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

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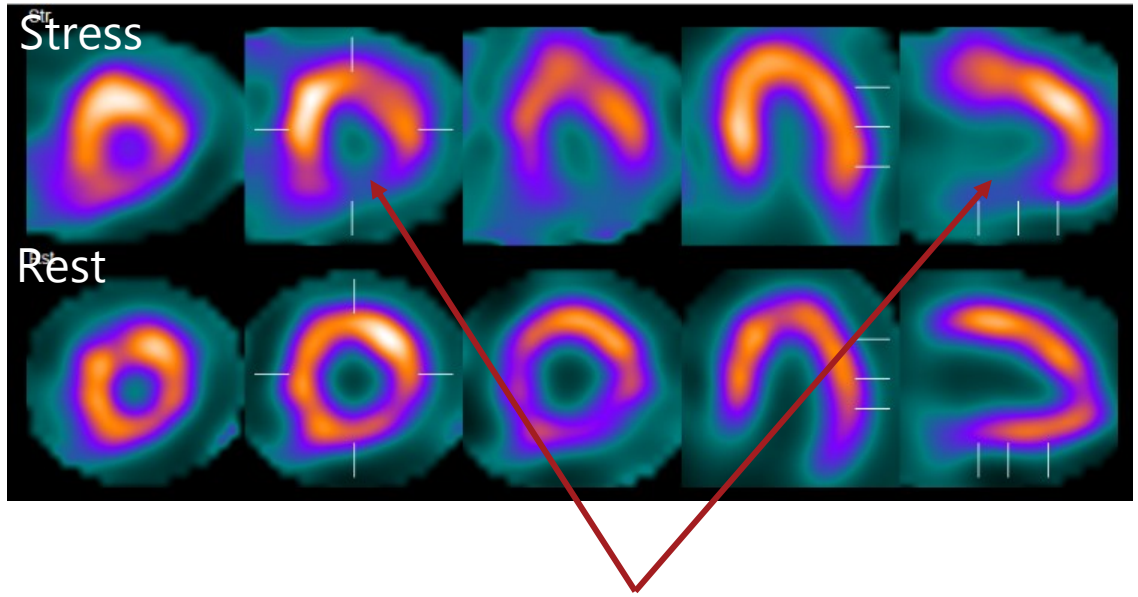
Quantitative cardiac perfusion in ischemic heart disease

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



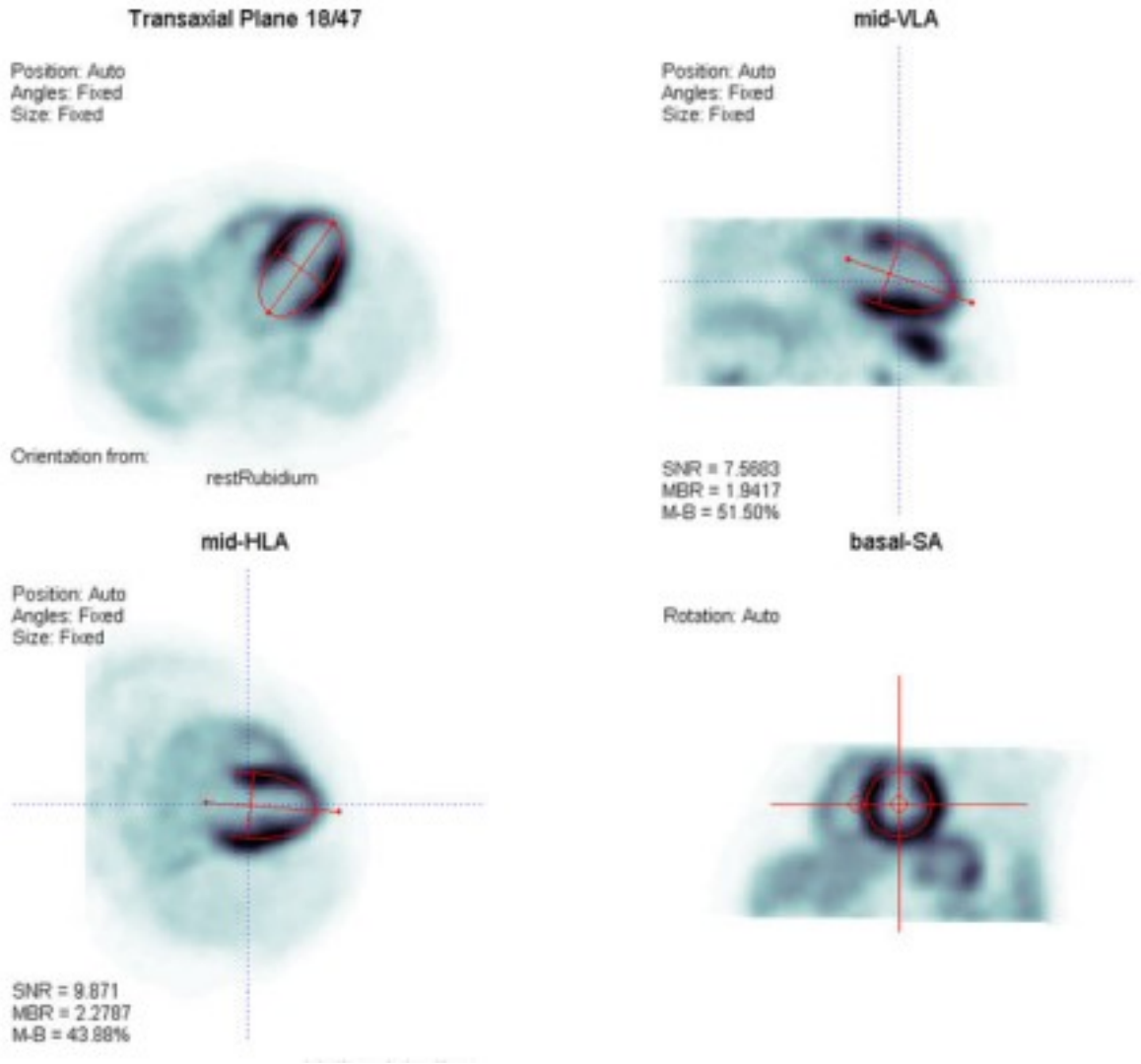
Stress defect in the inferior wall

^{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

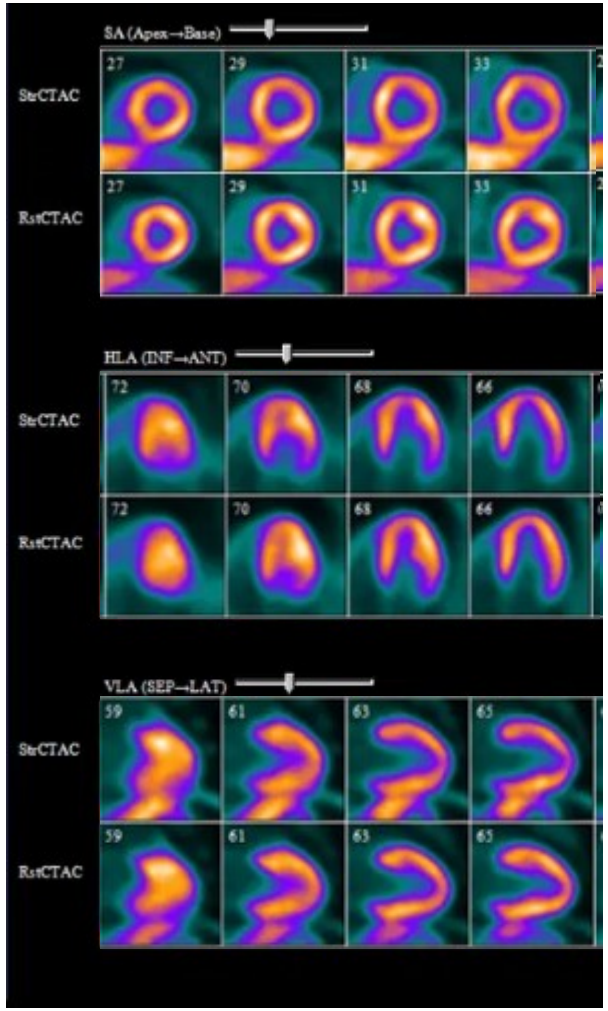
Cardiac perfusion measurements

Three planes are shown:

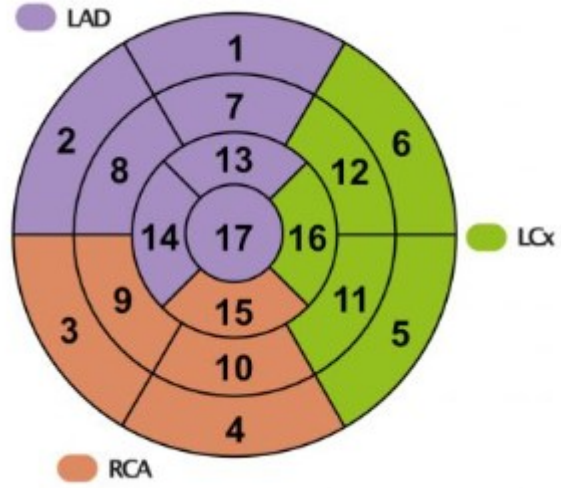
Top: short axis (perpendicular to the long axis), i.e. apex to base

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?

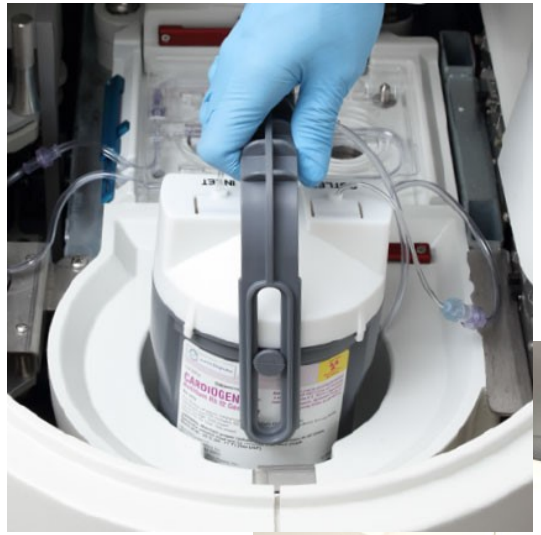
How do we stress the heart?

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.



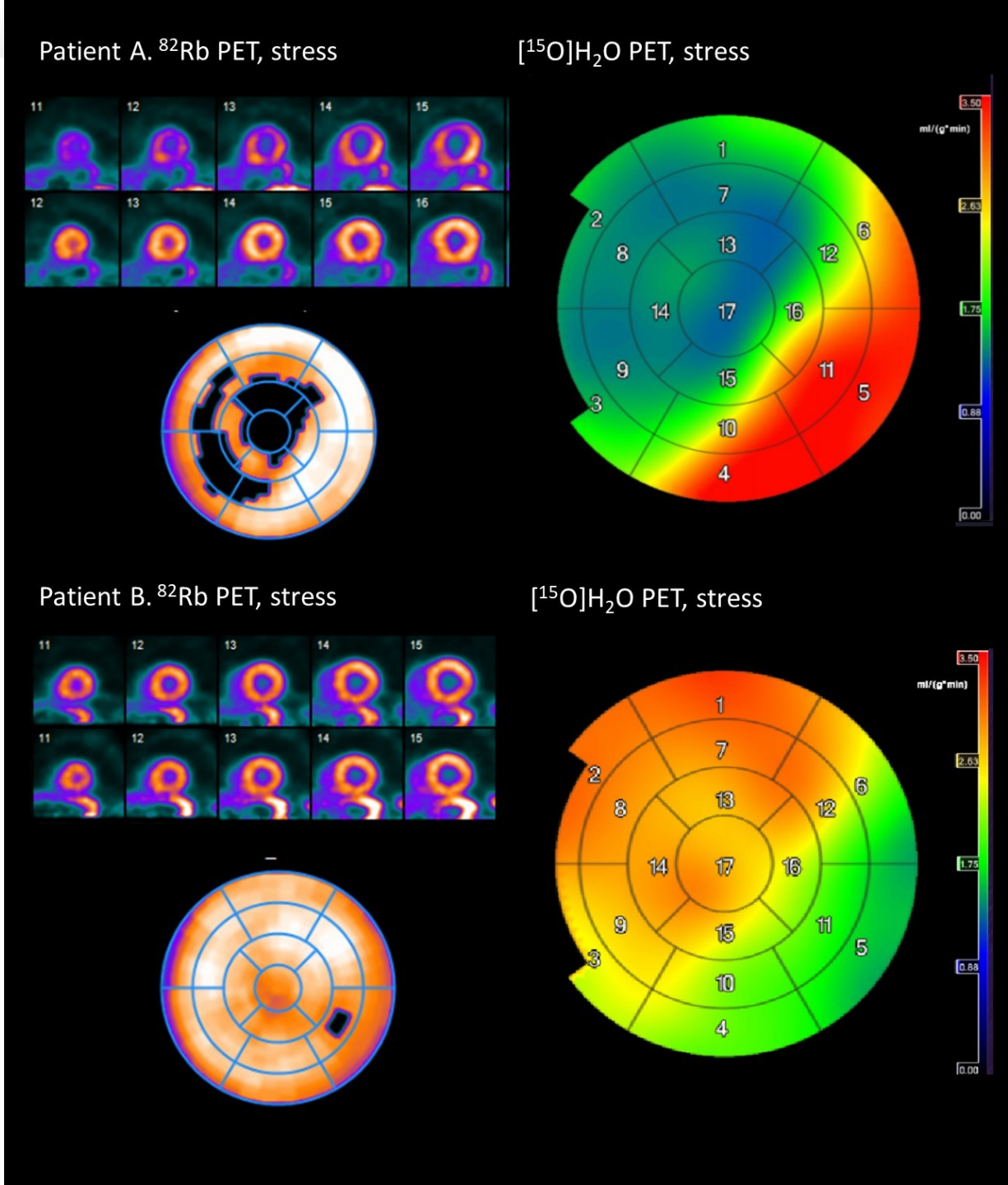
^{82}Rb vs. [^{15}O]H_2O

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?

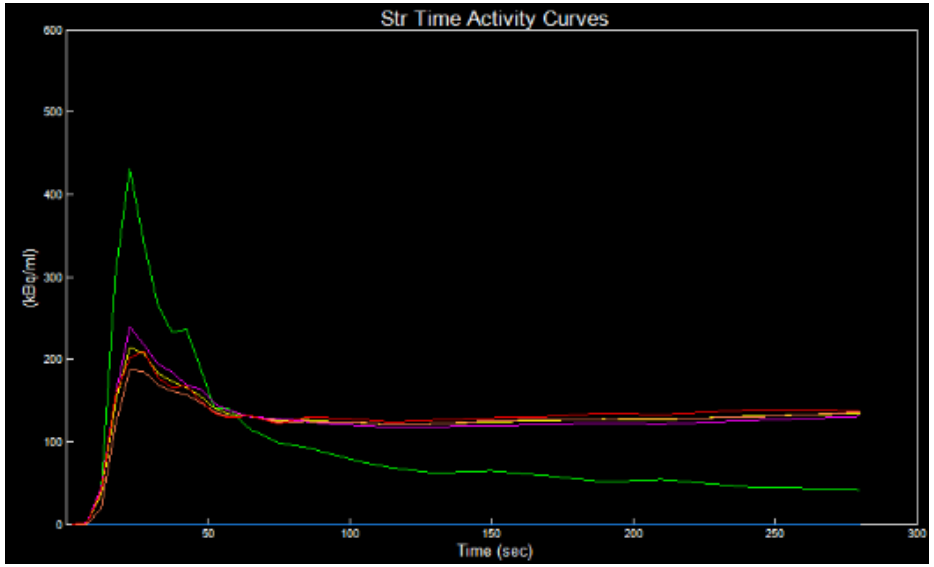
Are cutoffs the same?

	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

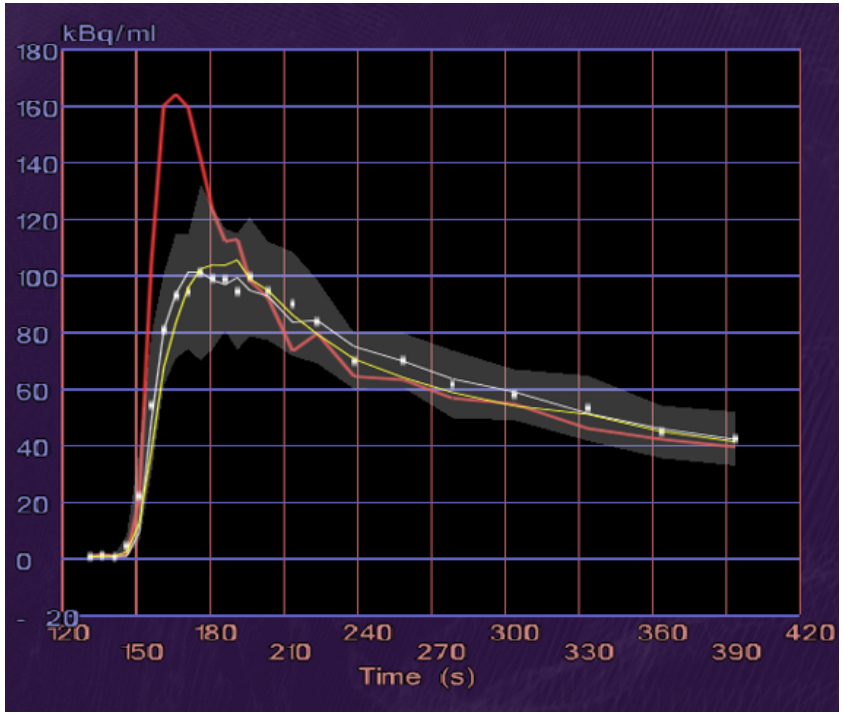
Cut-off [^{15}O]H_2O: Danad, I., et al., J Am Coll Cardiol, 2014. **64**(14): p. 1464-75.

Differences in tracer kinetics

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



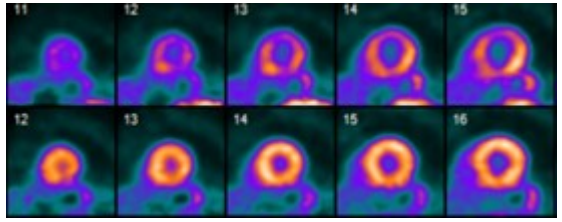
- $[^{15}O]H_2O$: reversible tracer – parametric imaging.



Differences in tracer kinetics

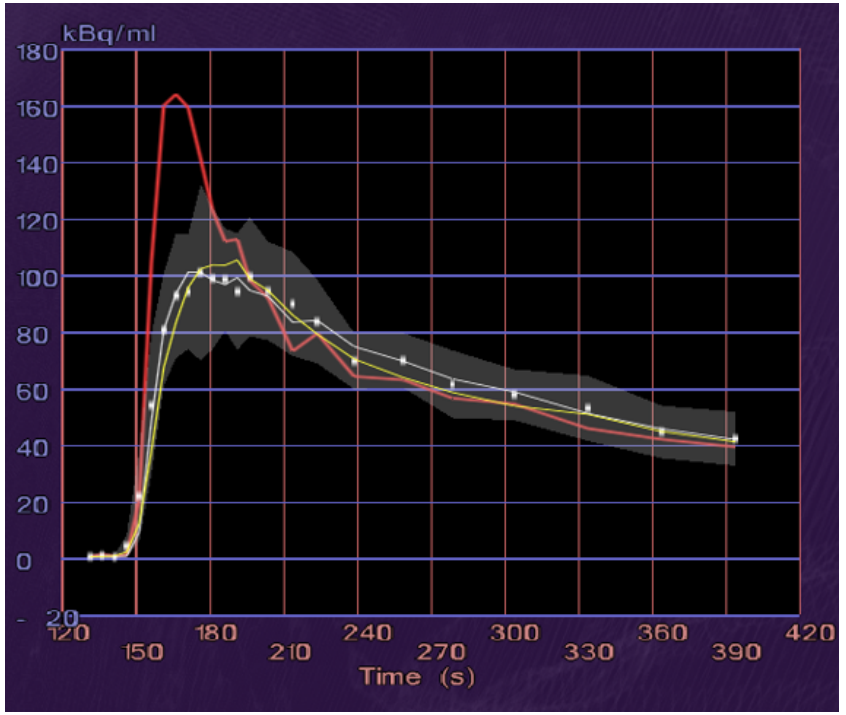
- ^{82}Rb: irreversibel tracer trapped in the myocytes – static imaging.

Visual assessment or



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

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

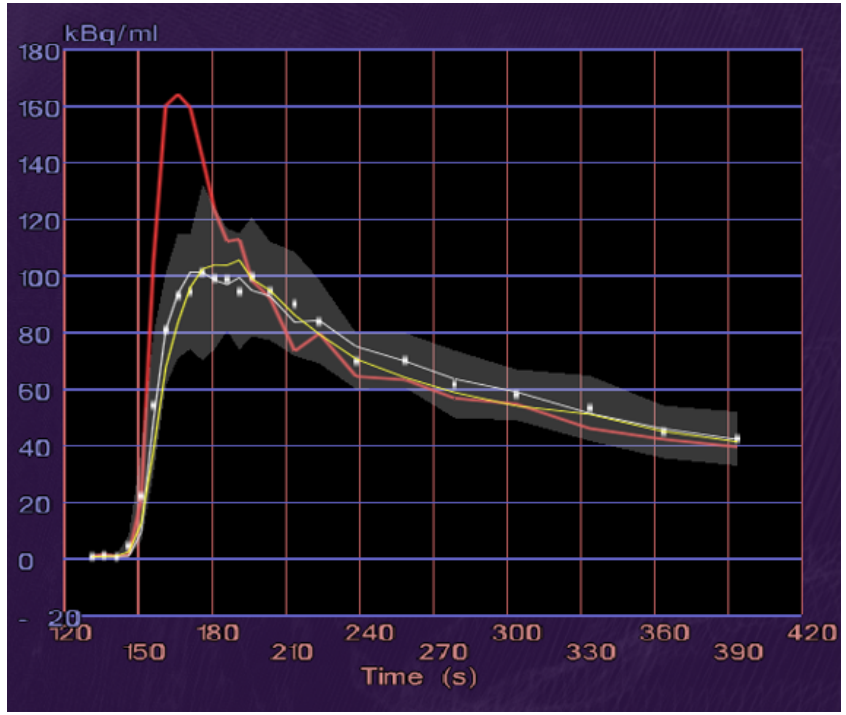


Differences in tracer kinetics

- ^{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 $k_2=f/p$

Differences in tracer kinetics

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Quantitative measures used for calculation of myocardial flow reserve

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

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

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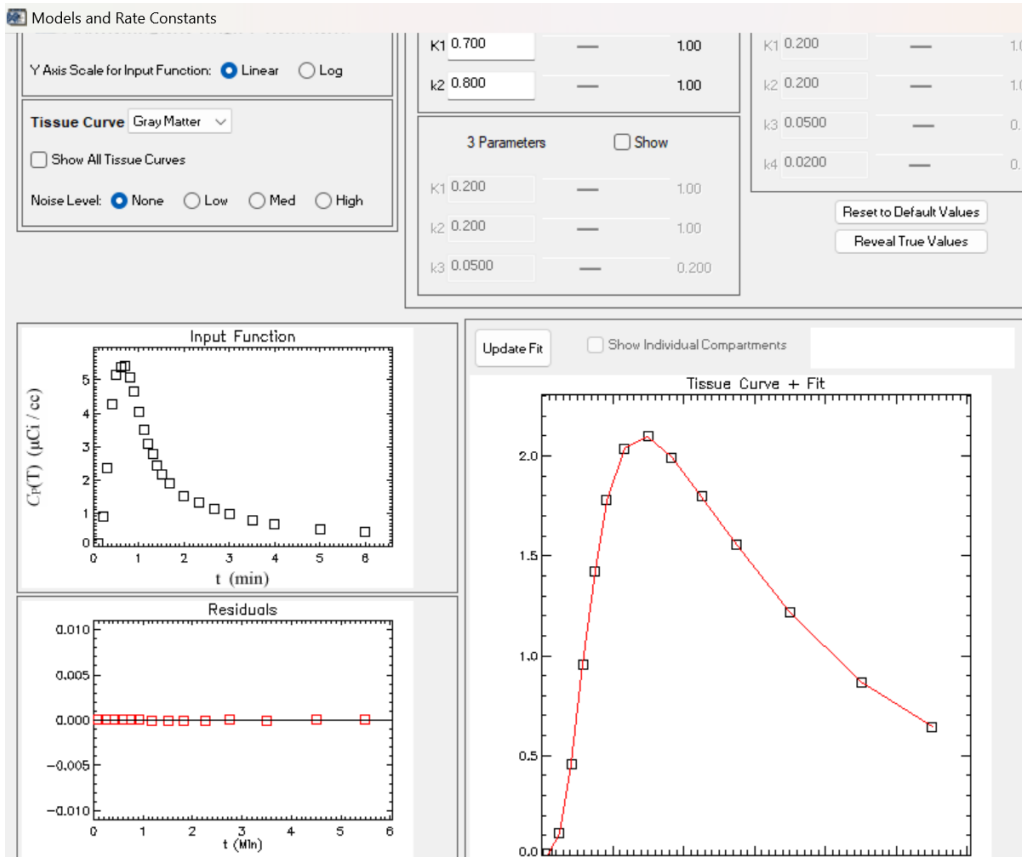
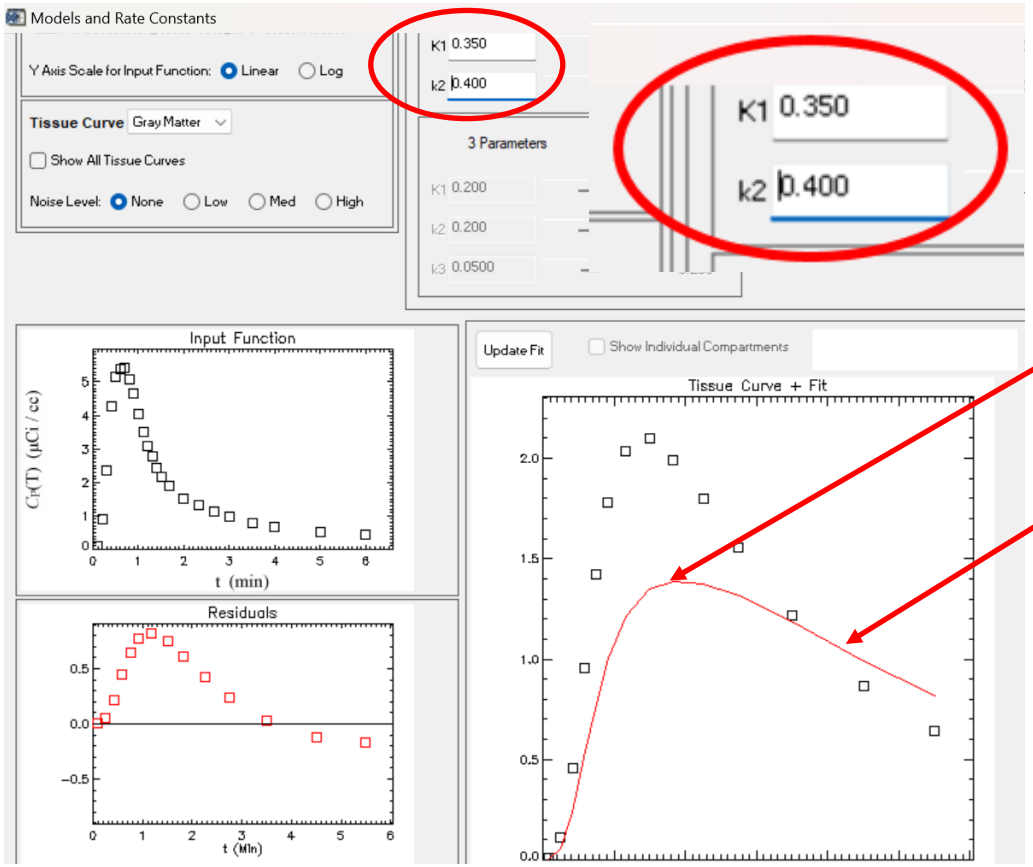


Cardiac flow is decreased by 50%:

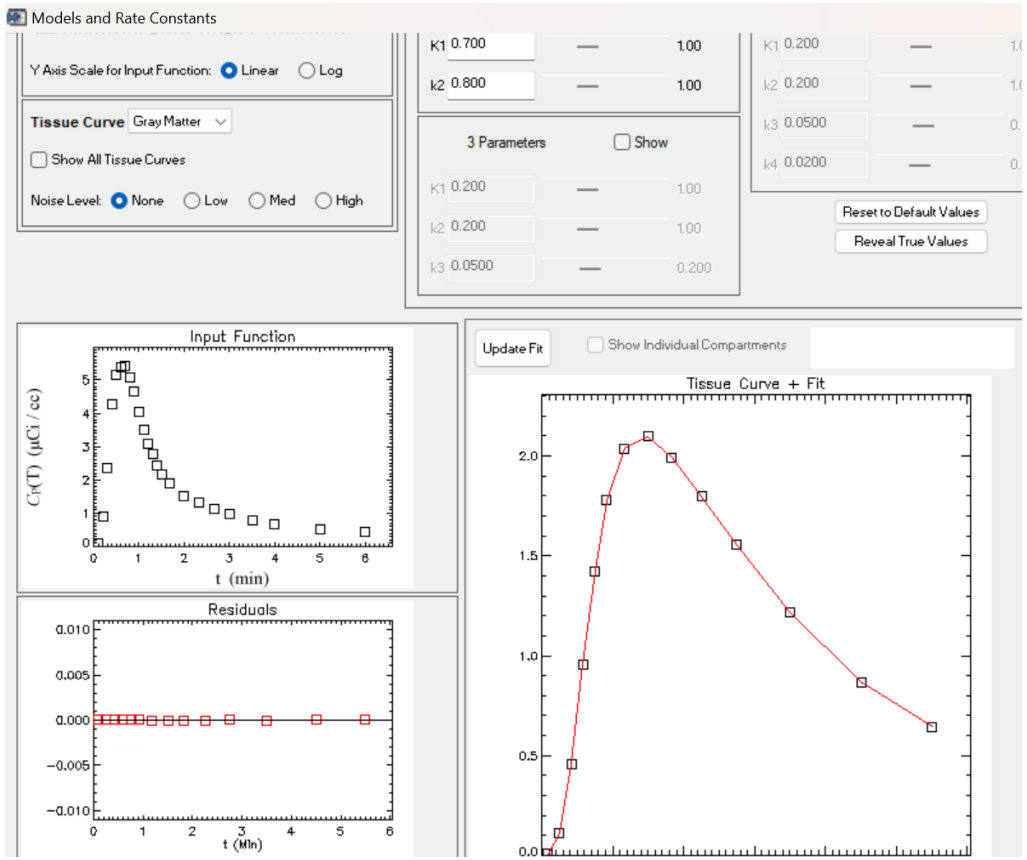


Peak decreased

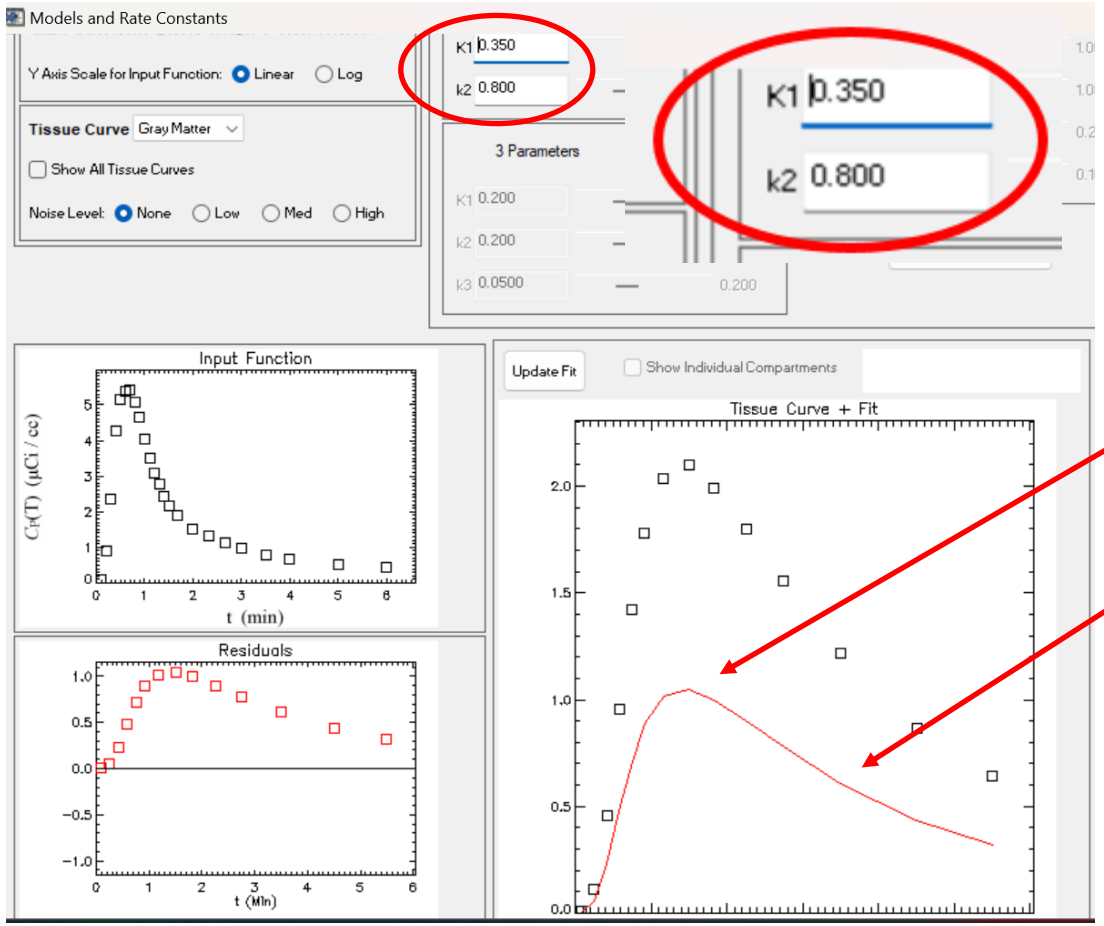
Washout decreased

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 $k_2 = f/p$

Using k_2 instead of K_1 to calculate the perfusion (f) allows to measure perfusion only in perfused tissue (ρ or PTF) .
-> Scarring, motion and AC correction affects the measured perfusion minimally.

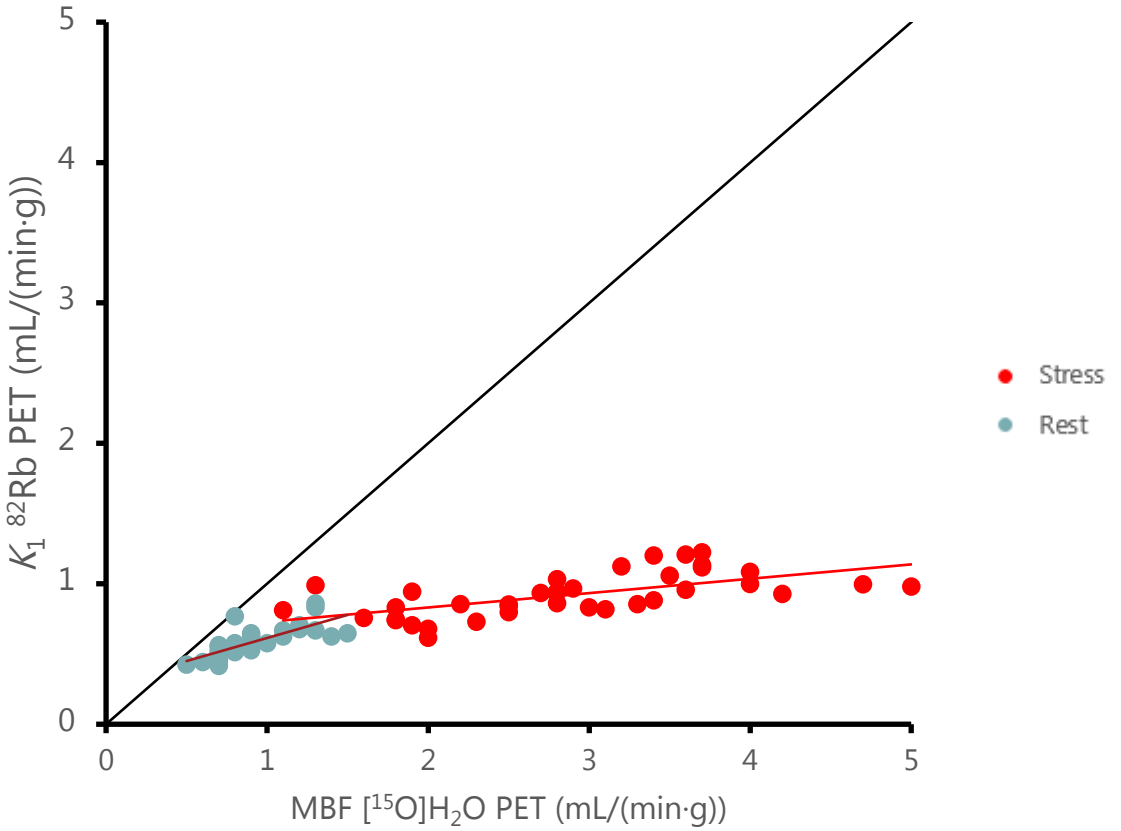
Scar tissue in the heart:

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



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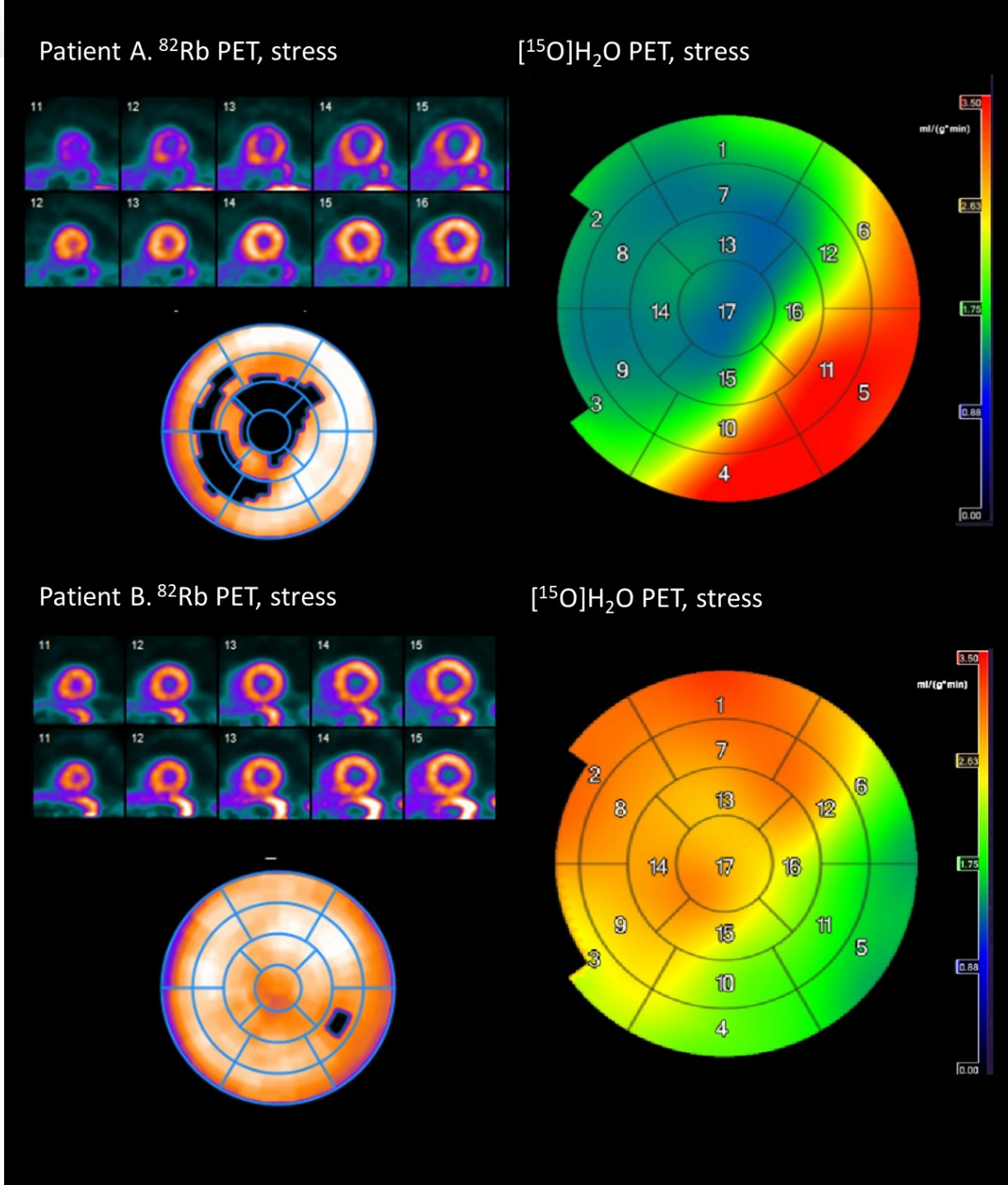
Disagreement

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

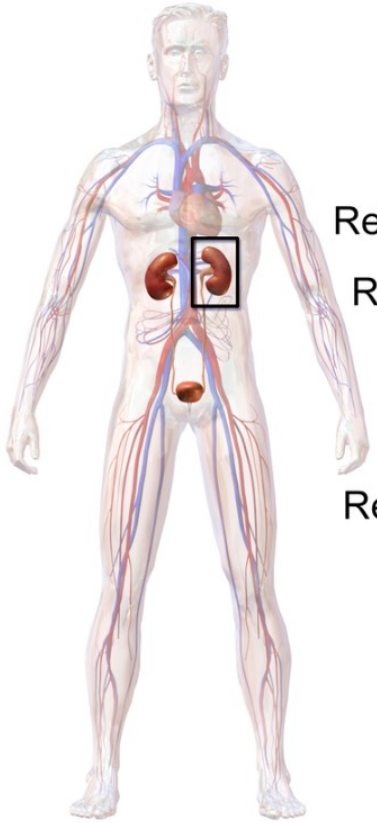
Thus, [^{15}O]H_2O PET is more sensitive to ischemia due to differences in extraction fraction!

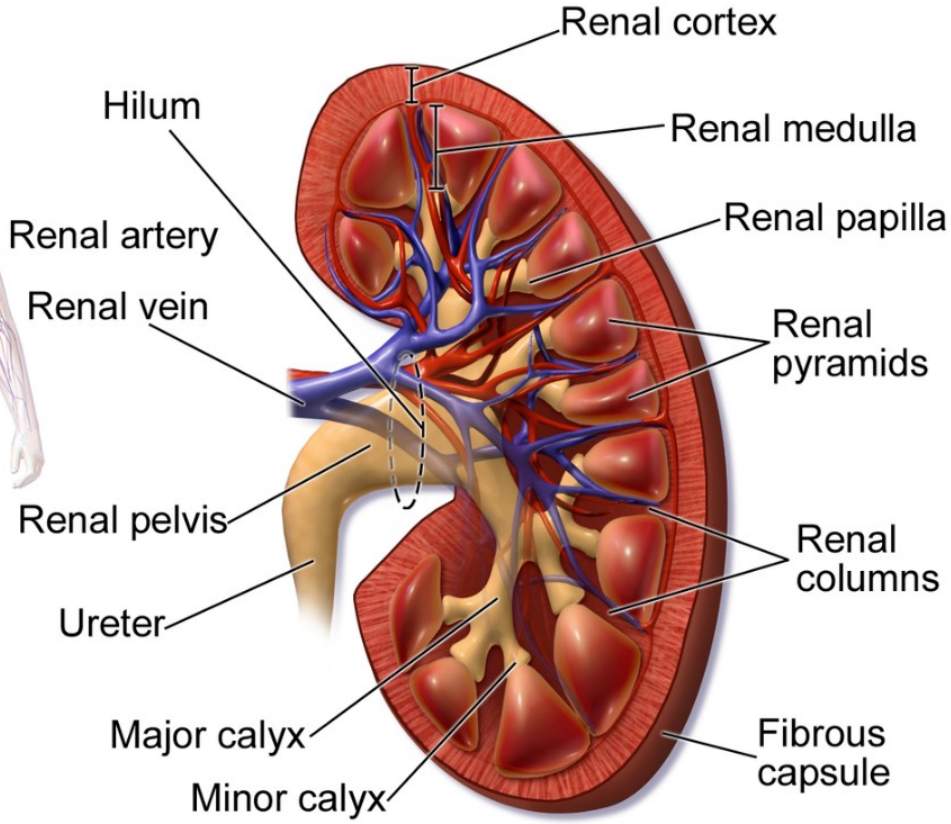


Kidneys

- 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
- Sodium, water and medication must be standardized to avoid confounders

Source: Turku PET Centre





Kidney Anatomy

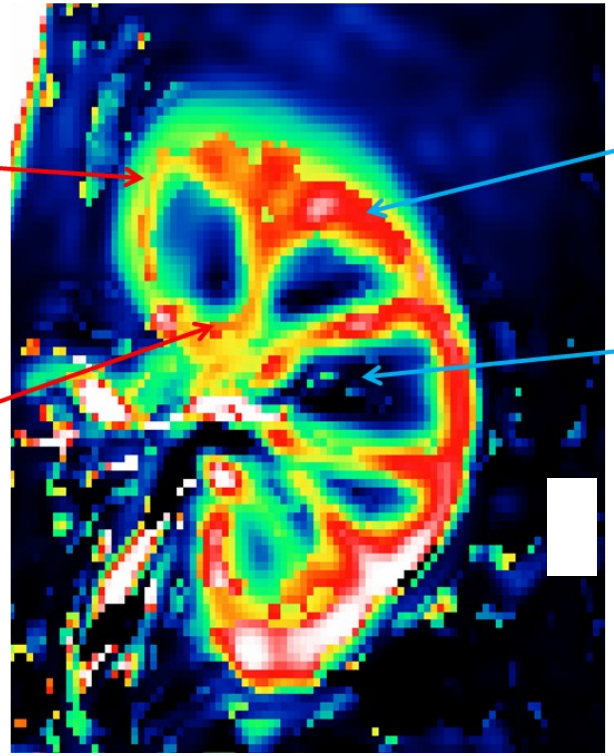
Source: wiki

Regional renal hemodynamics by MRI:

Perfusion

Cortex:
350-500
ml/ 100 g/ min

Medulla:
10-50
ml/ 100 g/ min



Oxygen tension

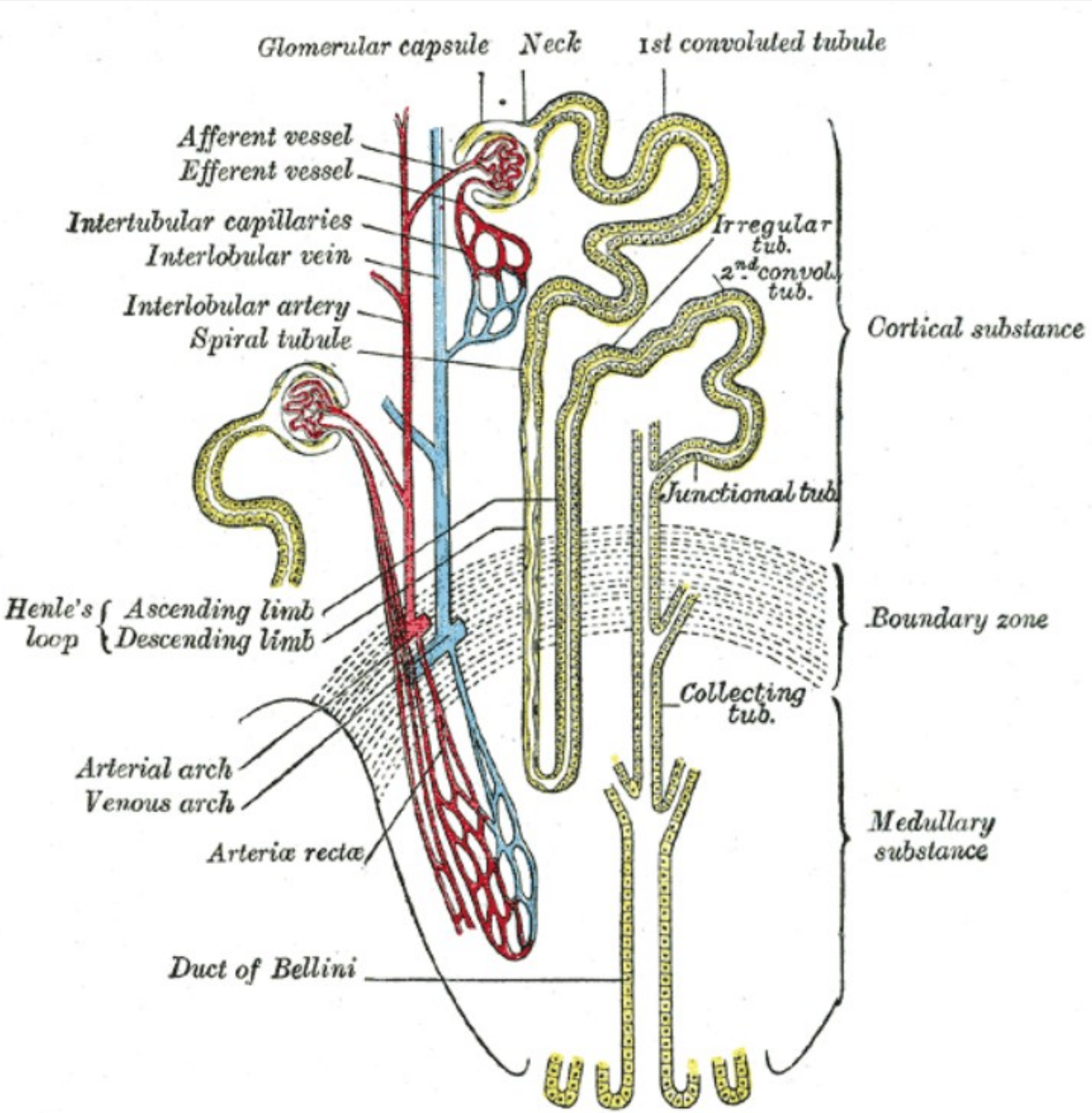
Cortex:
50 mm Hg

Medulla:
15 mm Hg

Haddock B & Asmar A.
JAHA. 2023 Feb 7;12(3):e027712.

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



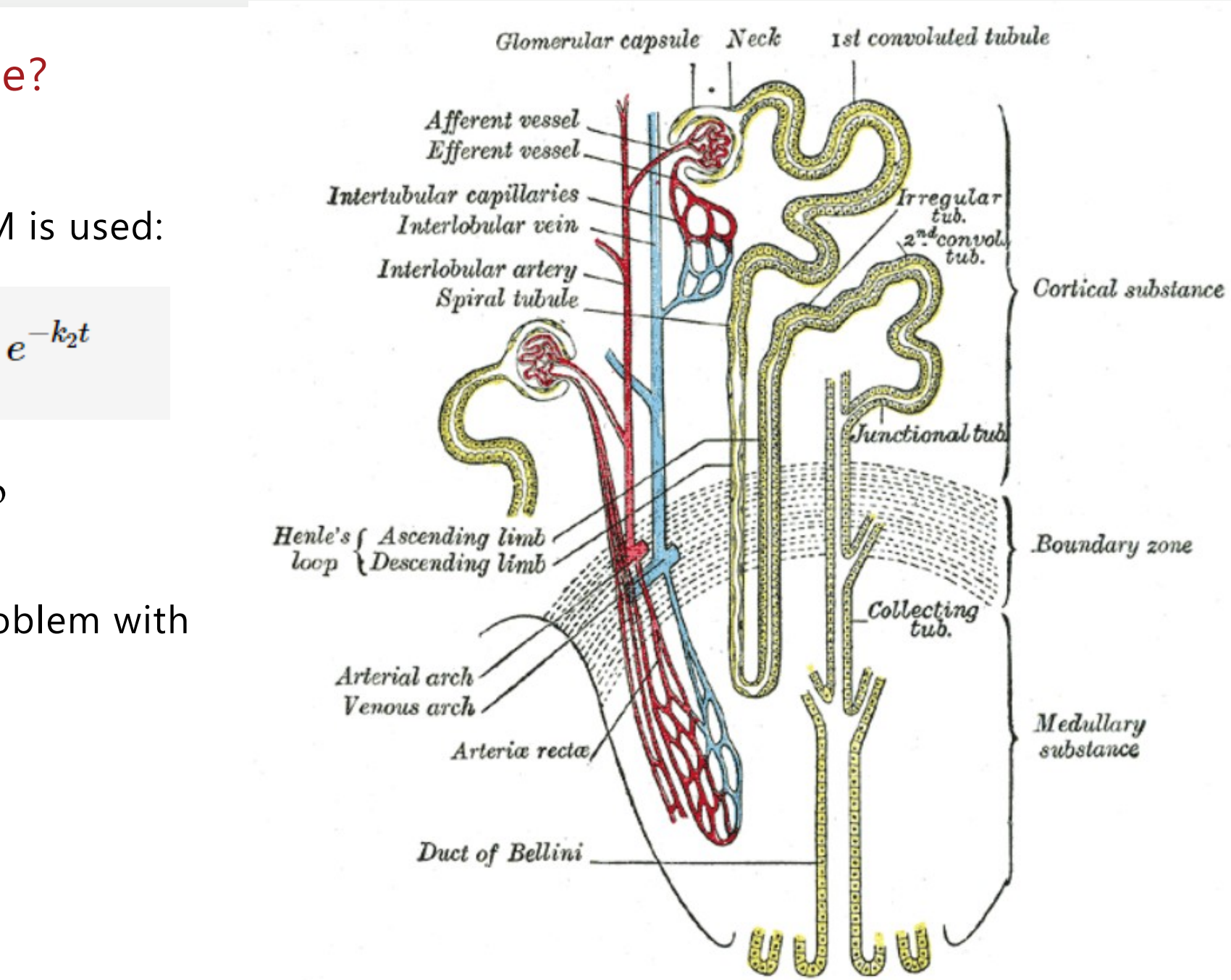
What model to choose?

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

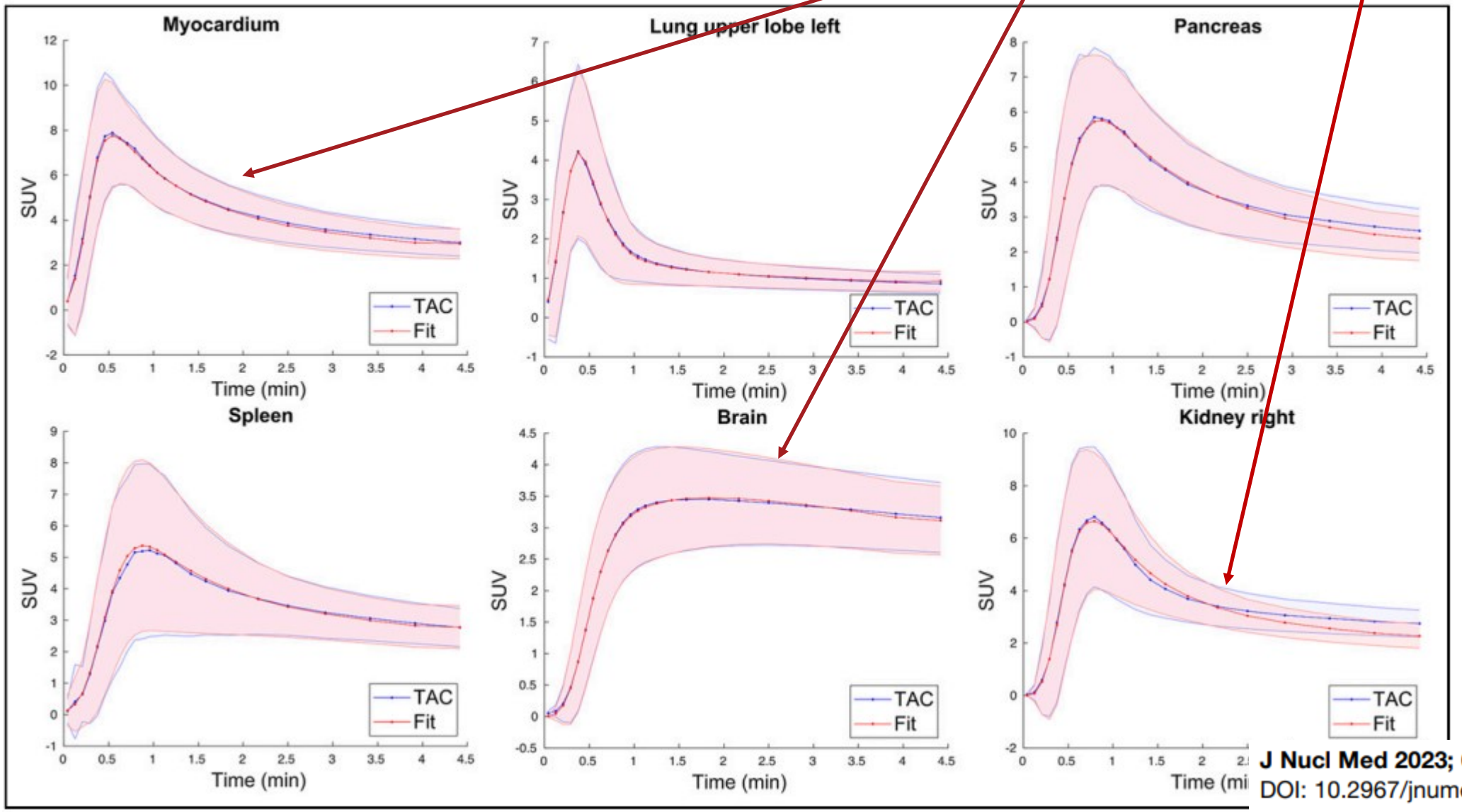
But what could be the problem with 1TCM?



What model to choose?

Perfect fits

Not perfect fit



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

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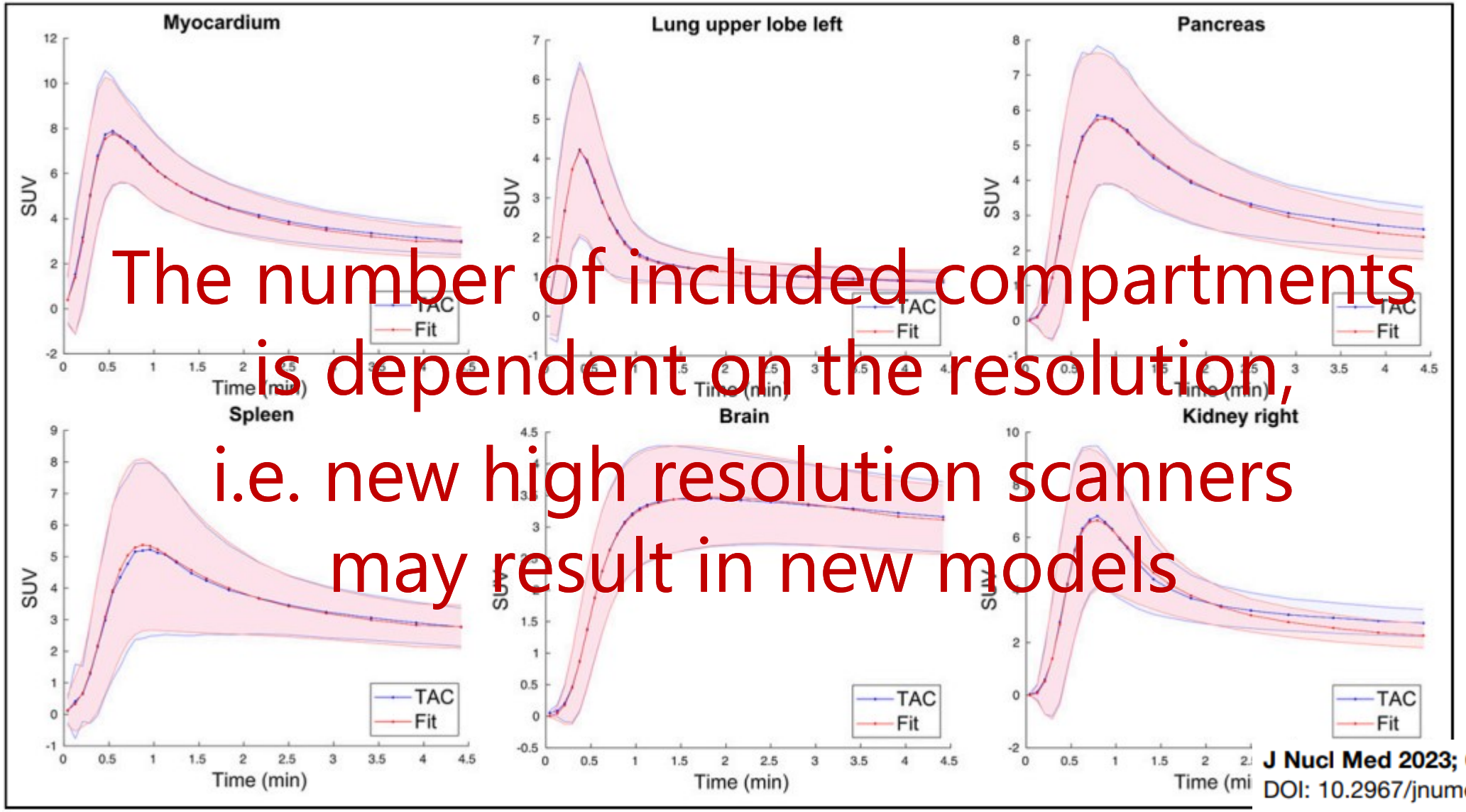

The number of included compartments is dependent on the resolution, i.e. new high resolution scanners may result in new models

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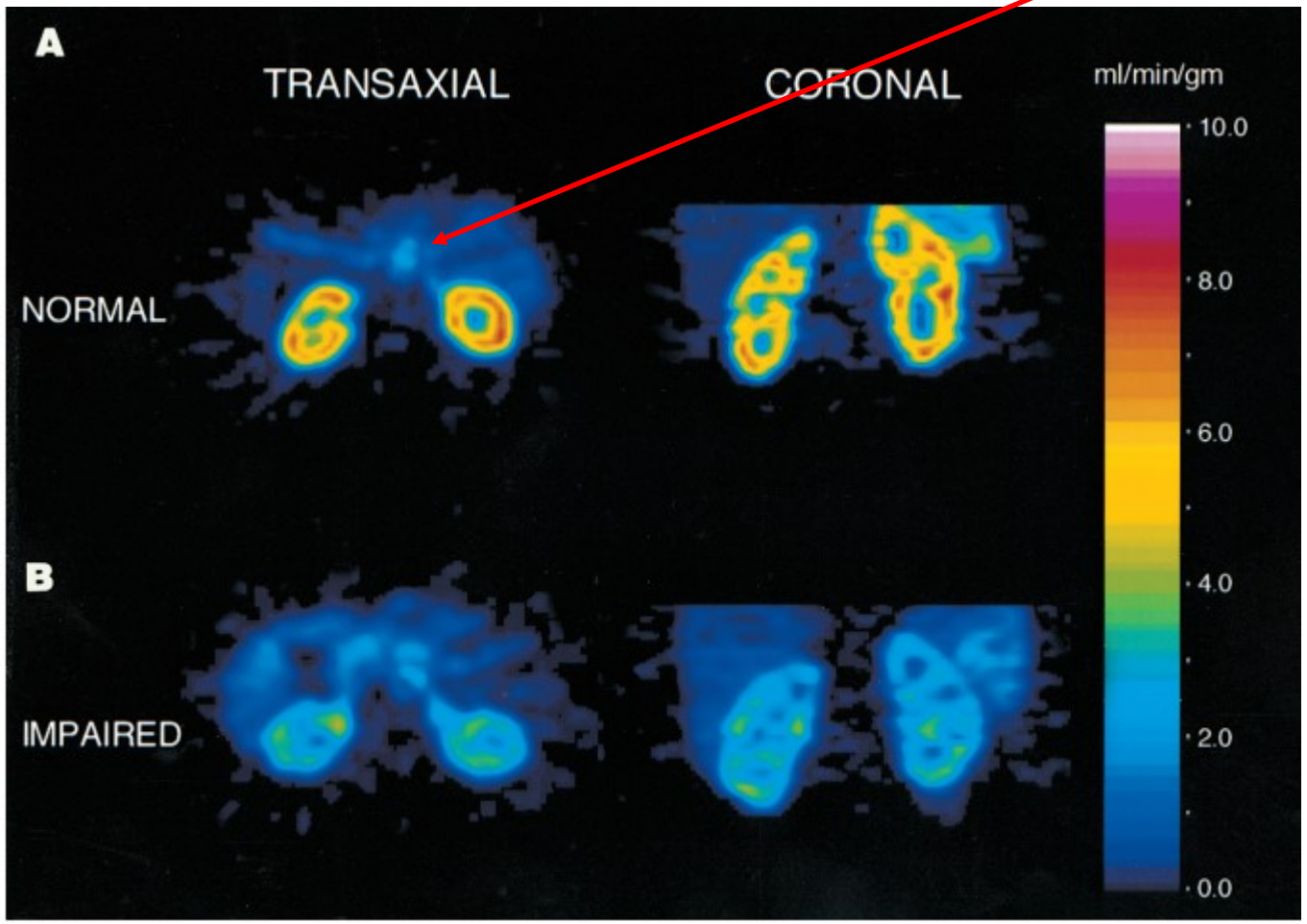
How to get the input function?



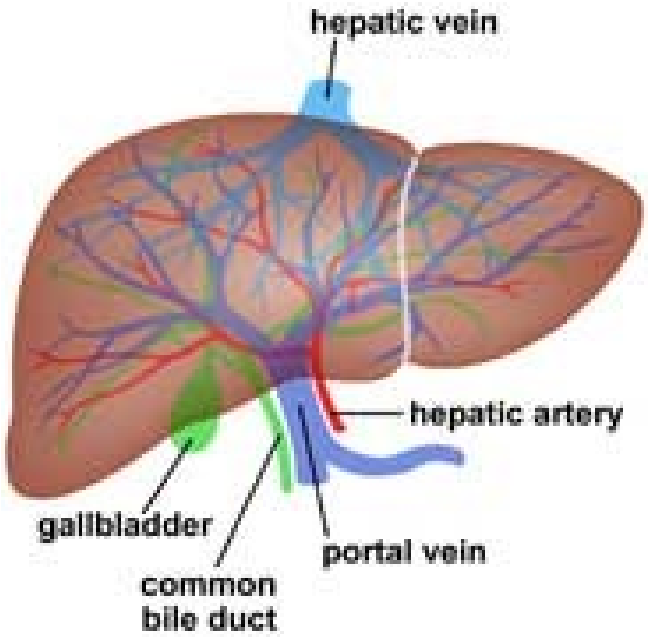
A 1-cm circular region of interest (ROI) was defined and used to measure the activity concentration averaged over each scanning interval

Alpert et al. 2002. Mapping of Local Renal Blood Flow with PET and $H_2{}^{15}O$. JNM 43:470-5

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

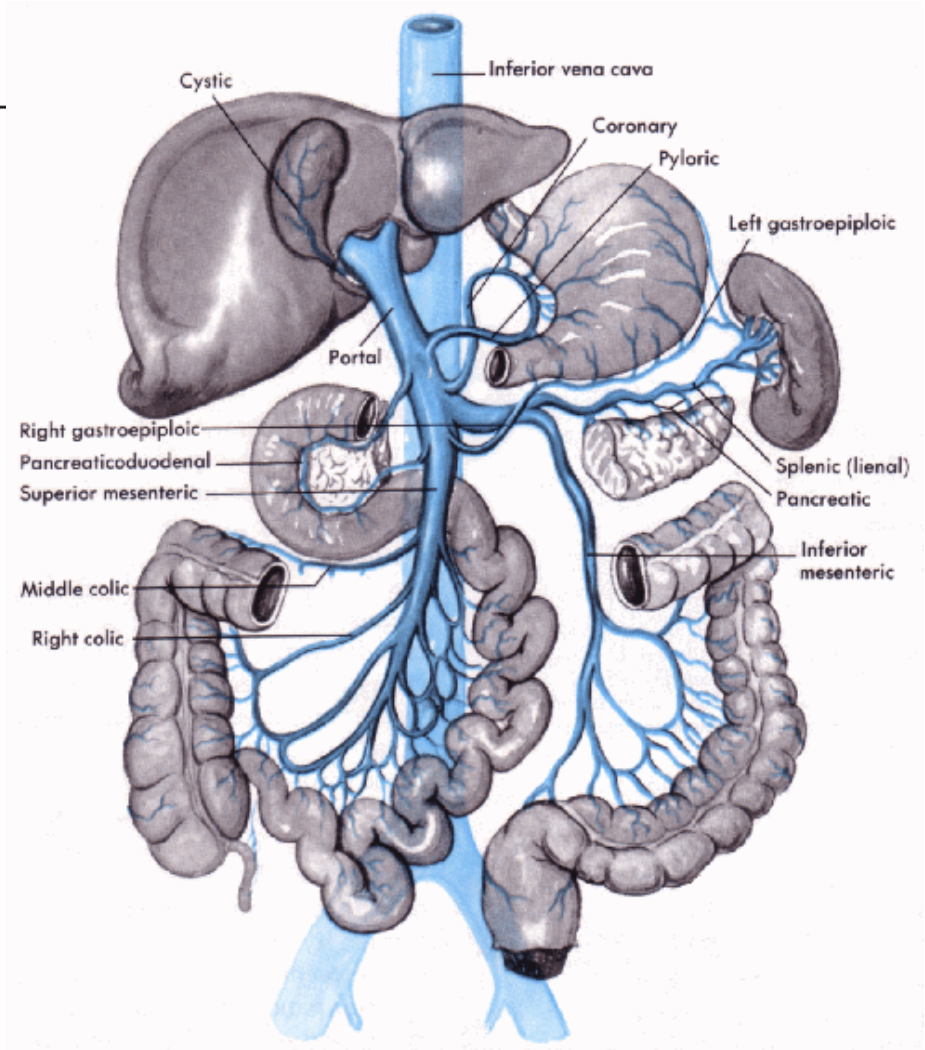
Eur J Nucl Med Mol Imaging (2008) 35:1899–1911
DOI 10.1007/s00259-008-0796-z

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

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



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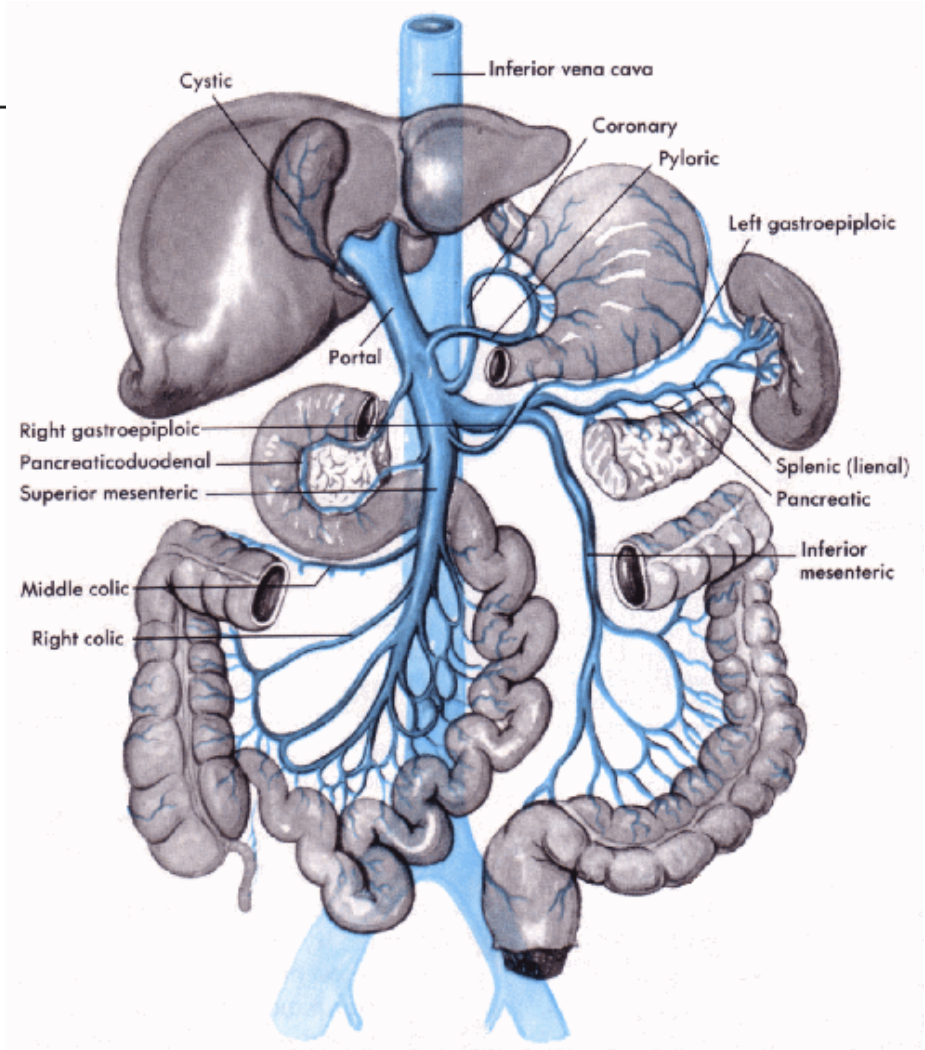
$$C_{TIS}(t) = (f_a C_A(t) + f_p C_P(t)) \otimes e^{-k_2 \cdot t}$$

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



Organ perfusion

Quantitative Perfusion Imaging with Total-Body PET

Juhani Knuuti[1,2], Jouni Tuisku[1], Henri Kärpijoki[1], Hidehiro Iida[1], Teemu Maaniitty[1,2], Aino Latva-Rasku[1], Vesa Oikonen[1], Sergey V. Nesterov[1], Jarmo Teuho[1], Maria K. Jaakkola[1], Riku Klén[1], Heli Louhi[1], Virva Saunavaara[1], Pirjo Nuutila[1], Antti Saraste[1,3], Juha Rinne[1], and Lauri Nummenmaa[1]

[1]Turku PET Centre, Turku University Hospital and University of Turku, Turku, Finland; [2]Department of Clinical Physiology, Nuclear Medicine, and PET, Turku University Hospital, Turku, Finland; and [3]Heart Center, Turku University Hospital and University of Turku, Turku, Finland

Although there are several works on lung (*57*) and liver (*56*,*58*) perfusion, the detection of input function from the bronchial artery and the portal vein has been difficult in previous PET scanners. This might be more feasible with total-body PET scanners, which provide better spatial resolution and higher accuracy in measuring a wide range of perfusion levels.

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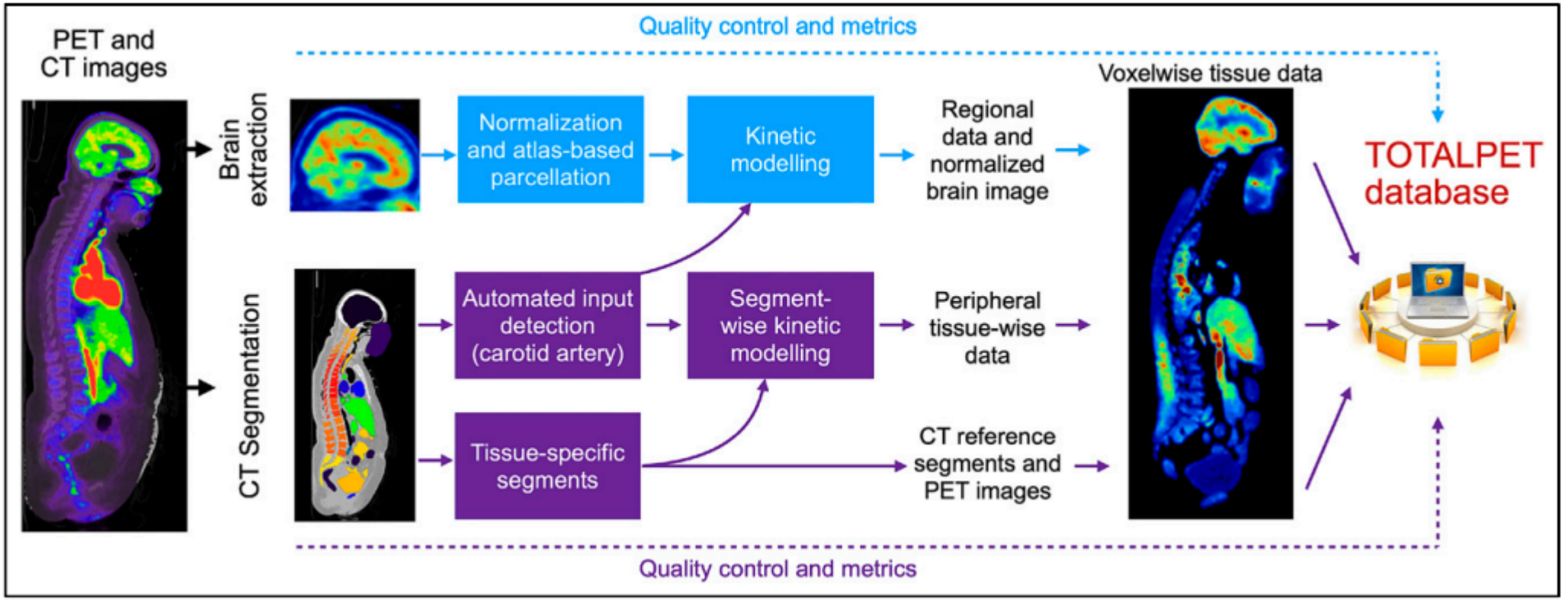
Organ perfusion

Quantitative Perfusion Imaging with Total-Body PET



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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?

Tommaso Volpi[1*], Lucia Maccioni[2], Maria Colpo[2,3], Giulia Debiasi[2,4], Amedeo Capotosti[2,5], Tommaso Ciceri[2,6], Richard E. Carson[1], Christine DeLorenzo[7], Andreas Hahn[8], Gitte Moos Knudsen[9,10], Adriaan A. Lammertsma[11], Julie C. Price[12], Vesna Sossi[13], Guobao Wang[14], Paolo Zanotti-Fregonara[15], Alessandra Bertoldo[2,3] and Mattia Veronese[2,16]

Increased use of quantitative PET?

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https://doi.org/10.1186/s13550-023-01050-w

EJNMMI RESEARCH

REVIEW **Open Access**

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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.