FFYS7086 Signal and Image Processing course

PET Modeling

13:15-14:00, 2022.05.11

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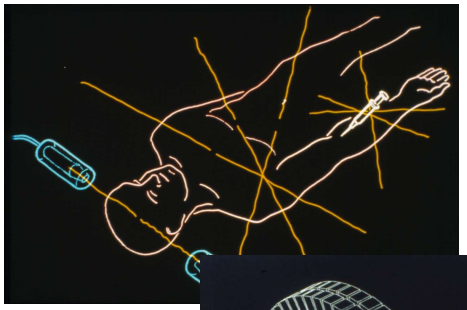
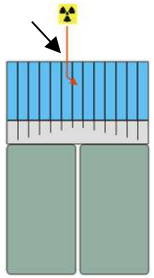
Positron Emission Tomography

Detector+electronics technology





- Block design (high packing rate)
- Energy resolution
- Time resolution
- Increased signals
- Electronics circuit (ASIC)
- Large scale storage

10^4～$10^{5\ \text{detectors}}$～10^9のLOR

Coincidence　Δt～nsec

～200ps for time-of-flight reso.

PET system

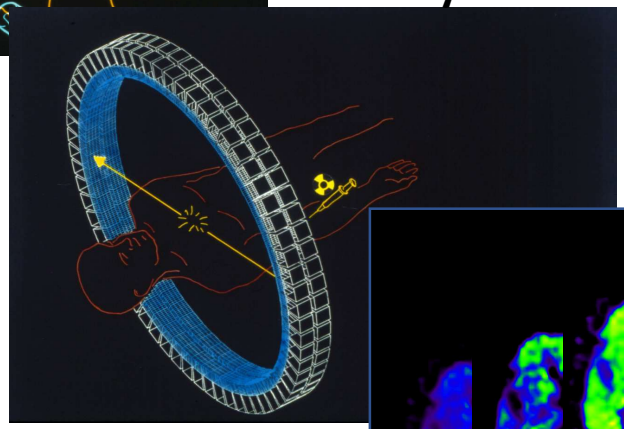
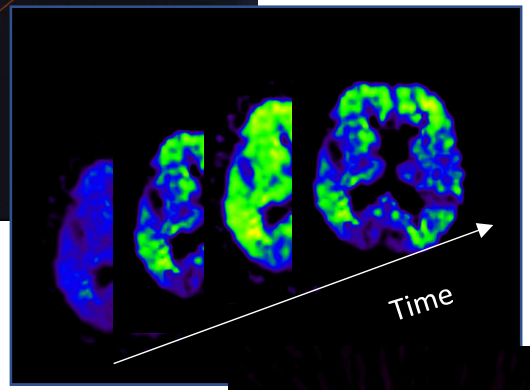
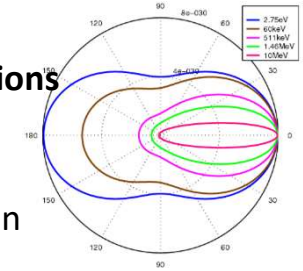


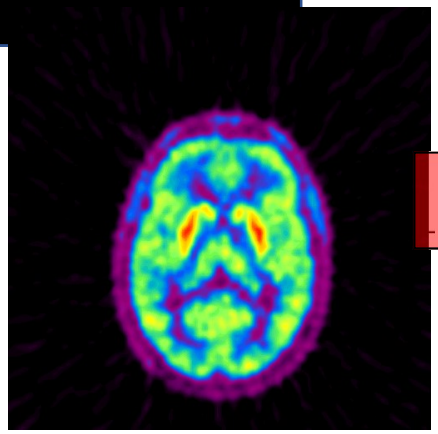
Image reconstruction



A number of corrections

- Random events
- Inhomogeneity
- Dead time
- Photon Attenuation
- Photon Scatter
- Partial Volume

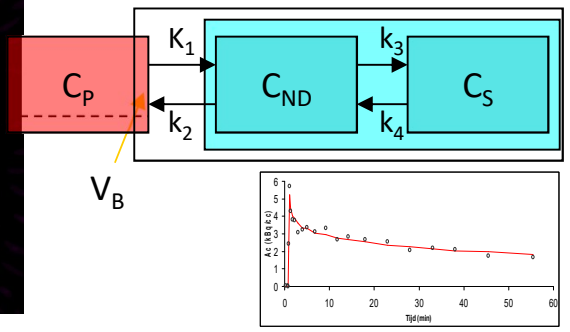




Modeling contribute:

- **Practical protocol design**
- **Radio-tracers development**
- **PET system design specifications**
- **Software specifications**

To extract biological information



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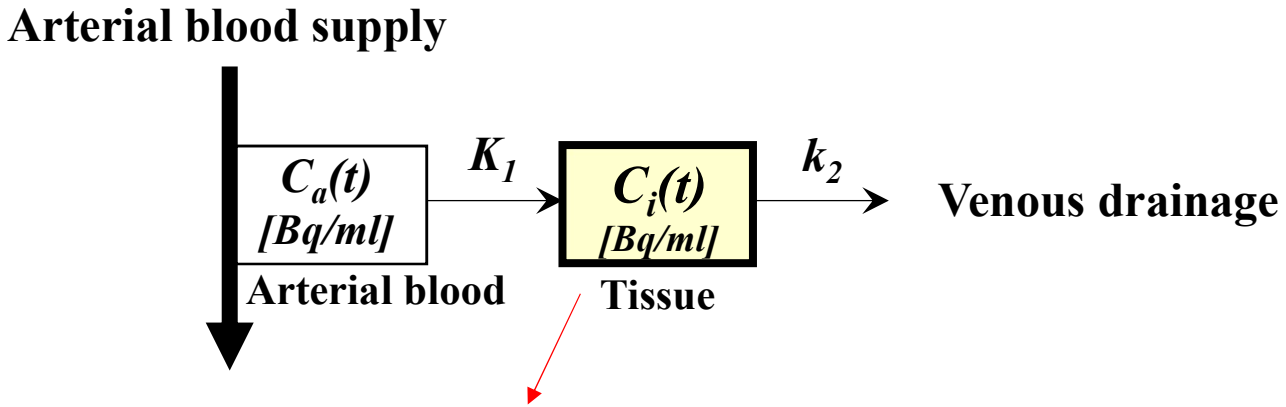
Contents

1. **Basis of the compartment model**
2. **Modeling of $H_2{}^{15}O$-based regional tissue perfusion**
   - Cerebral blood flow (CBF)
   - Myocardium blood flow (MBF)
3. **General concerns and future perspectives**

Exponential function
as the basis of the compartmental modeling

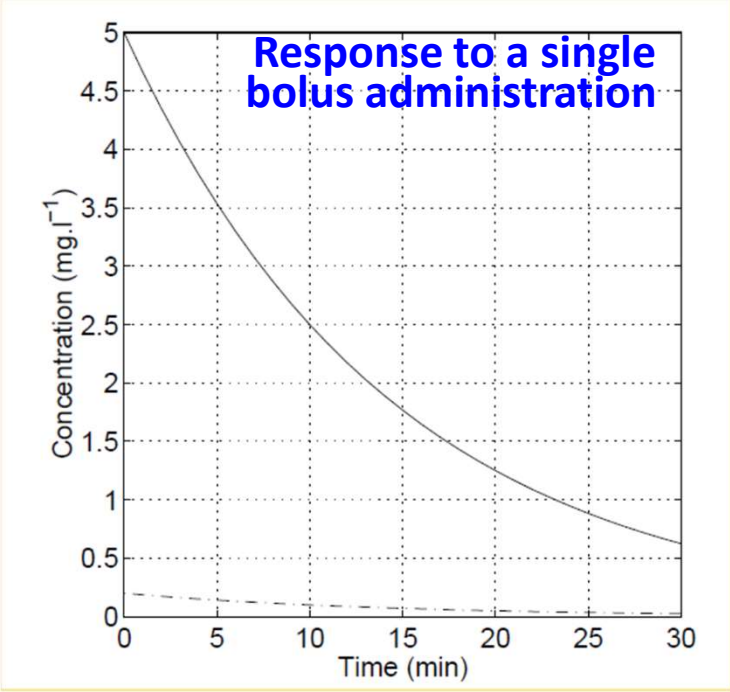


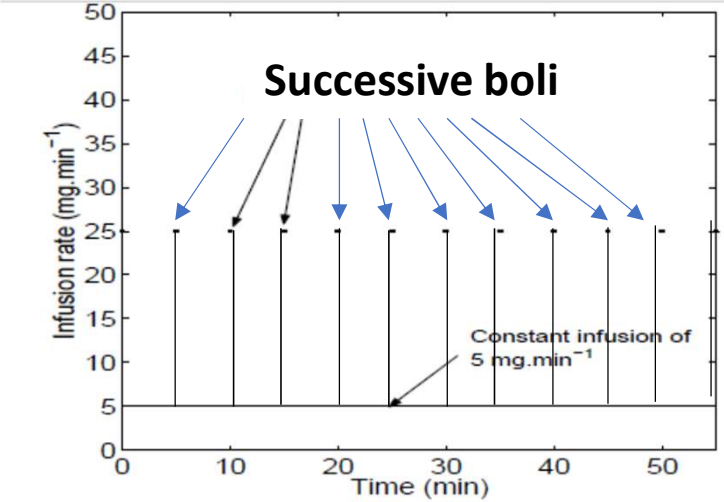
$$\frac{dC_i(t)}{dt} = K_1 C_a(t) - k_2 C_i(t) \qquad \text{- eq. (1)}$$

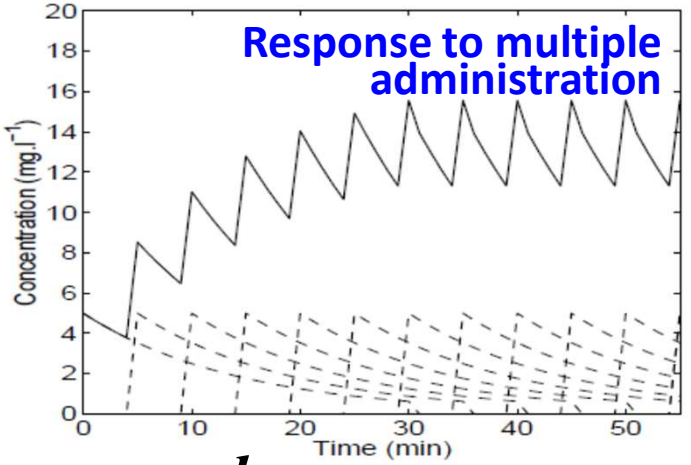
- After the tracer is introduced, the radio-labeled tracer in the arterial blood is carried to tissue, and from the tissue to the venous drainage.
- These transport flux is proportional to differences in concentrations at the boundary, where the carriage rate may be assumed at constant, under some circumstances. Instantaneous equilibrium in the tissue compartment is also an important assumption.
- The time balance of the tracer concentration in the tissue compartment may be expressed as eq. (1).

Solving the compartment model

$$\frac{dC_i(t)}{dt} = K_1 C_a(t) - k_2 C_i(t)$$



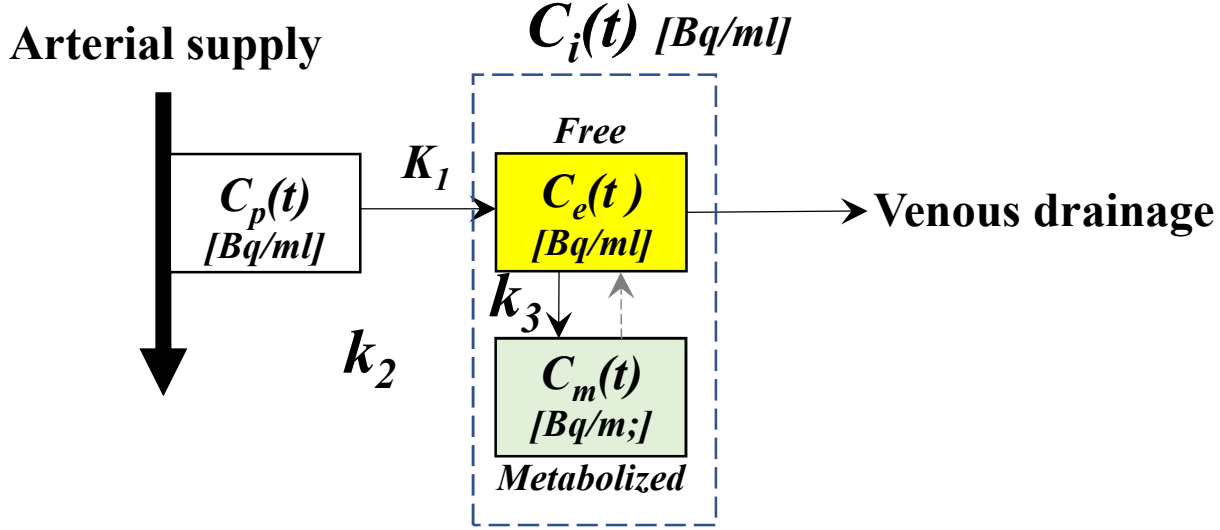




$$C_i(t) = K_1 \cdot C_a(t) \otimes e^{-\frac{k_2}{p} \cdot t}$$

$$= K_1 \cdot \int_0^t C_a(t-s) \cdot e^{-\frac{k_2}{p} \cdot s} ds$$

Exponential function
as the basis of the compartmental modeling



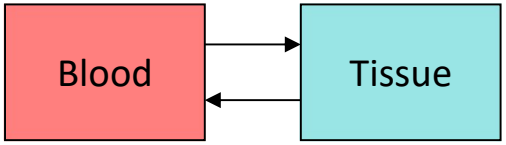
- $\frac{dC_e(t)}{dt} = K_1 C_p(t) - k_2 C_e(t) - k_3 Ce(t)$
- $\frac{dC_m(t)}{dt} = k_3 Ce(t)$

$$C_i(t) = Ce(t) + C_m(t)$$

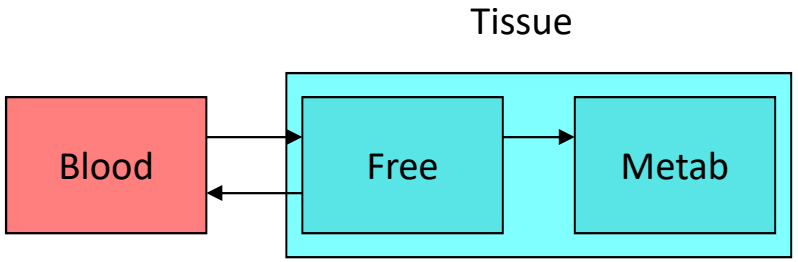
$$= \underbrace{\frac{K_1}{(\alpha_2 - \alpha_1)}\{(k_3 - \alpha_1)e^{-\alpha_1 \cdot t} + (\alpha_2 - k_3)e^{-\alpha_1 \cdot t}}_{C_e(t)} + \underbrace{\frac{K_1 k_3}{(\alpha_2 - \alpha_1)}(e^{-\alpha_1 \cdot t} - e^{-\alpha_1 \cdot t}\} \otimes C_p(t)}_{C_m(t)}$$

$$\alpha_{1,2} = \frac{1}{2} \cdot \left[(k_2 + k_3 + k_4) \mp \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2 k_4} \right]_p$$

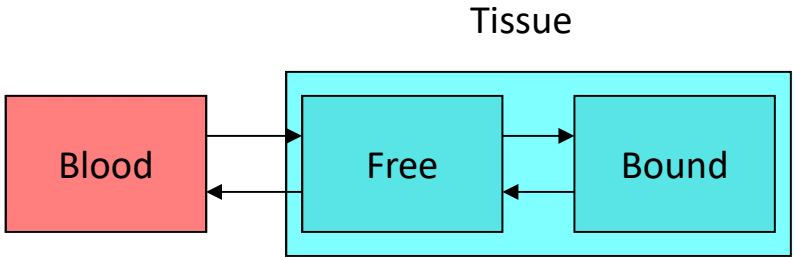
Common Compartment Models



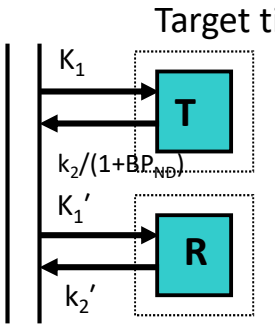
Blood flow tracer



Glucose metabolism



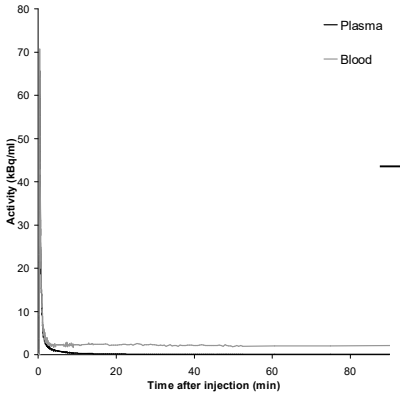
Receptor ligand



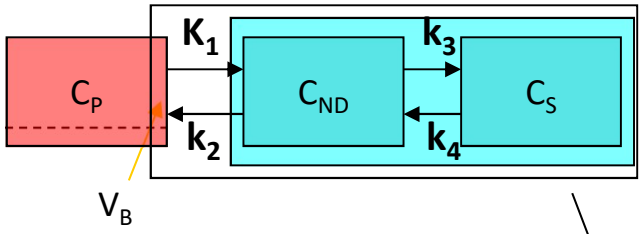
SRTM

Kinetic fitting to solve the inverse problem

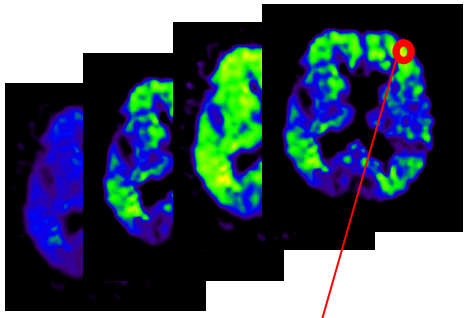
Input function



Kinetic model

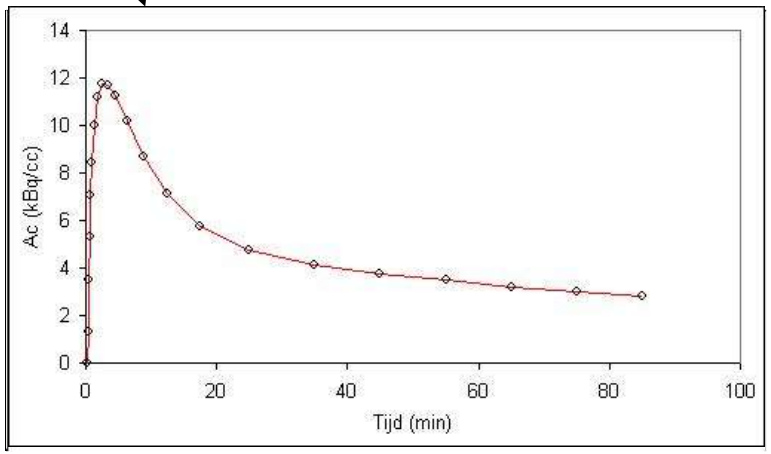


Dynamic PET images



Fitting routine

Tissue time-activity curve



Kinetic parameters

K_1: transport

K_3/k_4: binding potential

Optimization of parameter sets $(p_1, p_2, p_3, , ,)$

$$\boldsymbol{Counts}\left[\frac{\boldsymbol{Bq}}{\boldsymbol{ml}}\right]\boldsymbol{estimated\ using\ a\ formulae\ with\ given\ } K_1, k_2, k_3, , , \boldsymbol{values}$$

$$\boldsymbol{Counts}\left[\frac{\boldsymbol{Bq}}{\boldsymbol{ml}}\right]\boldsymbol{measured\ by\ PET}$$

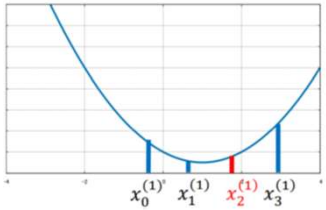
$$\chi^2 = \frac{1}{N} \cdot \sum_i \left(\frac{(\boldsymbol{Estimated\ data})_i^{\,2} - (\boldsymbol{Measured\ data})_i^{\,2}}{(\boldsymbol{Estimated\ error})_i^{\,2}} \right)$$

If the assumed model formula is adequate, and the data are acquired with suffieient accuracy, the minimal $\boldsymbol{\chi^2}$ value may reach unity.

- *"The minimal* $\chi^2 << 1$" means that the parameters determined are not reliable.
- *"The minimal* $\chi^2 >> 1$" suggests the need for improving the model formulation.

Numerical procedures to find the local minimum of χ^2

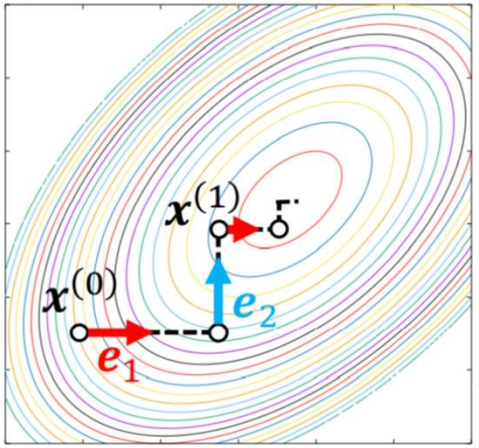
- **1-dimensional search to find a local minimum**



Golden section method, etc
(No way to find the "global" minimum!)

- **Multi-parameter search**
  - The steepest descent method
  - Conjugate gradient method
  - Newton's method
  - Gauss-Newton method
  - Marquardt method
  - Powell method, etc.
  - Simplex (Nelder-Mead) method ← **Works well!!**

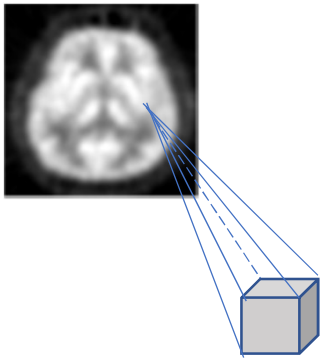
Combination with 1-dimensional search
+ updating the search direction



y)

- **Basis Function method accelerates the optimization**

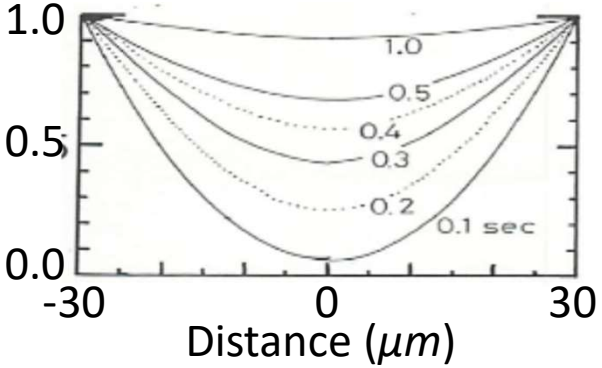
Modeling of ^{15}O-labeled water ($H_2{}^{15}O$) kinetics for cerebral & myocardial blood flow



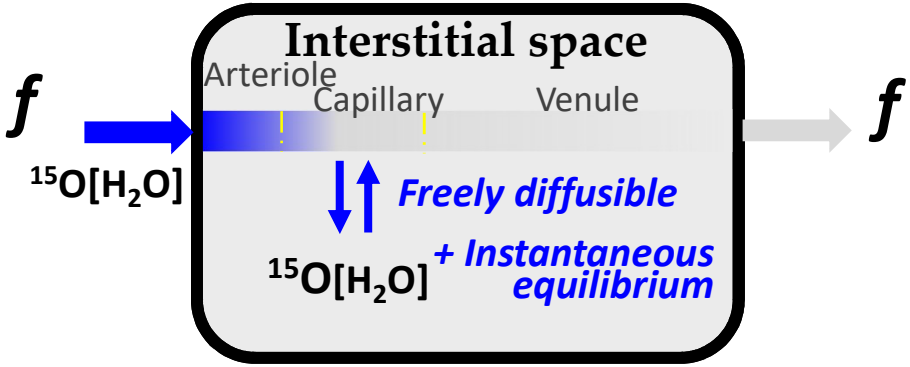
Capillary bed

Diffusion equation in the capillary bed

$$\frac{\partial u(t,r)}{\partial t} = D\frac{\partial^2 u(t,r)}{\partial r^2}$$



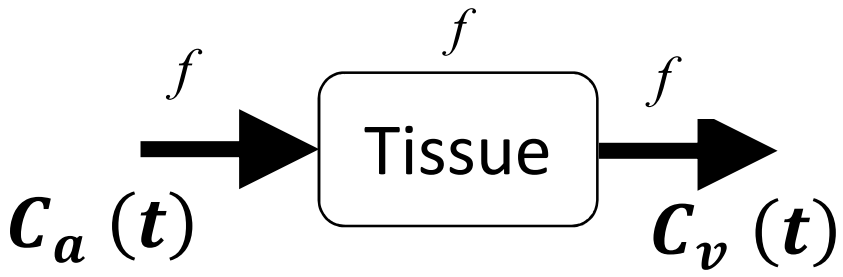
Single-tissue compartment model



Questions and proposals

- Gradient along the capillary
- Slowly exchanging water (binding water)
- Heterogeneity of blood supply

Mathematical model for $H_2{}^{15}O$ to quantitatively asses regional blood flow



$$\frac{dC_i(t)}{dt} = f \cdot C_a(t) - f \cdot C_v(t)$$

Assuming $C_v(t) = \frac{C_i(t)}{p}$

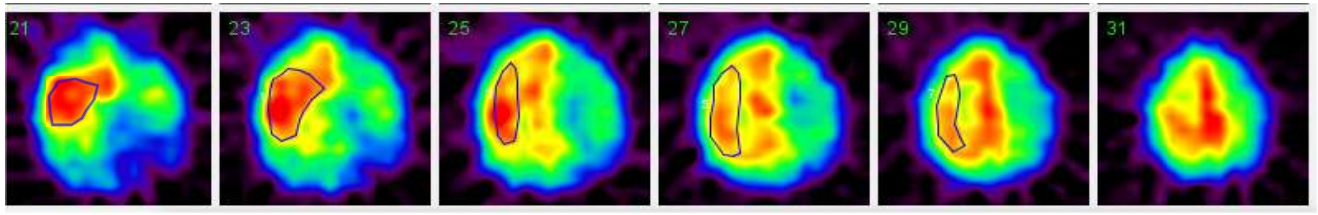
$\because p = \frac{Water\ content\ in\ tissue}{Water\ content\ in\ blood}$

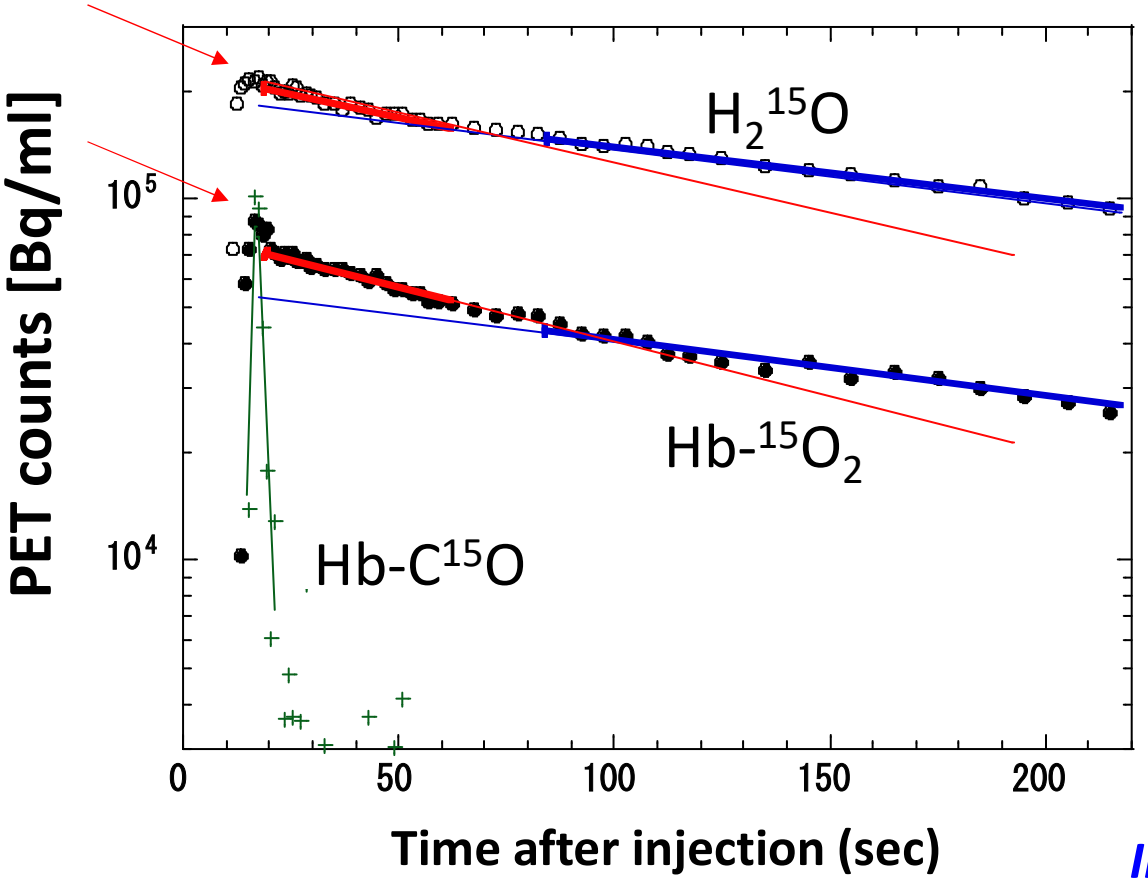
$$\Rightarrow \frac{dC_i(t)}{dt} = f \cdot C_a(t) - f \cdot \frac{C_i(t)}{p}$$

Solving eq. (1) gives

$$C_i(t) = f \cdot C_a(t) \otimes e^{-\frac{f}{p} \cdot t}$$

Clearance of radioactivity from cerebral tissue after bolus carotid injection of ^{15}O-water

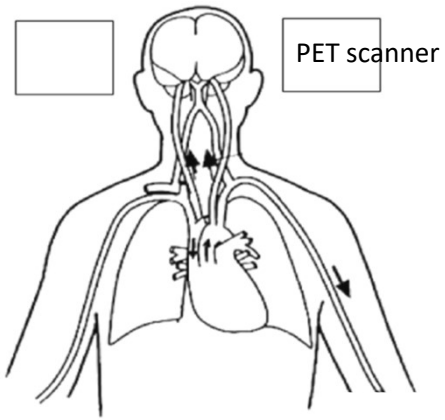




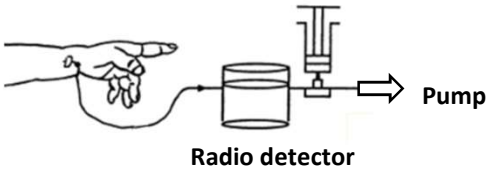
Iida et al., JCBFM 2014, 1-6

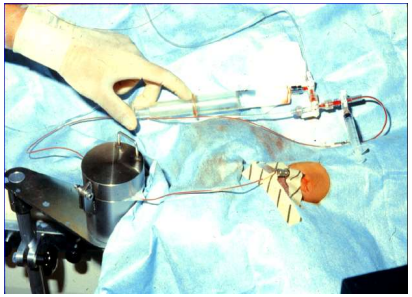
Delay and dispersion in the observed AIF occur in the arterial lines and in the catheter tubes.

A)

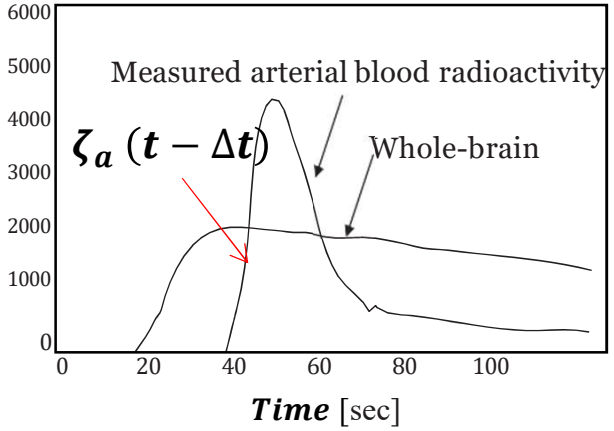


B)





C)



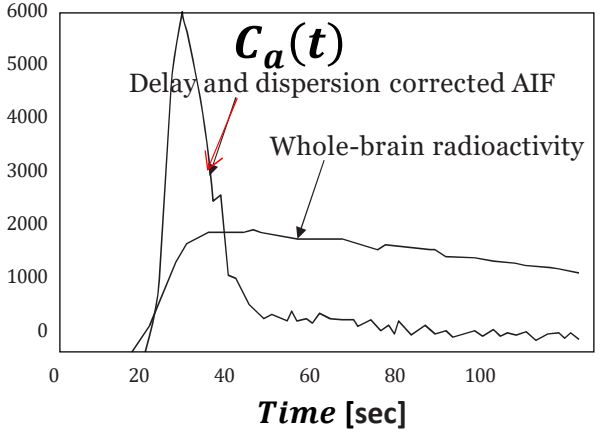
Dispersion function:

$$d(t) = \frac{1}{\tau}\cdot e^{-t/\tau}$$

Delayed & Dispersed AIF:

$$\zeta_a\,(t-\Delta t) = C_a\,(t) \otimes \frac{1}{\tau}\cdot e^{-t/\tau}$$

D)

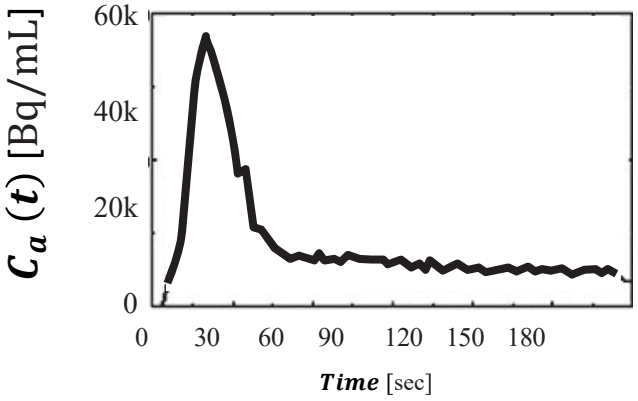


Delay & Dispersion corrected AIF:

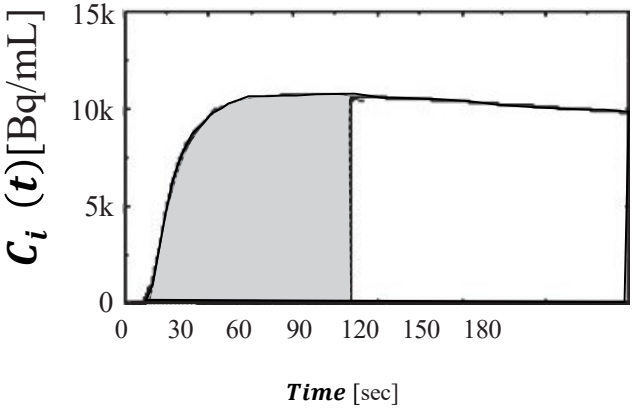
$$C_a(t) = \zeta_a\,(t-\Delta t) + \tau\frac{d}{dt}\left(\zeta_a\,(t-\Delta t)\right)$$

Procedures of the ^{15}O-Water Autoradiography

Arterial input function



Tissue TAC

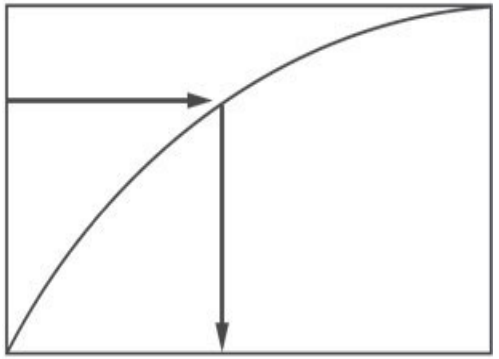


Pixel counts measured by PET

$$\int_0^t C_i\,(t)dt = f \cdot \int_0^t C_a\,(t) \otimes e^{-\frac{f}{p}\cdot t}dt$$

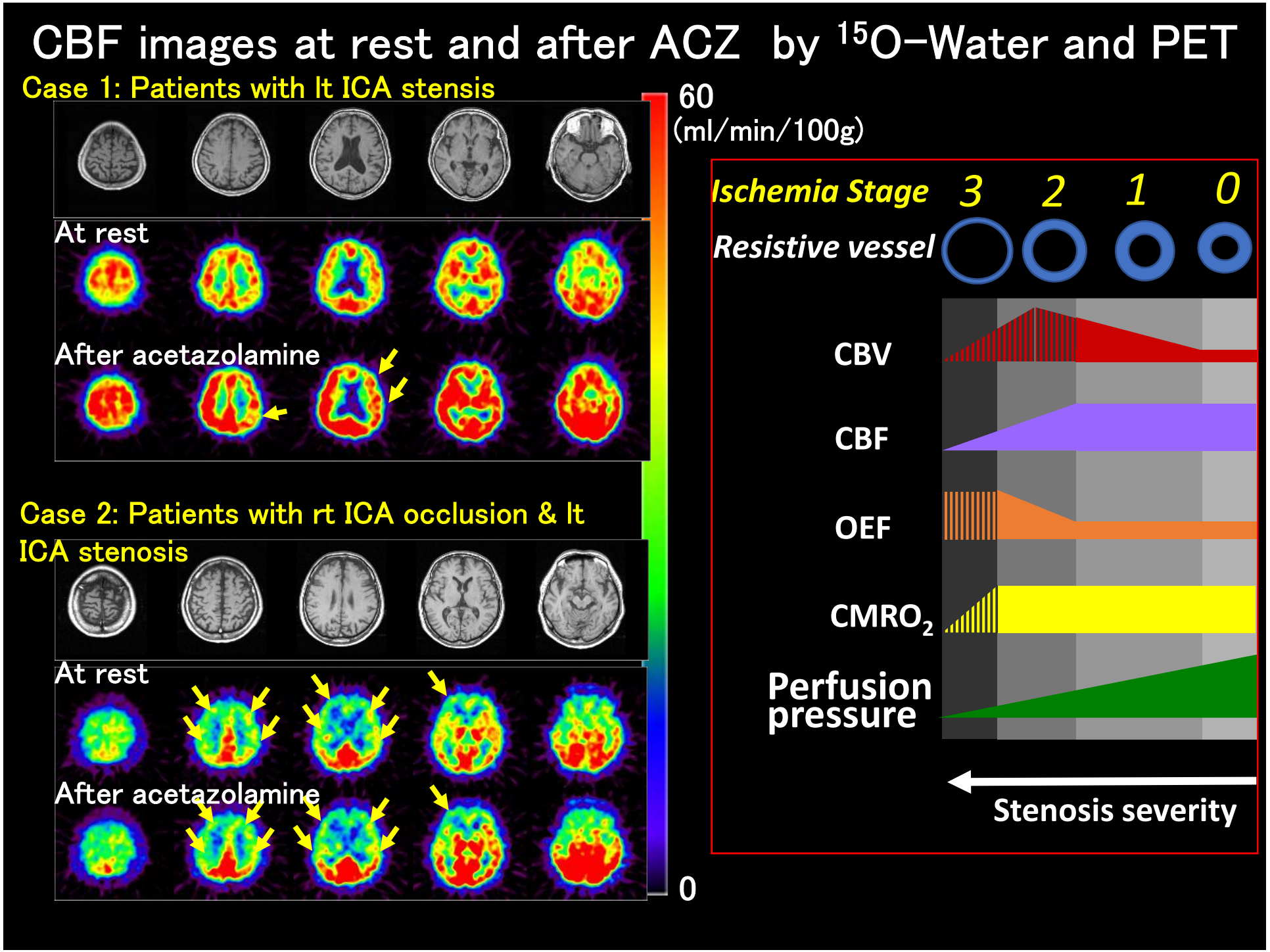
Assumed p-value

Calculation of CBF by Table-Look-Up



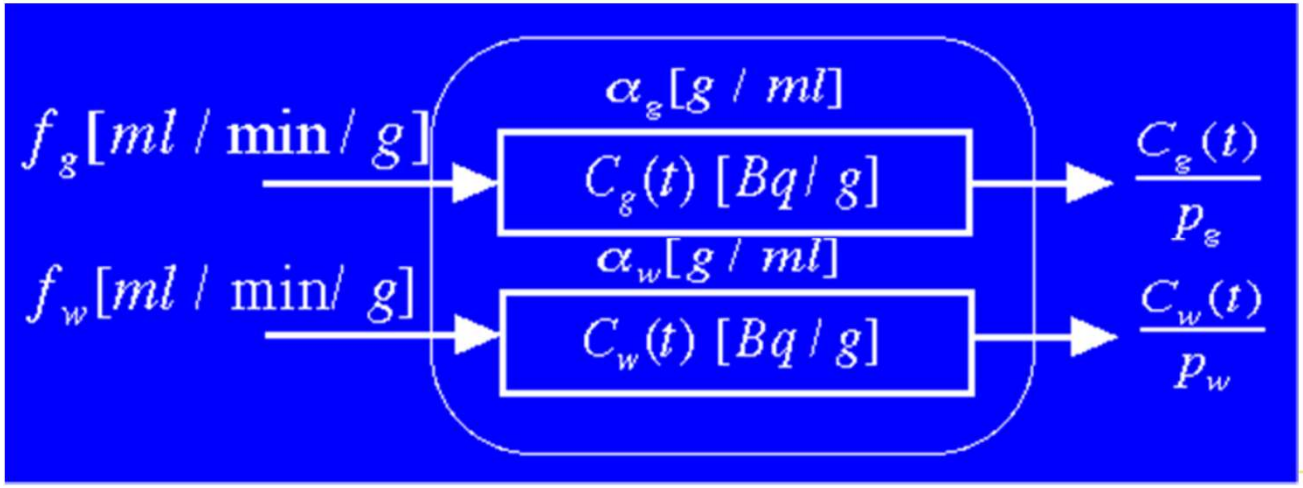
CBF image

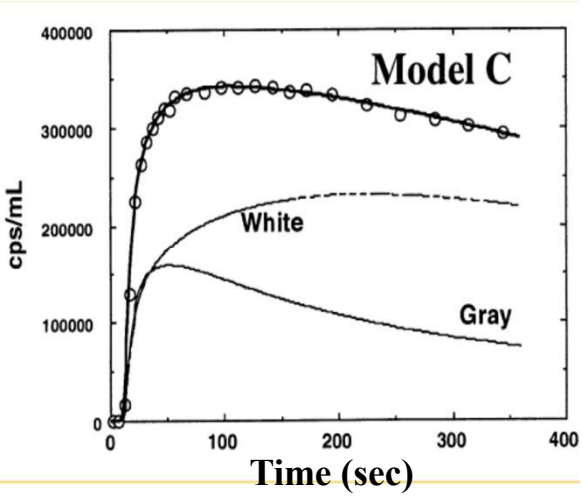
CBF images at rest and after ACZ by ^{15}O-Water and PET



Quantitation of rCBF corrected for Partial Volume Effect

using ^{15}O-Water and PET



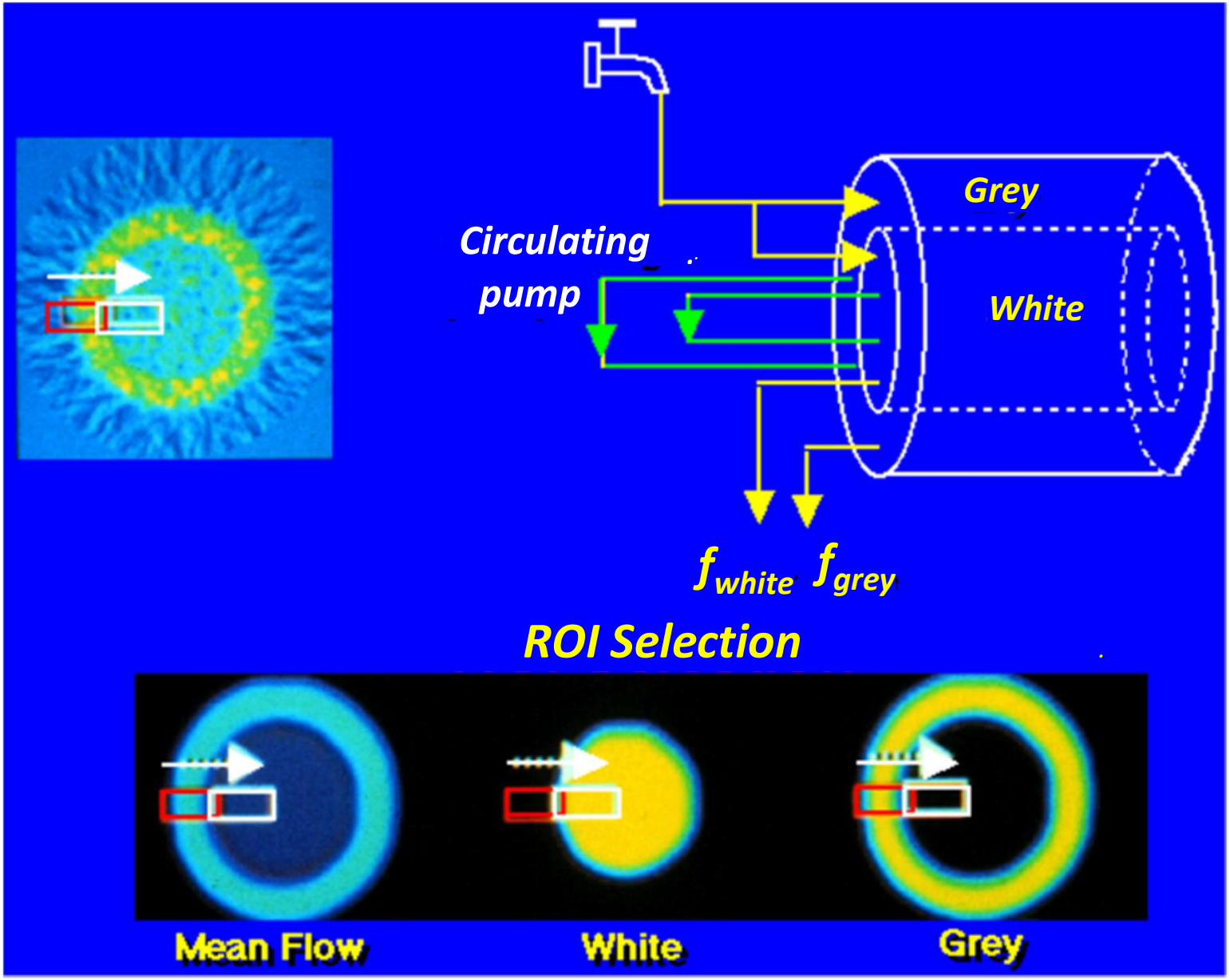


$$R(t) = \alpha_g \cdot f_g \cdot C_a(t) \otimes e^{-\frac{f_g}{p_g}t} + \alpha_w \cdot f_w \cdot C_a(t) \otimes e^{-\frac{f_w}{p_w}t}$$

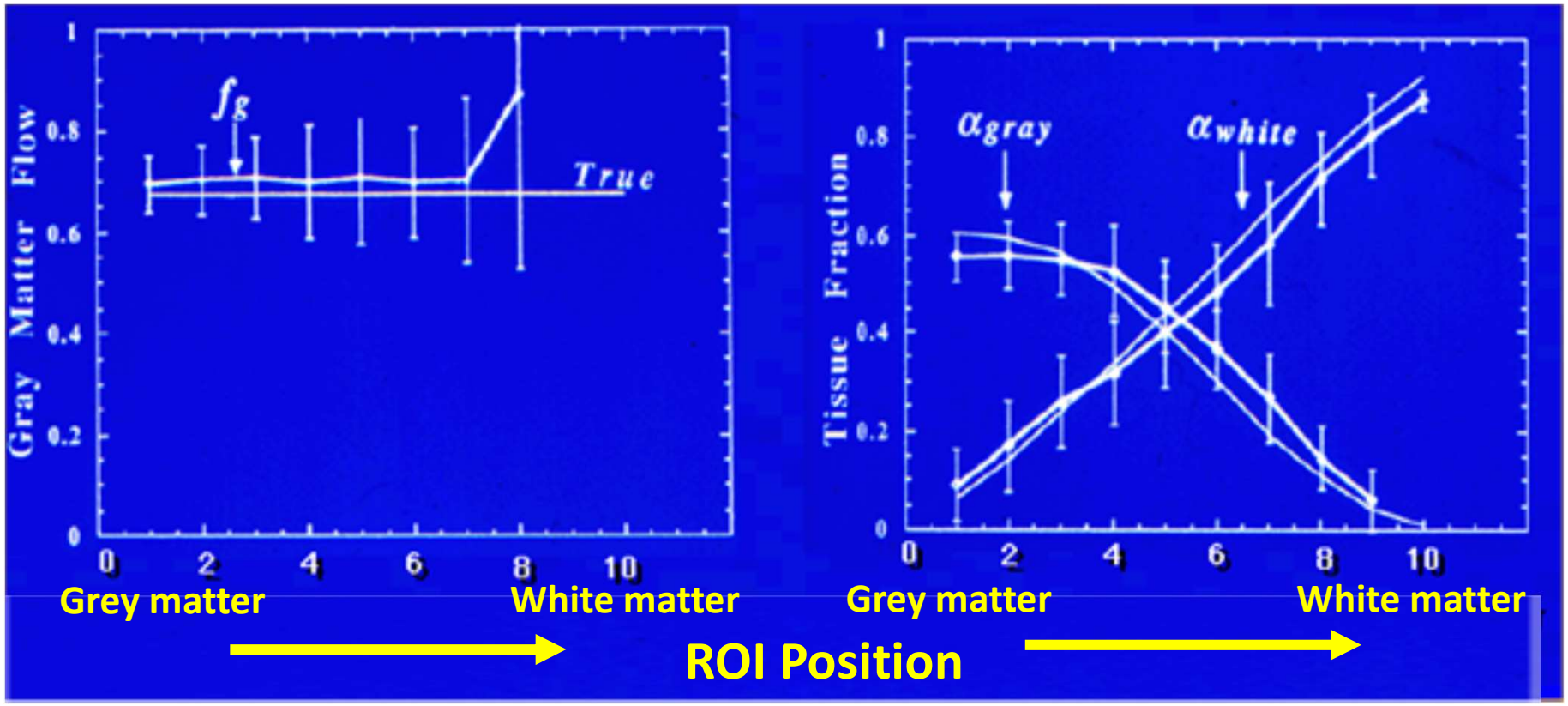
Iida H, Law I, etc, JCBFM 2000

Law et al., Iida et al. JCBFM 2000

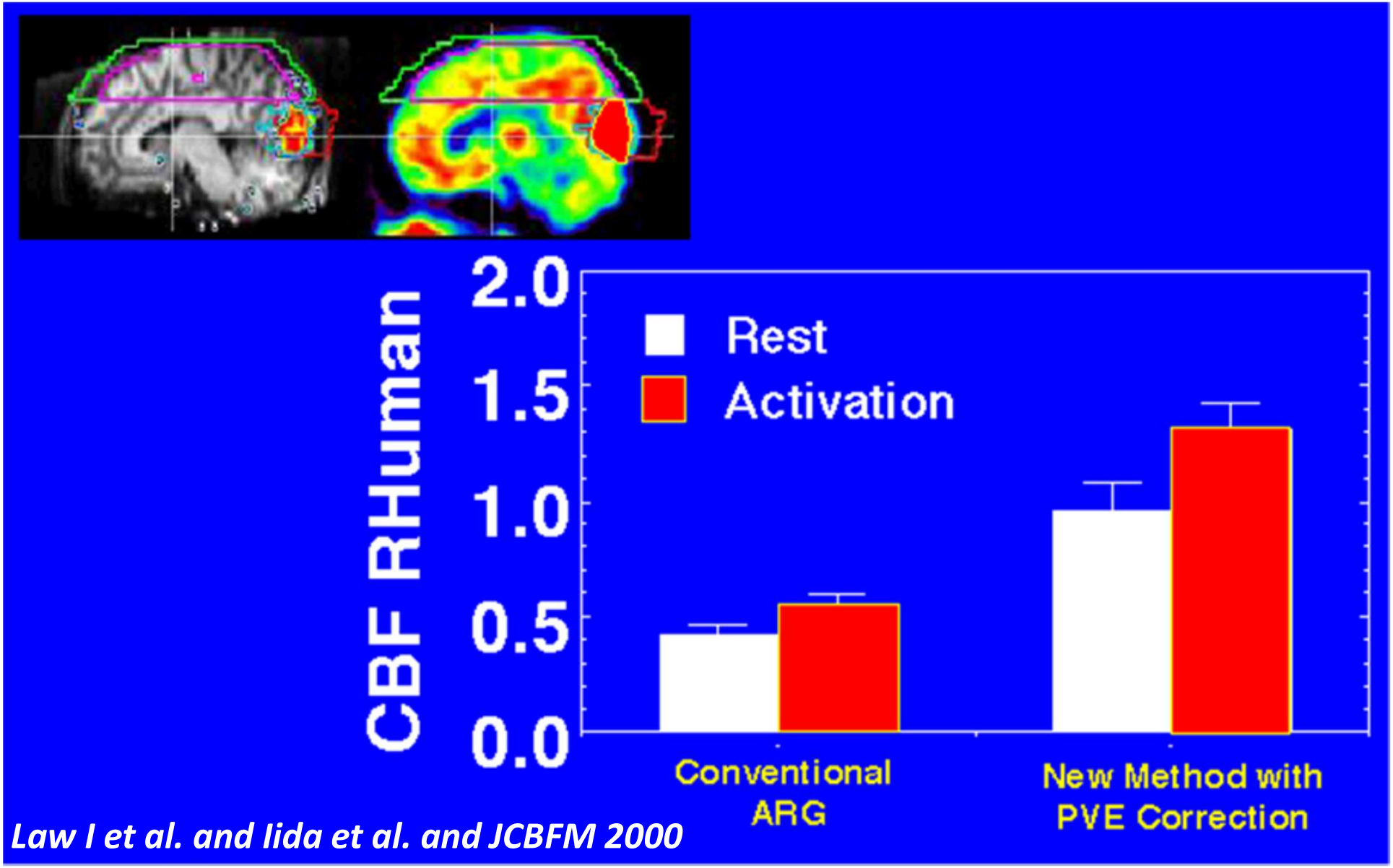
Validation using a dynamic equilibrium phantom



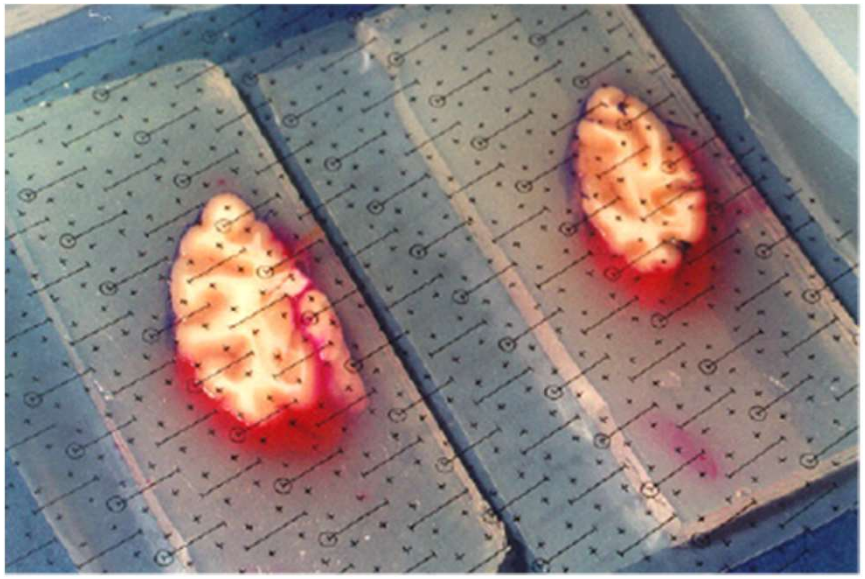
Results from a dynamic equilibrium phantom experiment



Impact of Partial Volume Correction on Absolute CBF in young healthy volunteers



Comparison of the gray matter volumes
- ^{15}O-water PET vs stereologic volumes -

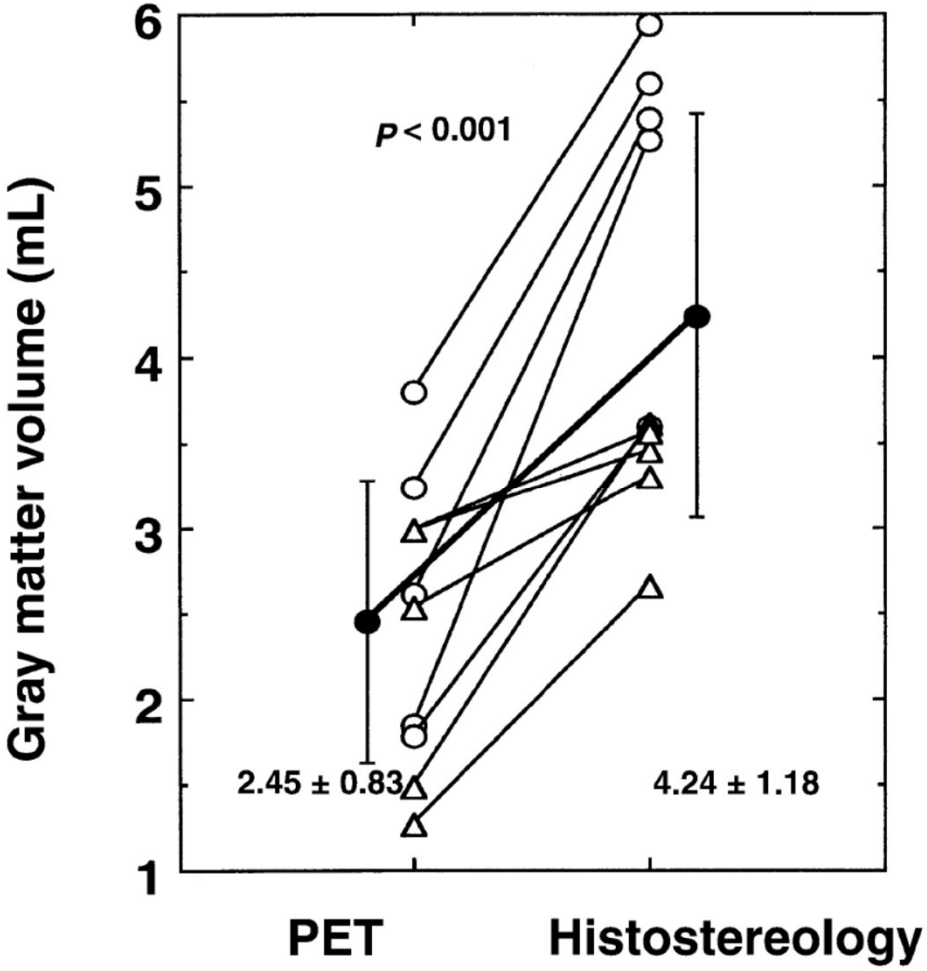


$$V = \bar{t} \times a(p) \times \sum p$$

$\bar{t}$ = average section thickness

$a(p)$ = area per point of the grid

$\sum p$ = the total number of points that fall on the object



Iida et al. abd Law I et al., JCBFM 2000

Quantitation of myocardial perfusion

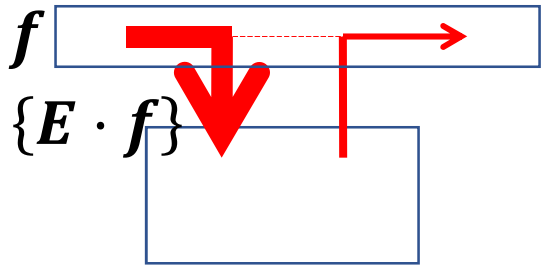
^{15}O-water as a gold standard

1. **Instantaneous equilibrium in tissue**
2. **Large first-pass extraction fraction**
3. **Chemically inert**
   - No retention
   - No metabolism
   - Adequate for math modeling

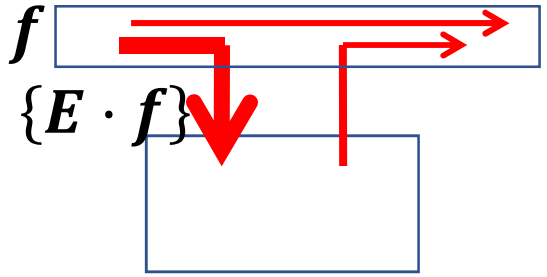
First-pass extraction fraction

$$\frac{dC_i(t)}{dt} = \{E \cdot f\} \cdot Ca(t) - \{E \cdot f\} \cdot C_v(t)$$

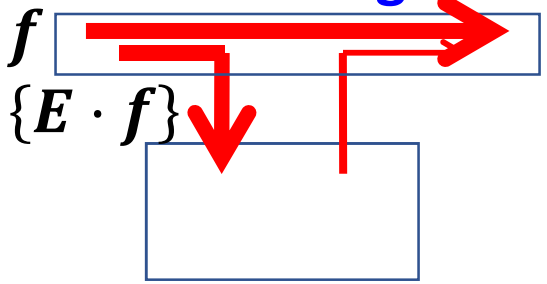
Ideal

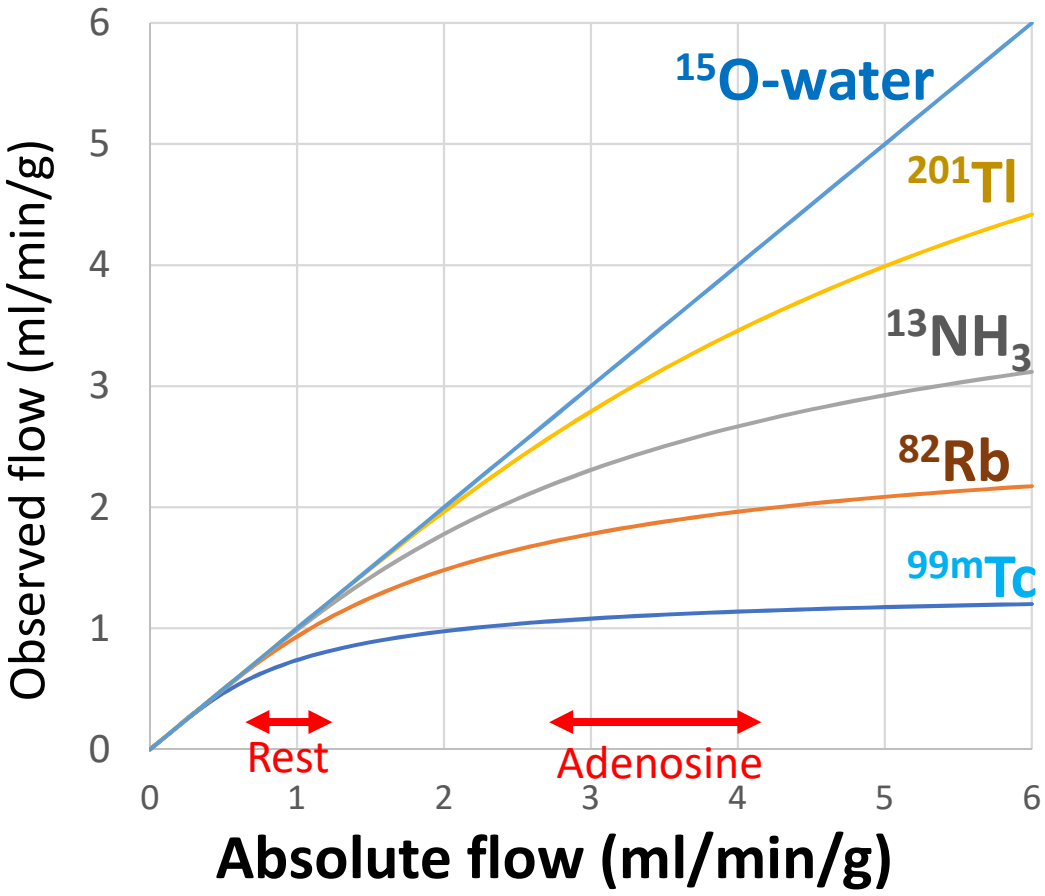


Limited EF at rest

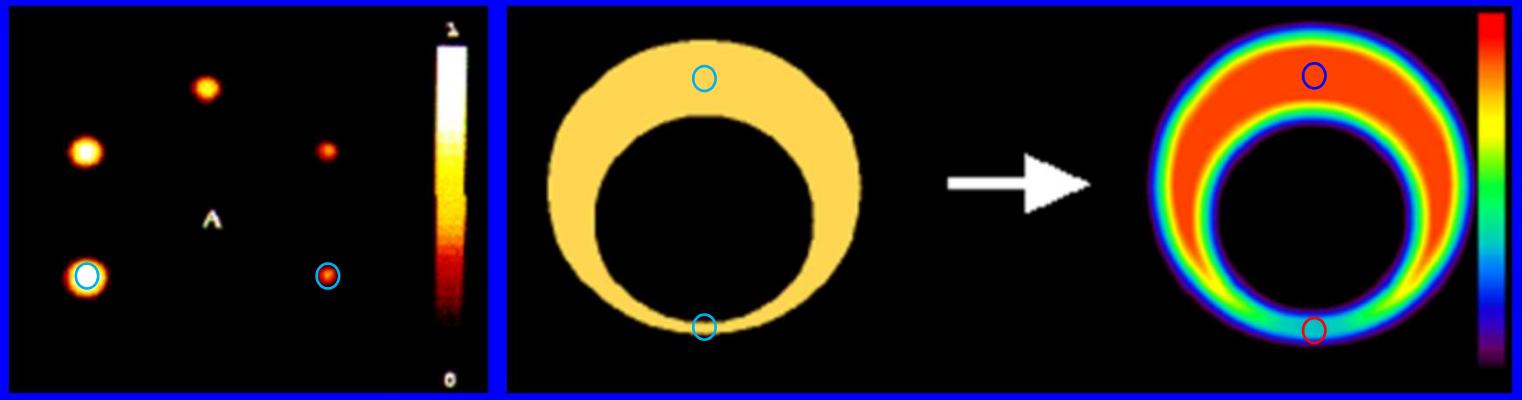


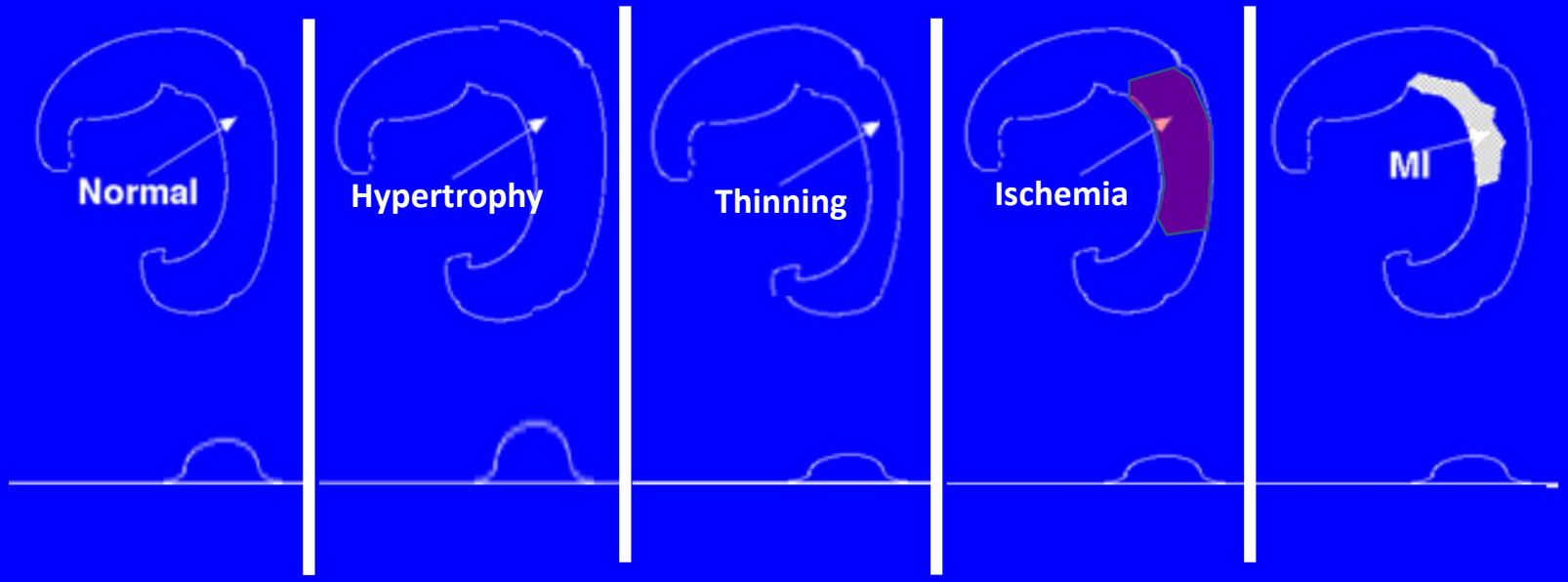
Limited EF during stress



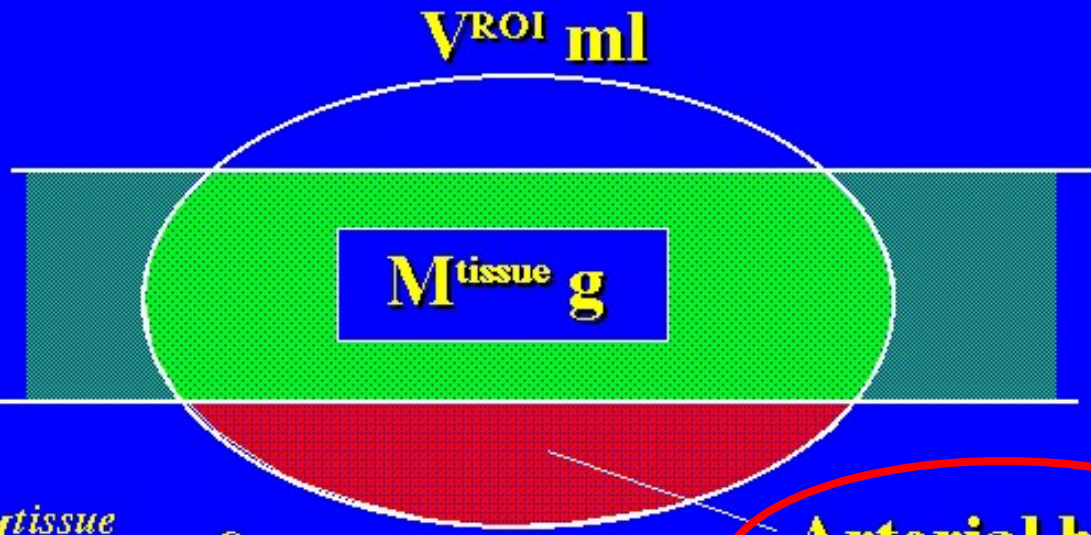


Systematic underestimation due to Partial Volume Effect (PVE) in Myocardial PET





Partial Volume Correction in Myocardial Blood Flow Quantitation



Recovery coeff.

$$\alpha = \frac{M^{tissue}}{V^{ROI}} \left[\frac{g}{ml}\right]$$

Arterial blood volume

$$\mathbf{R(t)} = \alpha \, f \cdot C_a(t) \otimes e^{-\frac{f_t}{p}} + V_a \, C_a(t)$$

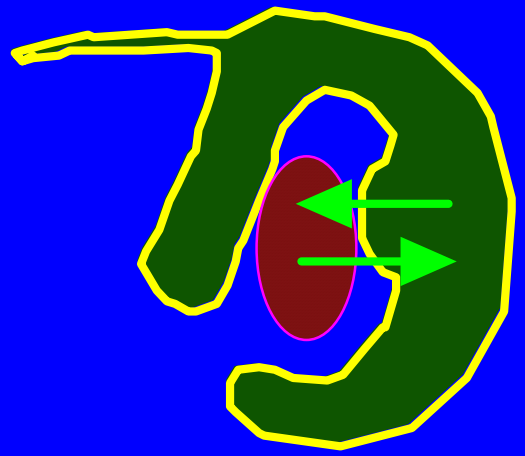
Water Perfusable Tissue Fraction (PTF)

Iida et al, Circulation, 1988

Use of LV TAC and Spillover Correction ^{15}O-Water Myocardial PET

Fitting f, α and V_a to R(t)

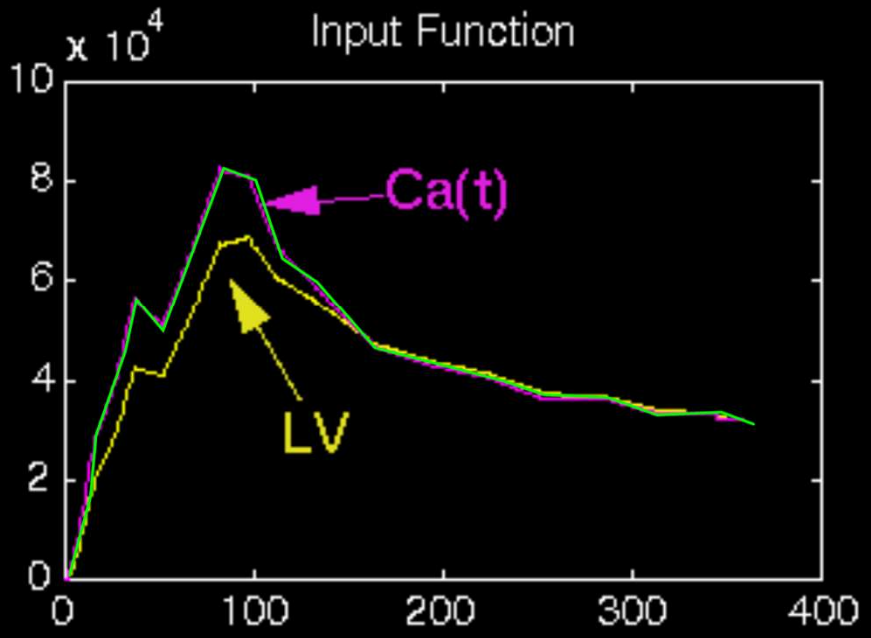
Spillover correction

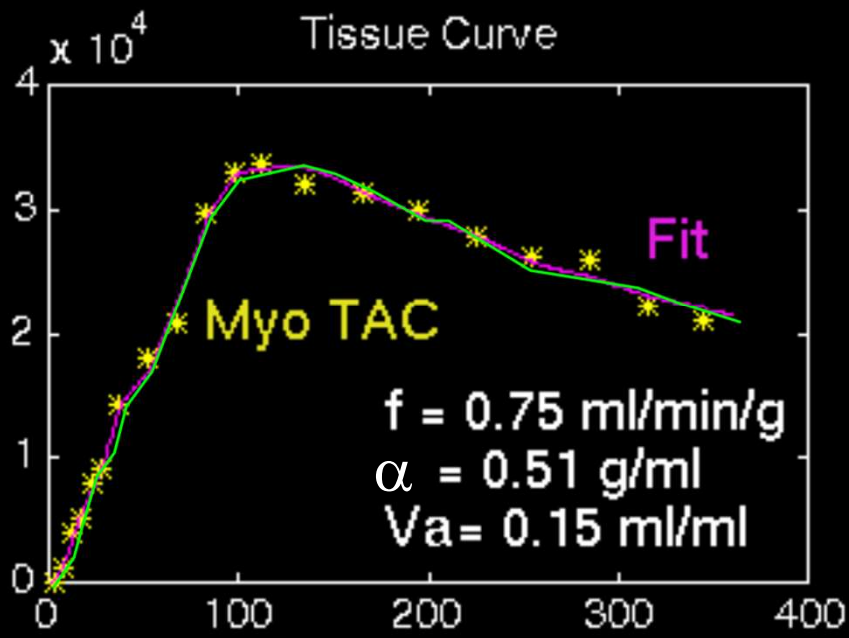


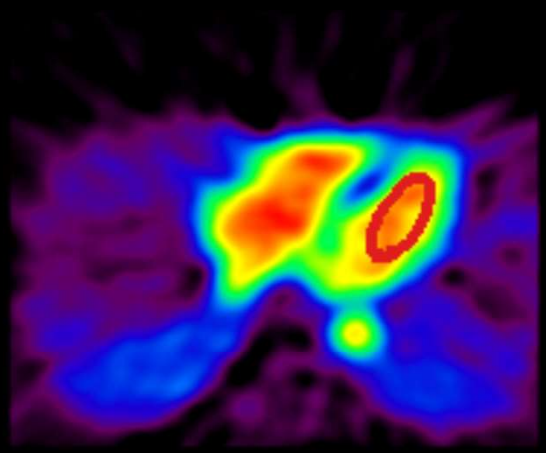
$$R(t) = \alpha C_i(t) + V_a C_a(t)$$

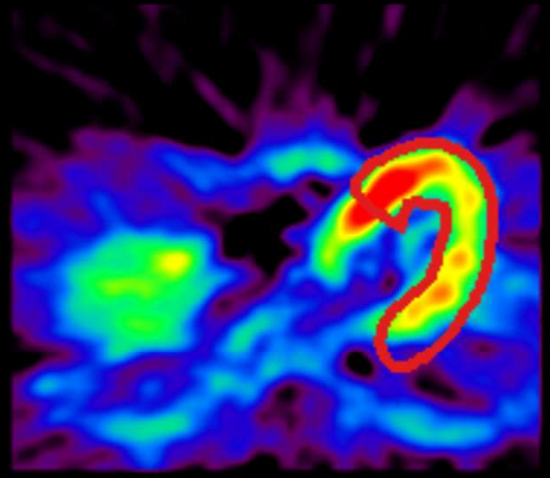
$$LV(t) = \beta C_a(t) + (1-\beta) C_i(t)$$

JNM 1992; 33:1669-1677
JNM 1995; 36:78-35





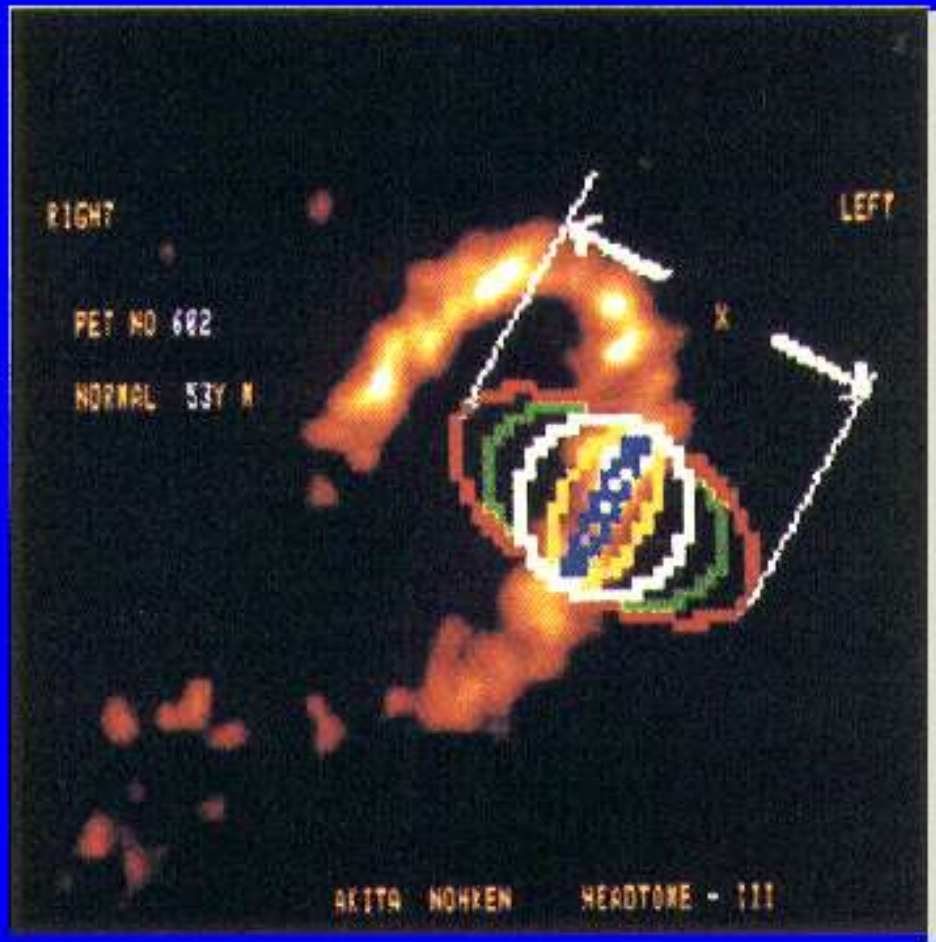


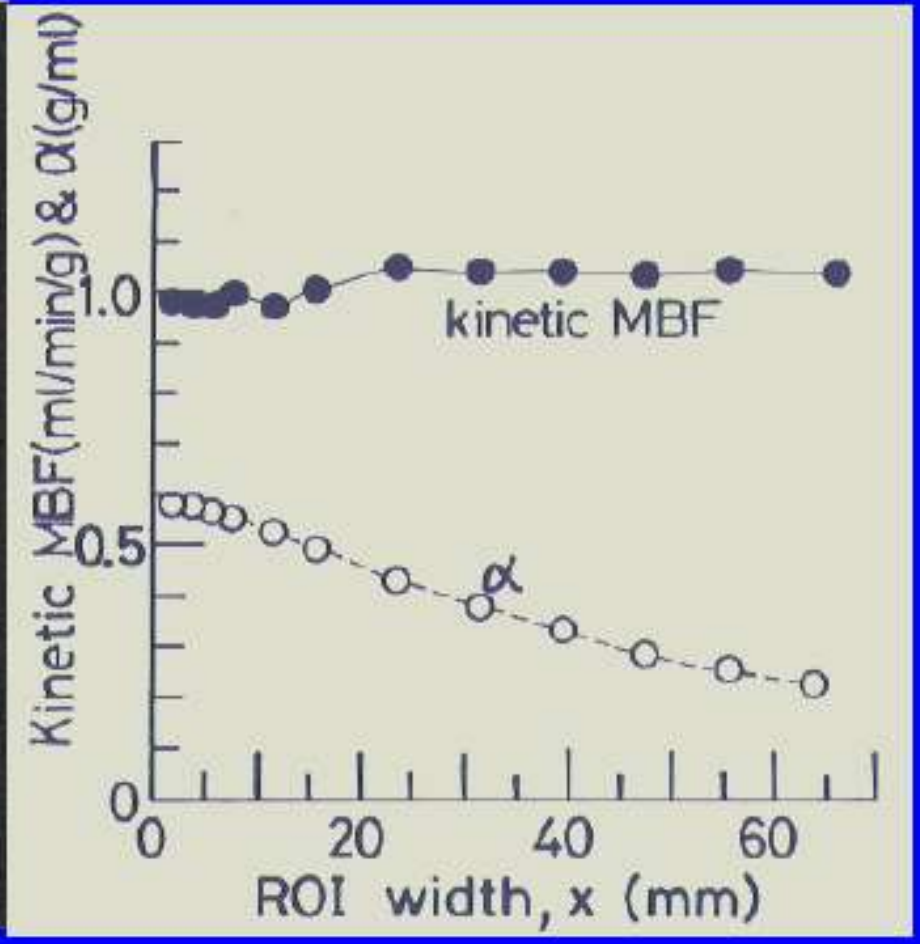


Iida et al., J Nucl Med 1992; 33:1669-1677

Validation of MBF Quantification by Use of O-15 Water

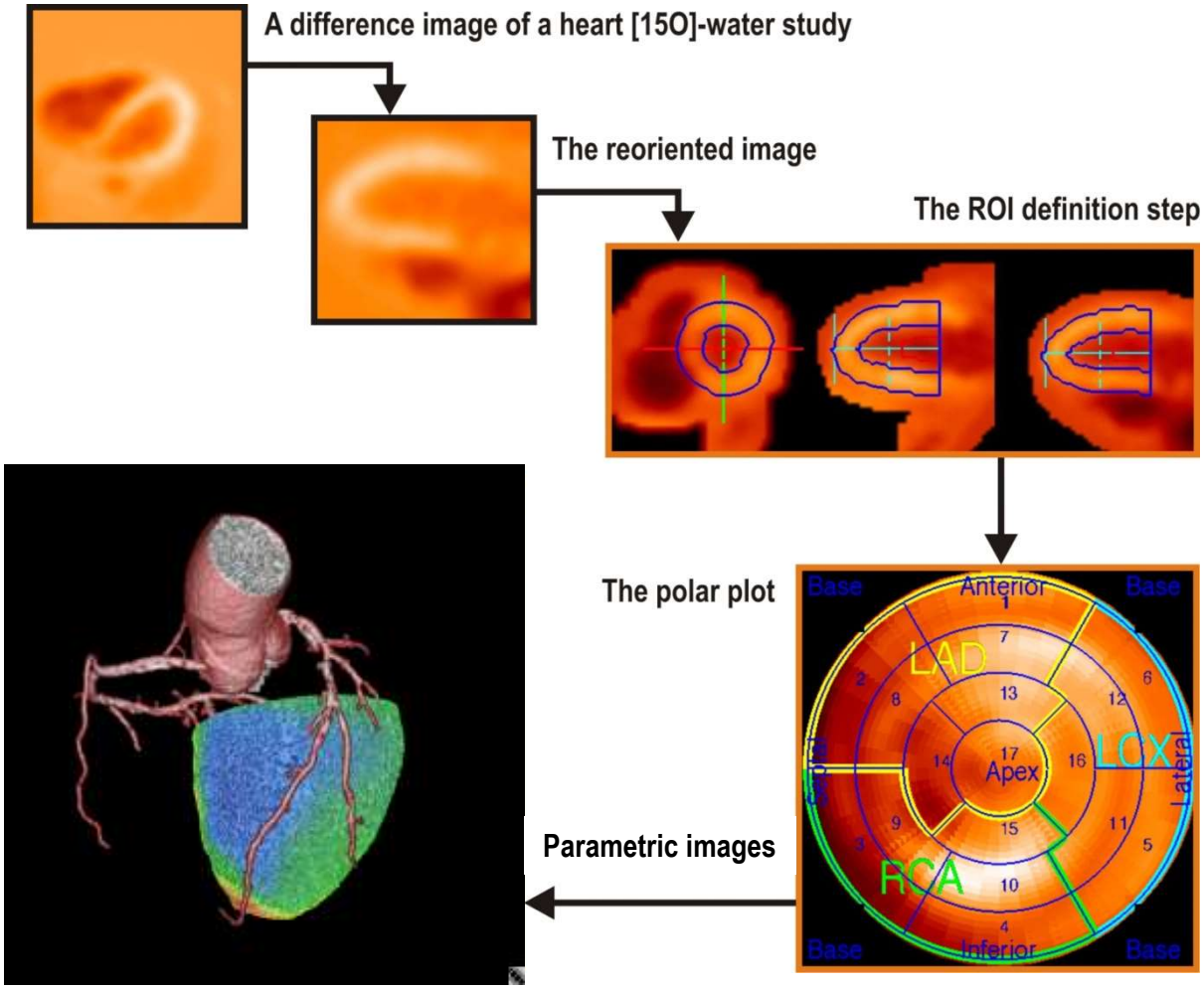
ROI Size Dependency of Estimated MBF





Iida et al Circulation 1988; 78:104-115

Analysis of PET myocardial perfusion study



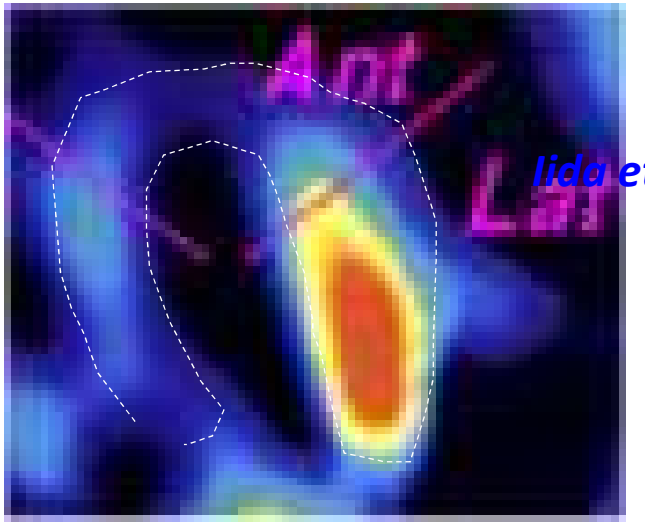
Carimas ™ / Turku PET Centre

Software packages for MBF quantification:

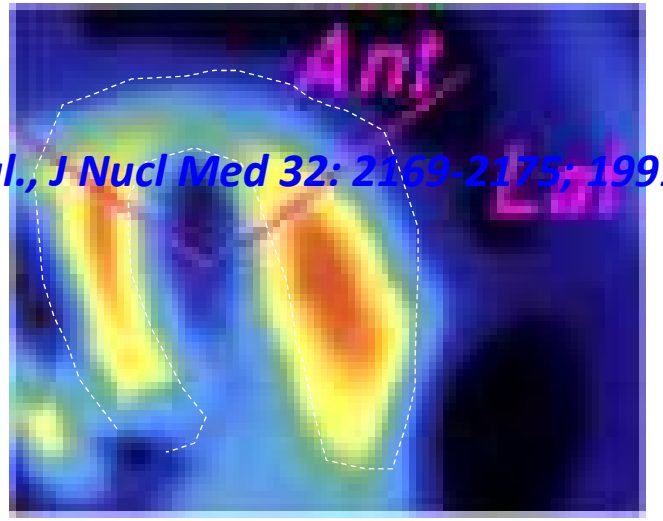
- aQuant
- Cardiac Vuer
- Munich Heart
- PMOD
- FlowQuant
- Carimas
- Syngo
- Hoquto
- QPET
- UW-QPP
- ImagenQ
- Corridor 4DM

Courtesy of Prof. J. Knuuti

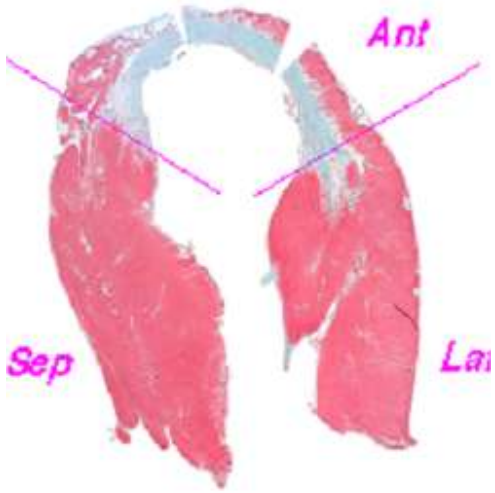
MBF and water-perfusable tissue (PTF) by ^{15}O-water PET in a K9 model of OMI



MBF
(ml/min/mL)



PTF
(g/mL)

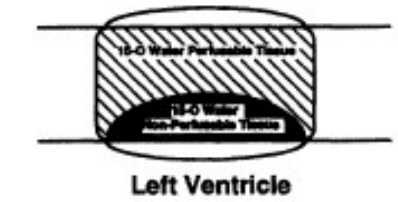


EM

Iida et al., J Nucl Med 32: 2169-2175; 1991

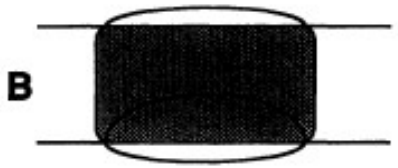
Iida et al J Nucl Med. 41:1737–1745., 2000

PTI as a Myocardial Viability Marker

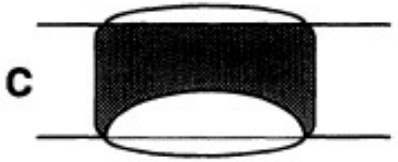


Myocardium

ROI



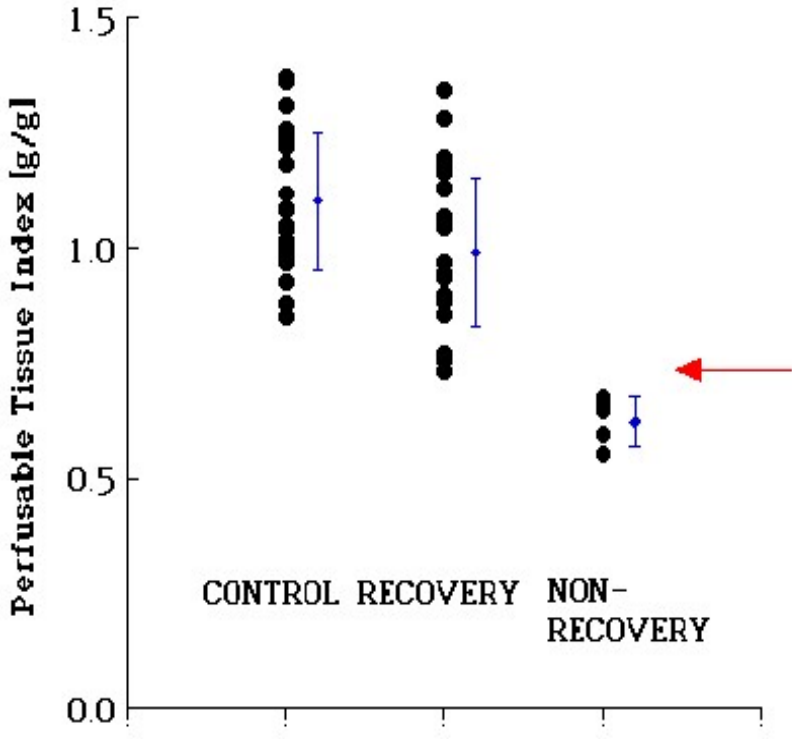
Total anatomical Tissue fraction (ATF) =B/A



Water-Perfusable Tissue fraction (PTF) = C/A

PTI = C/B (=PTF/ATF)

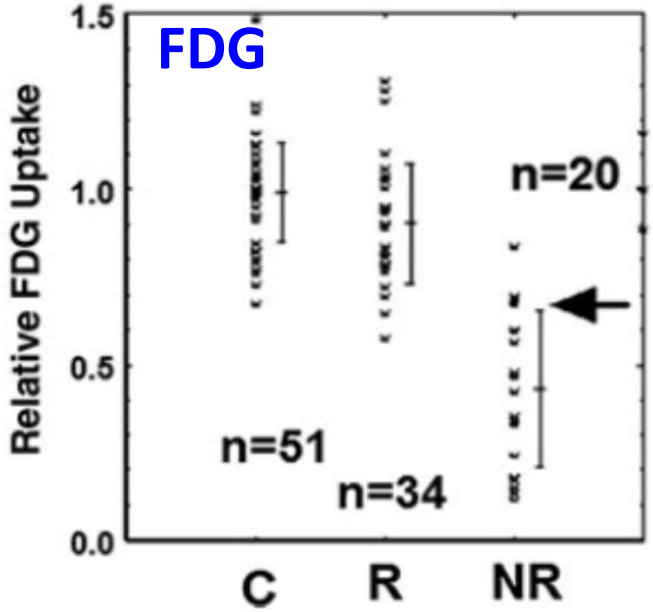
PTI values before CABG

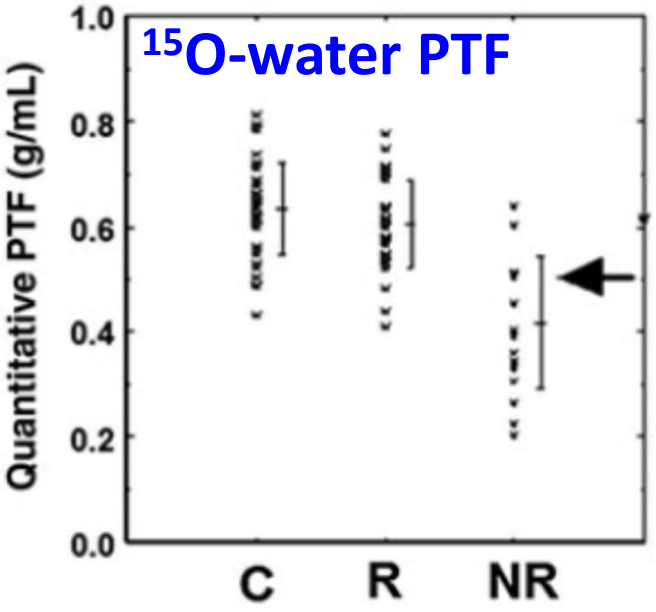


Yamamoto et al, Circulation, 1992

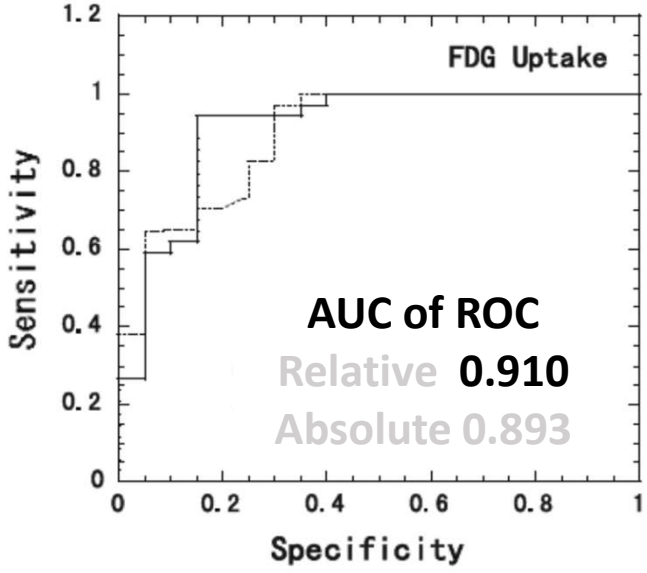
De Silva et al, Circulation, 1993

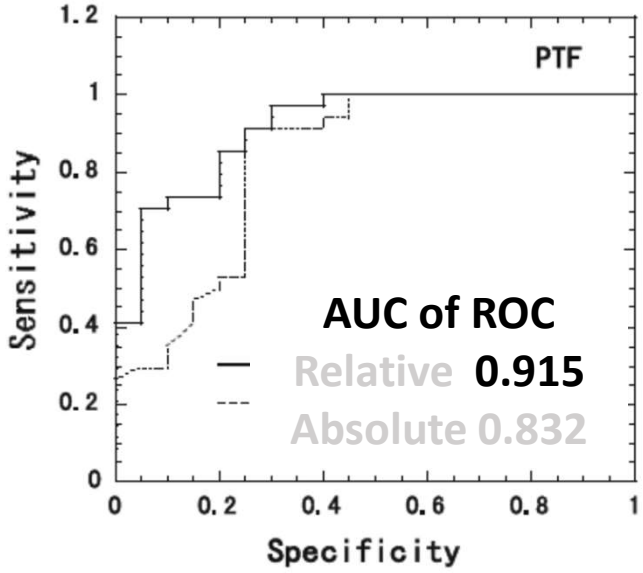
FDG & PTF as Myocardial Viability Marker





PTF: 70% of normal





16 Patients
128 ROIs

Iida et al Ann Nucl Med, 2012

Perfusable Tissue Index as a Potential Marker of Fibrosis in Patients with Idiopathic Dilated Cardiomyopathy

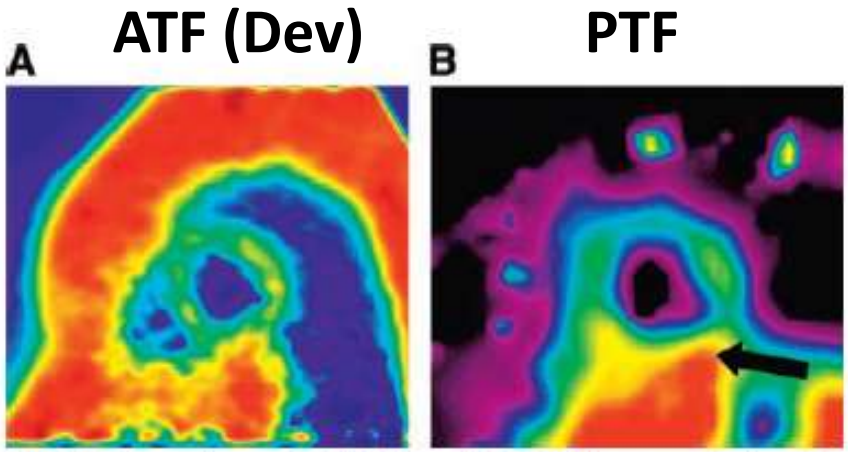


FIGURE 1. Short-axis ATF (A) and PTF (B) images of a healthy volunteer. Arrow in PTF image indicates inferior wall. Spillover effects from adjacent liver tissue are present.

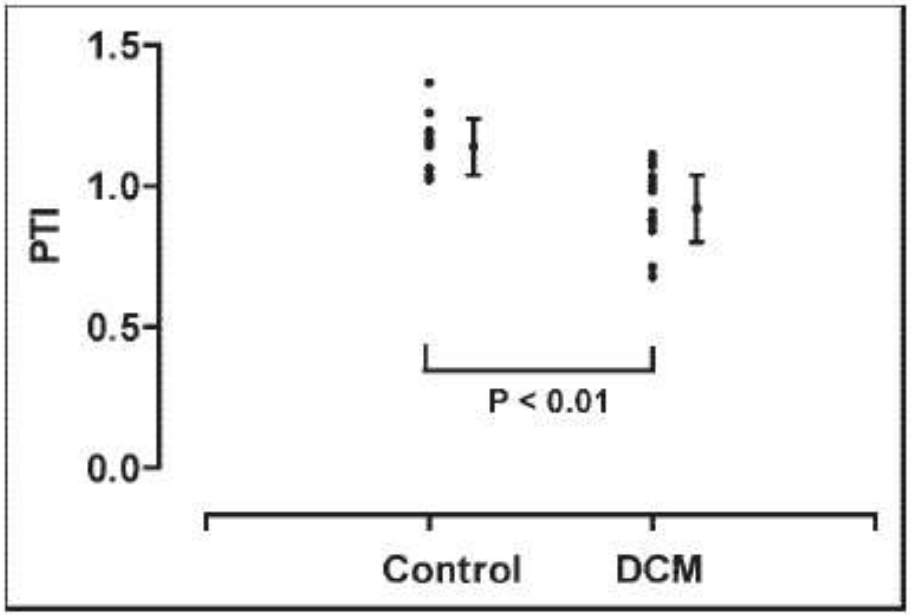


FIGURE 2. PTI for healthy control subjects and DCM patients.

Knaapen P et al., J Nucl Med. 45:1299–1304, 2004

Missing issues in this talk

1. Modeling for metabolic tracers, e.g., ^{18}F-FDG
2. Modeling for neuro-receptor ligands (reversible tracers) and application to drug development and evaluation.
3. Appearance of metabolized molecules in the blood
4. Examples where the existing compartment model is limited or does not work.
5. etc

Future perspectives

Mismatch between PET and CT images in attenuation correction
⇒ A novel approach for attenuation correction is needed

Metabolites in the AIF
⇒ Total body PET to estimate the metabolites in the arterial blood

Logistical complexity that made the usage of ^{15}O-oxygen inhalation PET difficult
⇒ Comprehensive automated radio-tracer production + inhalation system
⇒ Single Scan Dual Administration (SSDA) with sequential $^{15}O_2$ and $H_2{}^{15}O$

CT and PET mismatch

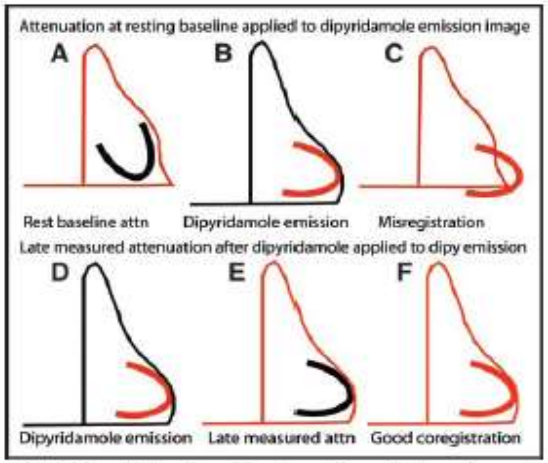
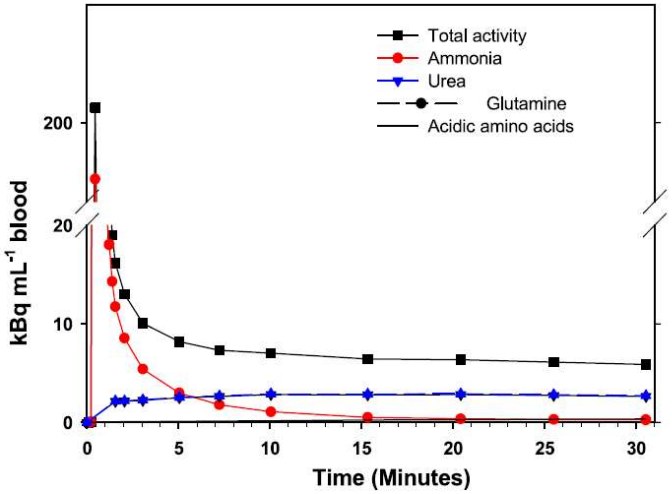
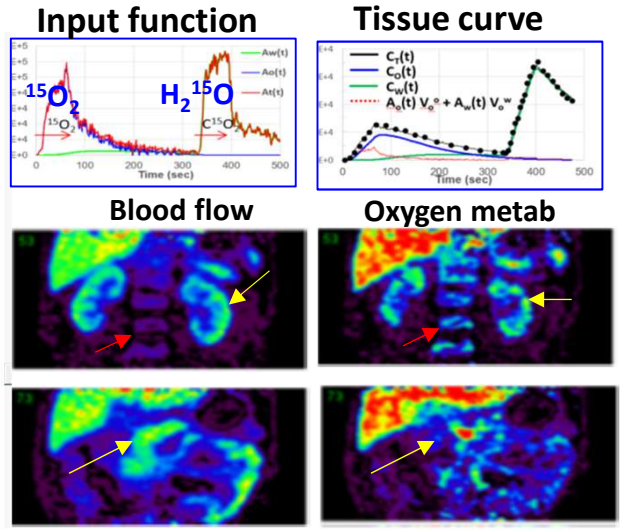


FIGURE 7. Mechanisms for attenuation artifacts using post-dipyridamole scan. Legend is the same as Figure 6.

Metabolites in AIF



SSDA ^{15}O-Gas PET



Total Body PET scanner with axial FOV of 106 cm

Biograph Vision Quadra - Siemens Healthineers