(t) &= M(1 - \exp(-Kt)) + N\exp(-Kt) + U \\ &= A - B\exp(-Kt) \end{aligned} \quad (3)$$

where N, M, A and B are constants, and K is the colloid clearance rate.

The liver uptake data were fitted by an iterative least squares regression to the function described in Eq. (3). A schematic liver curve is illustrated in Fig. 3. The fitting was carried out on data collected between 4 and 10 min following intravenous injection. Prior to 4 min it was assumed that full equilibration in the vascular space had not occurred. Data beyond 10 min were also excluded because by that time the liver curve was close to the plateau value and, when subtracted from the estimated plateau value in the iterative regression, gave rise to large errors. Since in general the curve had not reached its plateau value at the end of the measurement period

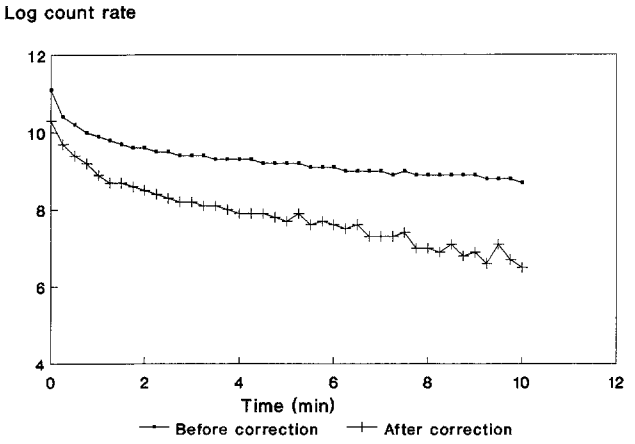

Fig. 4. Typical curves of log cardiac count rate before and after correction for extra-cardiac and unlabelled activity

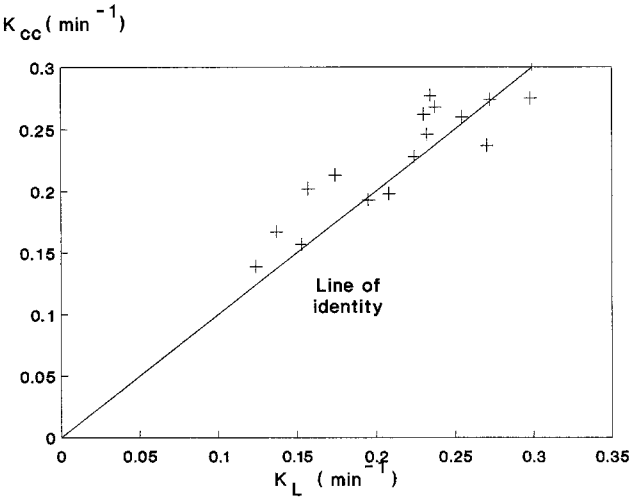

Fig. 5. Relationship between colloid clearance rate estimated from the cardiac curve after correction and that from the liver uptake curve

(T = 15.75 min), the fraction of colloid cleared by the that time was also calculated:

$$F = (A - L(T))/A$$

where $L(T)$ is the value of the liver uptake curve at time T.

The cardiac curve between 4 and 10 min was then fitted to a monoexponential function using linear regression on the logarithm of the count rate and the rate constant (K_{CU}) noted.

The cardiac curve [$C(t)$] was considered in terms of its four contributions:

$$C(t) = I(t) + E(t) + D + (G \cdot L(t) + J \cdot S(t))$$

$I(t)$ was due to true cardiac activity labelled to colloid, $E(t)$ was due to extra-cardiac activity, and D was due to cardiac activity not labelled to colloid which was assumed to be constant after equilibration in the vascular space had occurred. $G \cdot L(t)$ and $J \cdot S(t)$ represent the contribution to counts in the cardiac ROI due to scattered radiation from the liver and spleen, respectively. G and J are fractional constants and $S(t)$ the spleen time-activity curve.

The extra-cardiac and scatter contributions were removed by background subtraction. A composite background curve was created by adding the curve from the two background ROIs. This was subtracted from the cardiac region curve after scaling the curves according to the relative areas of the ROIs, giving a cardiac curve corrected for extra-cardiac contribution, $C_E(t)$, where

$$C_E(t) = I(t) + D$$

It was then necessary to subtract the contribution due to activity not labelled to colloid, D. This was estimated from the extra-cardiac subtracted count rate at the end of the measurement period, $C_E(T)$. However, a correction had to be made to allow for the fact that there was still some labelled colloid left in the blood at this time, I(T). This was evaluated by first estimating the count rate in the cardiac region that would have been obtained if equilibration in the vascular space had been instantaneous. The background subtracted cardiac curve $C_E(t)$ between 4 and 10 min was fitted to a monoexponential function using least squares regression and extrapolated back to zero time, giving count rate C_0. The count rate in the cardiac region at time T due to the colloid still in the blood was then given by $C_0 \cdot F$, where F is the fraction of colloid removed by time T as determined from Eq. (3) above. Therefore, the contribution due to unlabelled activity D was obtained from

$$D = C_E(T) - C_0 \cdot F$$

After subtracting constant D from curve $C_E(t)$, the remaining curve, which was the experimental estimate of $I(t)$, was fitted to a monoexponential function by least squares regression using the data obtained between 4 and 10 min following injection to obtain the rate constant of clearance (K_{CC}). A typical cardiac curve before and after correction is shown in Fig. 4.

Statistical analysis

The mean of each of the three estimates of colloid clearance rate from the liver curve and the cardiac curve before and after correction was calculated. In order to test for systematic differences between the two estimates obtained from the cardiac curve and that obtained from the liver curve, paired differences were tested for significance of difference from zero. Both cardiac curve values were also tested for linear correlation with the liver curve by calculating the correlation coefficients.

Table 1. Summary of the results of the estimation of the colloid clearance rate from the cardiac curve before and after correction compared with the values obtained from the liver uptake curve

	Colloid clearane rate mean (/min)	Significance of difference from liver clearance rate	Correlation coefficient with liver clearance rate	Standard error of estimate (/min)	Significance of correlation with liver clearance rate
Liver curve	0.212	–	–	–	–
Cardiac curve before correction	0.085	<0.001	0.40	0.047	NS
Cardiac curve after correction	0.222	NS	0.89	0.021	<0.005

Results

The results of the estimates of colloid clearance rate are summarised in Table 1. The values obtained from the cardiac curve before correction were significantly lower than those from the liver curve ($P<0.001$), whereas those from the corrected cardiac curve were not significantly different from the liver curve values. In addition, the cardiac curve clearance constant determined before correction (K_{CU}) was not correlated with liver curve values (K_L), whereas the post-correction values (K_{CC}) correlated significantly, with a linear correlation coefficient of 0.89 and standard error of 0.021/min. The relationship between estimates of colloid clearance rate from the liver curve and corrected cardiac curve are shown graphically in Fig. 5.

Discussion

The theory presented in this paper predicts that provided the extra-cardiac contribution to the cardiac curve is subtracted, the resultant curve provides an accurate representation of the shape of the organ arterial input function, covering both first-pass and equilibrium phases of a dynamic radionuclide study. This result is important in that it suggests that correction of the cardiac curve in this way will allow more accurate calculation of parameters which use processes requiring knowledge of the organ input function such as deconvolution. In particular, the matrix deconvolution algorithm (Diffey et al. 1976) is very dependent on the accuracy of the first few points of the input function. After correction, these points should have the appropriate value relative to the rest of the cardiac curve for use as an organ input function. Direct validation of these theoretical predictions would involve arterial blood sampling and is not presented in this study. However, in renography, computer simulations have shown that extra-cardiac correction improves the accuracy of deconvolution analysis without any significant effect on precision (Gullquist and Fleming 1987).

The experiment on the effect of extra-cardiac correction on the cardiac curve in radio colloid scintigraphy showed firstly that the cardiac curve without subtraction did not give a good assessment of plasma clearance of colloid. The values of colloid clearance rate from the curve were considerably lower than from the proven standard of the liver uptake curve and were also not correlated with the standard. This was due to the fact that the counts in the cardiac curve were not only due to the blood activity but also to unlabelled radionuclide and scattered radiation from the liver and spleen. These components have a very different variation with time from the blood activity, the former remaining approximately constant over the period of measurement and the latter increasing with time. Thus, their effect was to cause an underestimate in the measurement of clearance rate. The estimate of colloid clearance after correction was both accurate and precise with respect to the liver uptake curve values. This demonstrated the value and validity of performing the subtraction. In the case of radiocolloid imaging, it was shown to be necessary to subtract both the contribution due to extra-cardiac activity and that due to activity in blood not labelled to colloid.

Most forms of correcting by subtraction in radionuclide imaging give improved accuracy at the expense of reduced precision. This is also true for this technique when assessed by the variation in individual data points. Figure 4 demonstrates the greater point to point variability in cardiac curve values after subtraction. However, the value for colloid clearance rate obtained from the corrected cardiac curve using linear regression over a number of points is more precise as well as more accurate than the uncorrected curves.

The principle of correcting the cardiac curve for the extra-cardiac contribution is applicable to other radionuclide investigations, although details of the methods for correction may vary. For example, in renography

it is not possible to correct for the unlabelled activity, D, in the way described for colloid clearance, as the radiopharmaceutical is not trapped in the kidney. However, in renography, plasma clearance is far from complete over the typical period of the investigation so that the contribution of unlabelled activity is relatively small compared with the labelled activity still in the blood and therefore need not be subtracted. Techniques for subtracting the extra-cardiac contribution to the heart curve in renography have been described previously (Fleming 1977; Bell and Peters 1991).

In conclusion, this paper has demonstrated the theoretical and practical advantages of performing extra-cardiac correction in obtaining plasma clearance and organ input information from the cardiac curve in dynamic radionuclide imaging.

Acknowledgements. I would like to thank Ros Breen and her staff for performing the radionuclide imaging described in this paper and Sue Pitter for typing the manuscript.

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