Modeling for Quantitative Assessment of Regional Myocardial Blood Flow

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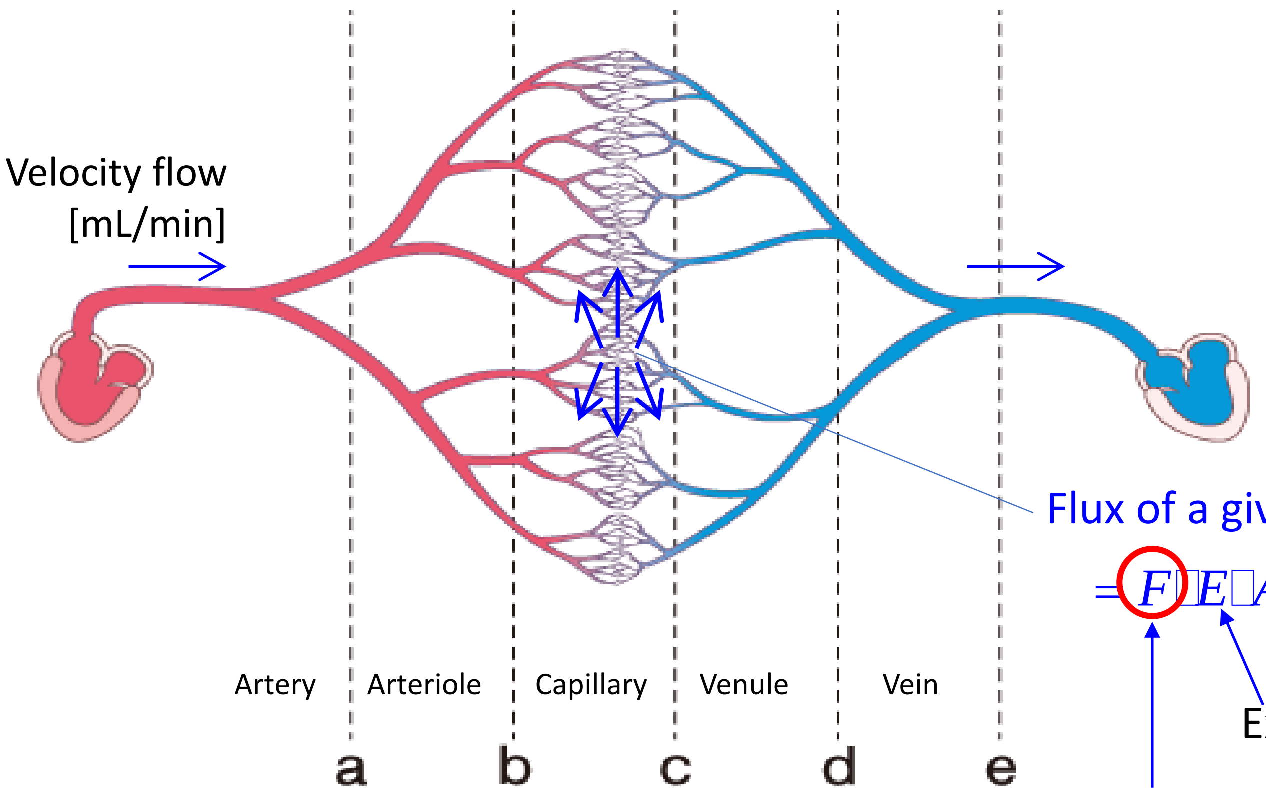
What is regional myocardial blood flow?

- **Blood flow (**Velocity flow of “blood”)

- **Regional tissue blood flow** (perfusion)
  A rate that supplies substrates to regional tissue with a separately defined extraction rate through the capillary membrane

What is regional myocardial blood flow?



Flux of a given substrate to tissue:

$$= F \cdot E \cdot A(t)$$

Extraction fraction

Regional blood flow [mL/min/g]

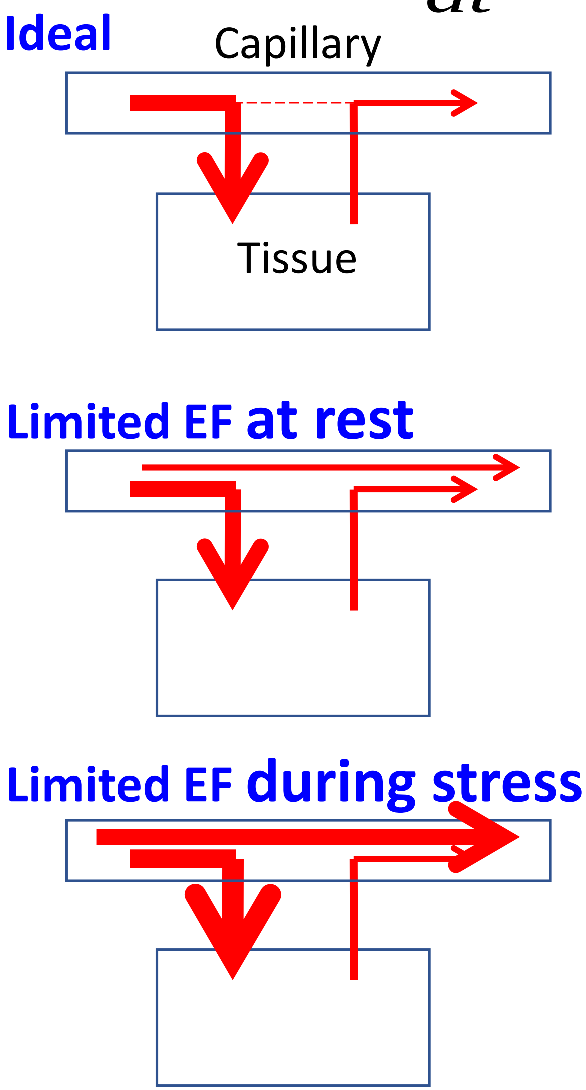
Given E of a radio-tracer, $F \cdot E$ is practically given as "regional blood flow"

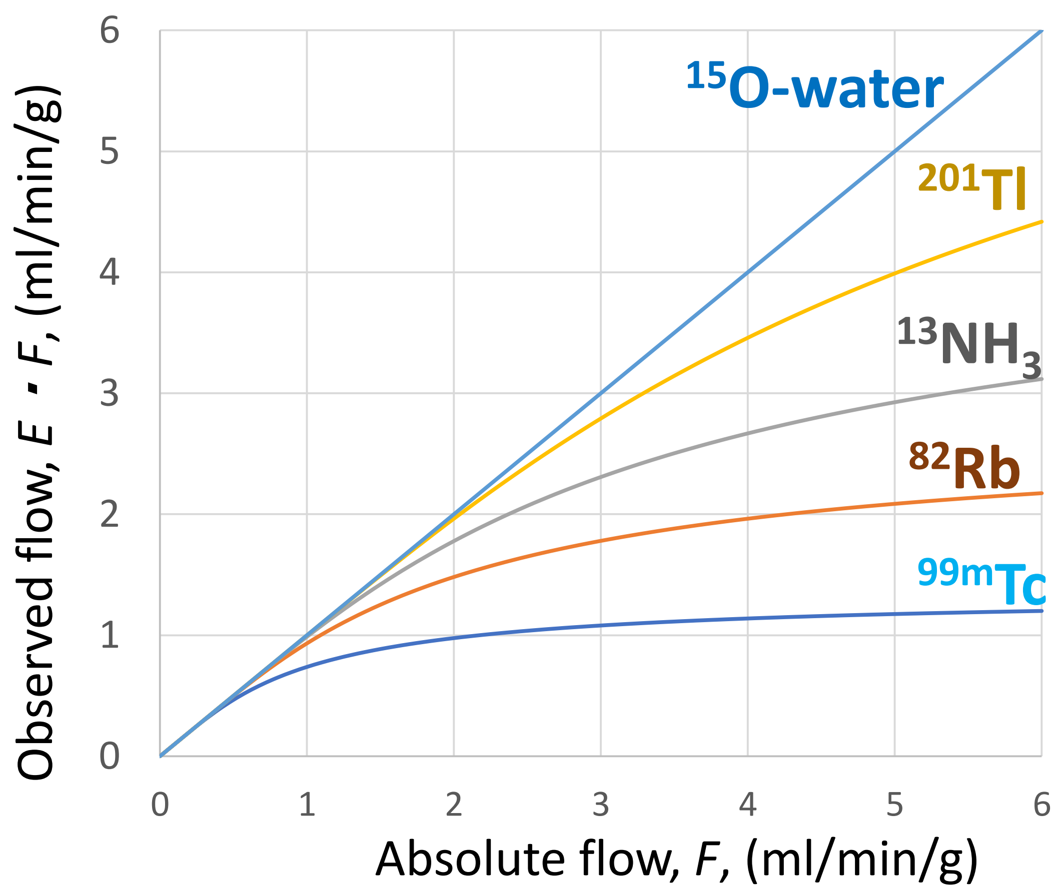
Radiotracers for myocardial perfusion in PET and SPECT

^{15}O-water	2.04 min (PET)	Onsite cyclotron
^{13}N-ammonia	9.96 min (PET)	Onsite cyclotron
^{18}F-flurpiridaz	109 min (PET)	Delivery/cyclotron
^{82}Rb	1.27 min (PET)	Generator
^{62}Gu-PTSM	9.74 min (PET)	Generator
^{201}Tl	72 hour (SPECT)	Delivery
^{99m}Tc-MIBI (^{99m}Tc-tetrofosmine)	6.01 hour(SPECT)	Generator/Delivery

First-pass extraction fraction

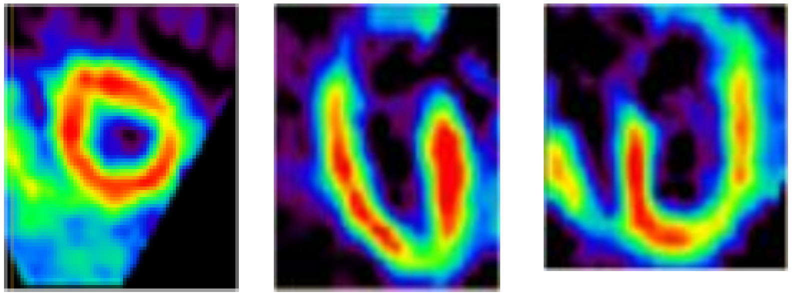
$$\frac{dC_i(t)}{dt} = \underbrace{E \cdot f}_{} \cdot Ca(t) - \underbrace{E \cdot f}_{} \cdot C_v(t)$$





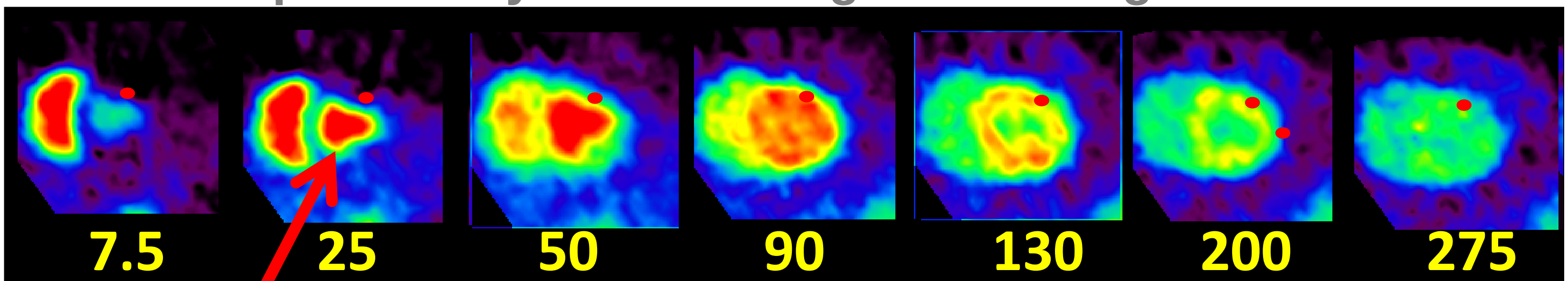
Use of ^{15}O-Water and PET for quantitative assessment of MBF

- Freely diffusible tracer
- Allows accurate quantitation of tissue perfusion including PVE correction
- Short half-life (2min)
- Allows repeated measurements
- Additional information of water-perfusable tissue fraction

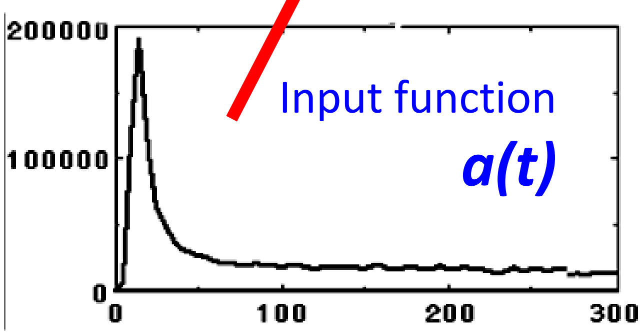


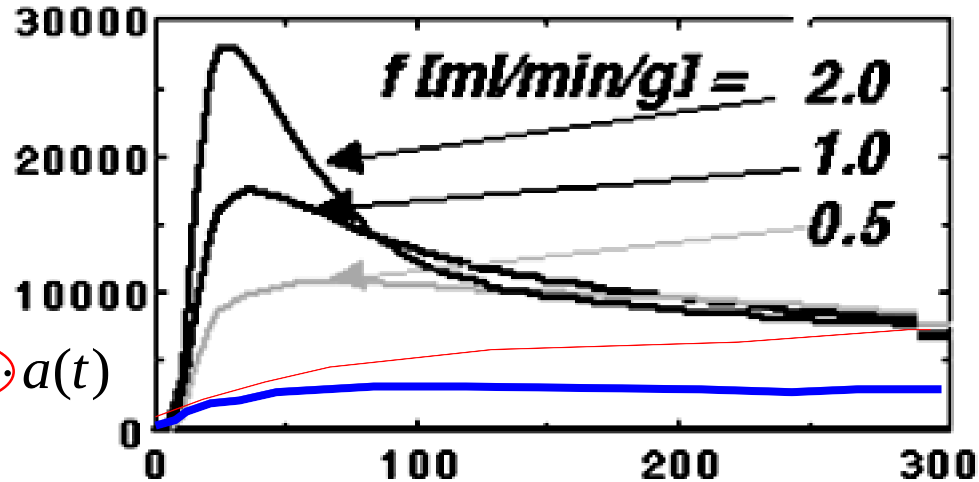
Kinetics of ^{15}O-Water in regional tissue

Sequential Myocardial Images following i.v.^{15}O-Water



Seconds after I.v. Injection



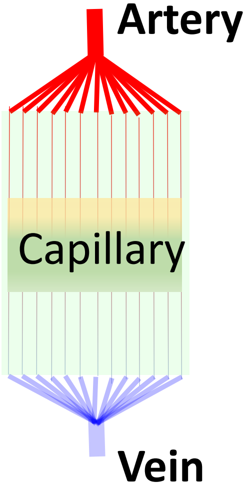


$$R(t) = PTF \cdot MBF \cdot a(t) \otimes e^{-\frac{MBF}{p}\cdot t} + V_a \cdot a(t)$$

MBF, PTF, V_a

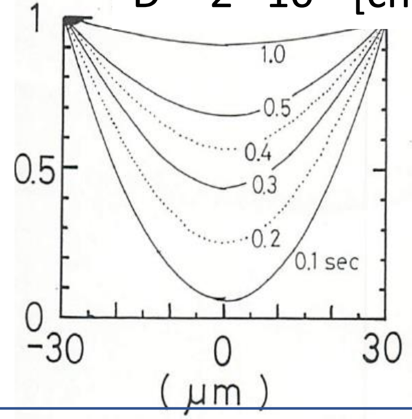
Instantaneous equilibrium of water in tissue

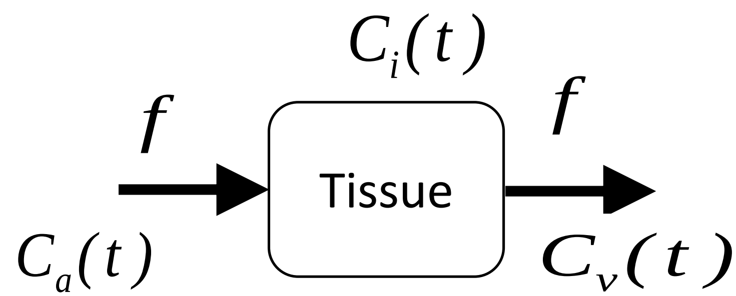
Small molecules reaches equilibrium distribution among capillary network



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

D〜2 · 10^{-5} [cm^2/s]





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

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

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

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

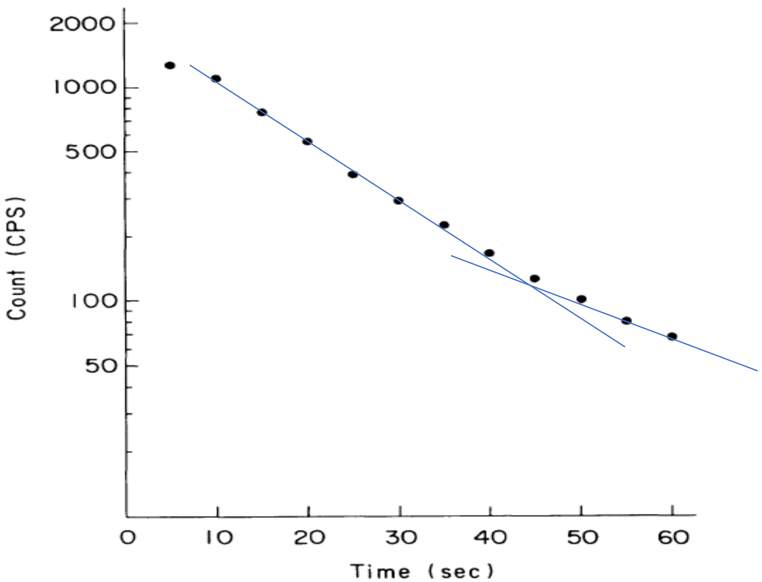
Tissue TAC

Input function

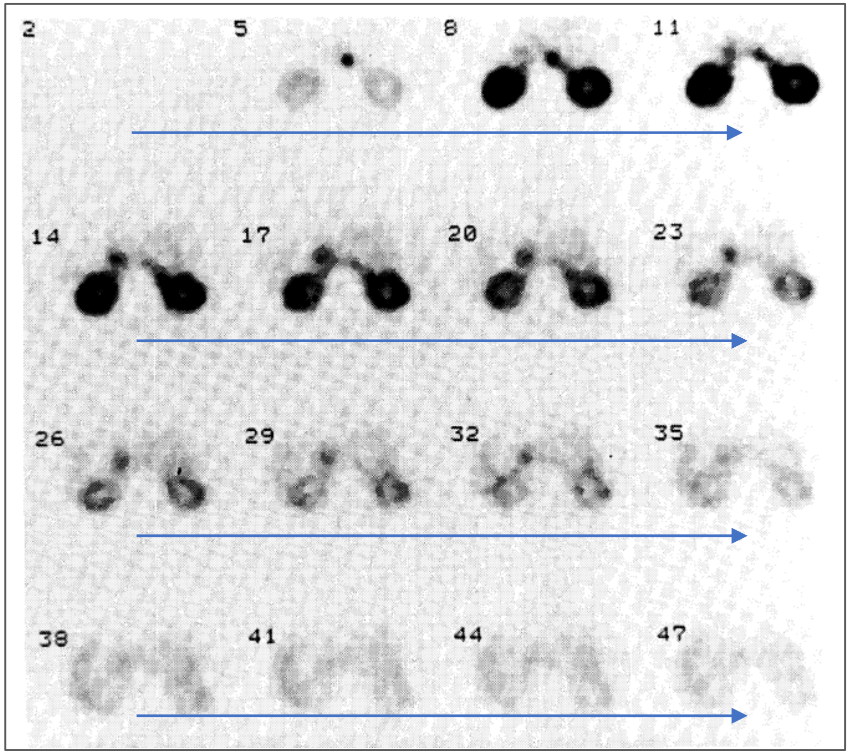
Regional flow

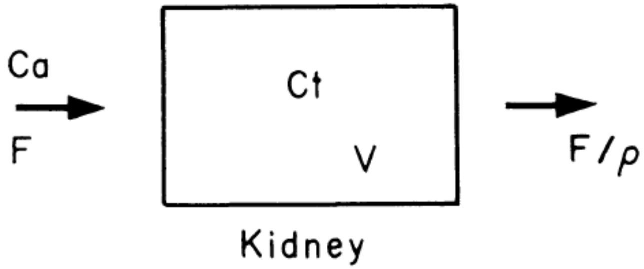
Kinetic model for regional kidney blood flow using ^{15}O-water and PET

Clearance curve after bolus injection of ^{15}O-water into Kidney artery



Sequential images after bolus injection of ^{15}O-water into Kidney artery



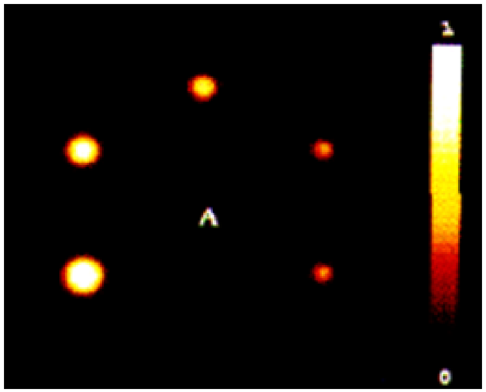


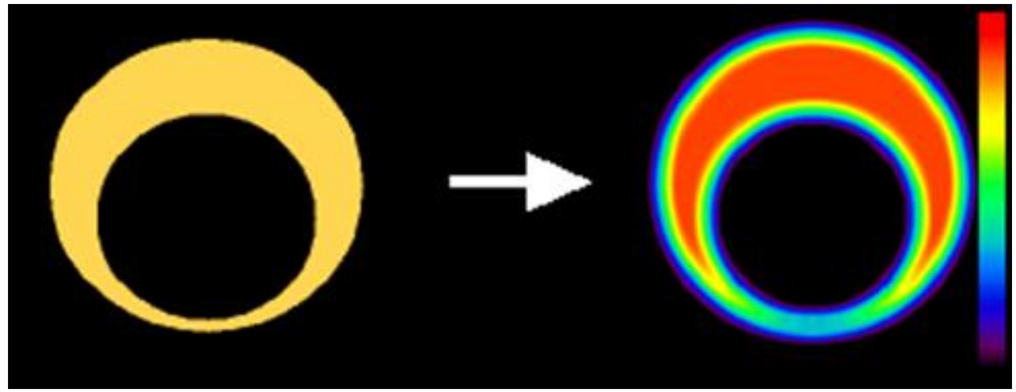
$$\frac{dC_t(t)}{dt} = F \cdot C_a(t) - \frac{F}{\rho} \cdot C_t(t)$$

or $C_t(t) = e^{-(F/\rho)\cdot t}$

Inaba et al., Tohoku J. Exp med, 1989, 159:283-289

Partial Volume Effect (PVE) in myocardial PET





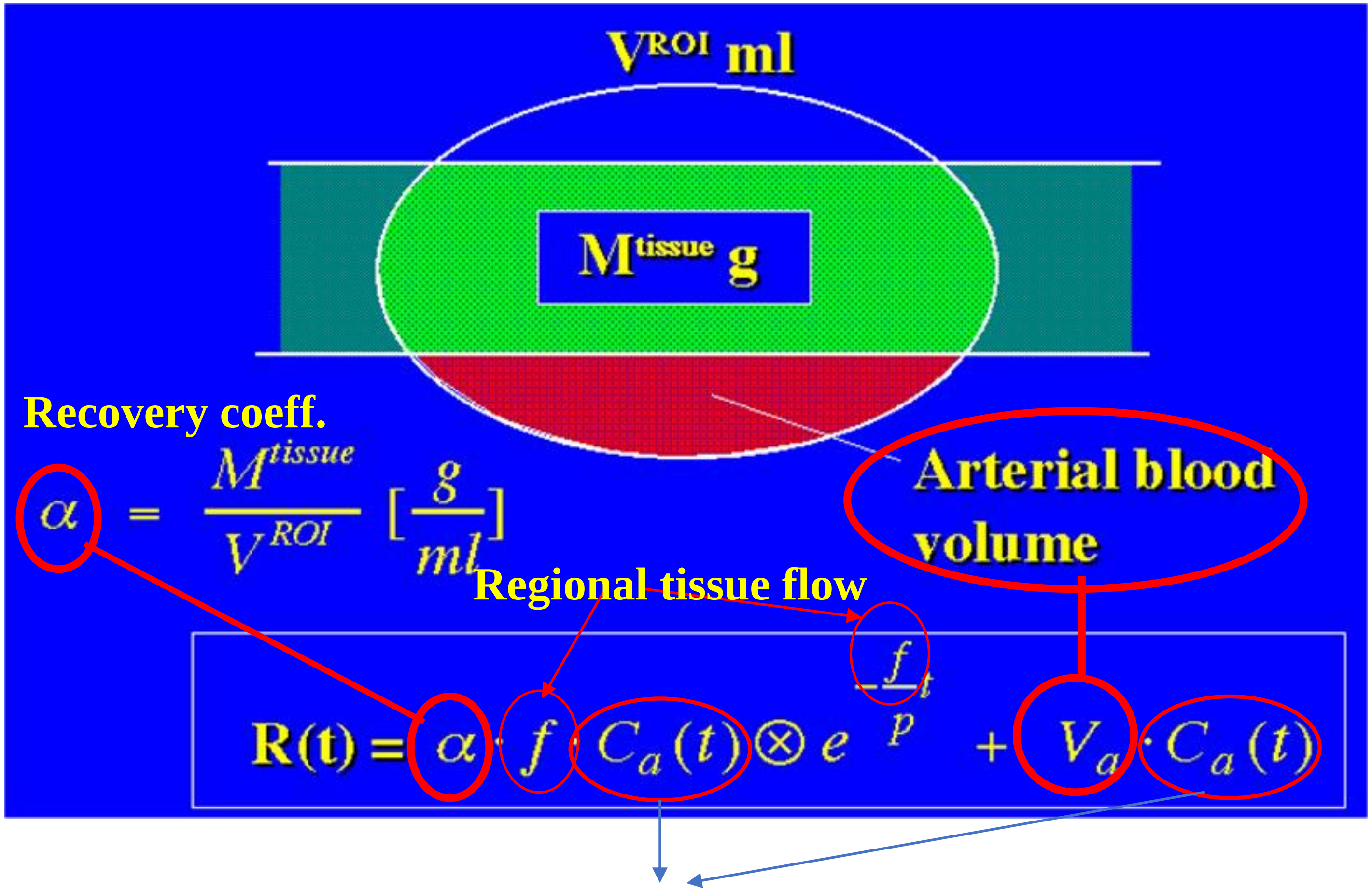
- PET provides radioactivity concentration in Bq per unit volume element [Bq/mL]

- For objects with small structure having the radioactivity concentration of Bq per unit mass [Bq/g-tissue], PET underestimats the radioactivity concentration:

$$PET\left[\frac{Bq}{mL}\right] = \alpha[\frac{g}{mL}] \cdot Tissue\,Concentration[\frac{Bq}{g}]$$

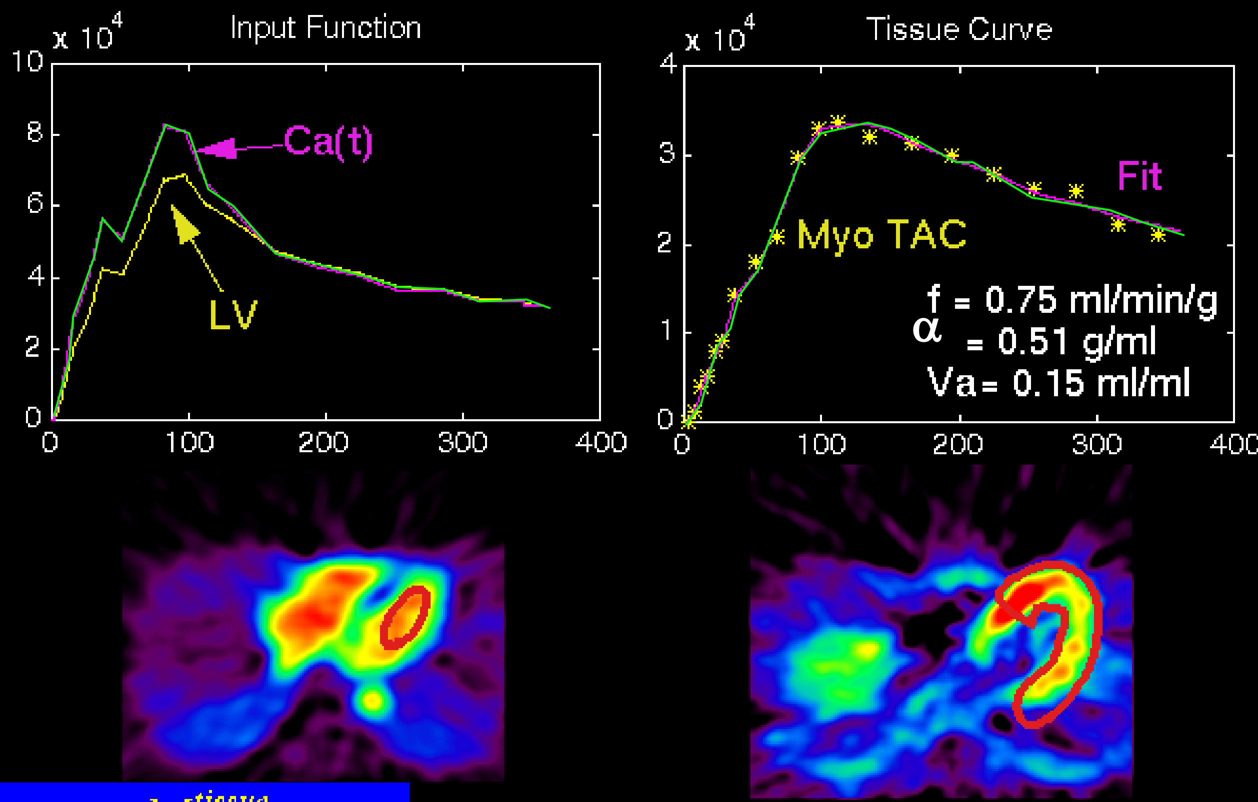
Compartment model for Myocardial ^{15}O-water PET

Unique approach to correct for partial volume effect



Can be estimated from LV chamber TAC on PET images

An example of data analysis for ^{15}O-Water PET for regional myocardial blood flow

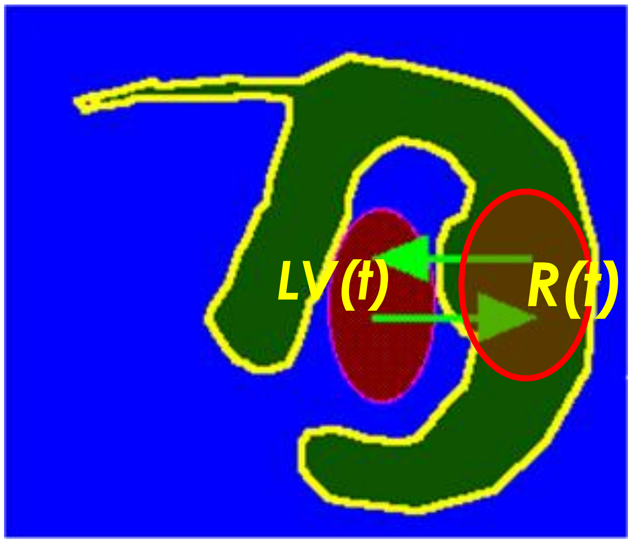


$$\alpha = \frac{M^{tissue}}{V^{ROI}} \left[\frac{g}{ml}\right]$$

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

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

Unique approach to correct for partial volume effect



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

$$LV(t) = \beta \cdot C_a(t) + \gamma \cdot C_i(t)$$

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

$$\because \beta + \gamma = 1$$

$$C_i(t) = \alpha \cdot f \cdot C_a(t) \otimes e^{-(f/p)\cdot t} + V_a \cdot C_a(t)$$

For a given β-value,

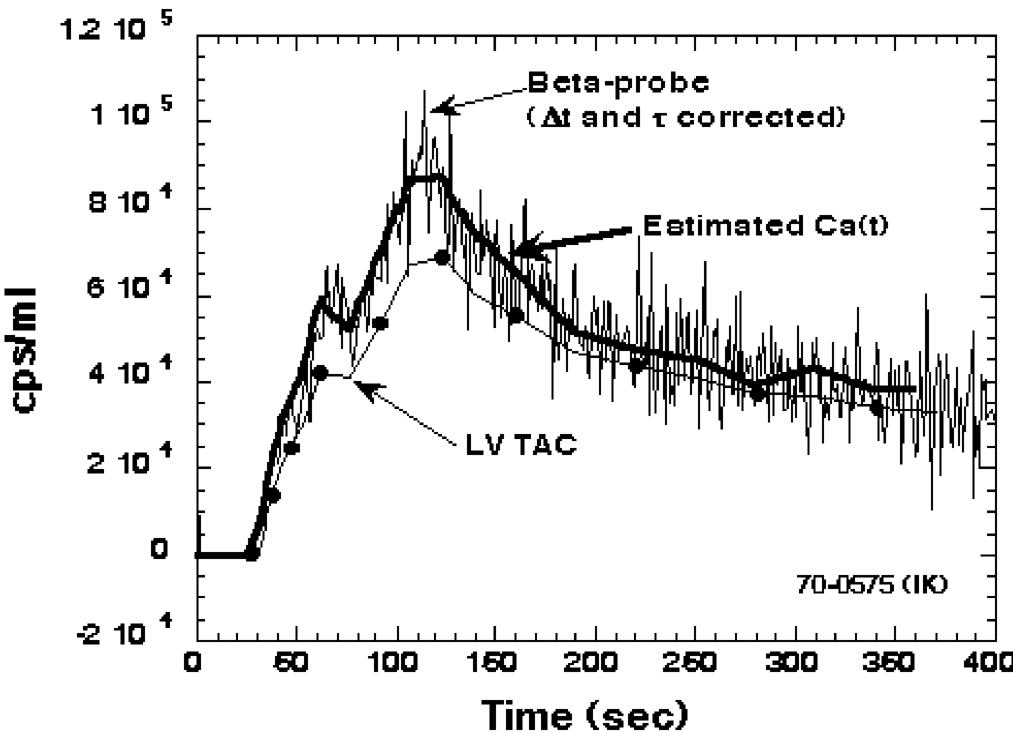
fitting f, α and V_a to R(t) and LV(t) enables estimation of Ca(t)

Important that a correct β value is given, and that $\beta + \gamma = 1$ is a good approximation

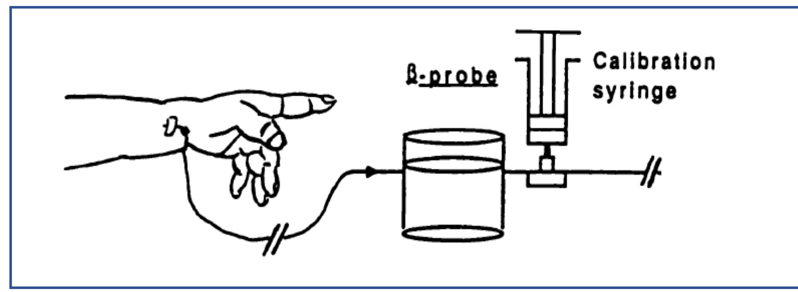
JNM 1992; 33:1669-1677

Validation of ^{15}O-Water PET for quantitation of regional myocardial blood flow

Validation of LV Input Function in O-15 Water PET

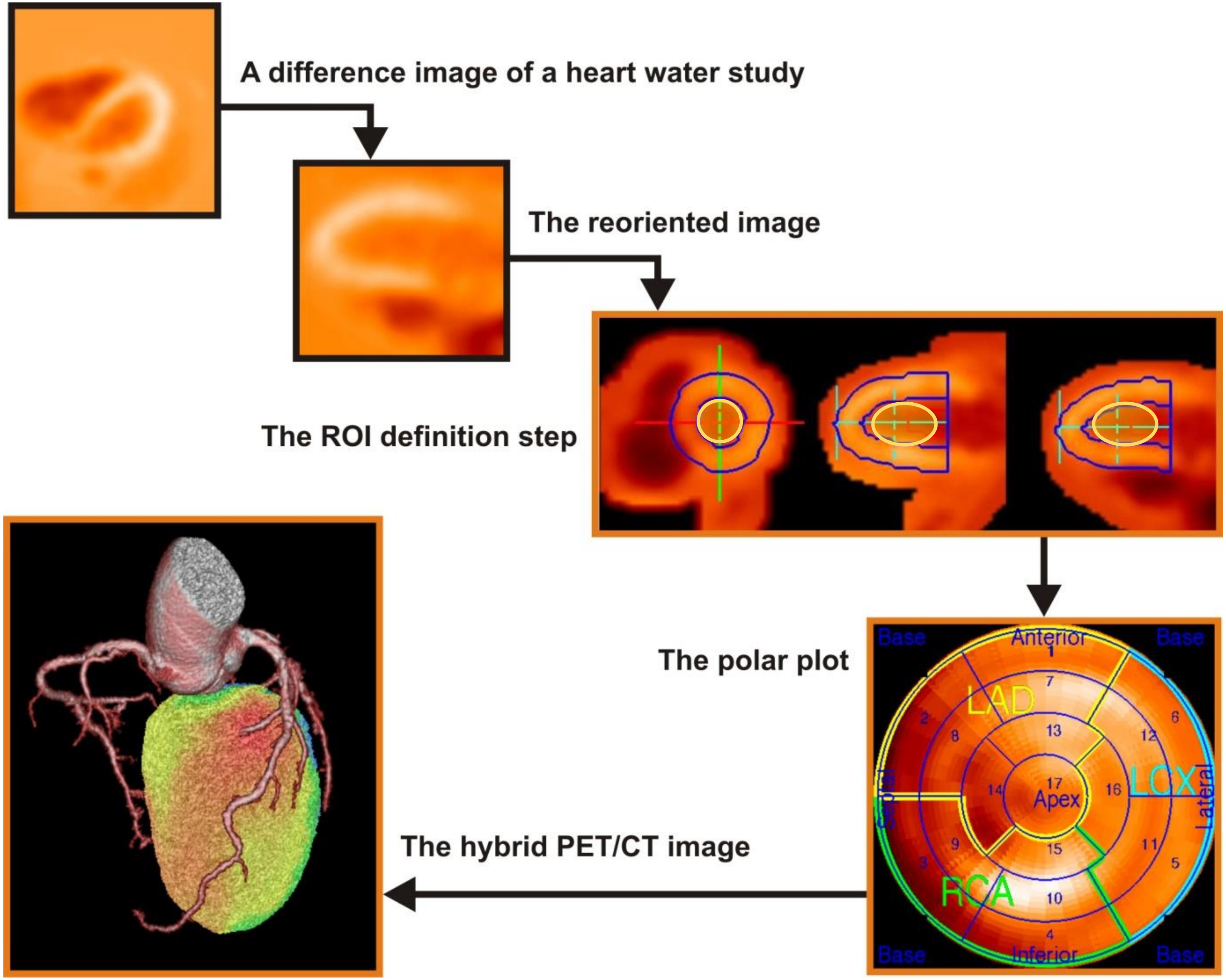


Continuous arterial blood sampling & monitoring radioactivity concentration in the catheter tube



From Iida et al., J Nucl Med 1998;39:1789-1798

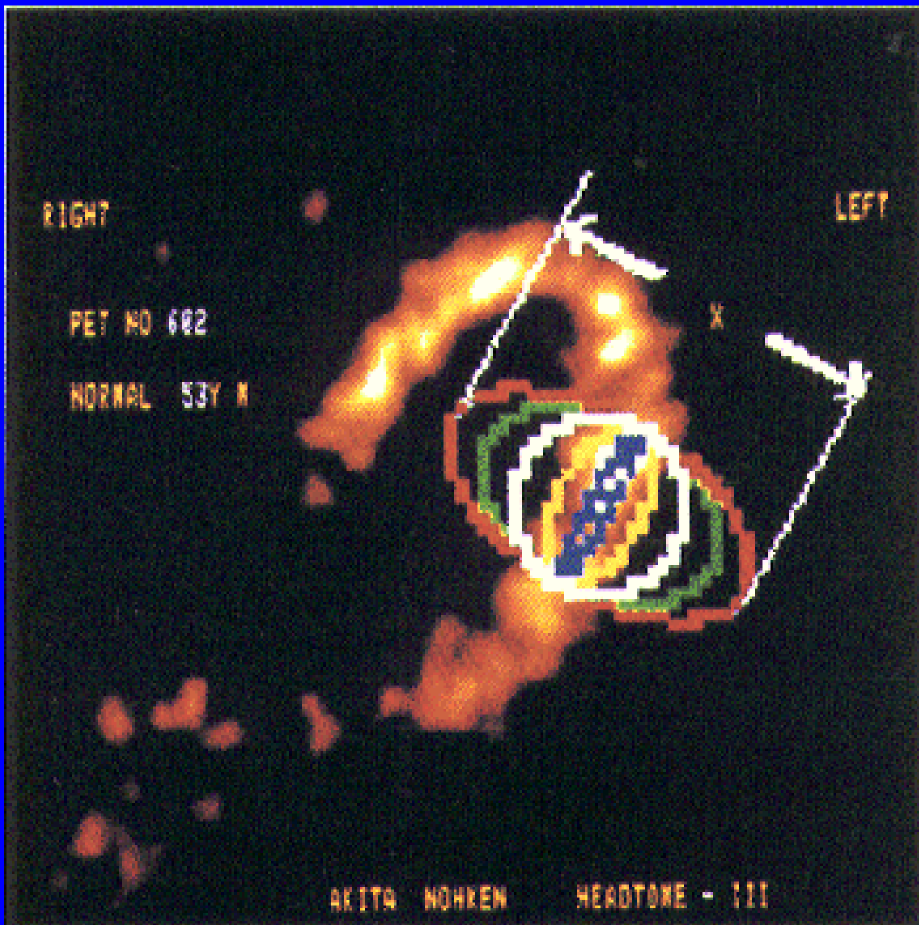
Analysis of dynamic PET Imaging: ^{15}O-water

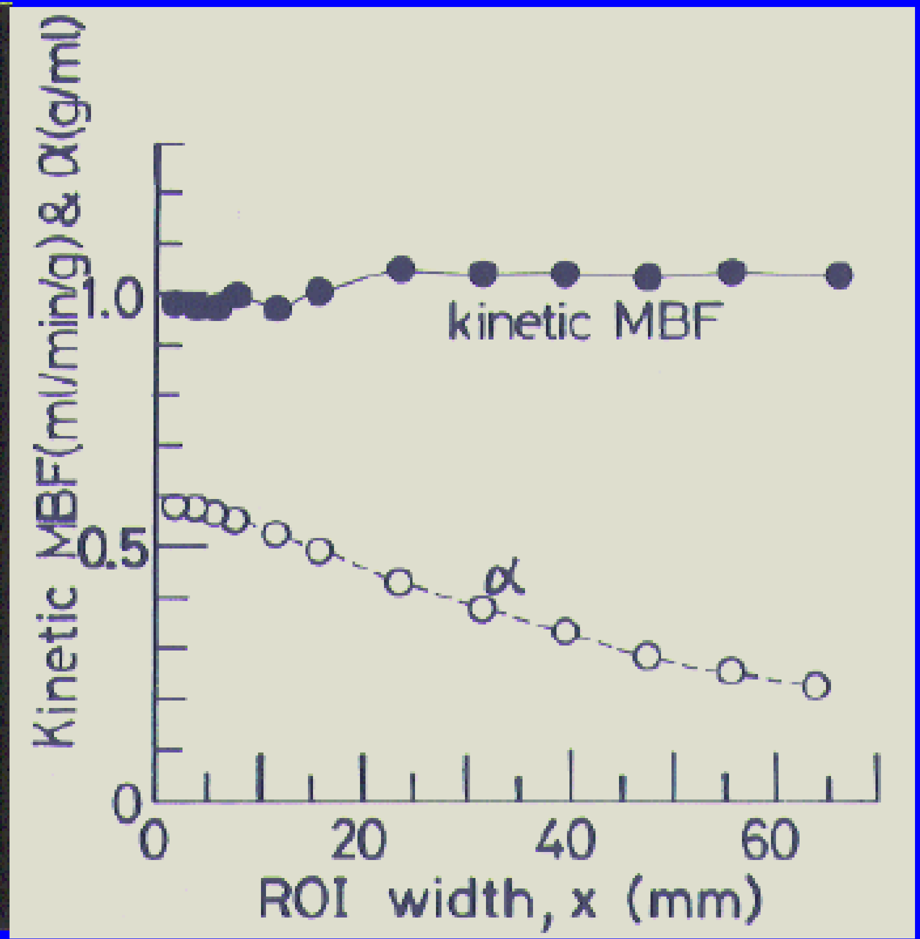


Turku PET Centre

Validation of MBF Quantification by Use of O-15 Water

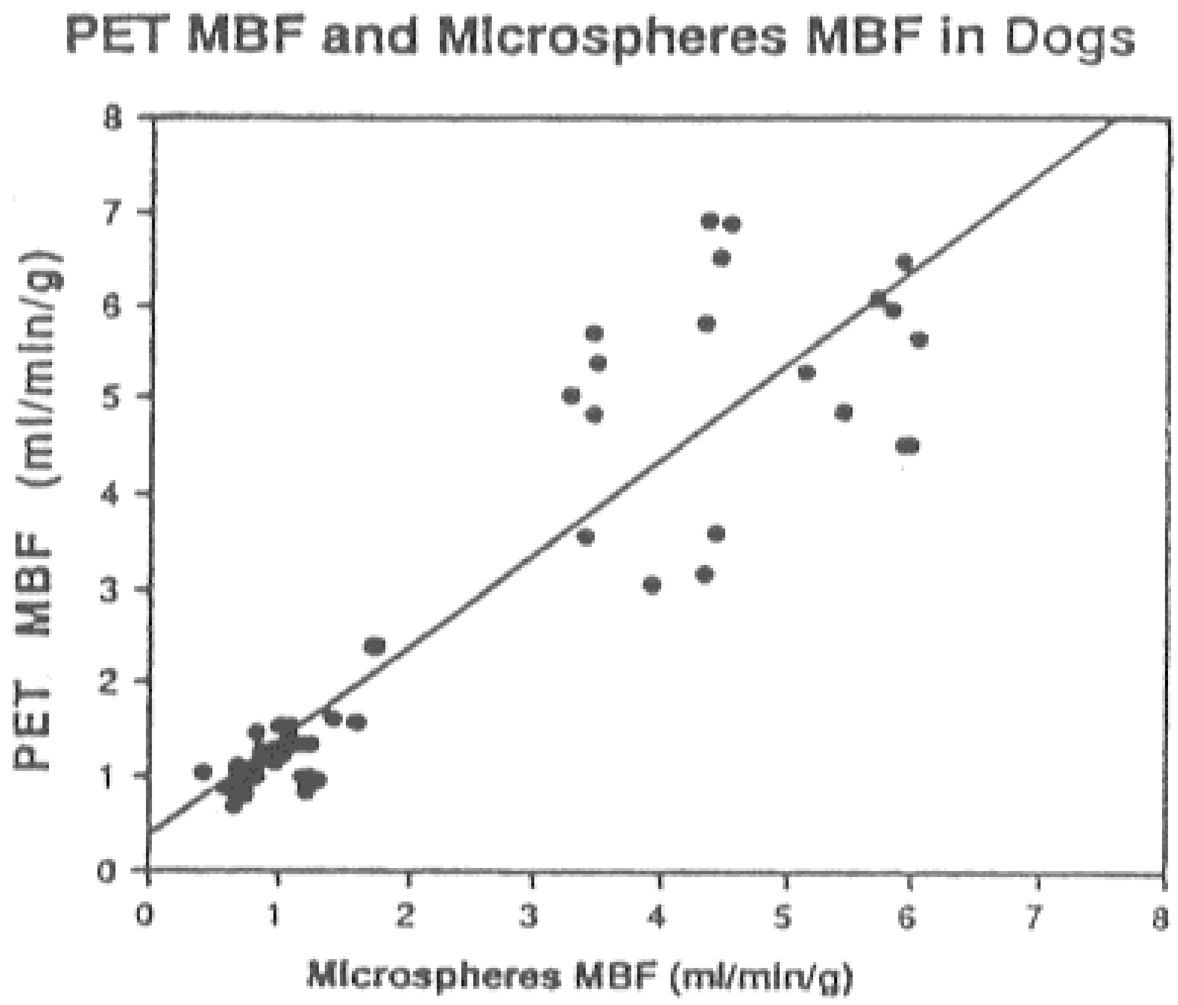
ROI Size Dependency of Estimated MBF





Iida H, Circulation 78:104-115, 1988

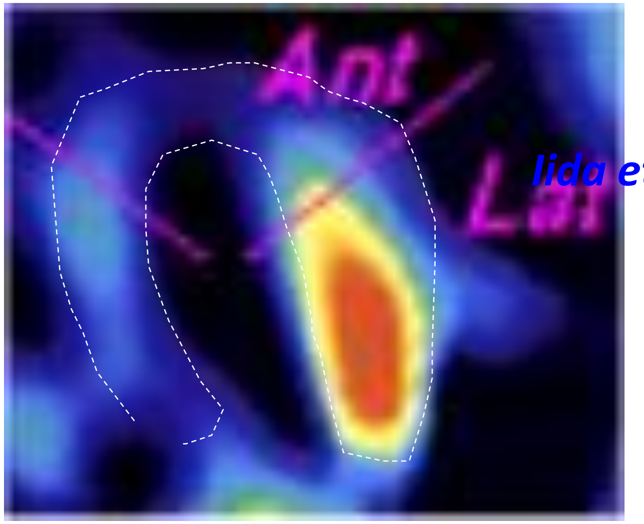
Validation of ^{15}O-Water PET for quantitation of regional myocardial blood flow



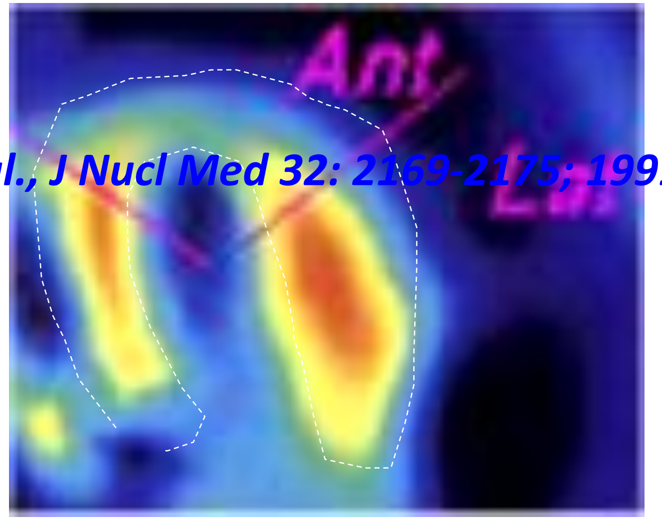
Araujo et al., Circulation 1989

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

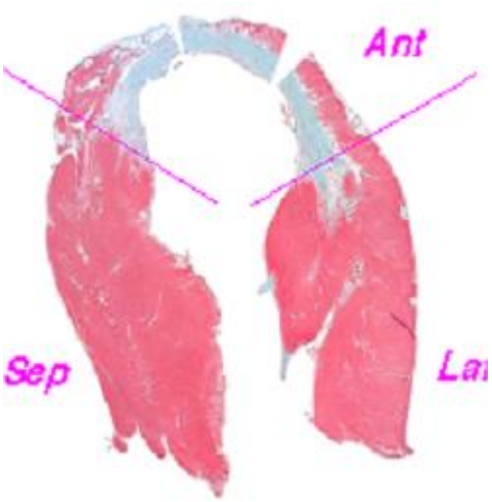
Iida et al., J Nucl Med 32: 2169-2175; 1991



MBF
(ml/min/mL)



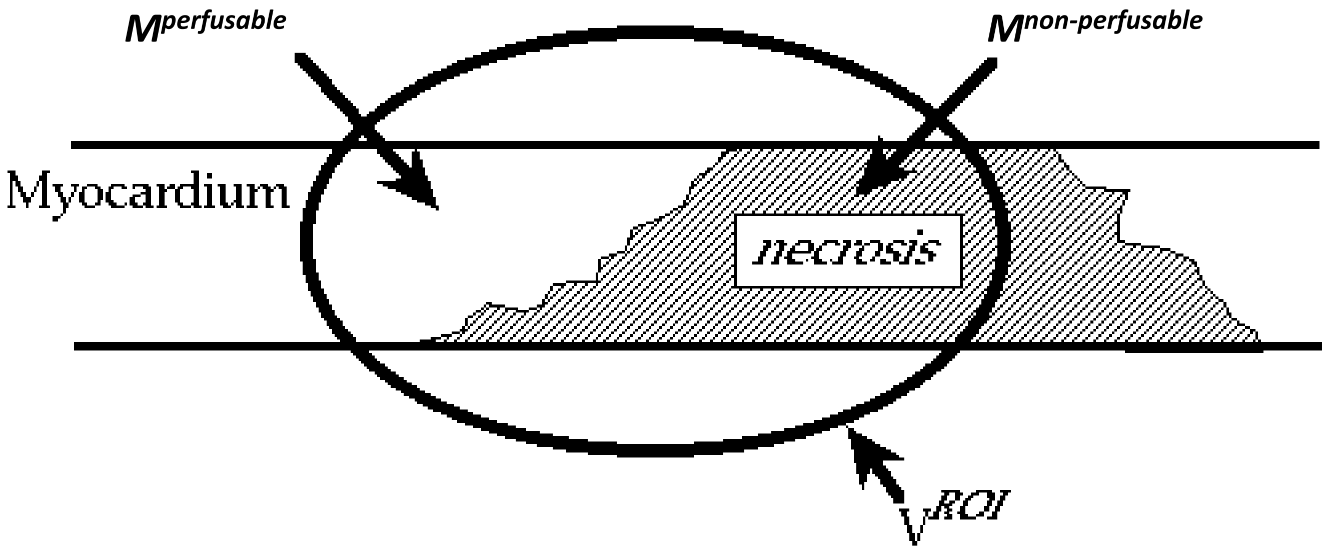
PTF
(g/mL)



EM

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

Water perfusable tissue fraction in the area of myocardial infarction



PTF (α) = $M^{perfusable}$ / V^{ROI}

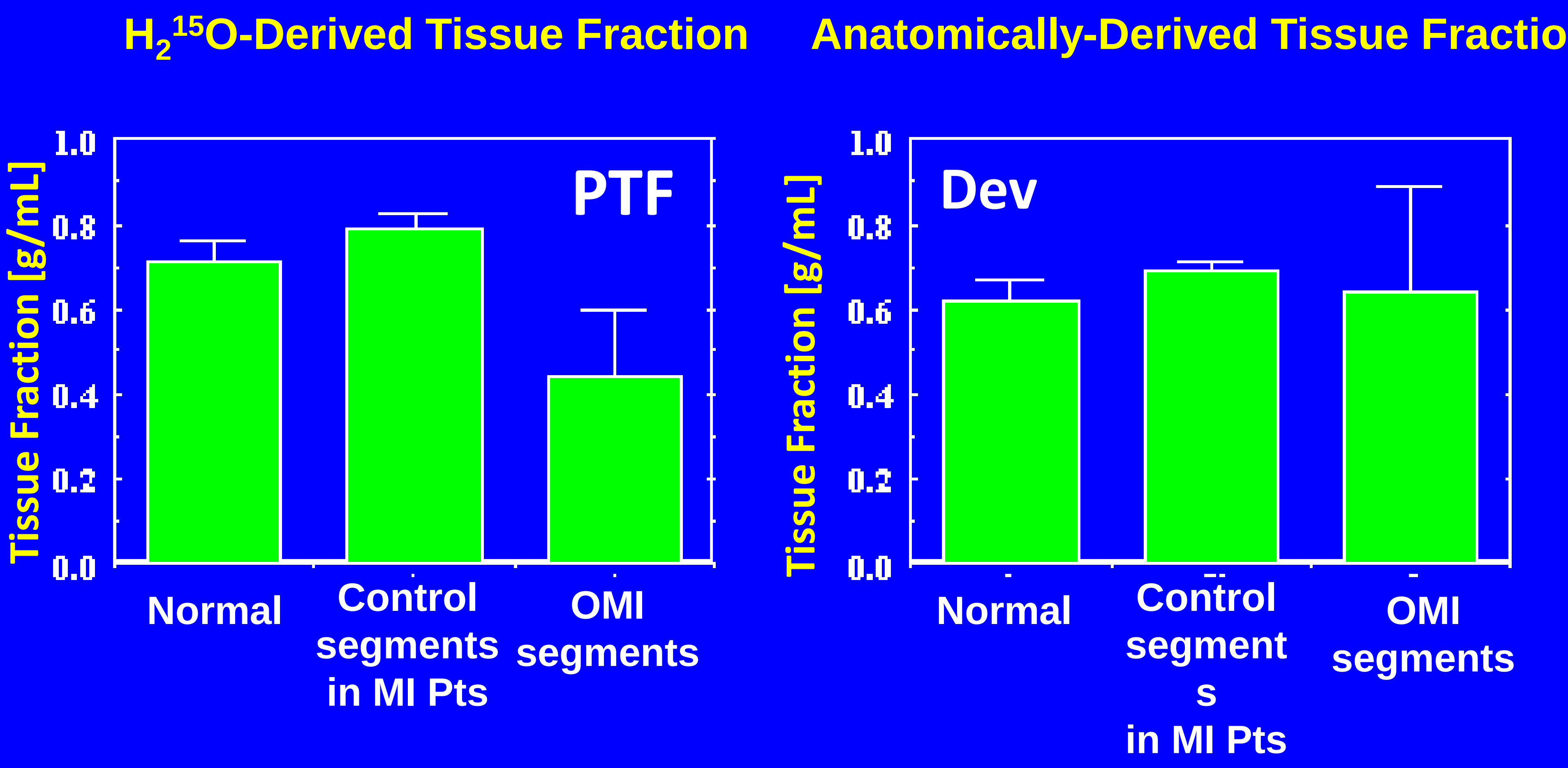
ATF (Dev) = ($M^{perfusable}$ + $M^{non\text{-}perfusable}$)/ V^{ROI}

PTF $\leq$ Dev

PTI $\equiv$ PTF/Dev = $M^{perfusable}$ / M^{total}

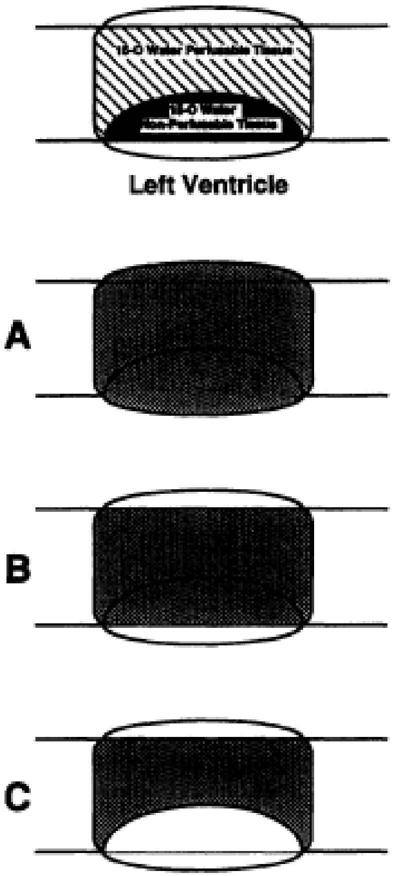
Iida et al., J Nucl Med 32: 2169-2175; 1991

Functional vs Anatomical PVE Correction Factor



Iida et al., J Nucl Med, 1991

PTI as a Myocardial Viability Marker



Myocardium

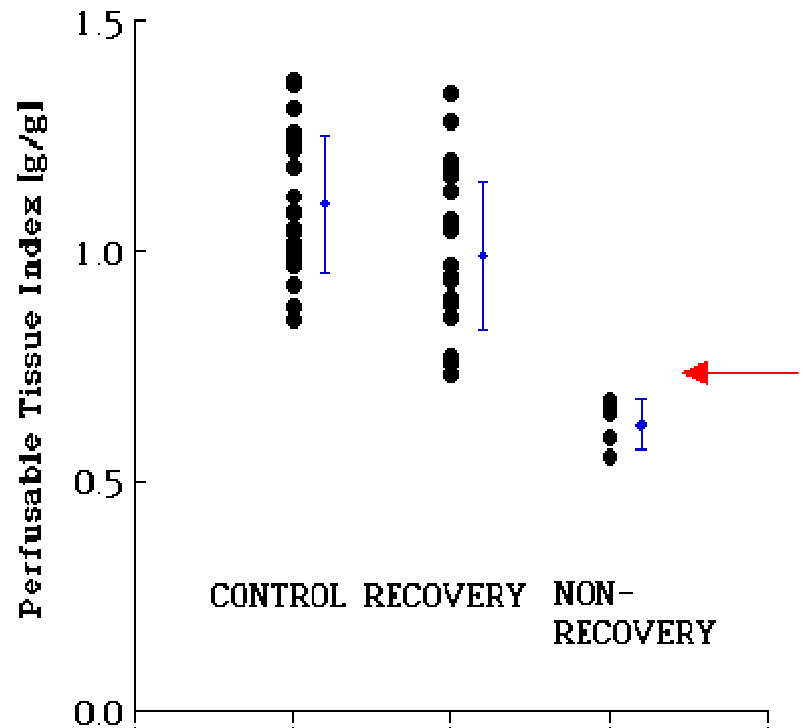
ROI

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

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

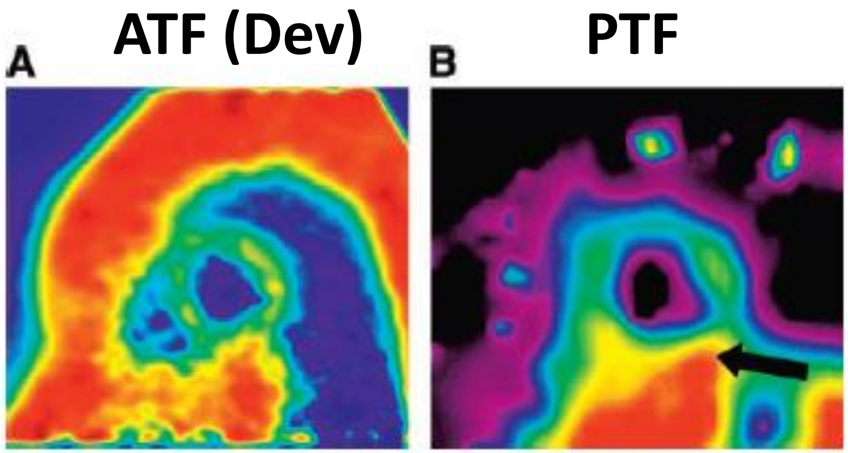


FIGURE 1. Short-axis ATF (A) and PTF (B) images of a healthy volunteer. Arrow in PTF image indicates inferior wall. Spillover effects from adjacent liver tissue are present.

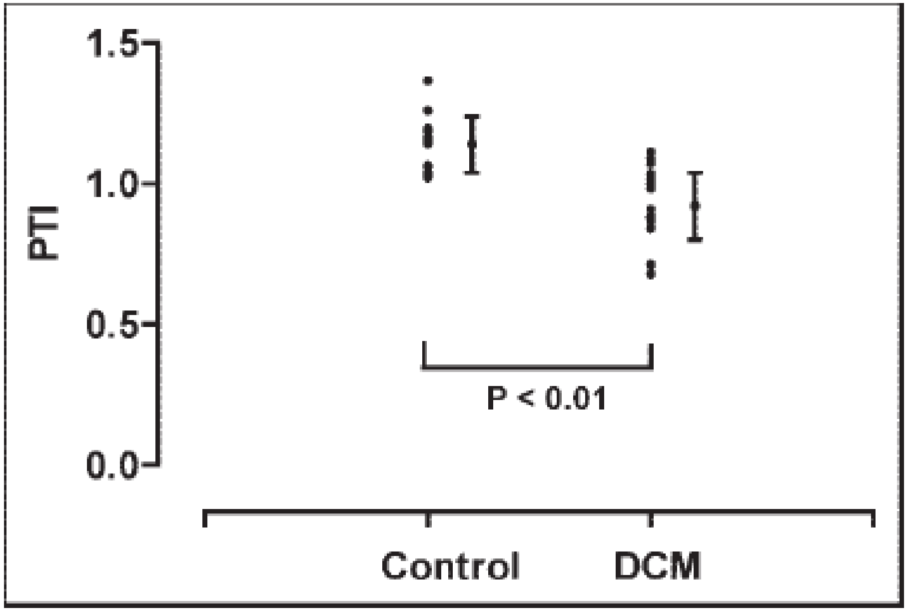
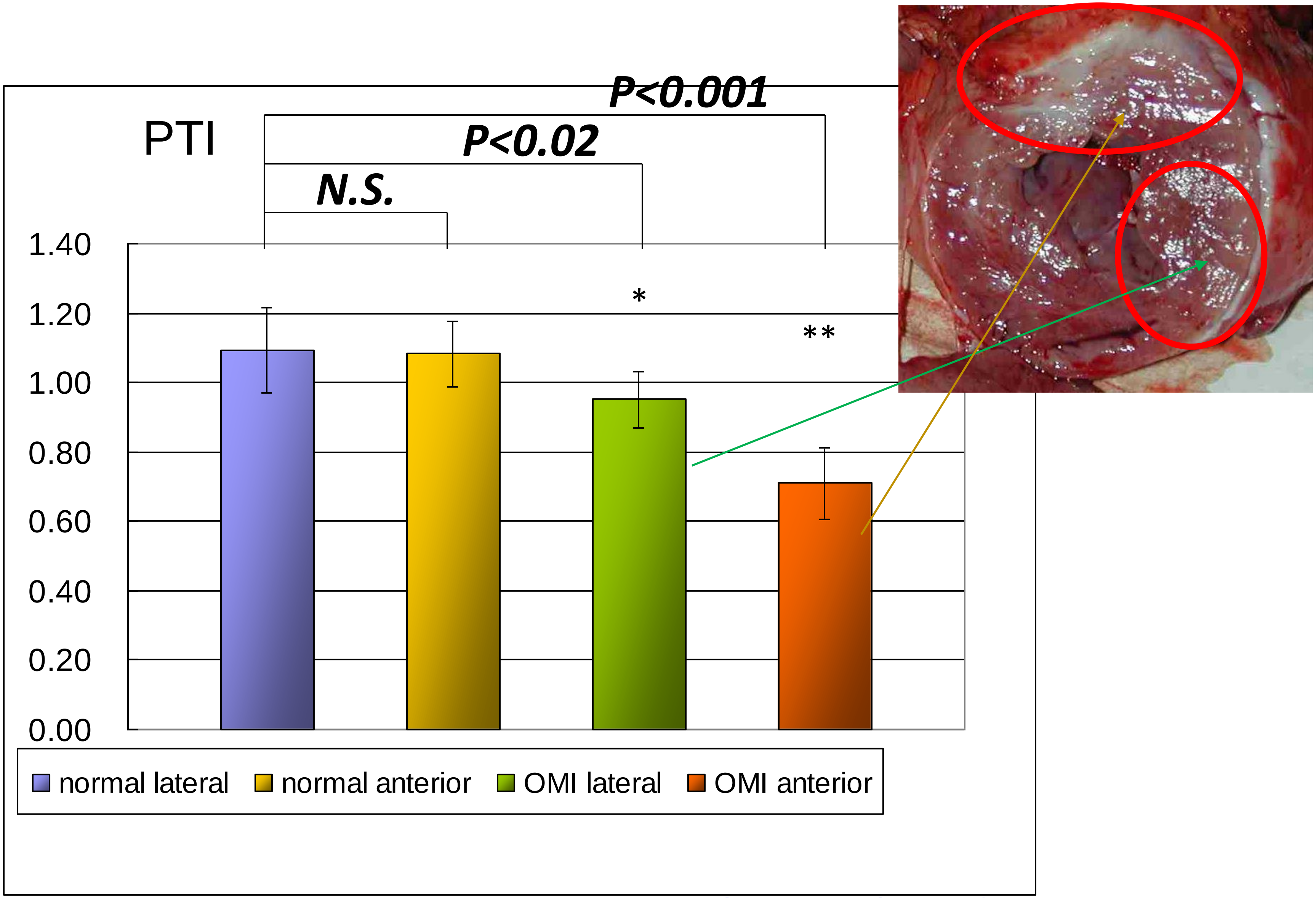


FIGURE 2. PTI for healthy control subjects and DCM patients.

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

PTI in Pigs with OMI

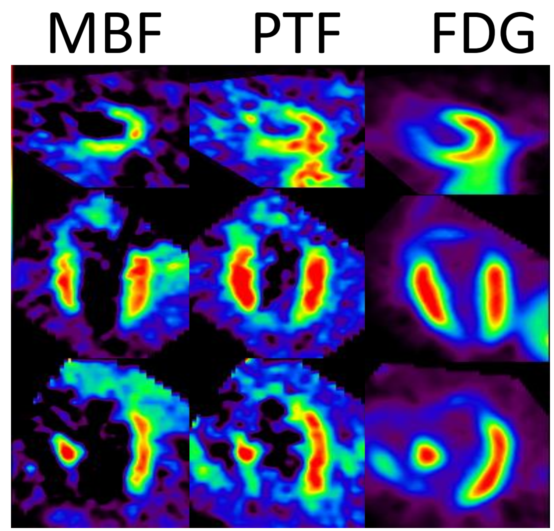


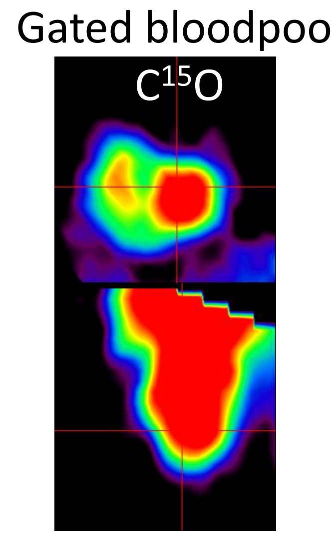
Teramoto et al., J Nucl Med 2011, 52:761–768

Sham-operated vs myoblast-transplanted myocardium in farm pigs with OMI

Sham operated

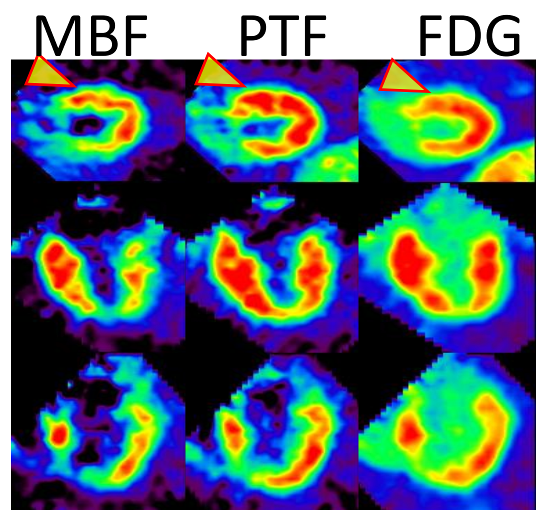
mpigh02_96n

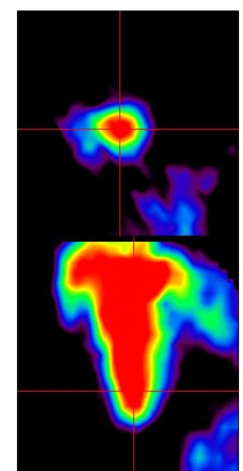




Autologous myoblast transplantated

mpigh22_9bp

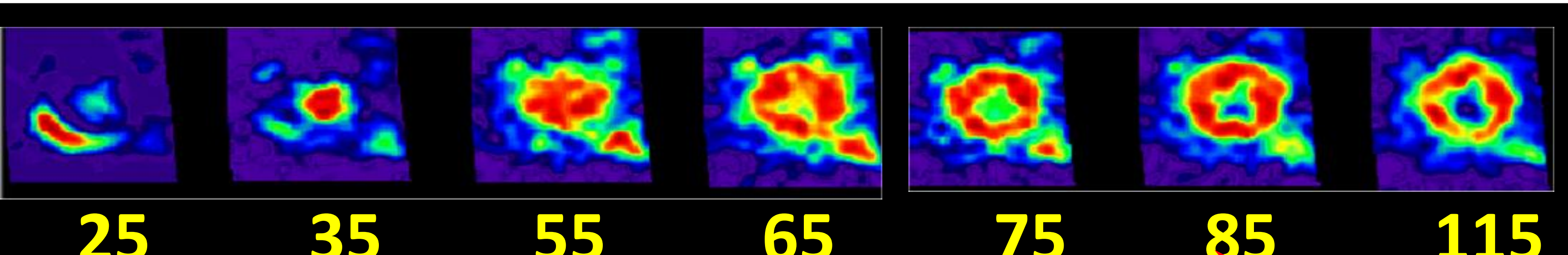




Miyagawa S et al., Transplantation, 90: 364-372, 2010

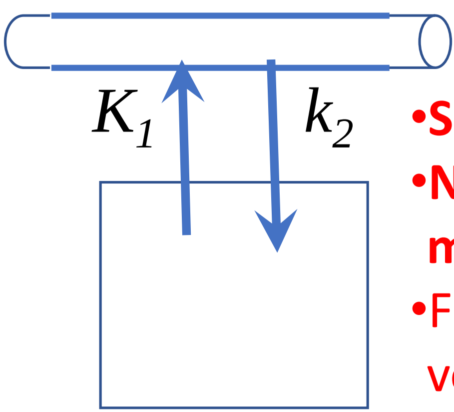
MBF quantitation with $^{13}NH_3$

metabolism-based accumulation



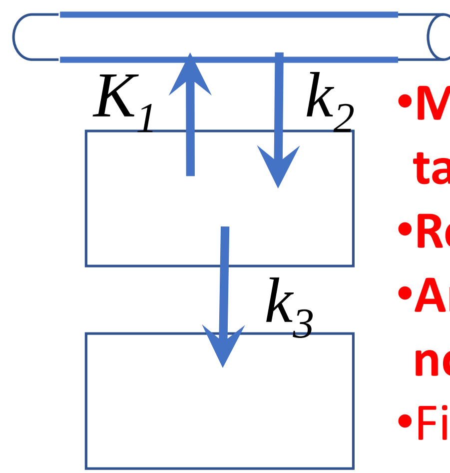
Seconds after I.v. Injection

2-tissue compartment model



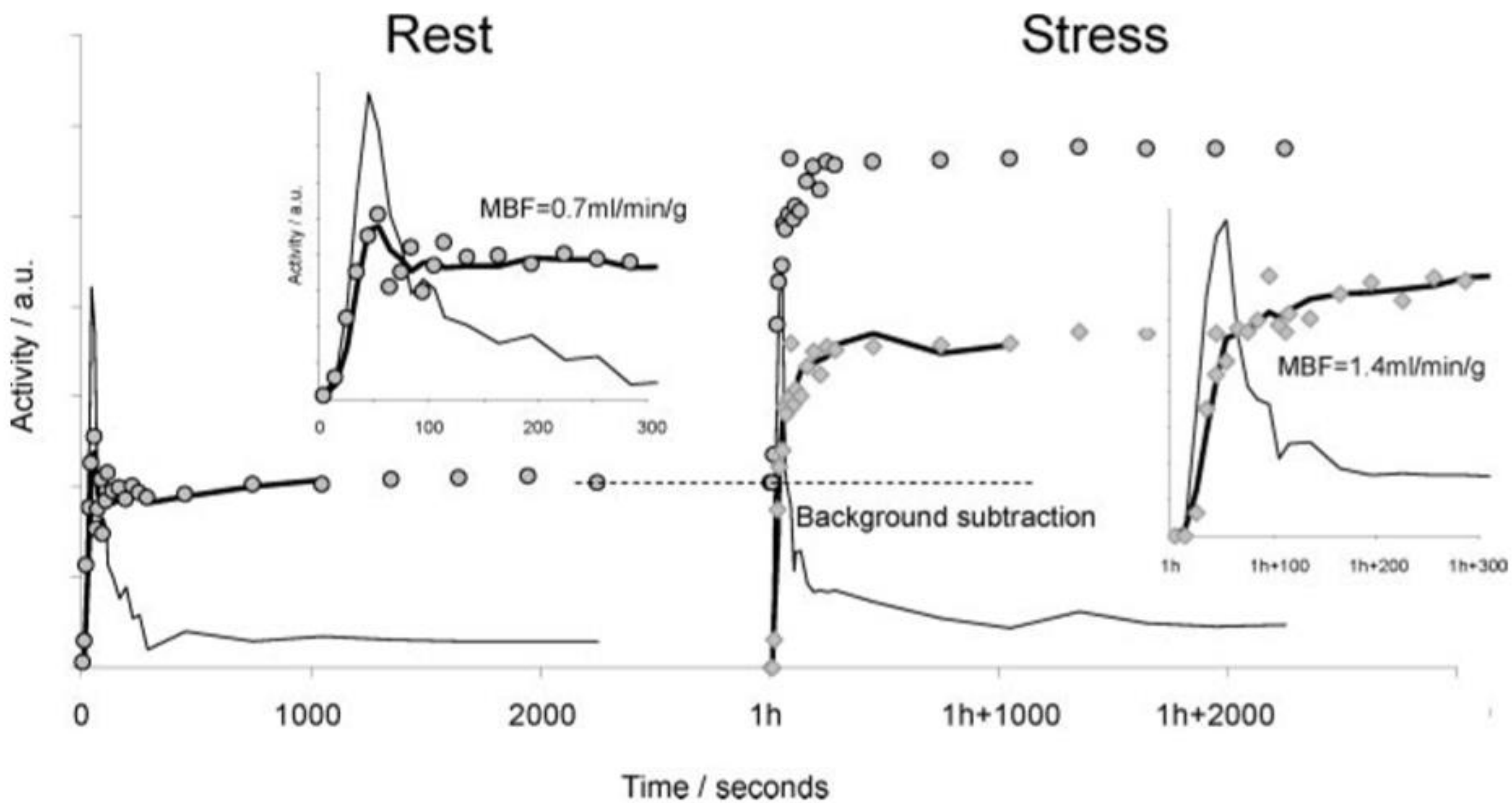
- **Short period scan**
- **Neglegible arterial metabolite**
- First-pass EF, partial volume effect, etc need to be corrected

3-tissue compartment model



- **Metabolic retention taken into account**
- **Requires longer scan**
- **Arterial metabolite not-negligible**
- First-pass EF, partial volume effect, etc need to be corrected

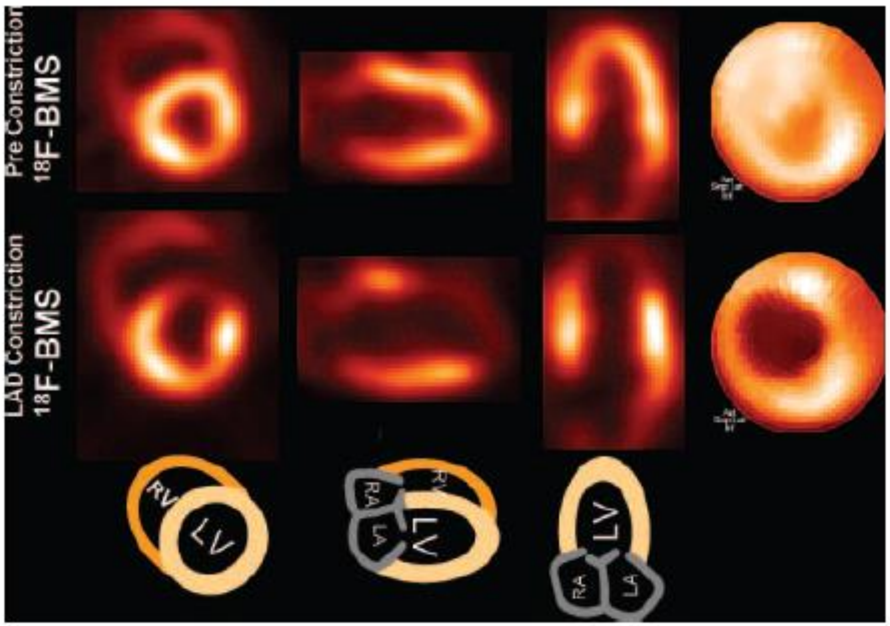
Kinetics of ^{18}F-BMS-747158-02 in myocardium

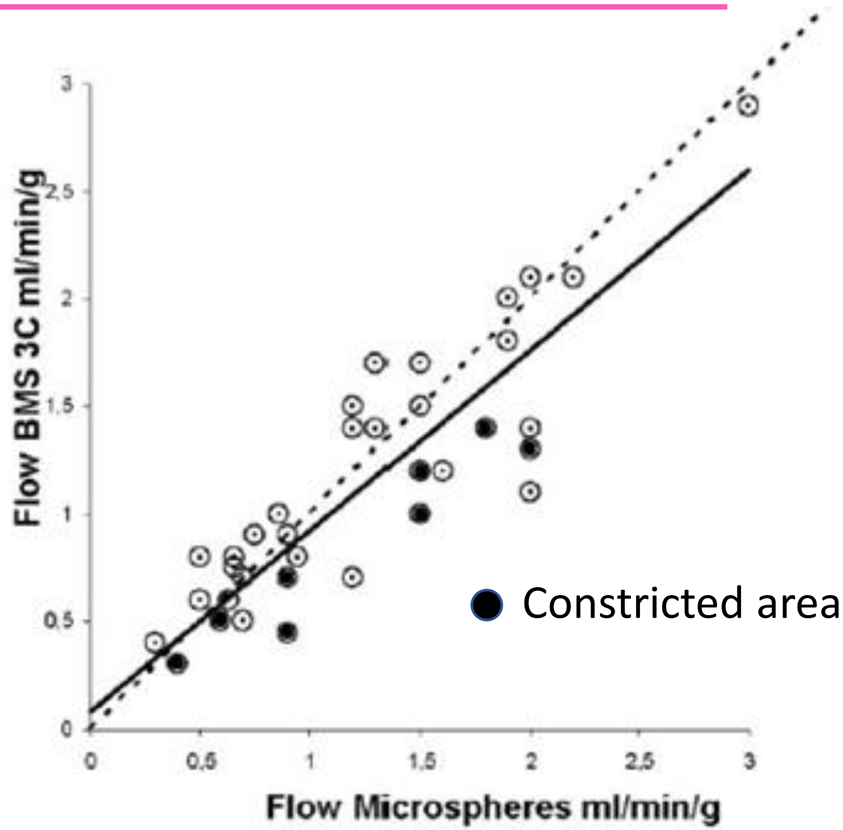


Nekolla et al., Circulation 2009, 119:2333-2342:

MBF comparison: ^{18}F-BMS-747158-02 vs microsphere

In normal and constricted LAD regions in pigs

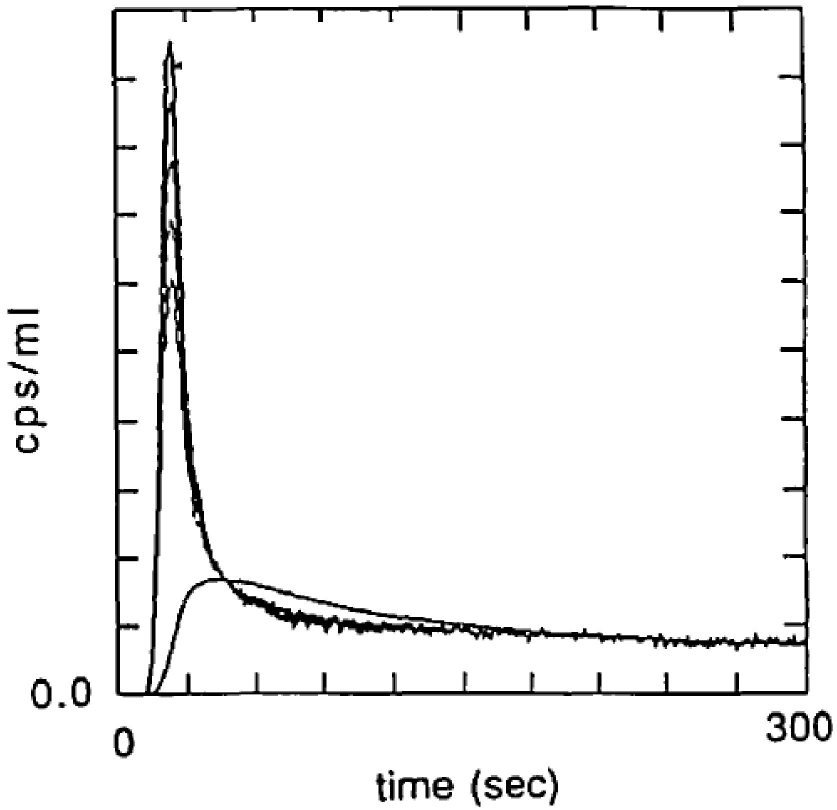


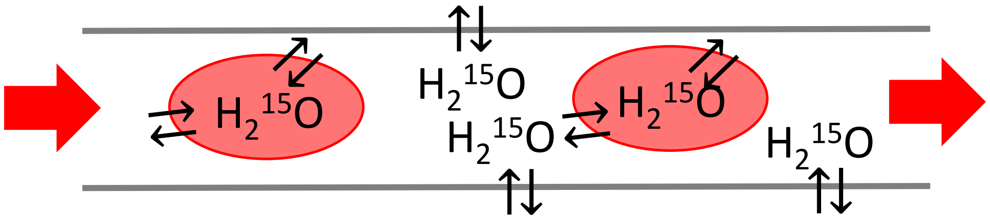


Reduced MBF in constricted area than microsphere

Nekolla et al., Circulation 2009, 119:2333-2342:

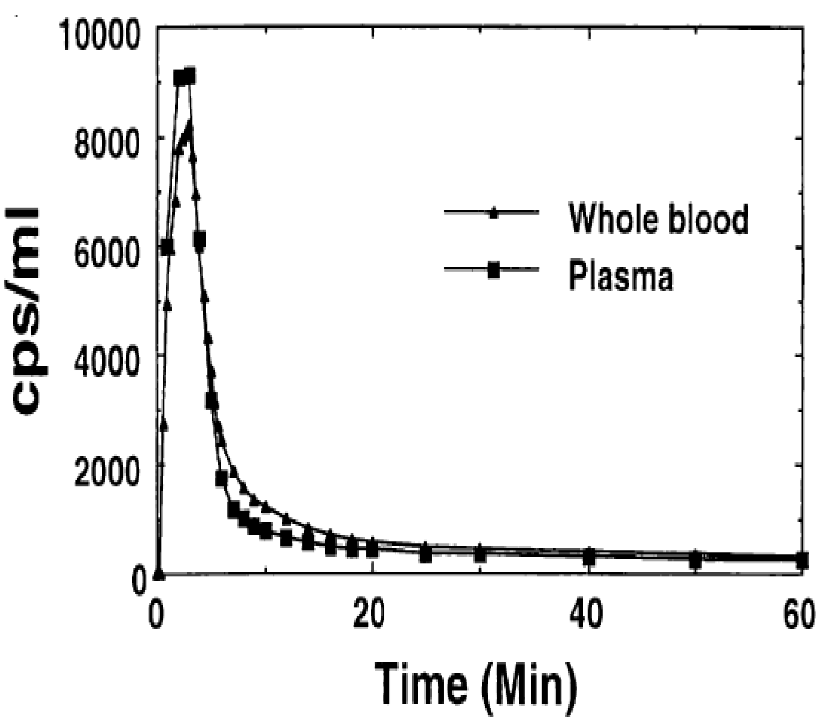
Whole blood radioactivity concentration as Input Function in $H_2^{15}O$



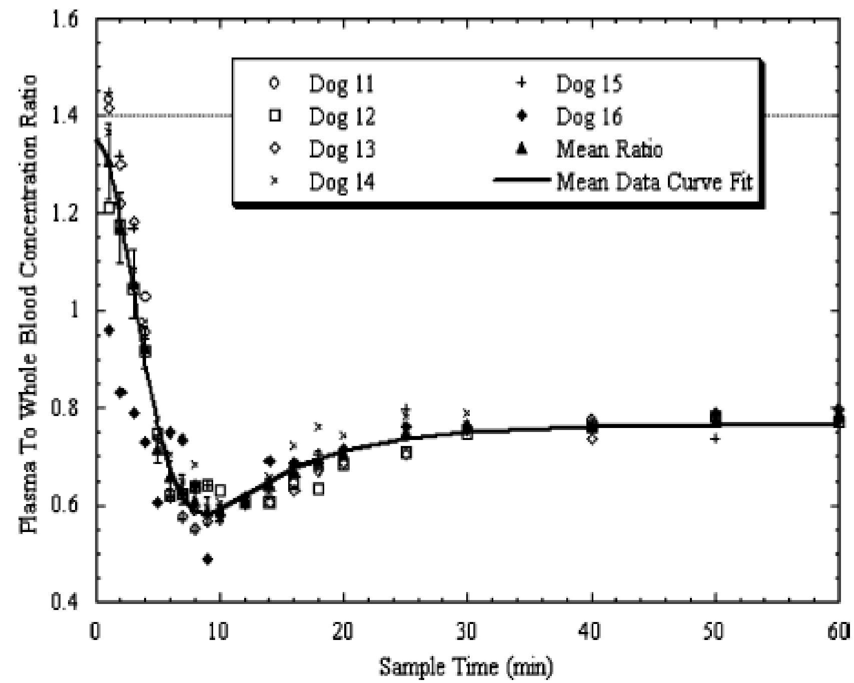


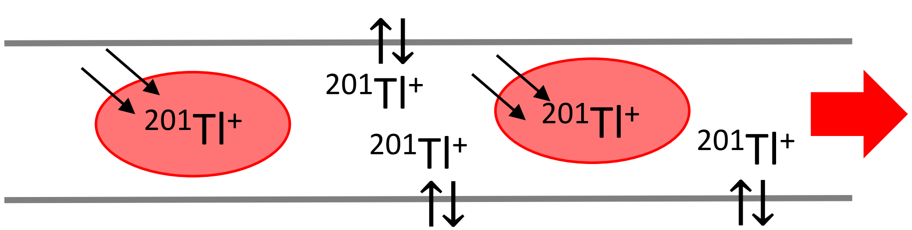
Plasma/whole blood ratio
^{201}Tl (also in ^{82}Rb?)

Arterial input functions



Plasma/whole blood ratio



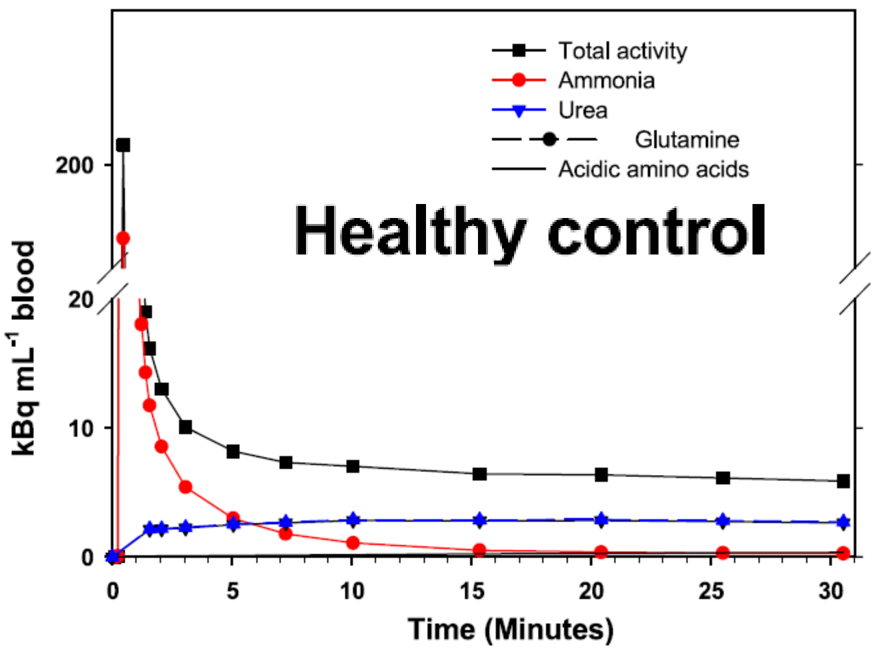


Iida et al., J Nucl Cardiol, 1998

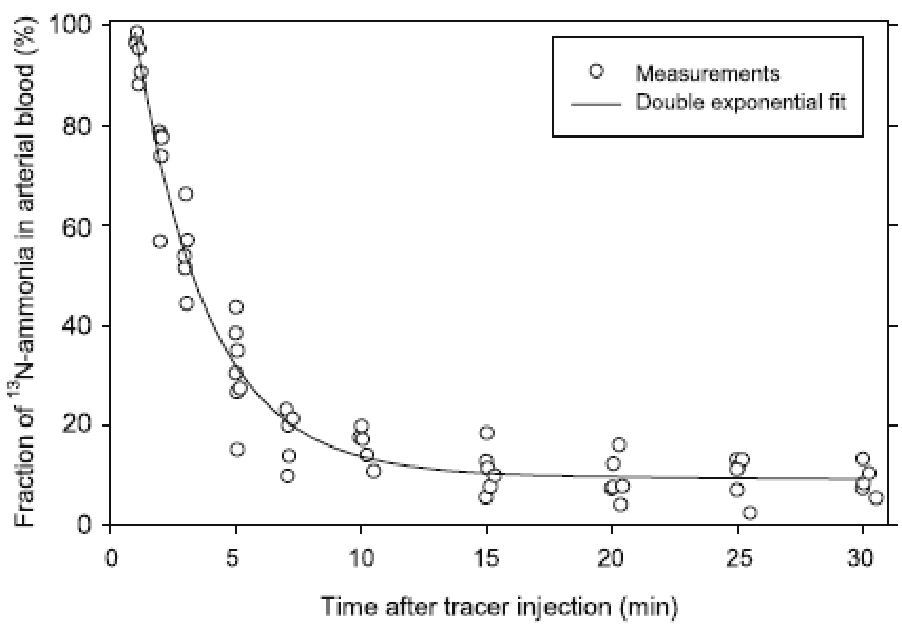
Iida et al., J Nucl Med 2009

Metabolites in arterial blood
in $^{13}NH_3$ PET

Arterial concentration (kBq/mL)



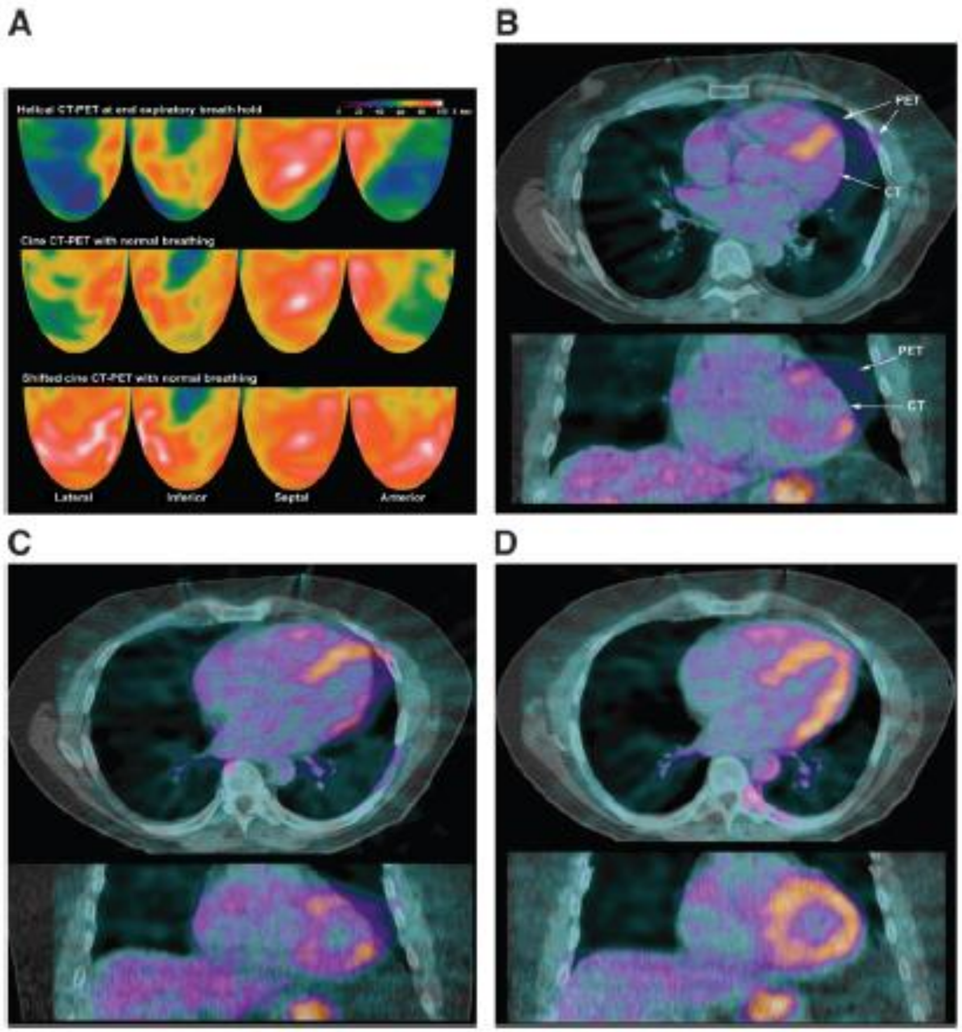
Fraction of $^{13}NH_3$ in blood (%)



Keiding et al., Metab Brain Dis (2010) 25:49-56

Frequent diagnostic errors in cardial PET/CT due to mis-registration of CTAC and emission PET images

CT-AC is often acquired during a breath hold, while PET assesses average over respirator &contractile motion



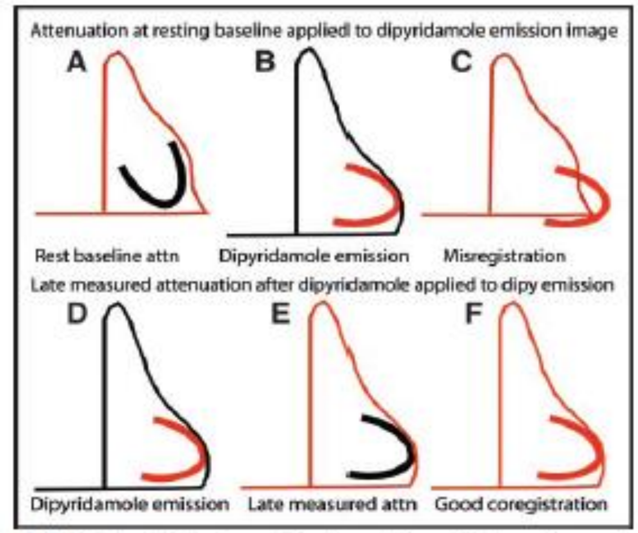


FIGURE 7. Mechanisms for attenuation artifacts using post-dipyridamole scan. Legend is the same as Figure 6.

Gould KL et al., JNM, 2007
Loghin C et al., JNM, 2004

Summary/comments

1. Regional myocardial blood flow as a flux of the tracer to/from tissue through the capillary membrane
2. Regional myocardial blood flow can be quantitatively assessed using PET and several radio-labeled tracers.
3. ^{15}O-water PET can provide accurate quantitative values and has been considered a gold standard
4. Step-by-step specification is encouraged not only for core software, but also for all intermediate processes including GUIs, by means of ISO13485 or equivalent processes
5. Mistmatch between CT-AC and PET needs further technological innovation and development