Measurements of tissue perfusion using [^{15}O]H_2O PET - kinetic models of heart, kidney and liver

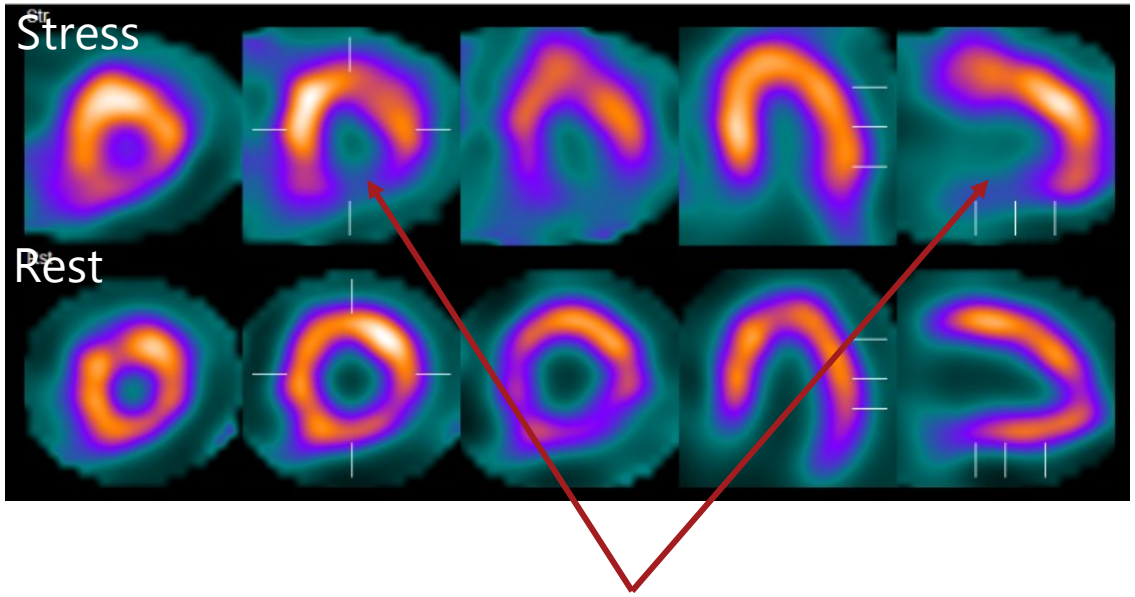
Lisbeth Marner, DMSc, PhD
Professor, Senior consultant
Department of Nuclear Medicine
Copenhagen University Hospital Herlev
Email: lisbeth.marner@regionh.dk

Quantitative cardiac perfusion in ischemic heart disease

Non-quantitative static imaging in rest and stress (bicycling or medicine) using SPECT has been used for decades for diagnosing ischemia.

What kind of tracer is used?

[^{99m}Tc]Sestamibi is an irreversible flow-dependent tracer



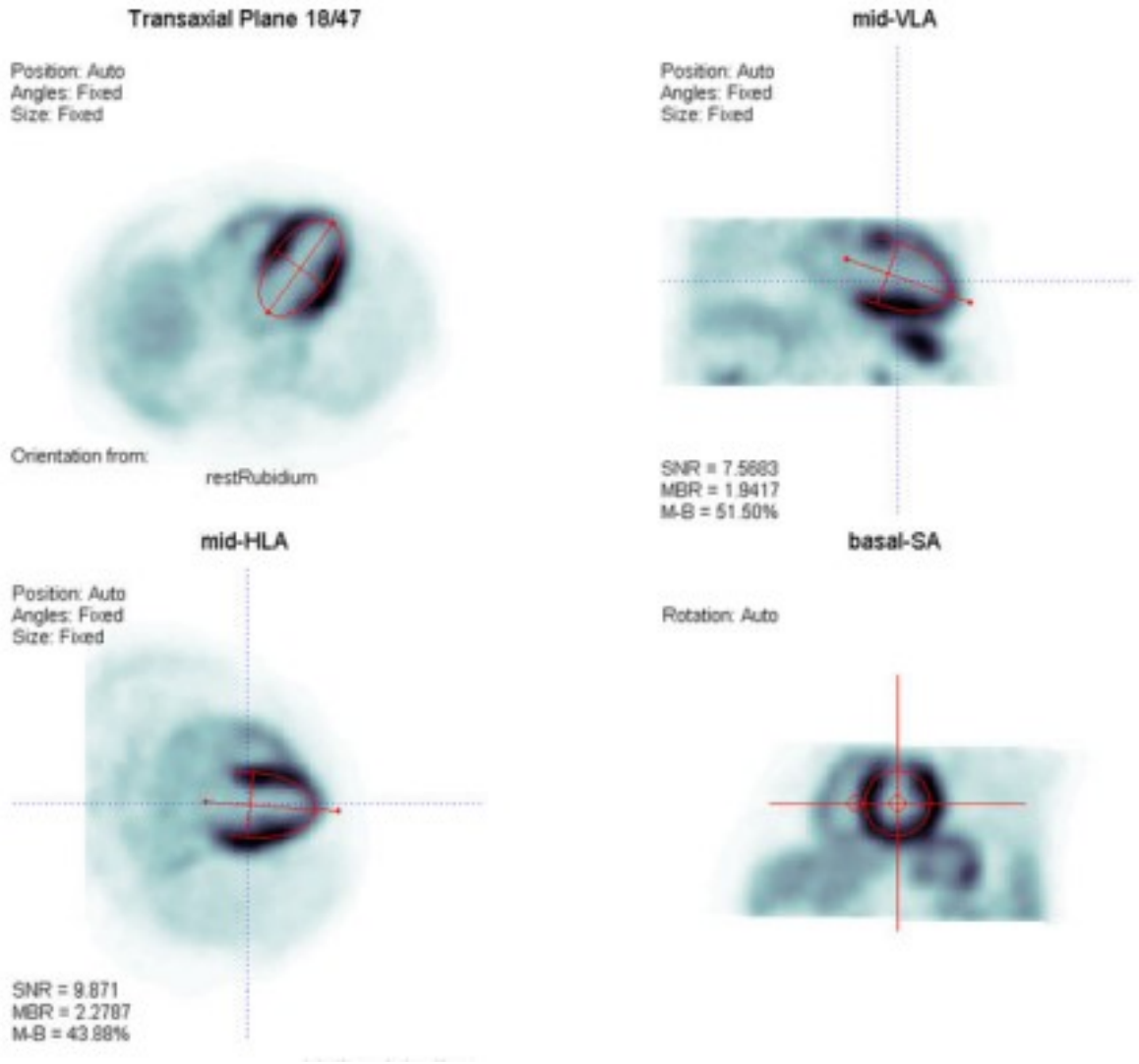
Stress defect in the inferior wall

^{82}Rb is a PET alternative – also an irreversible flow-dependent tracer – that allows for quantification

Cardiac perfusion measurements

The long axis of the left ventricle of the heart is oriented to ensure a normalization in 3D allowing for reproducible presentation of the walls of the heart.

A VOI in e.g. the left ventricle is placed to sample the input function.



Murthy et al. 2018. Clinical Quantification of MBF Using PET. J nucl Cardiol 25:269-97

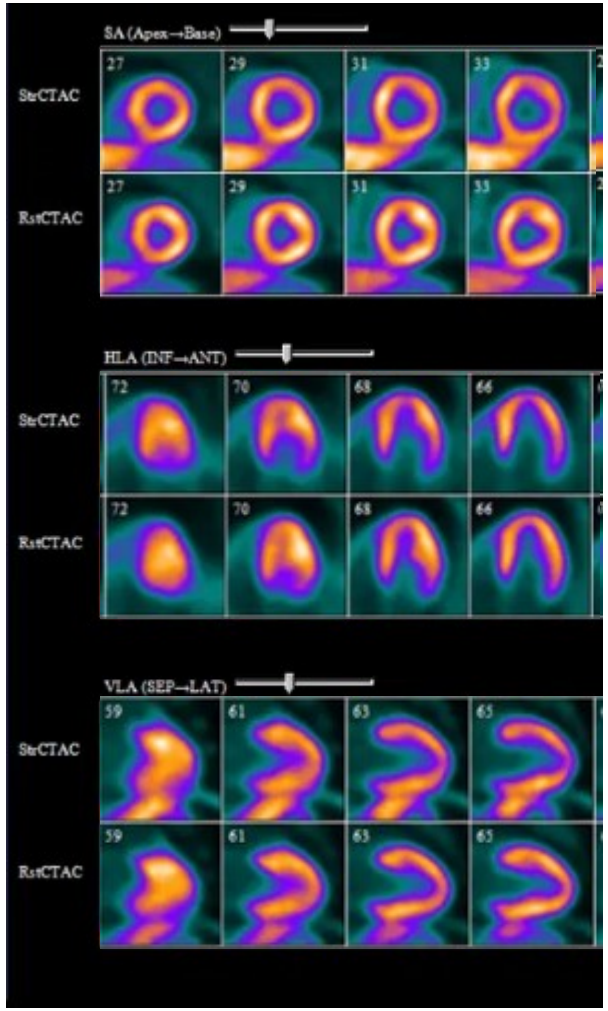
Cardiac perfusion measurements

Three planes are shown:

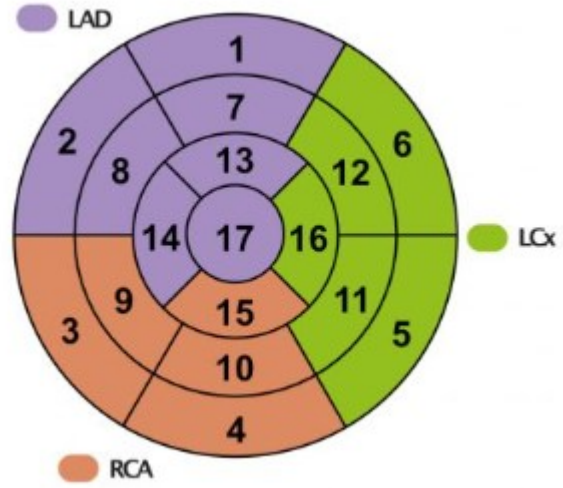
Top: short axis (perpendicular to the long axis), i.e. apex to base

Middle: Long axis: Inferior to anterior wall

Bottom: long axis: Septum to lateral wall



Bull's-eye plot of segments and coronary arterial territory



Basal segments	Mid-cavity segments	Apical segments
1. Basal anterior	7. Mid anterior	13. Apical anterior
2. Basal anteroseptal	8. Mid anteroseptal	14. Apical septal
3. Basal inferoseptal	9. Mid inferoseptal	15. Apical inferior
4. Basal inferior	10. Mid inferior	16. Apical lateral
5. Basal inferolateral	11. Mid inferolateral	17. Apex
6. Basal anterolateral	12. Mid anterolateral	

Cardiac perfusion measurements

As for brains we can increase detectability of ischemia by ‘stressing’ the heart.

Why is biking not useful for cardiac PET measurements?

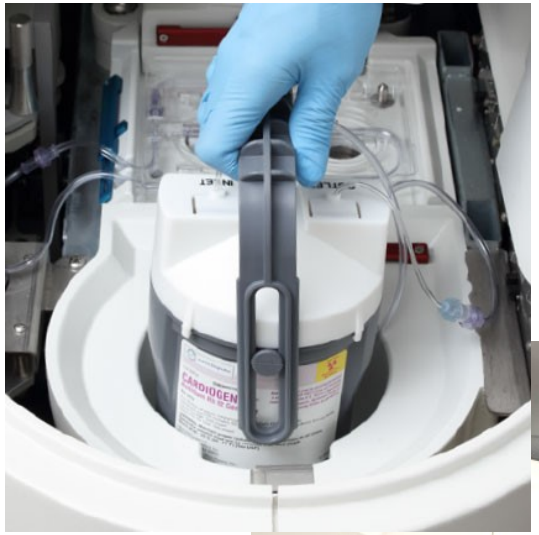
How do we stress the heart?

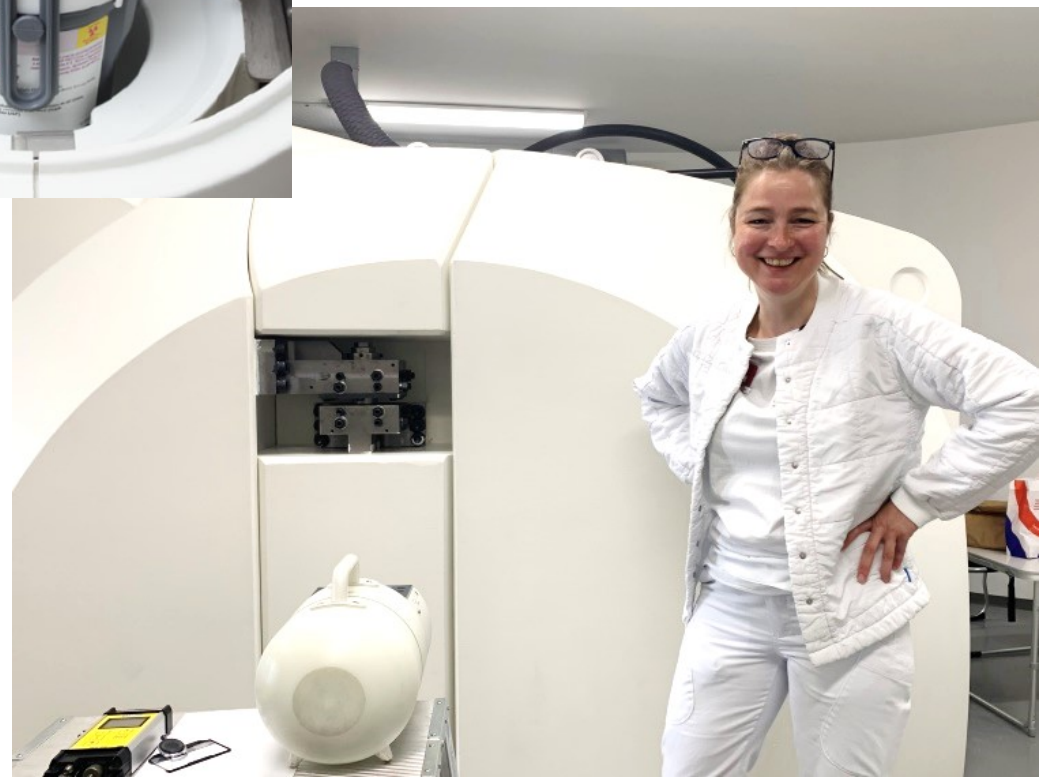
E.g. Adenosine infusion (halflife of <10 s)

Cardiac perfusion

During clinical transition from ^{82}Rb PET to $[^{15}O]H_2O$ PET, we performed a head-to-head comparison in a mixed population with suspected ischemic heart disease.

Surprisingly, we identified the **double amount of patients with ischemia** using $[^{15}O]H_2O$ compared to ^{82}Rb PET.





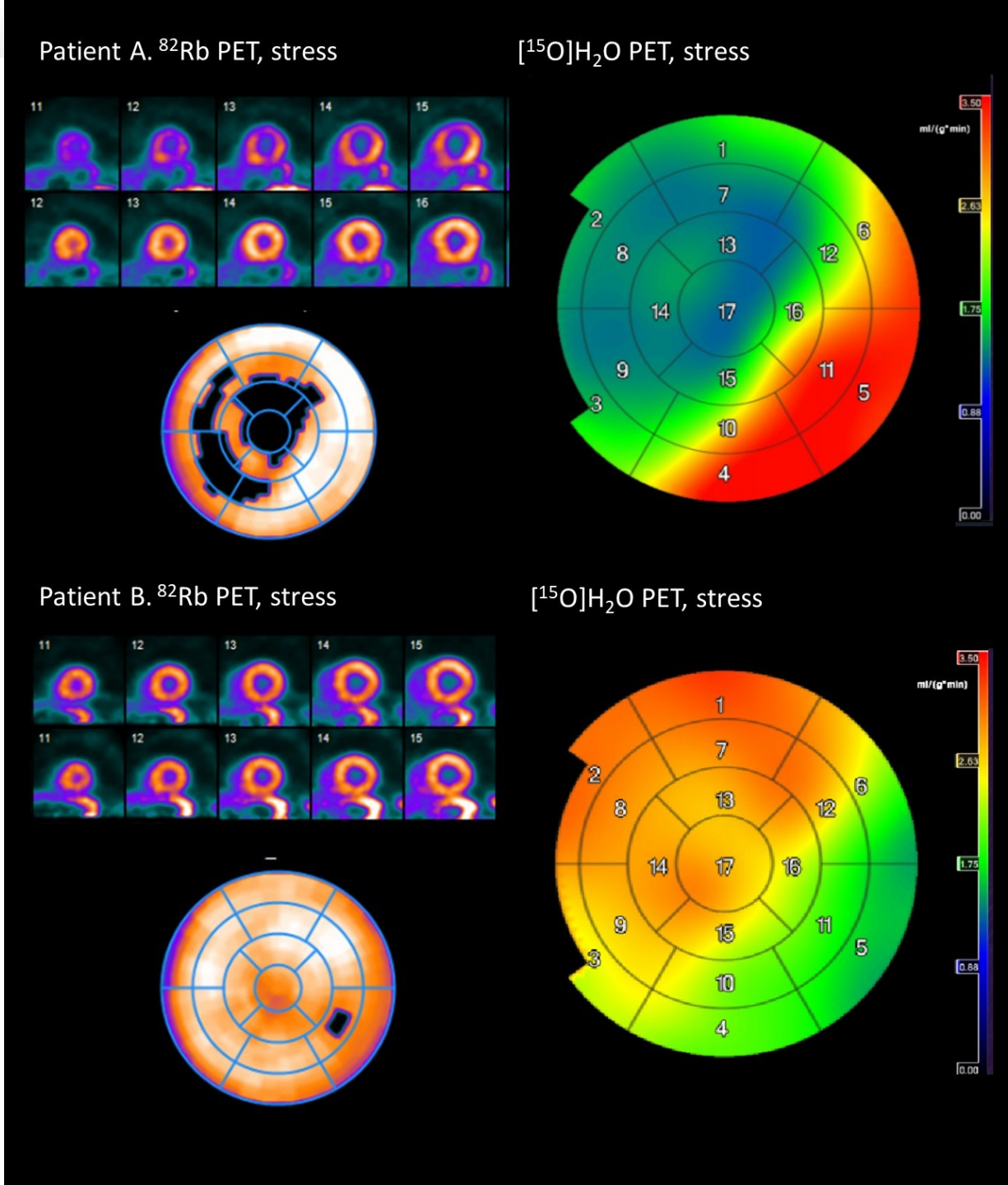
^{82}Rb vs. [^{15}O]H_2O

Agreement

- Patient A: 61 year-old-man without prior known heart disease and typical angina
  - ^{82}Rb PET: 25% defect
  - [^{15}O]H_2O PET: 54% defect

Disagreement

- Patient B: 74 year-old-man with angina and number of risk factors:
  - ^{82}Rb PET: homogenous
  - [^{15}O]H_2O: 15% defect



What explains the marked differences between ^{82}Rb and $[^{15}O]H_2O$?

- Are the cuttoffs the same?
- Differences in tracer kinetics?
- Differences in extraction fraction?

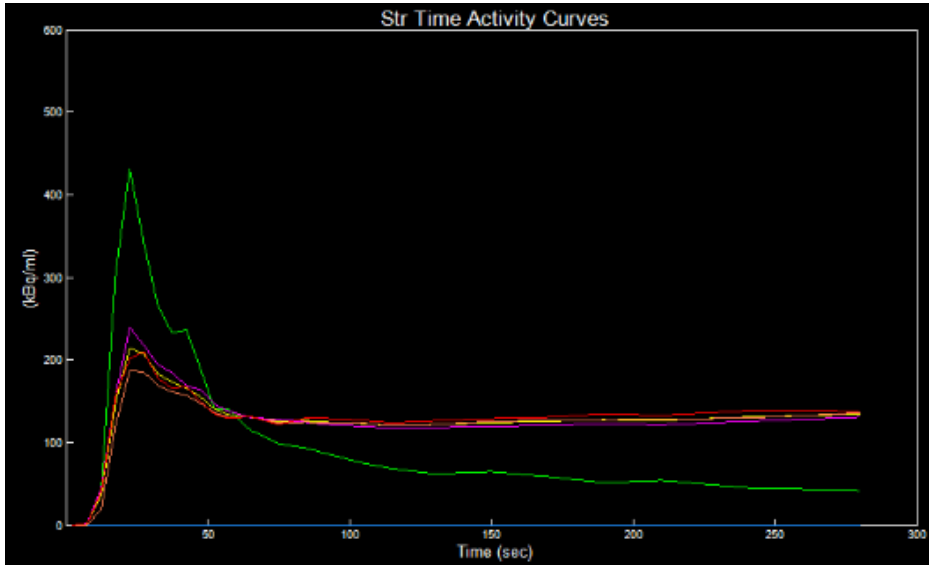
Are cutoffs the same?

	4 group classification				2 group classification	
	Normal	**Regional ischemia**	**Global reduction**	**Scarring**	**Normal**	**Regional ischemia**
^{82}Rb	Stress score defect <7/68	Focal stress score defect ≥7/68	CFR<1.8	Matched defects	Stress score defect <7/68	Focal stress score defect ≥7/68 or suspicion of triple-vessel disease
[^{15}O]H_2O	MBF_{stress} > 2.3 mL/(min·g)	≥ 2 neighboring segments with MBF_{stress}≤2.3 mL/(min·g)	MBF_{stress} ≤ 2.3 mL/(min·g)	Matched defects	Stress score defect <7/68	Focal stress score defect ≥7/68 or suspicion of triple-vessel disease

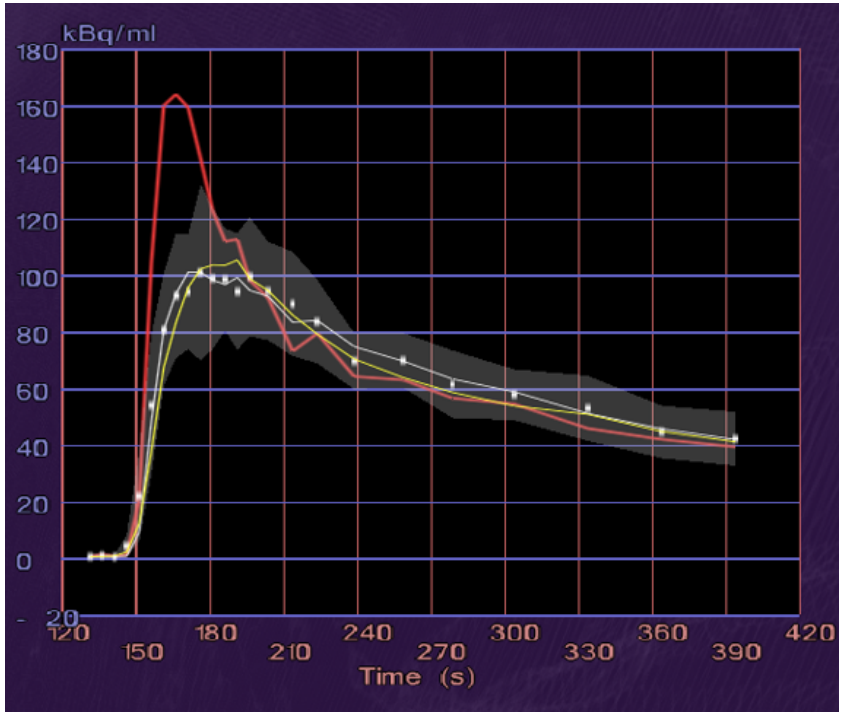
Cut-off [^{15}O]H_2O: Danad, I., et al., J Am Coll Cardiol, 2014. **64**(14): p. 1464-75.

Differences in tracer kinetics

- ^{82}Rb: irreversibel tracer trapped in the myocytes – static imaging.



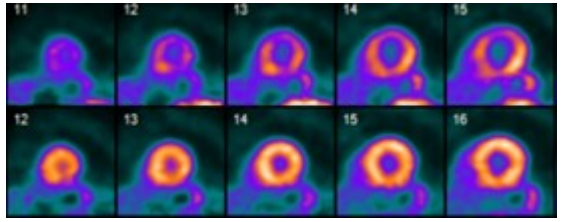
- $[^{15}O]H_2O$: reversible tracer – parametric imaging.



Differences in tracer kinetics

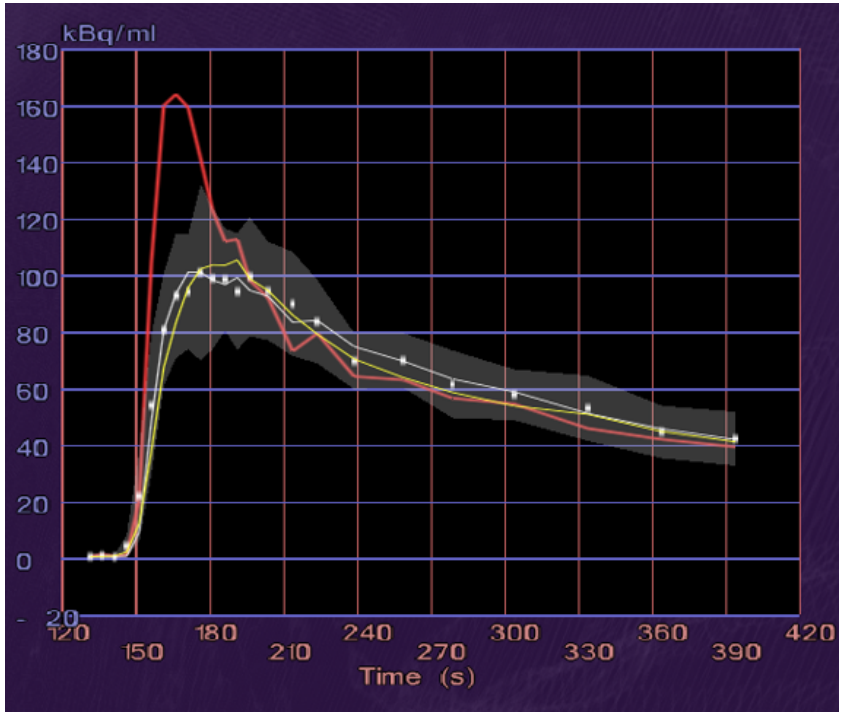
- ^{82}Rb: irreversibel tracer trapped in the myocytes – static imaging.

Visual assessment or



$$E \cdot F = \frac{P(t)}{\int_0^t Ca(x)\,dx}$$

- $[^{15}O]H_2O$: reversible tracer – parametric imaging.

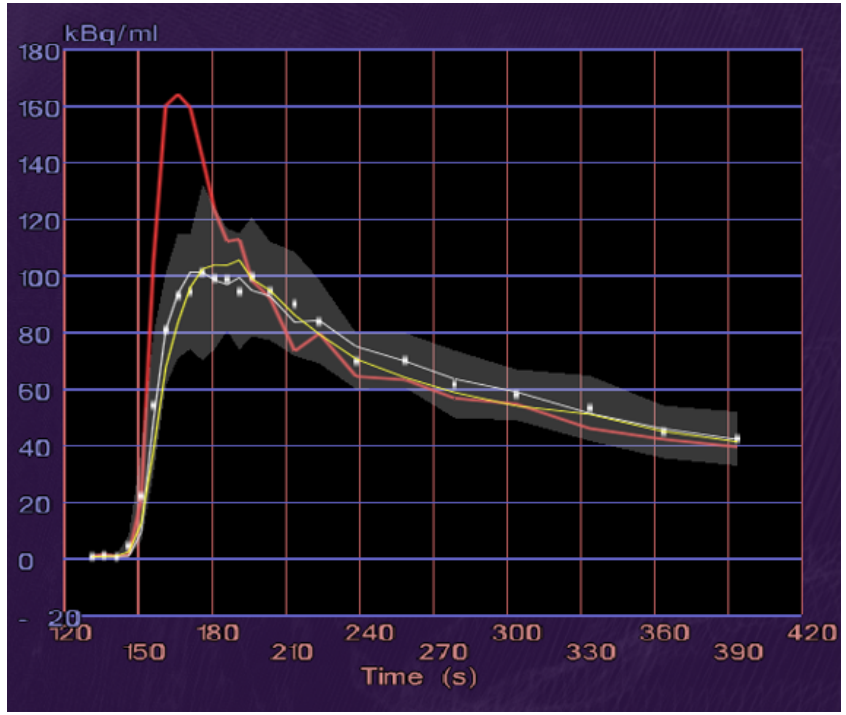


Differences in tracer kinetics

- ^{82}Rb: irreversibel tracer trapped in the myocytes – static imaging.

- $[^{15}O]H_2O$: reversible tracer – parametric imaging.

Quantitative measures used for calculation of myocardial flow reserve



Differences in tracer kinetics

- ^{82}Rb: irreversibel tracer trapped in the myocytes – static imaging.

- [^{15}O]H_2O: reversible tracer – parametric imaging.

Quantitative measures used for calculation of myocardial flow reserve

$$\frac{dC_T(t)}{dt} = f \times C_A(t) - \frac{f}{p} \times C_T(t)$$

$$C_T(t) = K_1 C_A(t) \otimes e^{-k_2 t}$$

with $K_1 = f$ and $k_2 = f/\rho$

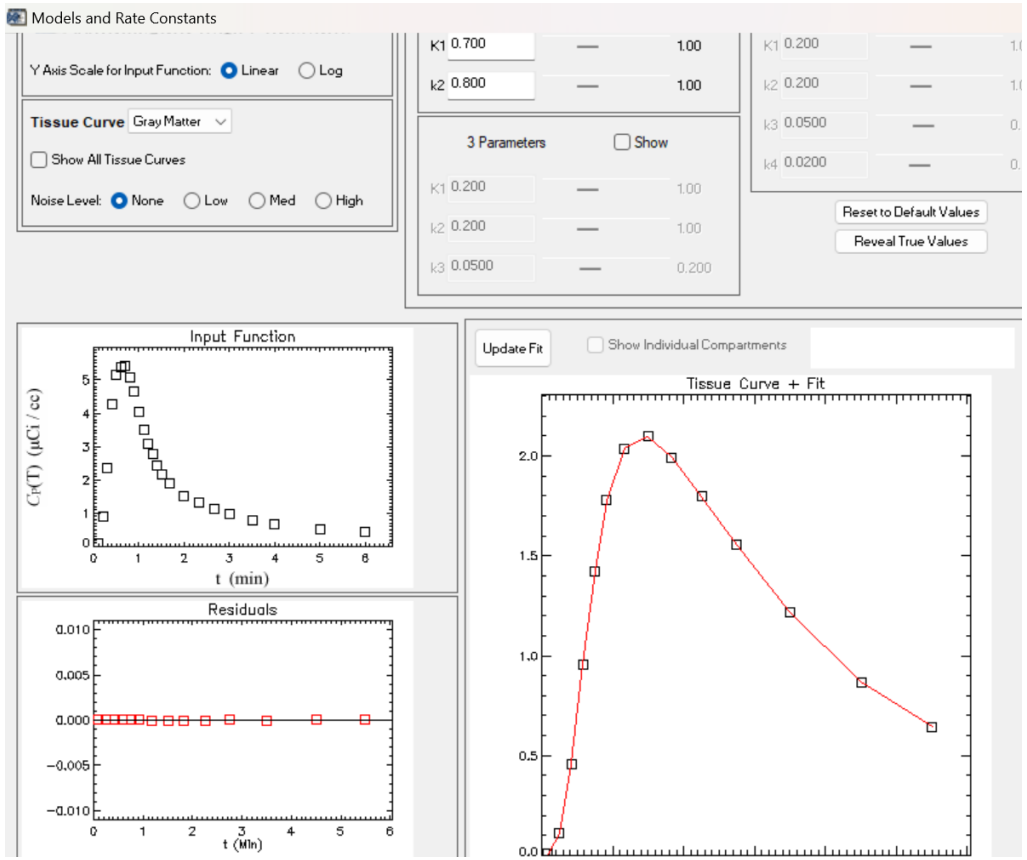
Why do we use k_2 instead of K_1 for cardiac perfusion, f?

$$C_T(t) = K_1 C_A(t) \otimes e^{-k_2 t}$$

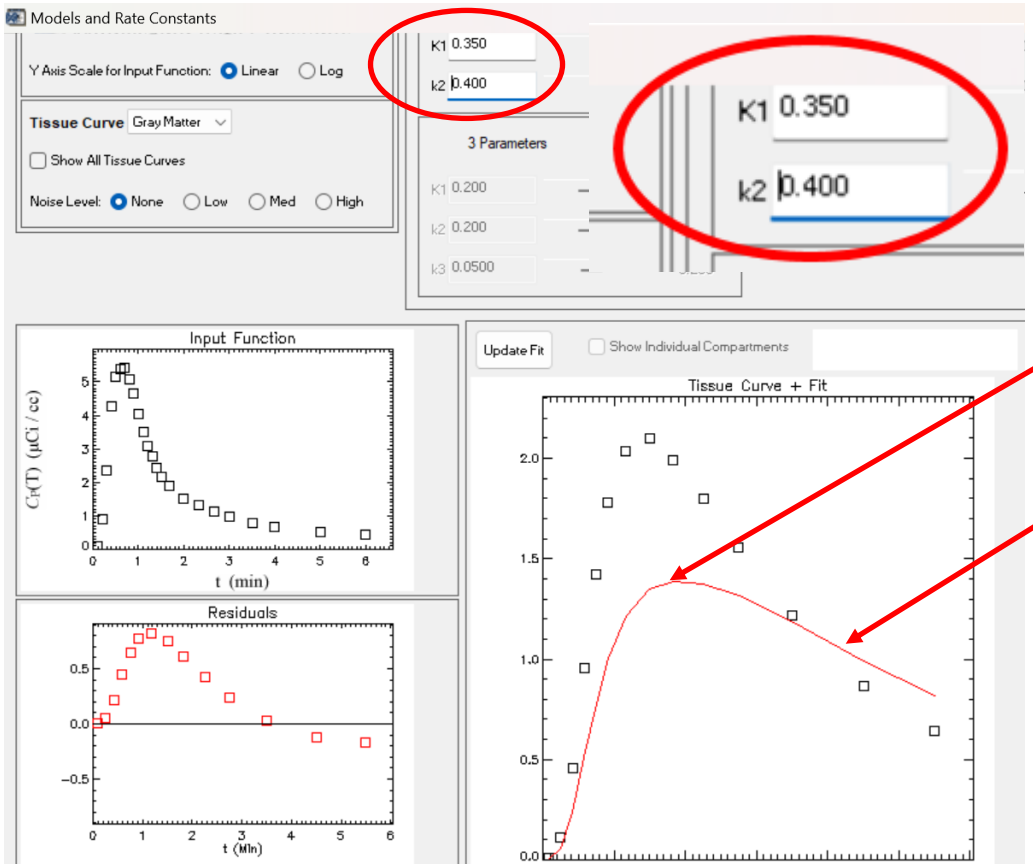
with $K_1 = f$ and $k_2 = f/\rho$

Why do we use k_2 instead of K_1 for cardiac perfusion?

$$C_T(t) = K_1 C_A(t) \otimes e^{-k_2 t}$$



Cardiac flow is decreased by 50%:

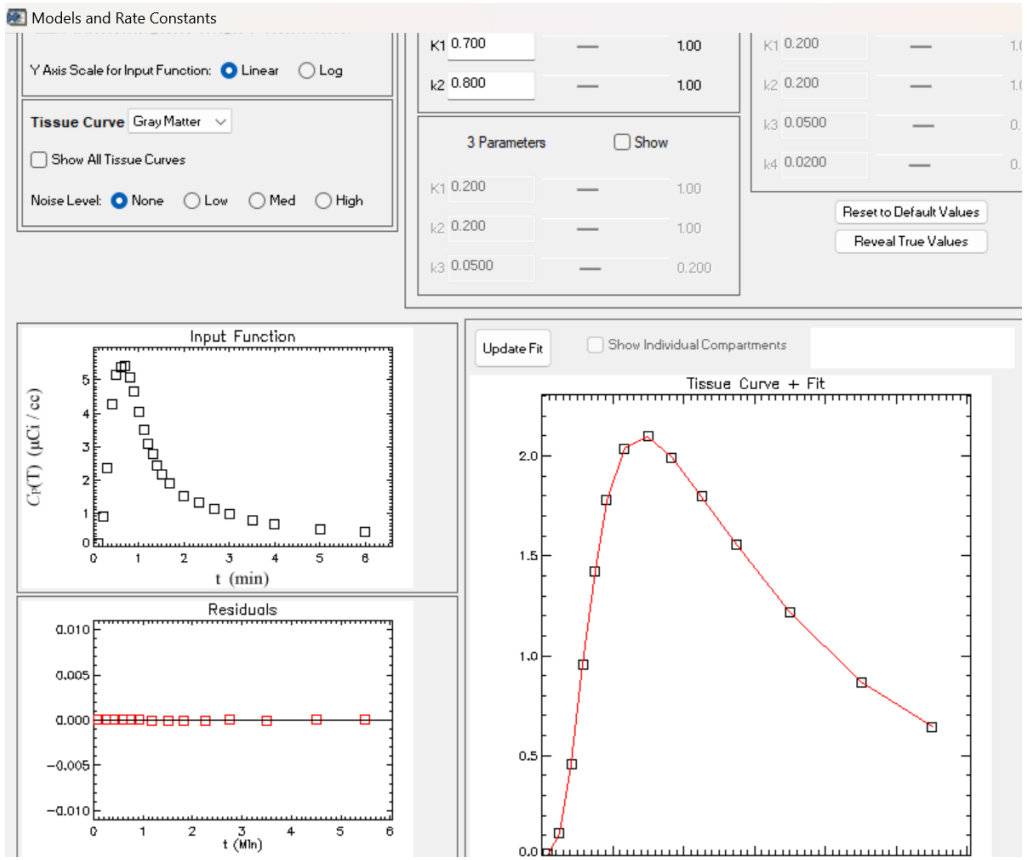


Peak decreased

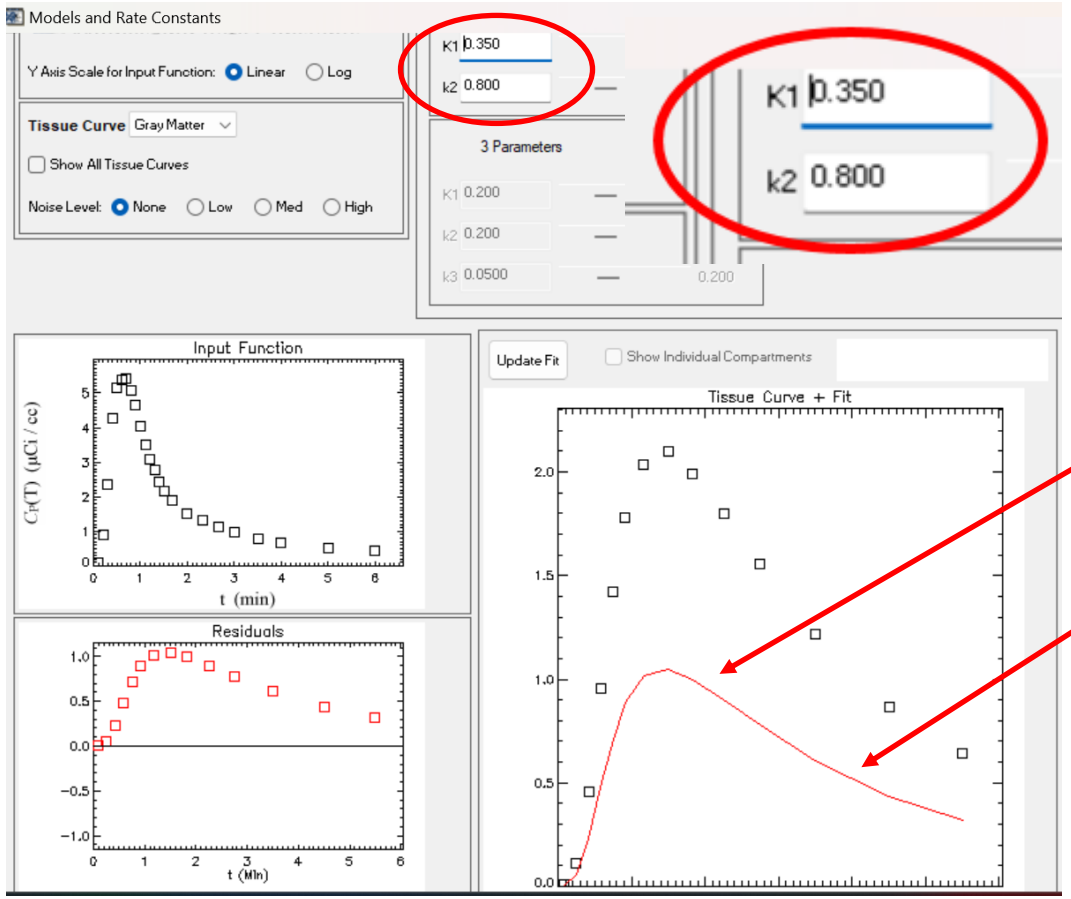
Washout decreased

Why do we use k_2 instead of K_1 for cardiac perfusion?

$$C_T(t) = K_1 C_A(t) \otimes e^{-k_2 t}$$



Cardiac flow is maintained, PTF decreased by 50%:



Peak decreased

Washout unchanged

PTF: perfused tissue fraction

Why do we use k_2 instead of K_1 for cardiac perfusion?

$$C_T(t) = K_1 C_A(t) \otimes e^{-k_2 t}$$

with $K_1 = f$ and $k_2 = f/\rho$

Using $k_2 = f/\rho$ allows for measuring perfusion only in perfused tissue (ρ or PTF).
-> Scarring, motion, partial volume, and AC correction affects the measured perfusion minimally.

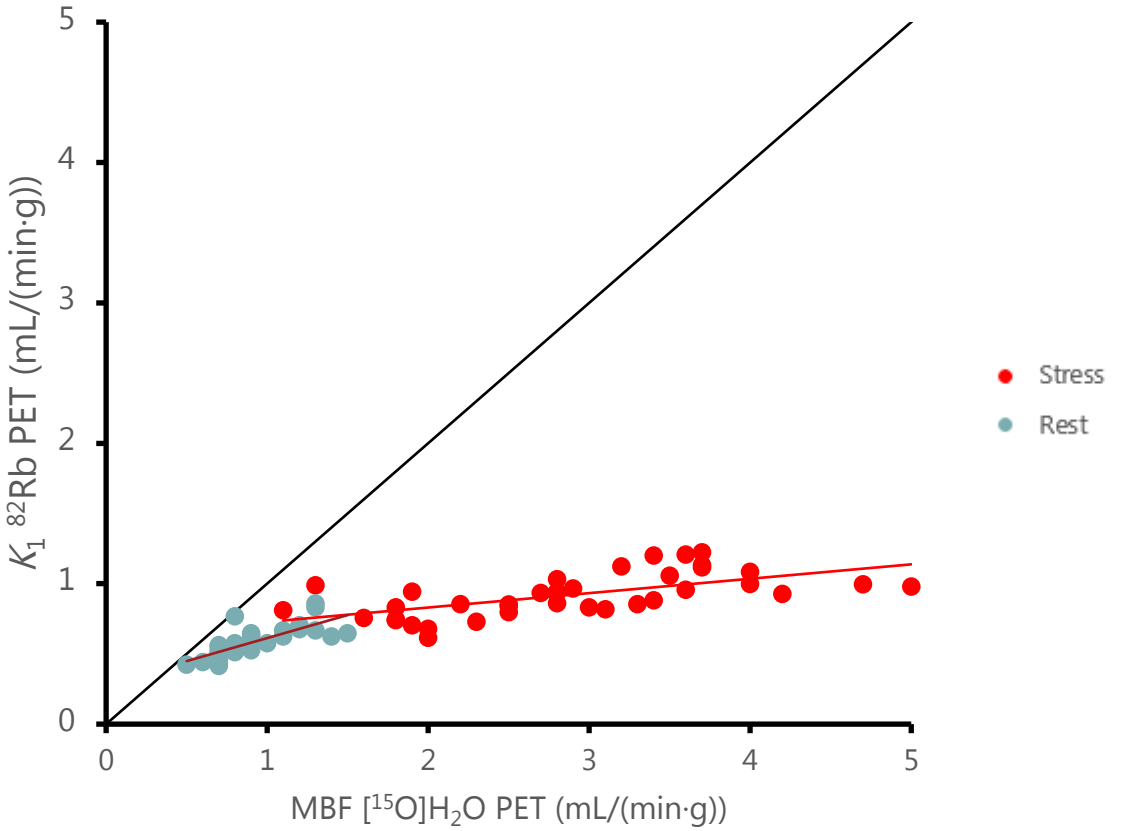
Scar tissue in the heart:

For ^{82}Rb, K_1 will be reduced in rest and stress – irreversibel defect.
For [^{15}O]H_2O, k_2 and f will be normal in rest and stress, PTH (ρ) will be reduced

Does kinetic differences increase sensitivity of [^{15}O]H_2O compared to ^{82}Rb PET?

Differences in extraction

- ^{82}Rb has a flow-dependent lower extraction into the myocytes
- Correspondance between calculated myocardial perfusion show slight underestimation using ^{82}Rb PET (corrected for extraction)
- Without correction, significant lower values was found with ^{82}Rb PET, especially for stress perfusion
- Splash and polar plots using ^{82}Rb are shown without correction, i.e. only severe reductions are visible



^{82}Rb vs. [^{15}O]H_2O

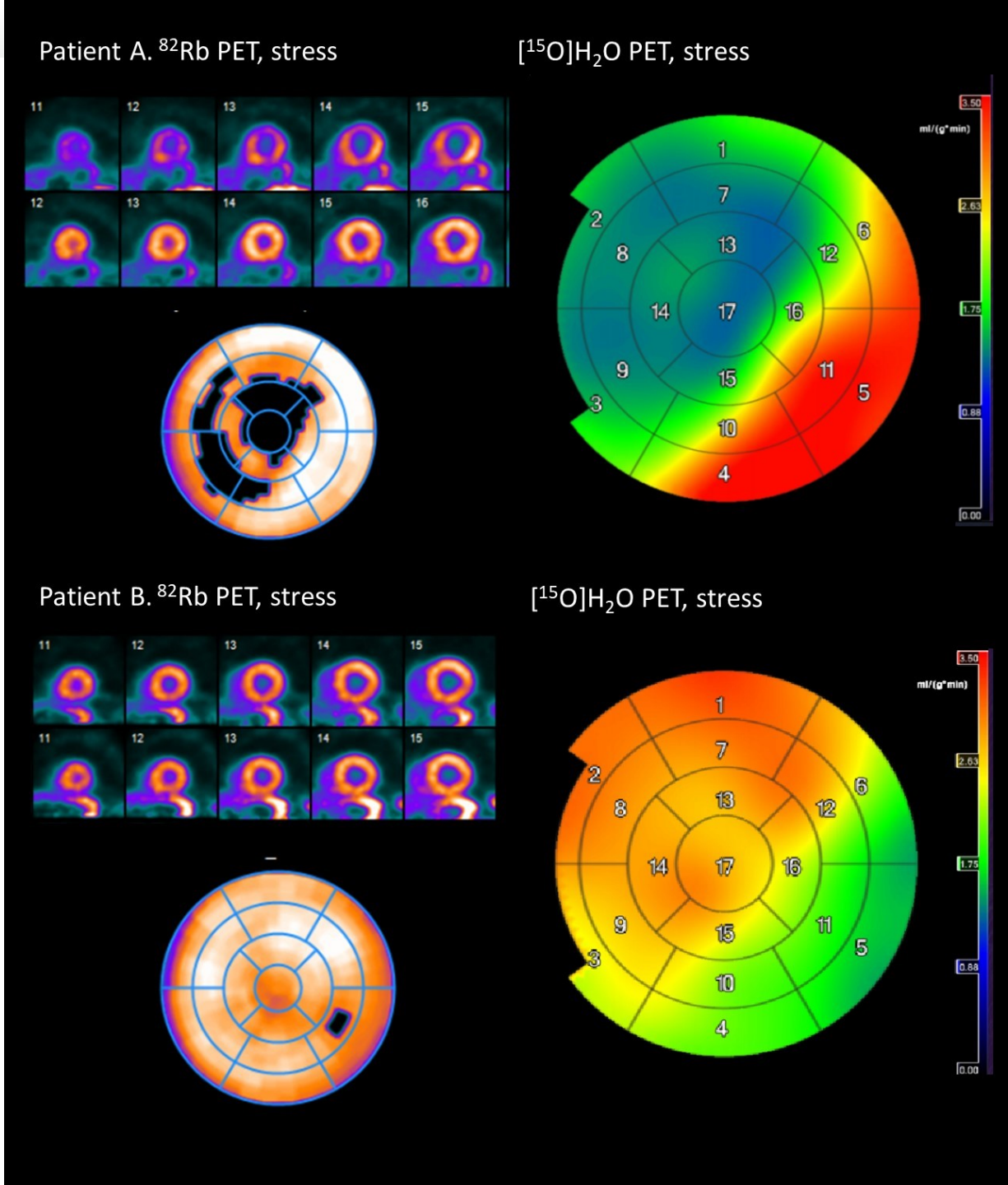
Agreement

- Patient A: 61 year-old-man without prior known heart disease and typical angina
  - ^{82}Rb PET: 25% defect
  - [^{15}O]H_2O PET: 54% defect

Disagreement

- Patient B: 74 year-old-man with angina and number of risk factors:
  - ^{82}Rb PET: homogenous
  - [^{15}O]H_2O: 15% defect

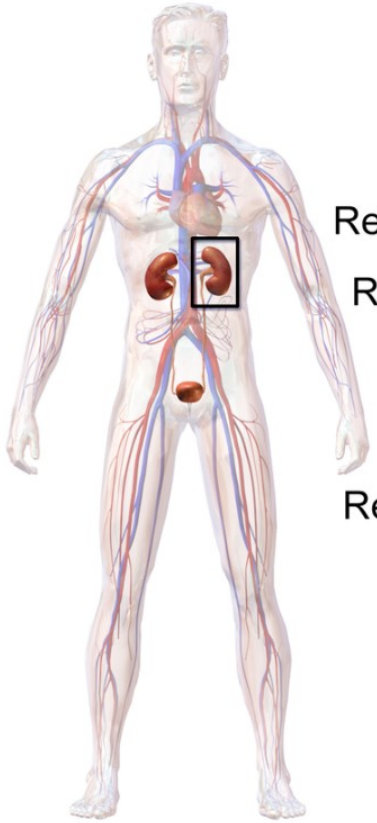
Thus, [^{15}O]H_2O PET is more sensitive to ischemia due to differences in extraction fraction!

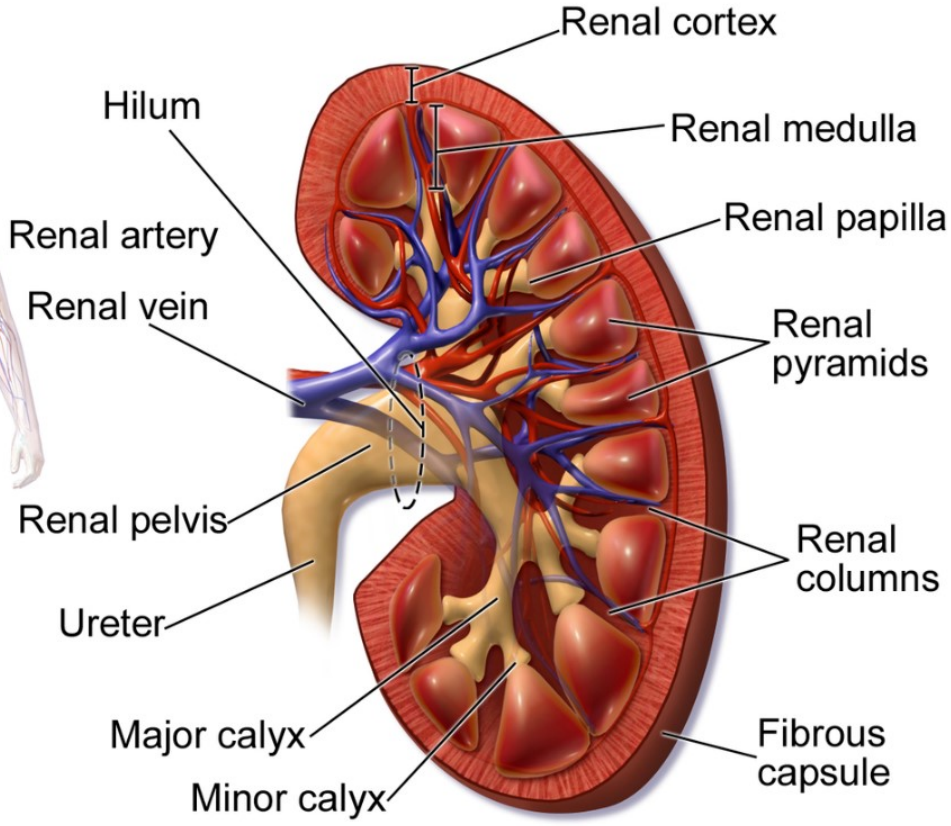


Kidneys

- Renal perfusion is high – 20-25% of cardiac output (<1% of body weight) – 4 mL/(min mL)
- Cortical perfusion compose 80-90% - regulated separately from medullary perfusion
- Vasodilator can increase perfusion
- Sympathetic nerve stimulation induced by e.g. hand grip can decrease perfusion (5%)
- Sodium, water and medication must be standardized to avoid confounders

Source: Turku PET Centre



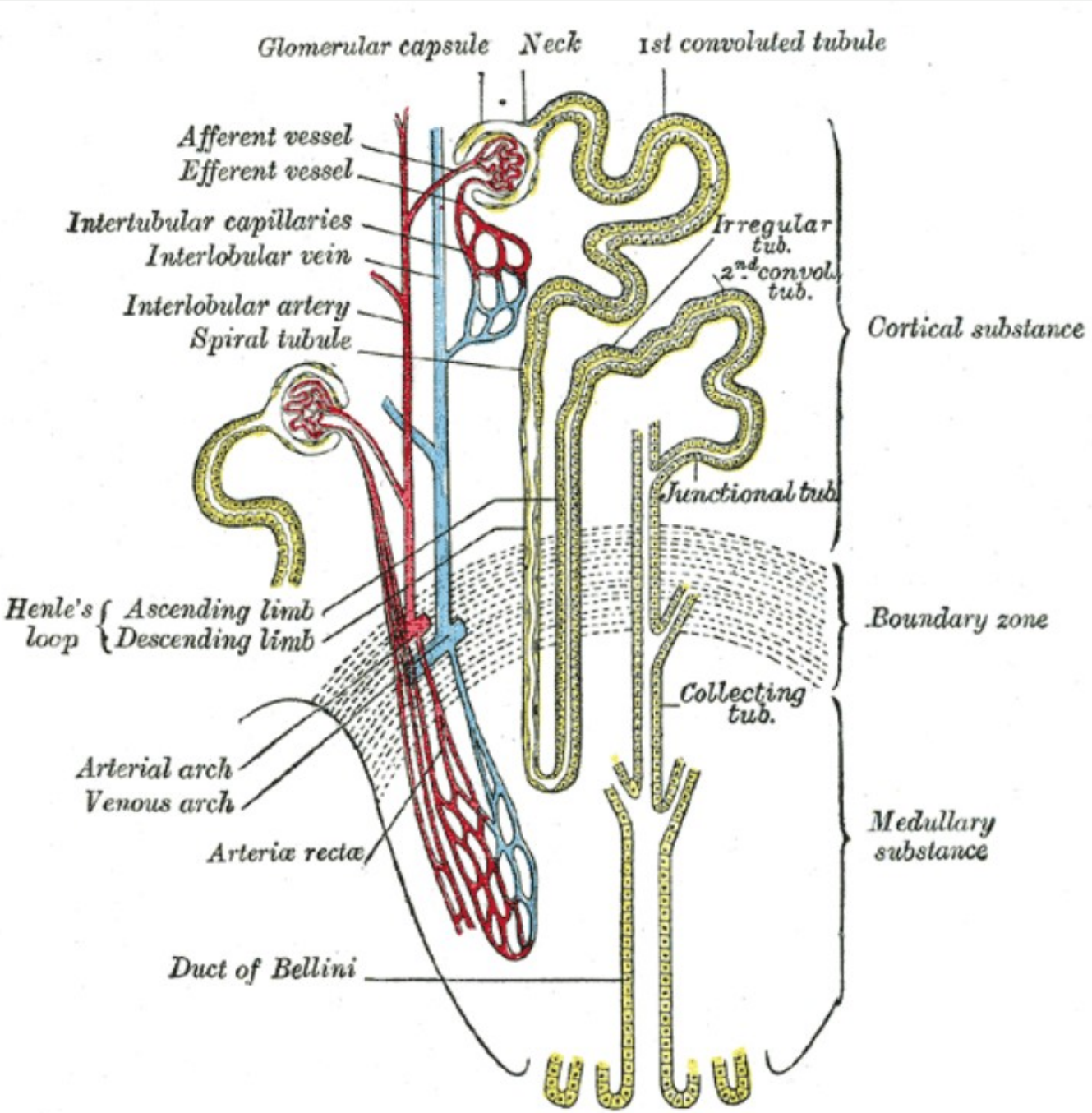


Kidney Anatomy

Source: wiki

Blood supply

- The renal artery gives rise to the afferent arteriole to the glumerulus
  - The glumerulus is the functional unit of the kidney that filters the plasma (~20%)
- The efferent arteriole leaving the glumerulus supplies the tubular portion of the kidney – the peritubular capillaries



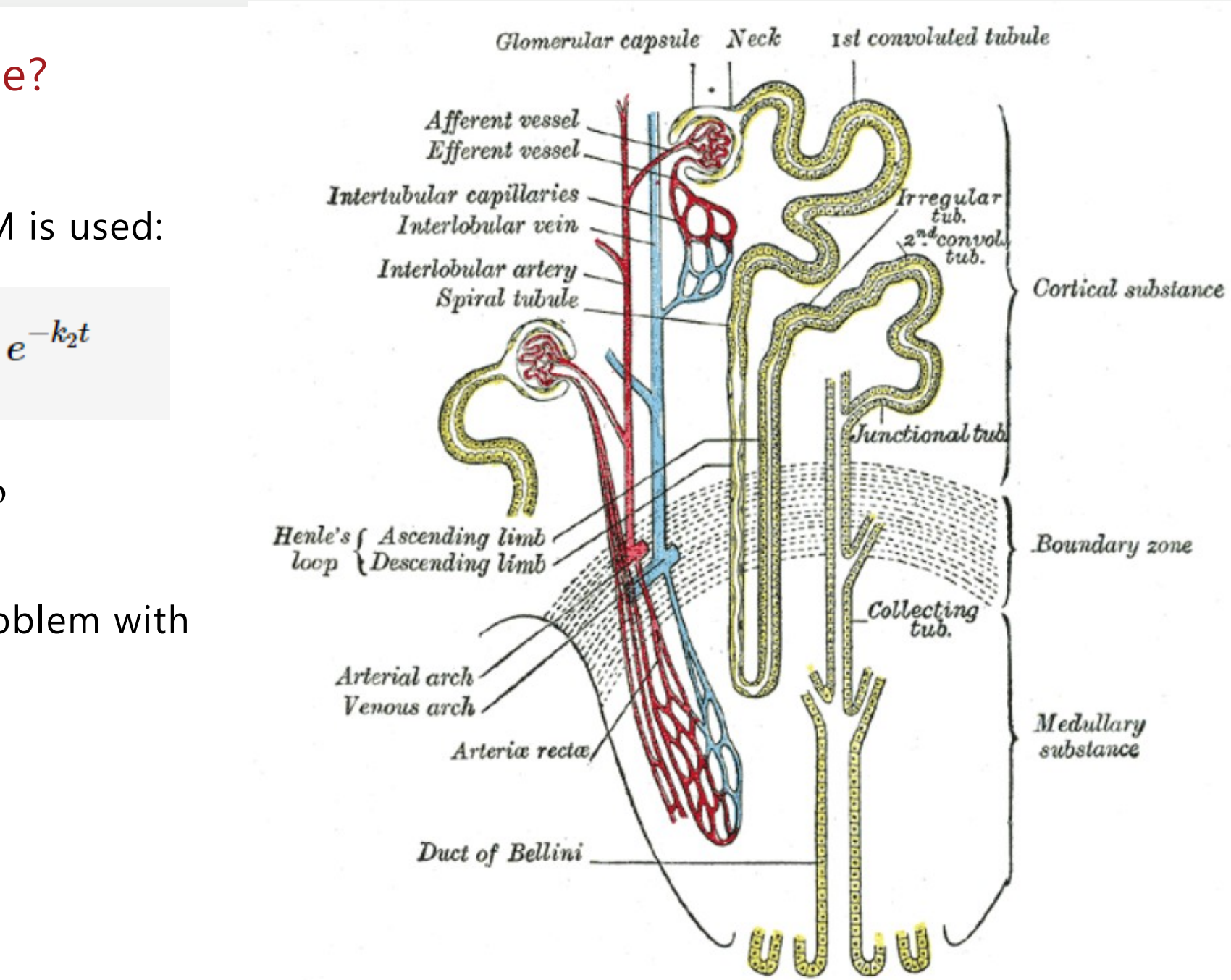
What model to choose?

In the literature, the 1TCM is used:

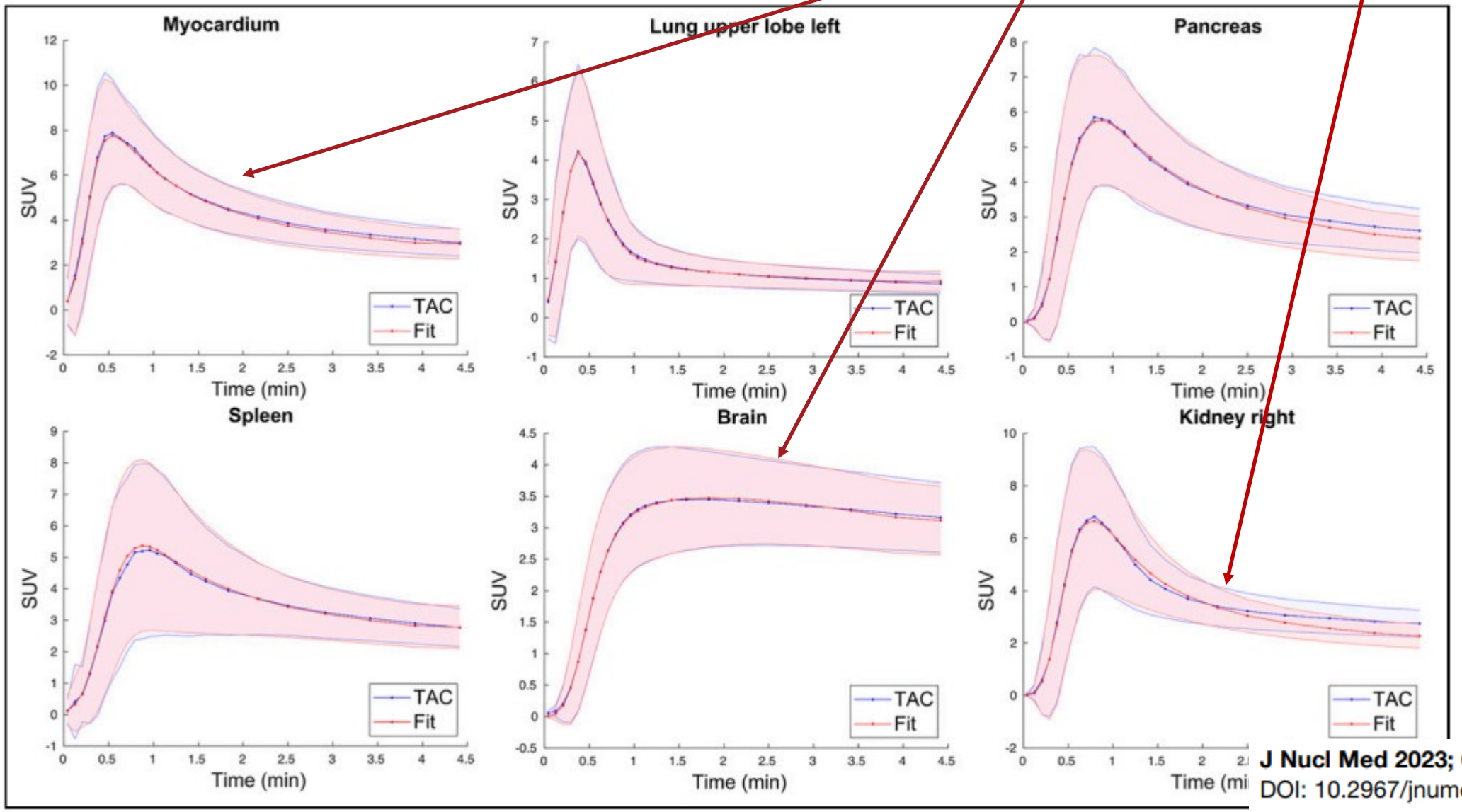
$$C_T(t) = K_1 C_A(t) \otimes e^{-k_2 t}$$

With either K_1=f or k_2=f/ρ

But what could be the problem with 1TCM?

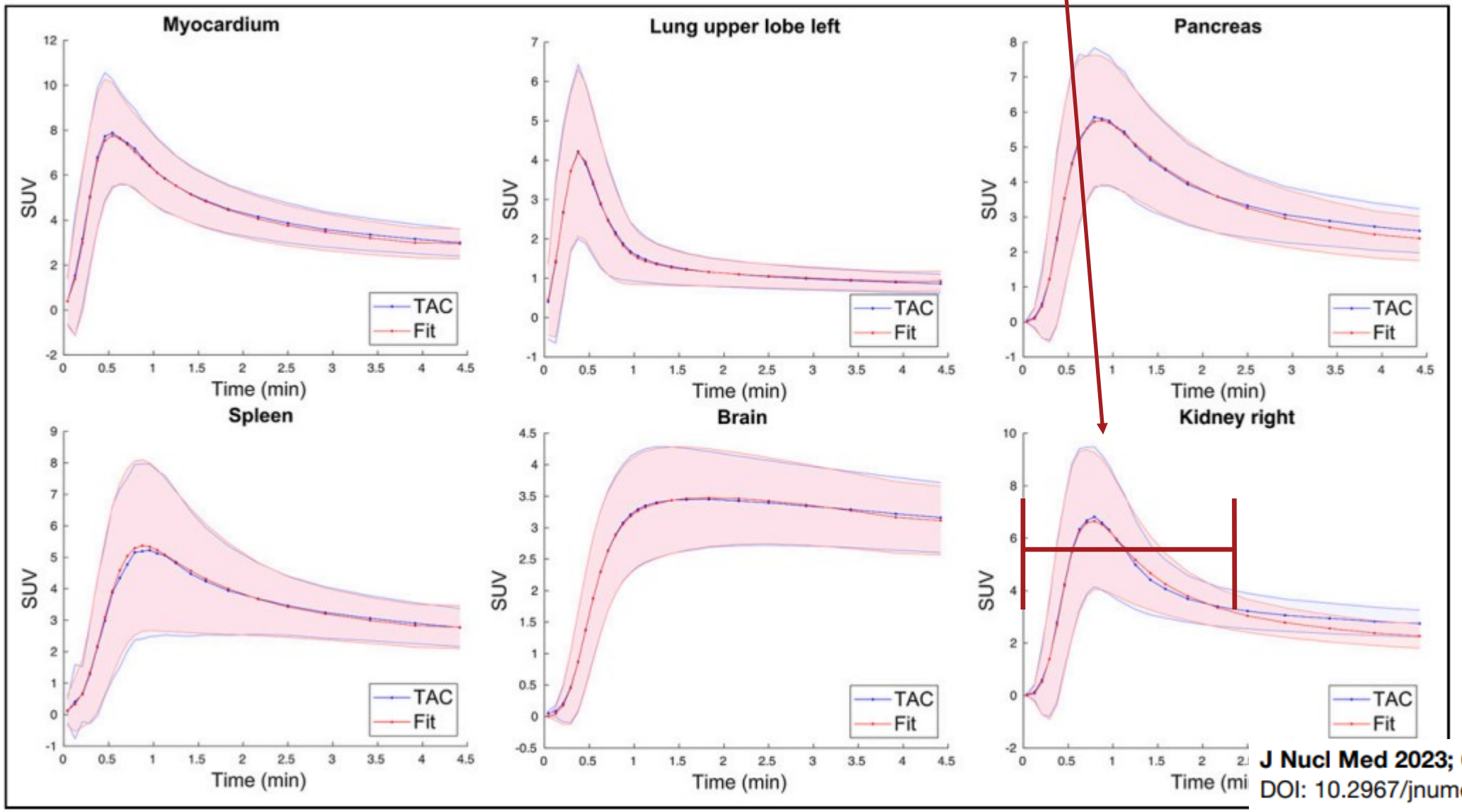


1-Tissue Compartment Model



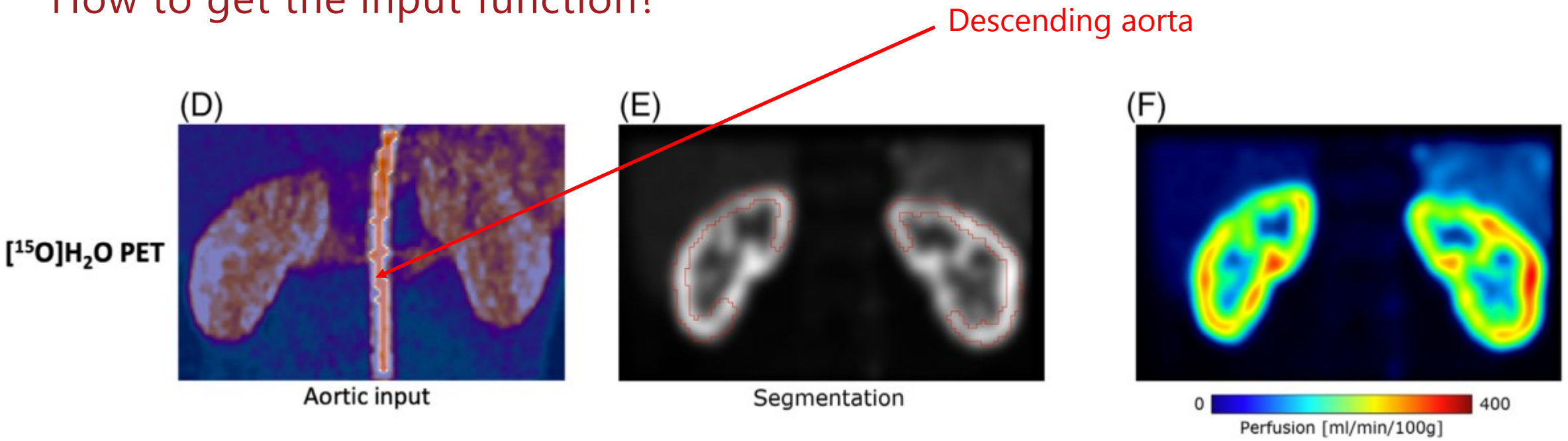
J Nucl Med 2023; 64:11S–19S
DOI: 10.2967/jnumed.122.264870

1-Tissue Compartment Model



J Nucl Med 2023; 64:11S–19S
DOI: 10.2967/jnumed.122.264870

How to get the input function?



Should we use K_1 or k_2?

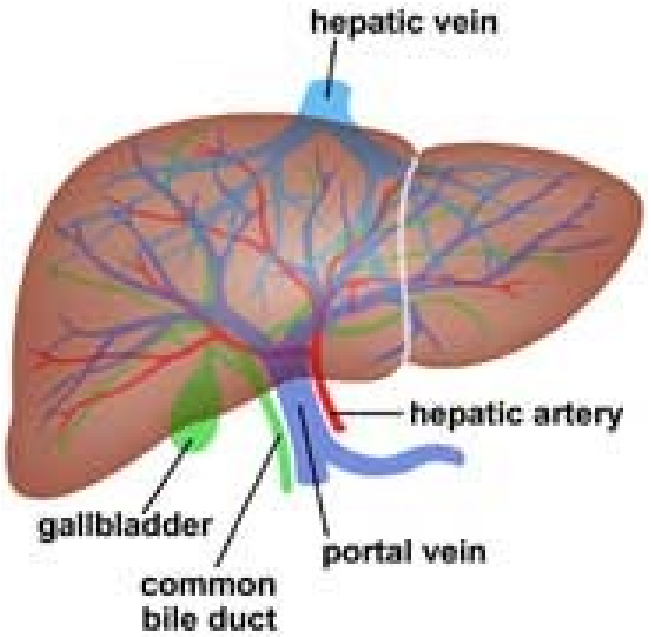
In this paper they used k_2 the first 150s a partition coefficient of ρ=0.94 mL/g.
Resting cortex perfusion: 1.8-4.7 mL/min/mL in young healthy subjects

Olsen et al. 2025. Measurement of renal cortex perfusion: A direct comparison of arterial spin labelling magnetic resonance imaging and [^{15}O]H_2O positron emission tomography. Magn Reson Med. 94:2537-49.

Liver perfusion

What is the problem with quantitative assessment of liver perfusion?

The liver is perfused through the portal vein and hepatic artery of which the portal vein has the largest diameter – dual input function



Liver perfusion

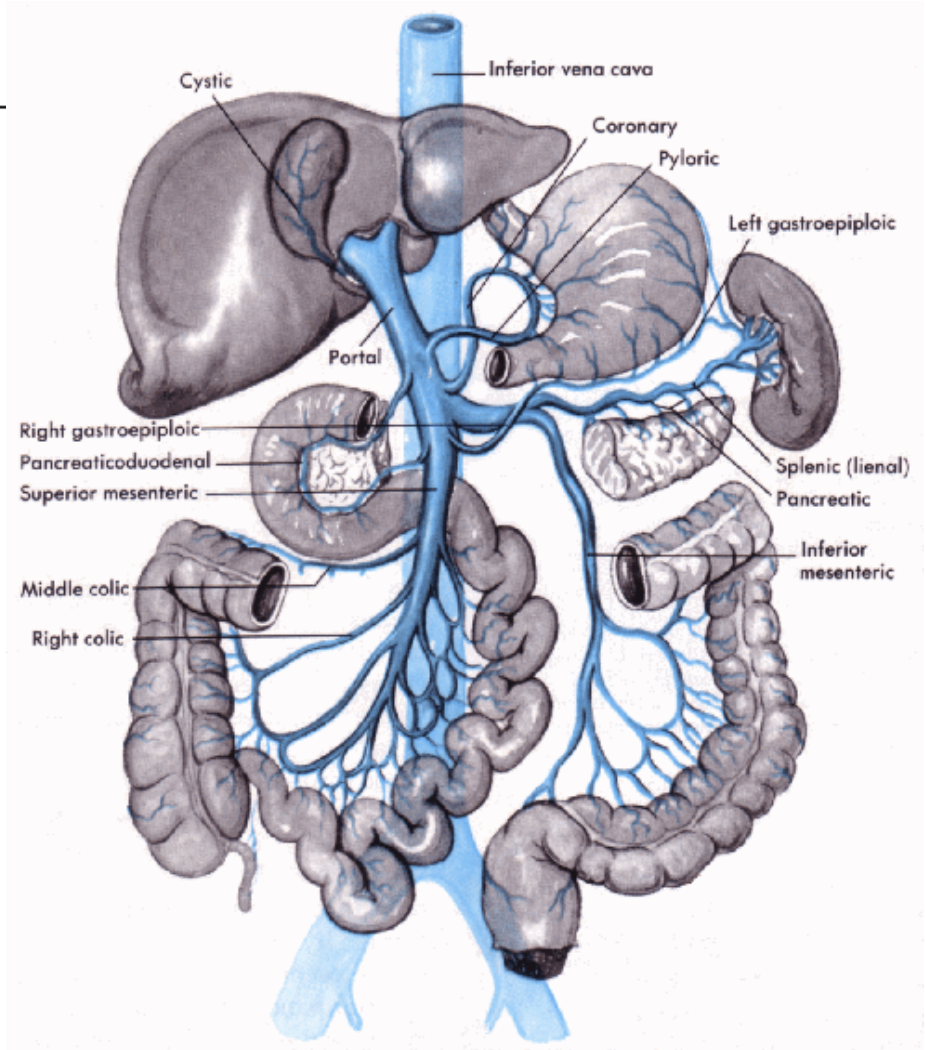
Eur J Nucl Med Mol Imaging (2008) 35:1899–1911
DOI 10.1007/s00259-008-0796-z

ORIGINAL ARTICLE

Non-invasive estimation of hepatic blood perfusion from $H_2{}^{15}O$ PET images using tissue-derived arterial and portal input functions

N. Kudomi · L. Slimani · M. J. Järvisalo · J. Kiss · R. Lautamäki · G. A. Naum · T. Savunen · J. Knuuti · H. Iida · P. Nuutila · P. Iozzo

$$C_{TIS}(t) = (f_a C_A(t) + f_p C_P(t)) \otimes e^{-k_2 \cdot t}$$



Liver perfusion

Eur J Nucl Med Mol Imaging (2008) 35:1899–1911
DOI 10.1007/s00259-008-0796-z

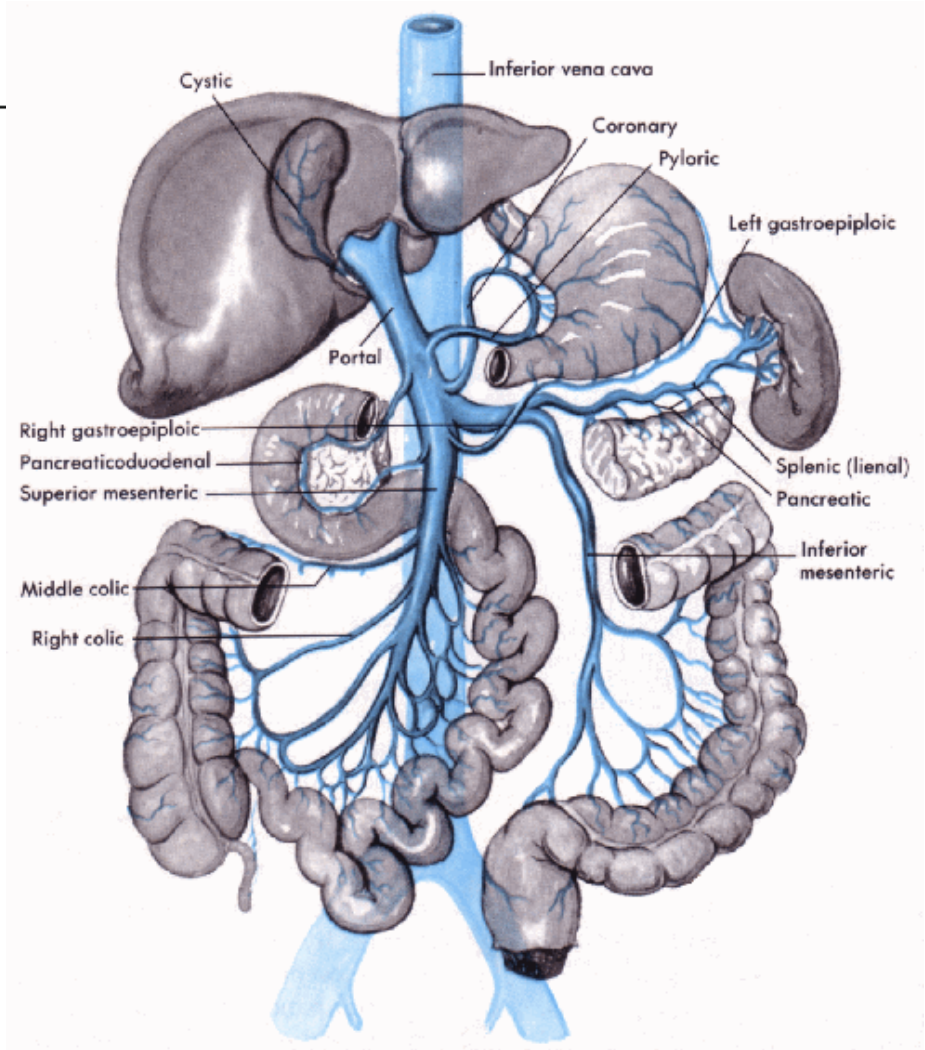
ORIGINAL ARTICLE

Non-invasive estimation of hepatic blood perfusion from $H_2{}^{15}O$ PET images using tissue-derived arterial and portal input functions

N. Kudomi · L. Slimani · M. J. Järvisalo · J. Kiss · R. Lautamäki · G. A. Naum · T. Savunen · J. Knuuti · H. Iida · P. Nuutila · P. Iozzo

$$C_{TIS}(t) = (f_a C_A(t) + f_p C_P(t)) \otimes e^{-k_2 \cdot t}$$

In this study from 2008, the IDIF could not be extracted from the image and a complicated model was used



Organ perfusion

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-026-07769-7

ORIGINAL ARTICLE

Automated long axial field of view PET image processing and kinetic modelling with the TurBO toolbox

Jouni Tuisku[1,2] · Santeri Palonen[1,2] · Henri Kärpijoki[1,2] · Aino Latva-Rasku[1,2,3] · Nelli Tuomola[1,2,3] · Harri Harju[1,2] · Sergey V. Nesterov[1,2] · Vesa Oikonen[1,2] · Hidehiro Iida[1,2] · Jarmo Teuho[1,2] · Chunlei Han[1,2] · Tomi Karjalainen[1,2] · Anna K. Kirjavainen[1,5] · Johan Rajader[1,4] · Riku Klén[1,2] · Pirjo Nuutila[1,2,3] · Juhani Knuuti[1,2] · Lauri Nummenmaa[1,2,6]

Organ perfusion

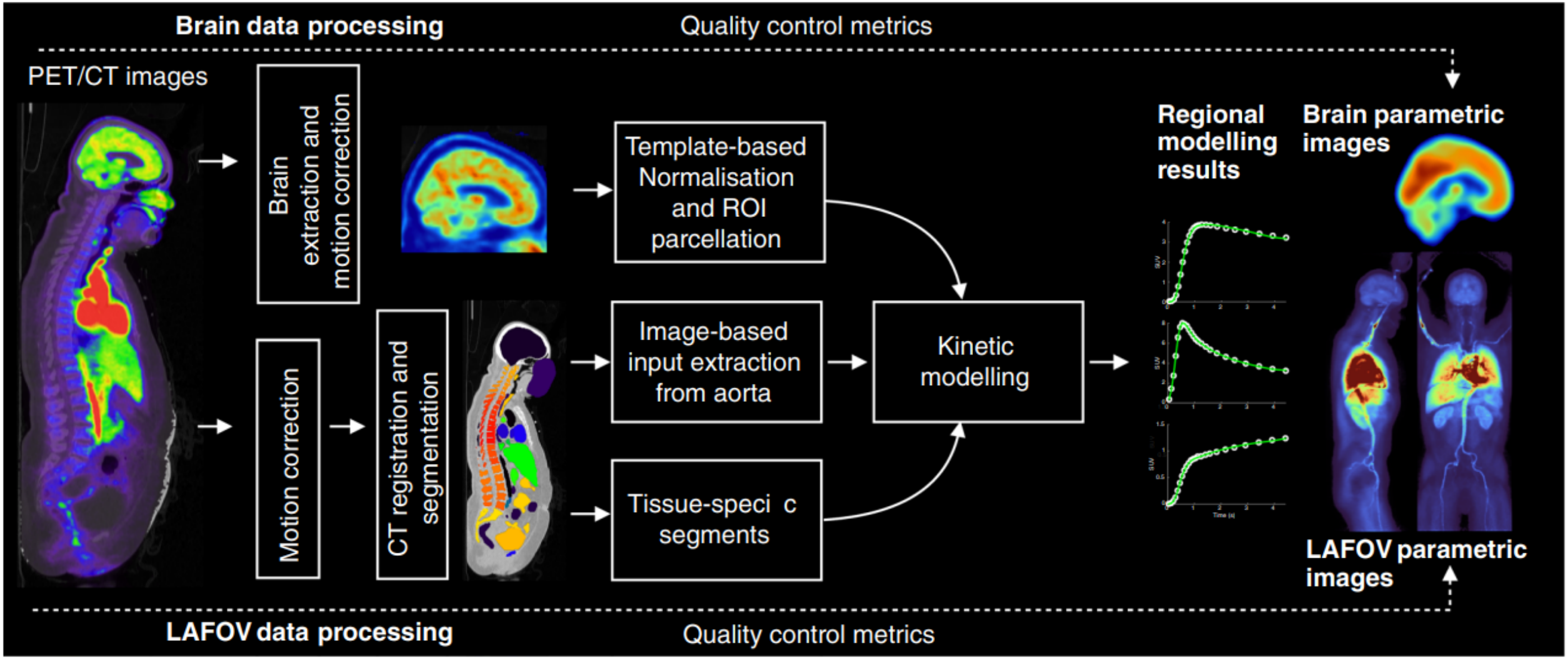


Fig. 1 Flowchart for the TurBO pipeline

How do they handle the liver input?

- Even with a total-body PET, an IDIF of the portal vein is noisy, thus the portal vein concentration C_{PV} is simulated from aorta IDIF, C_A:

$$C_{PV} = k_{GI} C_A \otimes \mathrm{e}^{-\mathrm{k_{GI}} t}$$

where k_{GI} represents the diffusion rate in the gut system [3].

- The arterial liver flow f_A and the portal vein flow f_{PV} is fitted from data to estimate the combined input curve:

$$C_{liverIF}(t) = \frac{f_A C_{IDIF}(t) + f_{PV} C_{PV}(t)}{f_A + f_{PV}}.$$

Increased use of quantitative PET?

Volpi *et al. EJNMMI Research* (2023) 13:97
https://doi.org/10.1186/s13550-023-01050-w

EJNMMI RESEARCH

REVIEW **Open Access**

An update on the use of image-derived input functions for human PET studies: new hopes or old illusions?

Conclusion Improvements in PET scanner technology and software for automated IDIF extraction may allow to solve some of the major limitations associated with IDIF, such as partial volume effects and poor temporal sampling, with the exciting potential for accurate estimation of single kinetic rates. Nevertheless, until individualized radiometabolite correction can be performed effectively, IDIF approaches remain confined at best to a few tracers.