N-13 Ammonia, F-18 FDG를 이용한 심근혈류량과 당대사율 정량화

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N-13 ammonia, a tracer of myocardial blood flow (MBF), and PET have been widely used for myocardial perfusion imaging and for quantification of myocardial blood flow. The accuracy of MBF estimates by N-13 ammonia and PET has been extensively validated at different institutions by comparison to microsphere based measurements of MBF. Noninvasiveness and technical convenience of N-13 ammonia and PET for quantification of MBF allow the use of this technique to explore important physiological questions such as the different drug effects and pharmacological and physical exercise effects on MBF. Moreover, N-13 ammonia and PET have been found to be clinically useful for the detection of coronary artery disease and for examining myocardial viability.

The myocardial metabolic rate of exogenous glucose (MRGlc) can be measured with PET and F-18 FDG using the three-compartment model originally developed by Sokoloff et al. (1977) for the measurement of cerebral glucose utilization. FDG competes with glucose for facilitated transport carriers and for hexokinase in the phosphorylation step. However, the phosphorylation product FDG-6-phosphate, unlike glucose-6-phosphate, is not metabolized any further. FDG-6-phosphate can leave the cytosol only by hydrolysis back to FDG by phosphatase, but FDG-6-phosphate is trapped inside the cytosol because phosphatase activity is low in the heart.

In order to accurately quantify MBF and MRGlc using PET various factors associated with the use of the tracer and the emission computed tomography need to be considered. The factors include:

1) partial volume effects on PET images
2) cross-contamination between blood and myocardium region due to spillover of activity
3) the non-linear relationship between the first pass extraction fraction of N-13 ammonia and MBF
4) contamination of the arterial input function by N-13 metabolites

Several different tracer kinetic methods have been proposed to address these problems and to improve the quantitative accuracy. Further, efficient analysis approaches have been developed to reduce the complexities and to facilitate the use of quantitative flow measurements in the clinical environment.

Image Acquisition and Reconstruction

A 10 min transmission scan for photon attenuation correction with $^{68}Ge/^{68}Ga$ pin sources is obtained. N-13 ammonia (550 to 740 MBq) and FDG (370 MBq) diluted in 10 ml saline solution is injected as a 30 second intravenous bolus by infusion pump. The intravenous line is then flushed by a 10 ml saline delivered at the same infusion rate again over a 30 second period to minimize residual activities in injection line.

Acquisitions of serial emission images begin just prior to the tracer injection. It consists of the

sequence of twelve 10-second, two 30-second, one 60-second, and one 900-second frames in N-13 ammonia studies and the sequence of twelve 10-second, four 30-second, two 300-second, and four 600-second frames in FDG studies.

The serially acquired multiplane (35) transaxial images are reconstructed employing a Shepp-Logan filter with a cut-off frequency of 0.96 cycles/cm, yielding a spatial resolution of about 10 mm FWHM in plane.

Image Analysis

The 35 contiguous transaxial images acquired serially after tracer administration are reoriented into left ventricular short axis. Regional myocardial time-activity curves are generated using dynamic images from sectorial region-of-interests (ROIs) defined by the two contours separated radially by 3 pixels (1.17 mm/pixel) and centered at the peak of myocardial circumferential activity.

Sectorial recovery coefficients for a given image spatial resolution, myocardial thickness and ROI thickness, in each imaging plane can be derived based on a myocardial activity thickness estimated by profile analysis of the activity across the myocardial wall on the resliced images.

The time-activity curves of the tracer activity concentrations in arterial blood, AB(t), can be derived from a small elliptical ROI (about 50 mm^2) assigned to the left ventricular blood pool on the dynamic images. These curves are generated from two mid-ventricular imaging planes and are averaged to reduce noise. The fraction of N-13 metabolites of the total N-13 activity in whole blood needs to be corrected in N-13 ammonia studies.

Calculation of Myocardial Blood Flow: Different Methods

Compartment modeling approach

The kinetics of N-13 ammonia in myocardium as observed by PET, have been described by several compartment models. While each modeling approach deals differently with several problems related to N-13 ammonia and PET, all share a basic model configuration as illustrated in Fig. 1. Compartment one in this model represents the concentration of N-13 ammonia in arterial blood and compartment two represents a space of freely diffusible N-13 ammonia including intravascular and interstitial spaces. Compartment three describes the metabolically bound N-13 activity (mostly in the form of N-13 glutamine) in the myocardium. First order rate constants k_1 to k_4 describe the rate of tracer exchange between compartments.

1. Two Parameter Model

In the two parameter model, the rate constant k_1 (ml/min/g) and k_2 (min^{-1}) represent myocardial blood flow (MBF) and MBF/V, respectively, where V is the distribution volume of N-13 ammonia in the free apace. k_3 (ml/min/g) represents

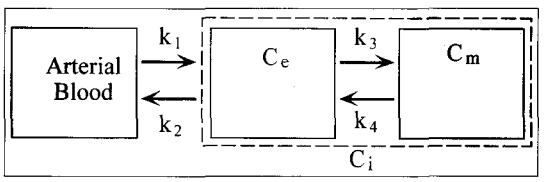

Fig. 1. A general N-13 ammonia compartment model. The first compartment represents the concentration of N-13 ammonia in arterial blood. The second and third compartments model free N-13 ammonia and metabolically bounded N-13 labeled metabolites, respectively. k_1 to k_4 are the first order rate constants.

the conversion rate of freely diffusible into metabolically bound radiotracer. k_4 (min^{-1}) is the clearance rate constant of N-13 activities from the bound to the free compartment.

The number of parameters estimated by model fitting was reduced to 2 in this model by fixing parameters to certain values and by using the relationship between parameters. During the model fitting, the relationship between k_3 and MBF (k_1),

$k_3 = MBF[1.65e^{(1.25/MBF)} - 1]$ Eq. 1,

is used to correct for the nonlinear relationship between the first pass extraction fraction of N-13 ammonia and MBF and to reduce the number of variable parameters. Eq. 1 is derived by equating the extraction fraction (E_m) from the model described in Fig. 1,

$$E_m = \frac{k_3}{k_3 + MBF} \quad \text{Eq. 2,}$$

to the extraction fraction (E_d) determined previously in dog experiments,

$E_d = 1 - 0.607e^{(-1.25/MBF)}$ Eq. 3.

The kinetic data obtained at 0 to 2 min after N-13 ammonia injection are used for the model fitting. k_4 and the distribution volume of free N-13 ammonia in the myocardium, V (ml/g), are fixed to 0 and 0.8, respectively. No minimum and maximum bounds of the parameters are applied during model fitting.

Partial volume effect related underestimation of myocardial N-13 activity concentrations by PET is corrected using recovery coefficient (RC). Spillover of activity from the ventricular blood pool into the myocardial ROI and blood activity in the myocardial vascular space is accounted for by an additional parameter (f_a) in the model:

$C_i(t)/RC = C_t(t) + f_aAB(t)$ Eq. 4,

where $C_i(t)$ is the measured myocardial N-13 activity concentration obtained from an ROI, $C_t(t)$ is the model predicted myocardial N-13 activity concentration and AB(t) is N-13 activity in arterial blood which is obtained from the left ventricular blood pool ROI. f_a represents the fraction of AB(t) measured in myocardium ROI due to the spillover from blood-pool activity into the myocardium ROI and the blood volume in myocardium ROI.

2. Modified Two Parameter Model

The approach is identical to the original two parameter model except for correction of partial volume and spillover effects by use of a geometrical model:

$C_i(t) = (1-f_b)C_t(t) + f_b \cdot AB(t)$ Eq. 5,

where fb is the spillover of blood-pool activity into the myocardium ROI.

3. Four Parameter Model

The four parameter model also derived from the compartment model shown in Fig. 1. The representation of the compartments is the same as in the two parameter method. The rate constants, k_1 (ml/min/g) represents the processes of the delivery of N-13 ammonia to the myocardium by blood flow and the extraction of the tracer across the capillary-tissue interface in a single capillary transit. k_2 (min^{-1}) and k_3 (min^{-1}) represent the N-13 ammonia washout rate and N-13 glutamine formation rate constant, respectively. k_4 is excluded in this model. MBF is obtained from the estimated k_1 using the relation shown in Eq. 6:

$k_1 = MBF \cdot E = MBF(1 - e^{-PS/MBF})$ Eq. 6

where PS is the permeability-surface area product for N-13 ammonia and found to be 1.08 + 2.34MBF in canine myocardium. The initial transcapillary first pass extraction fraction, E for N-13 ammonia is high (>90%) over a wide range of flow. It is therefore assumed that the rate constant k1 represents MBF with a small error (8% in 4.6 ml/min/g). Because this method has four parameters to be estimated, as compared to two parameters in methods 1 and 2, kinetic data

over longer time periods (about 10 min) are needed for model fitting. All variable estimates are constrained to positive values during the model fitting. Partial volume and spillover effects compounded in PET measured myocardial concentrations are corrected for using the geometrical model of ROI representation.

$$C_i(t) = (1-fb)C_t(t) + f_b \cdot AB(t) \qquad \text{Eq. 7.}$$

Non-compartment modeling approach

4. Graphical Analysis

In order to simplify the calculation of MBF by avoiding the nonlinear regression required for the compartment model approaches, a graphical analysis has been employed for estimating MBF with the assumption of unidirectional tracer uptake:

$$\frac{C_i(t)/RC}{C_a(t)} = K\frac{\int_0^t C_a(\tau)d\tau}{C_a(t)} + \frac{MBF^2V}{(MBF+k_3)^2} + f_b\frac{AB(t)}{C_a(t)} \qquad \text{Eq. 8}$$

where K, the slope of the straight portion of the plot, representing the transport of tracer from the arterial input function to the precursor pool times the fraction trapped in the bound pool, is expressed as follows:

$$K = MBF\ [1 - 0.607e^{(-1.25/MBF)}] \qquad \text{Eq. 9.}$$

Assuming of k_4 to be 0, MBF can then be measured by estimating the slope, K, of the straight portion of the graph, $\frac{C_i(t)/RC}{C_a(t)}$ (vertical (Y) axis) versus $\int_0^t C_a(\tau)d\tau / C_a(t)$ (horizontal (X) axis), and by using the relationship described in equation 9. The intercept of the plot is constrained within 0.43 - 0.65 based on previous studies.

5. First-Pass Extraction Method

The product of first pass extraction fraction (E) and MBF can be estimated using the following equation with the assumption of unidirectional tracer uptake:

$$MBF \cdot E = \frac{C_i(t)}{RC} / \int_0^t C_a(\tau)d\tau \qquad \text{Eq. 10.}$$

MBF is then calculated from the flow-extraction fraction relation (Eq. 3) as determined previously in canine myocardium. Myocardial kinetic data points recorded at t = 2 or 3 min post injection are used to estimate MBF by Eq. 10.

6. Dose Uptake Index

Dose uptake index (DUI) is employed:

$$DUI = \frac{C_i(t)}{RC} / \left(\frac{Dose(mCi)}{Weight(kg)}\right) \qquad \text{Eq. 11.}$$

Myocardial kinetic data points recorded at t = 2 or 3 min post injection are used to estimate DUI by Eq. 11.

Quantification of Myocardial Glucose Metabolism Using F-18 FDG

The input function, used in the 3-compartment FDG model, can be reliably obtained from the left ventricular chamber in a series of myocardial FDG images. With the known input function, individual rate constants, k_1 (ml/min/g), k_2 (min^{-1}), k_3 (min^{-1}) and k_4 (min^{-1}), of a myocardial sector can be estimated by fitting the time-activity curve generated from the corresponding sector to the 3-compartment FDG model.

MRGlc can then be estimated using:

$$MRGlc\ (\mu mmol/min/g) = \frac{C_P}{LC}\ \frac{k_1 k_3}{(k_2+k_3)}$$

where, C_p is the plasma glucose concentration and LC is the lumped constant.

The macroparameter, K, and, hence, MRGlc

can be estimated using Patlak graphical analysis with the assumption of $k_4 = 0$. This approach will allow to generate parametric image of MRGlc since it requires computationally simple linear regression.

The LC is a correction factor that accounts for the differences in the transport and phosphorylation steps between FDG and glucose. The LC value of 0.6 obtained from the experiment performed with the isolated perfused rabbit septum is commonly used for the calculation of MRGlc. Whether the LC value, however, is truly constant under all physiologic and pathophysiologic conditions remains unclear.

SUMMARY

Regional MBF and MRGlc can be accurately estimated with N-13 ammonia and FDG PET using tracer kinetic methods including compartmental and non-compartmental approaches. Compartment modeling approaches are physiologically well characterized, but are methodologically more complicated. Noncompartmental analysis are easier to implement while the limitations and assumptions of the methods should be understood prior to the application of the method.