Portasystemic Shunt Fraction Quantification with Colonic Iodine-123 Iodoamphetamine

C.-K. Yen, M. Polycove, R. Crass, T. H. Lin, R. Baldwin, and J. Lamb

Departments of Nuclear Medicine and Surgery, San Francisco General Hospital Medical Center and University of California, San Francisco; Department of Nuclear Medicine, Presbyterian Hospital of San Francisco; and Medi-Physics, Inc., Richmond, California

Portasystemic shunting was quantified in dogs with $^{123}$Iodoamphetamine (IMP) administered transrectally into the colon and monitored externally with a gamma camera. IMP was absorbed rapidly and unchanged from the colon. After direct injection into the portal vein, IMP was almost completely extracted by the liver on the first pass, and the washout half-life was ~60 min. Based on these kinetic data, computer simulation of this biologic system was carried out. Errors associated with simplified models are calculated. The simplest model with insignificant error, which assumed that the tracer behaved like microspheres, was used to quantitate portasystemic shunt fraction in animals with surgically created shunts. Results were compared with the standard of $^{99m}$Tc-labeled macroaggregated albumin infused into a branch of inferior mesenteric vein. For shunt fractions ranging from 0 to 100%, an excellent correlation was seen, indicating that this approach is potentially a simple, noninvasive method of portasystemic shunt fraction quantification.


P ortal systemic shunting (PSS) is a major consequence of portal hypertension. Quantitative measurement of this shunting helps in understanding the pathophysiology of the various liver diseases and in following patients after selective and total portacaval shunts, and allows rational selection of treatment for patients with portal hypertension. The portal vein carries blood from one capillary system in the splanchnic viscera into another capillary system, the hepatic sinusoids. Direct access to this system is difficult. Transrectal administration into the colon of radioactive tracers has been proposed to circumvent this difficulty (1–4). Because iodine-123-labeled N-isopropyl-p-iodoamphetamine ($^{123}$IIMP) has high first-pass extraction by multiple organs, slow washout, and favorable imaging properties (5–7), this agent may be useful for PSS quantification. We report here the kinetic study and validation of a method to quantitate PSS after transrectal administration of IMP into the colon. The kinetics of absorbed isotopes were evaluated. Computer simulations were performed to evaluate different models appropriate for this biologic system and to estimate possible errors associated with these models. PSS calculations based on the simplest model with insignificant errors were carried out in experimental studies and validated against the standard of microsphere infusion.

MATERIALS AND METHODS

Iodine-123 IMP obtained commercially had specific activity calibrated to be 1 mCi of $^{123}$I per cc of solution containing 0.15 mg of carrier at time of use. The usual dose administered per experiment was 2–3 mCi.

Dogs weighing between 30 and 45 lb were used in the experiments. The animals were anesthetized with i.v. phenobarbital, intubated, and ventilated with a mechanical ventilator. Colonic IMP was administered transrectally through a thin catheter into the sigmoid colon with the animal in the left lateral decubitus position. This position minimized the flow of tracer into the rectum. The colonic absorption rate of IMP was determined by imaging the sigmoid colon using a gamma camera with a parallel hole collimator after tracer administration. Portal blood samples were obtained with catheters placed close to the root of the portal vein through a branch of the portal venous system. Systemic venous samples were obtained with catheters placed in the area of the right atrium through
the femoral vein. The volume of the catheters was measured prior to placement. During blood sampling, the initial portion containing twice the catheter volume was discarded. A portasystemic shunt was created surgically either with a portacaval anastomosis or a diversion of part of the portal blood flow from the splenic vein into the femoral vein using an extracorporeal roller pump.

Blood samples taken at different times after colonic administration were extracted four times with octanol, and the solvent and blood phases were counted in a scintillation well counter to determine the octanol extraction fraction. The activity in the extracted phase was analyzed with thin layer paper chromatography utilizing precoated silica gel strips. Ethyl acetate/ethyl alcohol in 1:1 mixture was used as the solvent. Each chromatography paper contained, in addition to the blood samples, a sample of IMP similarly extracted with octanol that served as the control. The paper was then cut into sections and counted in a well counter.

The single-pass hepatic extraction and washout of IMP were assessed after bolus injection of IMP into the portal vein. The hepatic time-activity curve was monitored with a scintillation detector equipped with a collimator. The extraction fraction is obtained in the following fashion: The time at which the time-activity reaches its initial peak is first defined as T; the portion of the time-activity curve after 2 min is fitted to a single exponential which is then back extrapolated to T and represents the washout of tracers extracted by the liver; the extraction fraction is calculated as the ratio of the height of hepatic time-activity to the height of washout curve at time T (8–9).

After absorption of IMP from the colon, the tracer is delivered to the liver and, in the presence of PSS, to the lung as well. From these organs, the tracer washes out and recirculates to additional organs (Fig. 1). Shunt fraction quantification then requires knowledge of tracer activities in multiple organs. If sampling is sufficiently early, recirculation can be ignored and the tracer can be assumed to behave exactly like microspheres. The shunt fraction can be expressed simply as:

\[
\text{l lung activity/(lung + liver) activity. (1)}
\]

However, early sampling results in only limited tracer activity in the liver and lung which increases statistical error. Therefore, the ideal sampling time using the above formula is a compromise between the two errors. With more complex formulations, which take into account more of the recirculations, both of the above errors can be reduced at the cost of requiring additional measurements. A more complex model, which takes into account the washout of hepatic tracer activity into the lungs, is also evaluated. Assuming that the tracer activities in the different organs can be represented by compartments, the shunt fraction can be expressed by:

\[
1 - \frac{Q_1(t)(k_2 - k_1)/k_1}{Q_2(t)'(e^{-k_1T} - e^{-k_2T})},
\]

where \(Q_1(t)\) and \(Q_2(t)\) represent tracer activity, and \(k_1\) and \(k_2\) are the washout half-life, for the colonic and the hepatic tracer activities, respectively.

To estimate the error associated with the above methods of shunt fraction calculation, computer simulation was carried out. The system was assumed to have a preselected shunt fraction. The tracer activity for each organ was assumed to be represented by a single exponential and the activities for the different organs in the system were represented by a set of different equations. The parameters obtained from kinetic studies were used in these equations. Assuming that the system advanced in time by small increments, the time-activity curve for each organ was generated. Using formulas 1 and 2, shunt fractions were calculated as a function of time. The differences between the preselected shunt fraction and the calculated shunt fraction represented the error secondary to ignoring some or all of the recirculation. The ideal sampling time could then be chosen as the time when this error was negligible while sufficient activity was present in the organs to minimize statistical error.

Experimental PSS fractions were obtained by imaging over the liver and lung of the animals with a gamma camera equipped with a high resolution, low-energy collimator. For IMP, images were obtained immediately after colonic administration at the rate of 1 frame/min. Regions of interest (ROIs) were drawn over the liver and lung. Background region was obtained by drawing a one-pixel-thick region surrounding the liver or the lung, respectively. After background subtraction, time-activity curves were obtained and shunt fractions calculated as a function of time. Macroggregated albumin (MAA) labeled with technetium-99m was infused over a 1–2 min period into a branch of the inferior mesenteric vein draining the sigmoid colon. Imaging was carried out at 1 frame/min for 5 min. ROIs and background were then obtained in the same manner as for the IMP study and shunt fraction was calculated using Eq. (1). This served as the standard for comparison with the IMP results.
RESULTS

Kinetics of IMP After Colonic Administration

After transrectal IMP administration, the colonic tracer activity demonstrated a steady decrease that was monoexponential. The half-life of tracer disappearance, equivalent to the absorption half-life, was dependent on the level of anesthesia and ranged from 25 min in lightly anesthetized animals to over 50 min in heavily anesthetized animals.

The activities of the octanol-extracted blood samples and the IMP control were evaluated with paper chromatography. The extracted blood samples showed a single peak located at the same spot as the IMP. This was similar to the results obtained after i.v. IMP injection and indicated that extracted tracer activity represented IMP (5). The octanol extraction fractions for the portal and systemic venous blood samples were plotted as a function of time and compared with that of IMP (Fig. 2). Up to 10 min post-tracer administration, the extraction fractions of the portal blood samples were similar to that of IMP, indicating that the tracer was absorbed unchanged. The octanol extraction fractions of the systemic venous samples were very different, indicating that the systemic activity resulted from washout of IMP and/or its metabolites from the liver.

The hepatic time-activity curve after bolus injection into the portal vein was plotted on semilog paper and analyzed (Fig. 3). The extraction fraction was >90%, and the washout appeared to be monoexponential with a half-life of 60 min.

In the intact animal, imaging over the liver and lung after colonic IMP administration revealed prompt hepatic tracer uptake (Fig. 4A). Very little lung activity was seen until 12–15 min after administration (Fig. 4B), indicating high hepatic extraction and slow washout, consistent with the results outlined above.

Sampling-Time Selection

The results of computer simulations are shown in Fig. 5 where shunt fractions calculated with Eqs. (1) and (2) are plotted as a function of time. Using Eq. (1), the calculated shunt fractions deviate from the preset shunt fractions with time (Fig. 5A). The largest and smallest shunt fractions demonstrate greatest deviation. At between 5 and 10 min the error is small for all shunt fractions. Since the absorption half-life is ~25 min and the hepatic and pulmonary activities are well visualized beginning at 5 min after colonic IMP administration, the ideal sampling time for this approach appears to be between 5 and 10 min after IMP administration.

Equation (2) takes into account the washout of hepatic tracer activity. Therefore, the error for this approach is expected to be small for small shunts. For large shunts, the error is expected to approach that of Eq. (1). This is indeed the case, as shown in Fig. 5B.

Portasystemic Shunt Quantification

Five animals had successful portasystemic shunt surgery performed. Scintiphotos of these animals demonstrated prompt pulmonary uptake (Fig. 6). With end-to-side portacaval anastomosis which resulted in 100% shunting, there was no hepatic activity until the 10-min image (Fig. 6A), while both hepatic and pulmonary activity were seen promptly with an intermediate shunt fraction (Fig. 6B). The IMP shunt fractions were calculated with Eq. (1) and demonstrated changes with time. The changes were largest for the very high and very low shunt fractions (Fig. 7). The shunt fractions calculated with IMP and sampled at between 5 and 10 min were compared with MAA shunt fractions in Table 1. A similar experiment was carried out in an
FIGURE 4
A: Imaging over liver and lung of intact animal after trans-rectal IMP administration. Images were obtained at 1 frame/min and go from left to right and top to bottom. First image is body contour. Liver is visualized initially at 3 min and lung activity is not appreciable until 10–12-min image. B: Time-activity curve over liver and lung of same animal showing prompt hepatic and delayed lung activity.

FIGURE 5
A: Computer simulation of shunt fractions calculated with Eq. (1) as function of time (–•–•) for different preset shunt fractions (––). B: Same calculations using Eq. (2) (•••••••). Shunt fractions are closer to preset shunt fractions than in Fig. 7, particularly for small shunts.
intact animal that served as the control and the result was included in Table 1 as the animal with 0% shunt by MAA. The two methods demonstrated good correlation over the entire range of shunting. The largest error was 7%, for the animal with end-to-side portacaval anastomosis.

DISCUSSION

The results of our study indicate that after colonic administration, IMP is absorbed unchanged. It is also nearly completely removed by the liver on the first pass. Since pulmonary extraction of IMP is also high (7), this method of tracer administration can be utilized to measure fractional portal blood flow to the liver and lung. By sampling early, the effects of back diffusion and recirculation are minimized. In this case, IMP behaves like microspheres and PSS can be quantified with a very simple formulation.

Computer simulation of the biologic system was carried out to estimate errors for different models. Based on error estimation, the ideal sampling time can be selected to minimize the errors. In addition, errors due to different models can be compared. A rational decision can be made to select the appropriate model for PSS quantification. The appropriate experimental approach can then be designed to obtain the desired results. In our study, the simplest model, which assumes IMP to behave like microspheres, appears to yield acceptable error over the entire range of shunt fraction. However, the largest and the smallest shunt fractions have the largest error. If accuracy needs to be improved in these instances, more complex models may be appropriate. Our simulation results have demonstrated that small shunt fractions can be quantitated more accurately by taking into account the washout of hepatic tracers. The accuracy of quantitating large shunt fractions is expected to be improved by taking into account pulmonary tracer washout.
In our studies, 99mTc-labeled MAA, infused slowly into a branch of the inferior mesenteric vein draining the colon, served as the standard. Since the photons emitted by 99mTc and 123I have similar energies, the difference in attenuation by the organs is small. Shunt fractions computed from the two tracers can be directly compared with minimal error. To obtain absolute shunt fractions with IMP, absolute tissue activity quantification is necessary.

A number of tracers has been given intestinally to evaluate portal system hemodynamics. Routes of administration include transrectally into the colon and orally into the stomach and small bowel, using both radioactive and nonradioactive tracers (1–4,10). These techniques unfortunately yield only an index of PSS. With transrectal delivery of radioactive tracers such as xenon, ammonia or thallium, the hepatic tracer activity is compared to either pulmonary or myocardial tracer activity. However, the myocardial activity represents only a small fraction of the total amount of shunted tracer activity. These tracers are not retained in the lungs to any significant degree or for any amount of time. PSS quantification is difficult and the relationship between the PSS and the index derived from these studies is complex. The use of digital plethysmography after oral glyceral as an index of PSS is interesting and potentially quantitative. However, additional data is needed to measure the variability in individual response to this agent. The main advantage of our approach is that both the liver and the lung extract this tracer almost completely on the first pass, with slow washout. The pulmonary and hepatic tracer activity can be compared directly. The relationship between PSS and the observed tracer activity in these organs is simple. Therefore, PSS can be quantitated simply and directly.

FOOTNOTES

* Medi-Physics, Inc., Richmond, CA.
† Pulmolite, DuPont NEN Medical Products, No. Bilerica, MA. Pulmolite contains 3.6 to 6.5 × 10^6 particles in 8 ml. The size of at least 90% of the macroaggregated albumin is between 10 and 90 μ and no microsphere is larger than 150 μ.

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REFERENCES