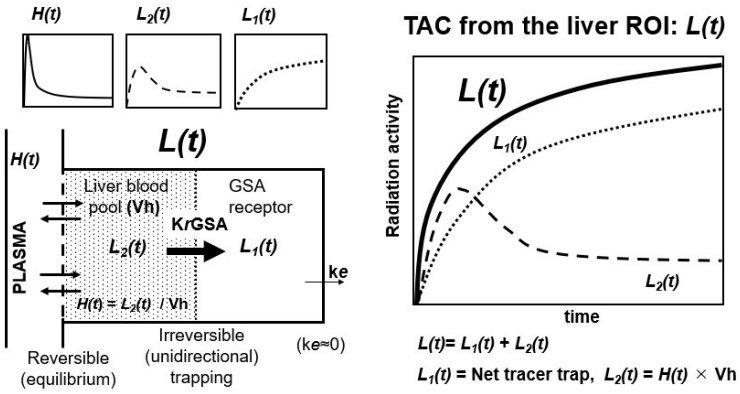
Supplementary Material 1: Calculation of the Uptake Rate Constant

In a one-compartment kinetic model, after a single bolus dose, the tracer reaches the liver through the plasma, is distributed in liver blood pool and binds to the receptor. Among these processes, movement of the tracer between plasma and the liver blood pool is assumed to be in a steady state; however, that between the liver blood pool and the receptor is an irreversible unidirectional trap.



Schematic representation of a one-compartment kinetic model. Time activity curves (TAC) are illustrated after bolus administration of the tracer, where three unknown parameters are GSA receptor uptake rate (K*r*GSA), total excretion rate (k*e*), liver blood pool (Vh). *H(t)* and *L(t)* indicate blood tracer concentration and tracer amount in the liver at time *t*, respectively. k*e* is assumed to be negligible during measurement within 30 min for ^{99m}Tc-GSA scintigraphy. Vh is estimated as 0.25 of liver volume. *H(t)* is calculated as whole heart tracer activity over whole heart volume.

Here, three parameters, namely, GSA receptor uptake rate (K*r*GSA), total excretion rate (k*e*), non-specific volume of distribution in the liver (Vh), are unknown, but k*e* is assumed to be negligible during measurement within 30 minutes of bolus injection for ^{99m}Tc-GSA scintigraphy. $H(t)$ and $L(t)$ represent plasma tracer concentration and tracer amount in the liver at time t, respectively. When a steady state between plasma and the liver blood pool is assumed, $H(t)$ represents tracer concentration in the liver blood pool as well and $L(t)$ is the radioactivity count from the region of interest (ROI) that is set to encompass the entire liver at time t.

TAC from the liver ROI captures total hepatic radioactivity $L(t)$, but is the sum of the tracer trapped by the receptor, $L_1(t)$ and that present in the liver blood pool, $L_2(t)$, where the $L_2(t) = H(t) \times \mathrm{Vh}$. These variables cannot be distinguished from each other on the TAC of the liver ROI. On the other hand, the $L_1(t)$ curve can be deemed to follow a first-order reaction because the binding process of the tracer (^{99m}Tc-GSA) to the receptor (asialoglycoprotein receptor) is irreversible, i.e., $L_1(t) = L_1(\infty) \times (1 - \mathrm{Exp}(-kt))$.

Although the desired TAC is $L_1(t)$, subtraction of $L_2(t)$ from $L(t)$ is not a simple mathematical operation because the $L_2(t)$ curve is dynamic and complex, especially in the initial stages, and a theoretical expression of the actual curvature of the $L_2(t)$ curve is quite complex because of difficulties in evaluating the arrival time of the tracers and the ratio of the tracers that reaches the liver through both the hepatic artery and portal vein. However, we can confirm that the shape of the $L_2(t)$ curve is similar to the one shown in the figure above. In the initial stages, the tracer is predominantly present in the plasma but will constantly enter the liver, either via the hepatic artery and the portal vein or both, leading to its rapid decrease in the plasma. After a certain period, the amount of tracer is close to its steady state concentration due to various transfer processes, including receptor binding and excretion; at this point, $L_2(t)$ becomes almost constant and is negligibly flat. Therefore, at steady state, $H(t)$ concentration at time t can be estimated from the TAC of the heart ROI with minimum error, even though volume of the liver blood pool (Vh) and the blood volume of the heart ROI (Vc) are unknown. To arrive at the best estimate of these parameters, we calculated the volume of interest (VOI) for the liver and heart from the SPECT data. Here, the blood volume of the heart is almost equal to the heart volume, but the liver blood pool is about 25% of the liver volume [1,2]. Therefore, we assumed that Vh / Vc ≈ 0.25 × [liver VOI volume] / [heart VOI volume], and consequently, $L_2(t)$ = [radioactivity of the heart ROI at time t] × (0.25 × [liver VOI volume] / [heart VOI volume]). The constant k denotes receptor binding rate of GSA (K*r*GSA) and was calculated by best fitting it to the equation $L_1(t) = L_1(\infty) \times (1 - \mathrm{Exp}(-kt))$ using actual time activity of $L_1(t)$ obtained by dynamic scintigraphy and a free add-in mathematical optimisation programme of Solver on Microsoft Office Excel® (Microsoft Inc., Redmond, WA, USA). Time points for measurement were set at 10, 20 and 30 minutes after injection of ^{99m}Tc-GSA because the decrease in radioactivity in the heart ROI achieved steady state and was almost negligible by 10 minutes.

For the actual time radioactivity counts at ROIs, those from 9 to 10 minutes, 19 to 20 minutes and 29 to 30 minutes after injection of ^{99m}Tc-GSA were used for the 10, 20 and 30 minute timepoints, respectively.

References

1 Greenway CV, Stark RD. Hepatic vascular bed. Physiol Rev. 1971; 51:23–65.

2 Lautt WW, Greenway CV. Conceptual review of the hepatic vascular bed. Hepatology. 1987; 7:952–63.