CE20: Quantitative PET for Liver Diseases

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Dynamic Liver PET: Kinetic Modeling and Clinical Translation for NASH Imaging

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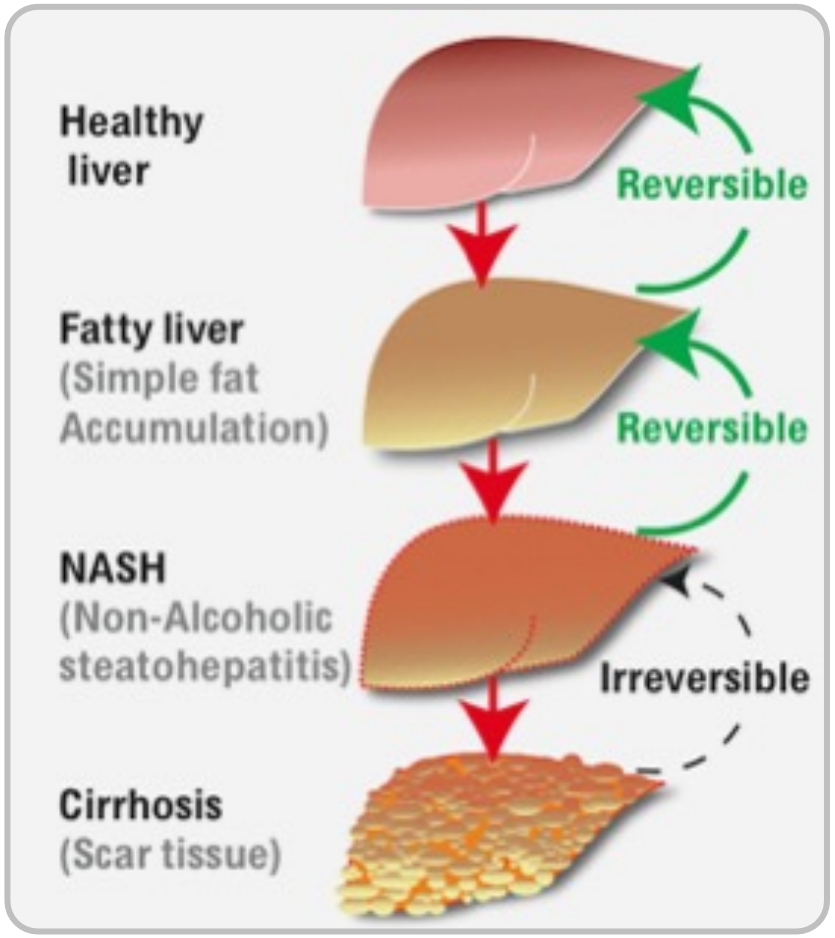
Disclosure

- University of California Davis has a revenue sharing agreement and a research agreement with United Imaging Healthcare (UIH)

Nonalcoholic Steatohepatitis (NASH)



http://www.sydneynwgastro.com.au/

- 5-10% of nonalcoholic fatty liver disease patients develop NASH
- Diagnostic hallmark of NASH is **liver inflammation** in the setting of steatosis

Gap in Clinical Imaging of NASH

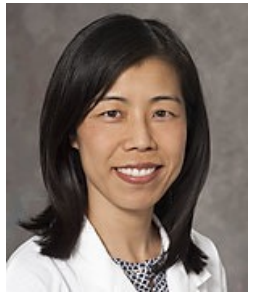
Disease Characteristics	Clinical Imaging
Liver Steatosis	Magnetic Resonance Proton Density Fat Fraction (MR-PDFF) or Computed Tomography (CT)
Liver Inflammation	?
Liver Fibrosis	Magnetic Resonance Elastography (MRE), Ultrasound Elastography

Development and Translation of PET Methods for NASH Imaging

- A **team** of MDs and PhDs at UC Davis Medical Center

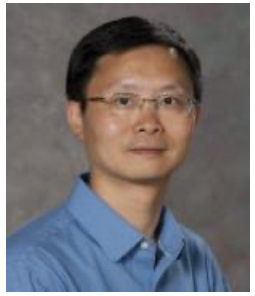

Sarkar S, MD


Corwin M, MD


Matsukuma K, MD

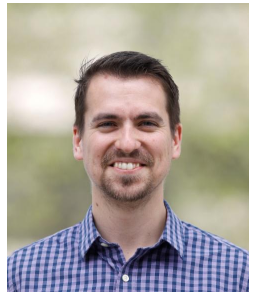

Lyo V, MD


Medici V, MD


Wang GB, PhD


Badadwi RD, PhD

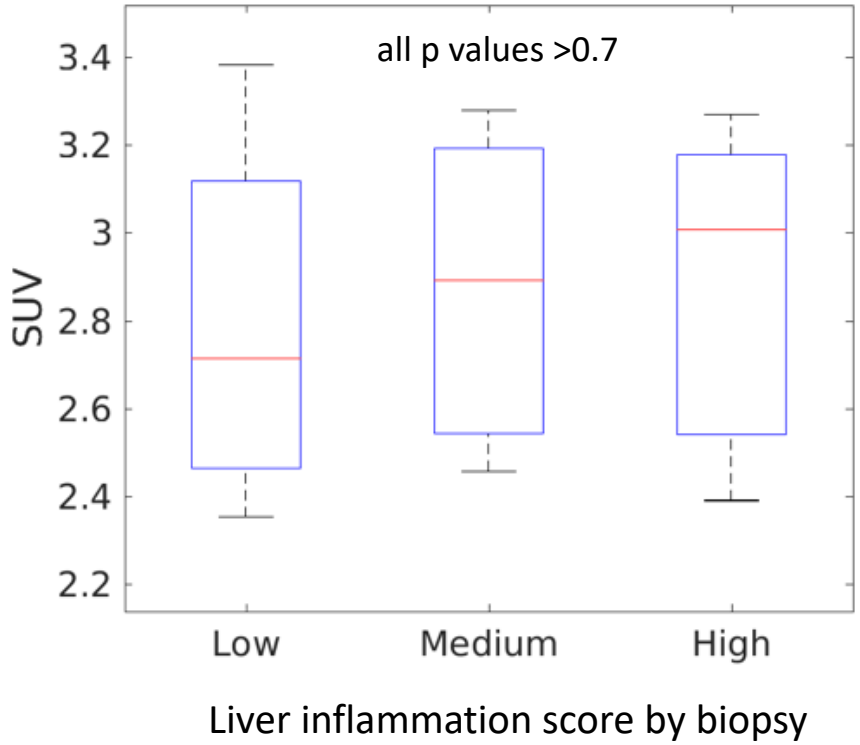

Chen S, PhD


Spencer BA, PhD


Tran Q, PhD

Standard ^{18}F-FDG PET for Evaluating Liver Inflammation?

- Liver is the primary organ to store and regulate glucose
- ^{18}F-FDG PET is mainly used for assessing glucose metabolism
- Standard FDG PET measure did not correlate with liver inflammation

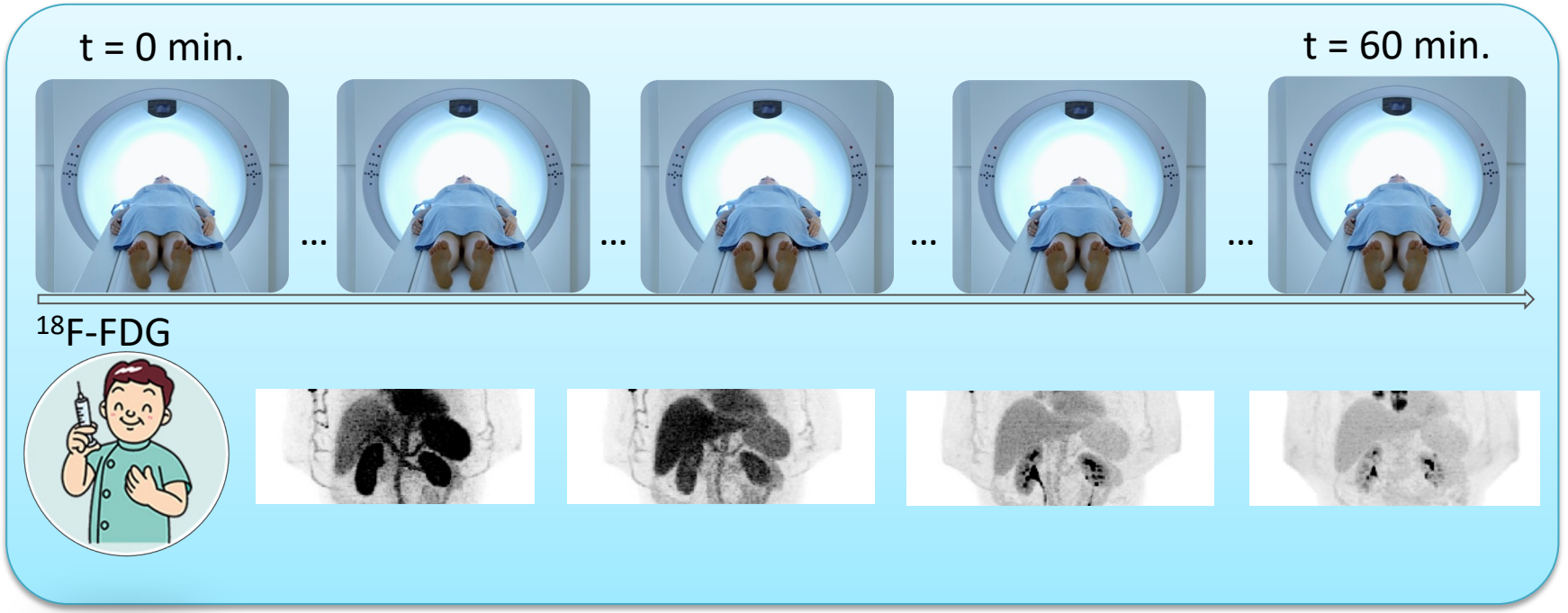


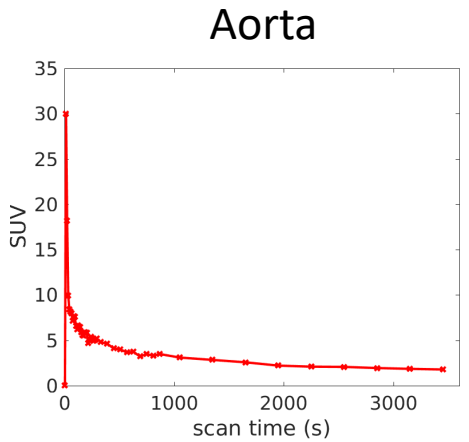
Liver inflammation score by biopsy

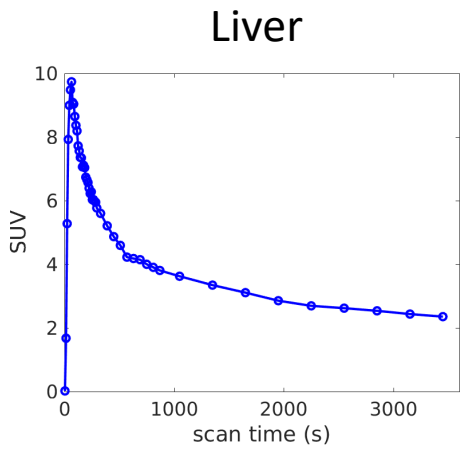
Wang *et al* PMB 2018; Sarkar *et al*. AJR 2019

Dynamic ^{18}F-FDG PET Imaging

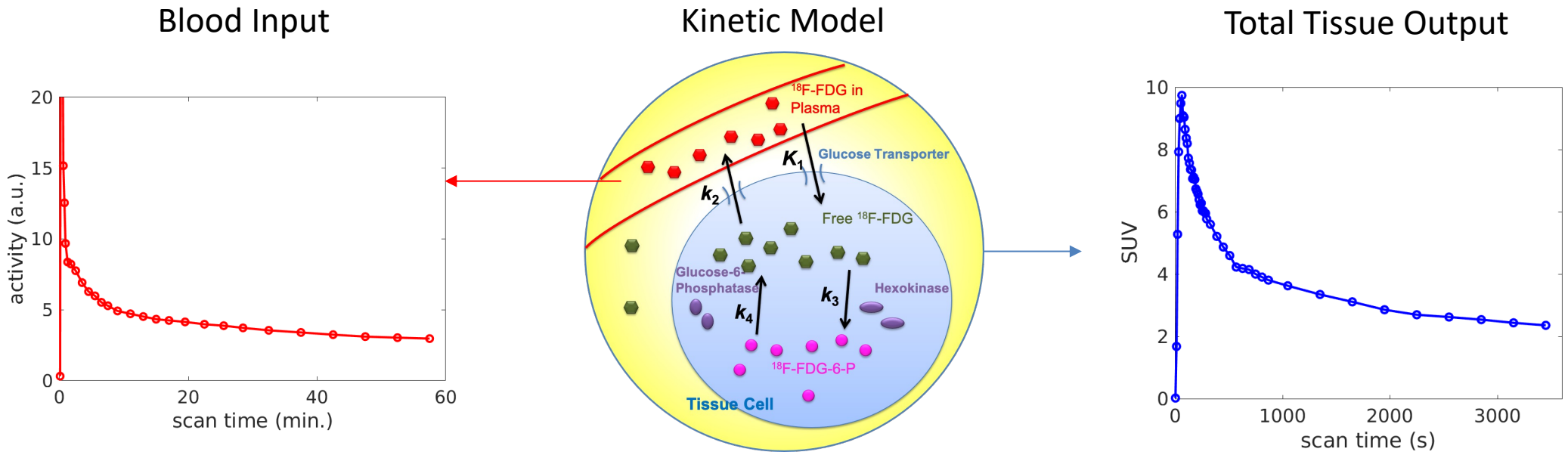
- Dynamic PET monitors both spatial and temporal change of tracer uptake, creating a functional “movie”







Kinetic Quantification by Time Activity Curve (TAC) Fitting



- For FDG, conventional focus is on glucose metabolism

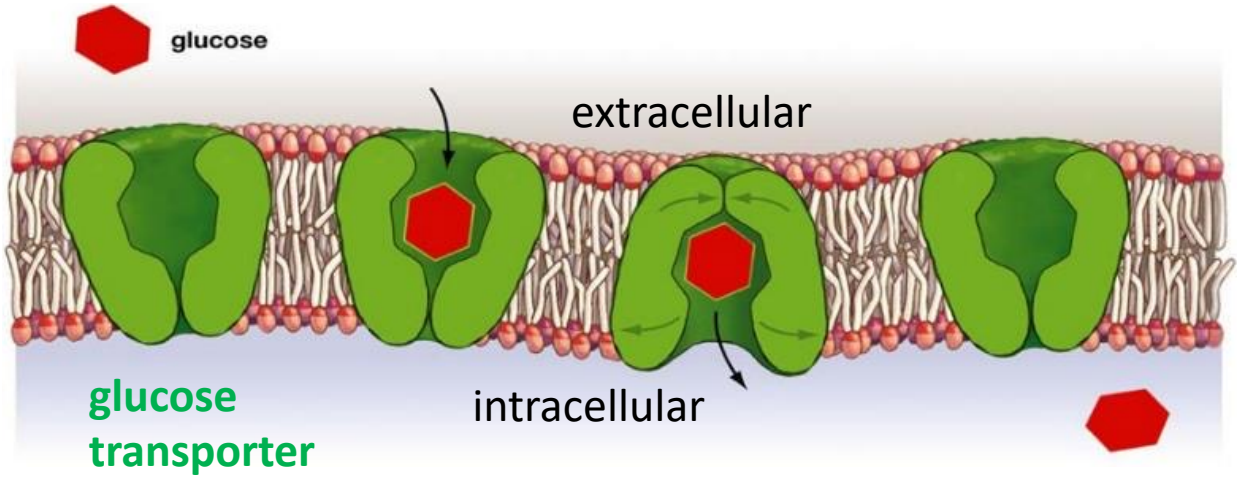
$$\text{Net influx rate } K_{\text{i}} = \frac{K_1 k_3}{k_2 + k_3}$$

- We call attention to glucose transport rates (e.g., K_1) as well

A Glucose Transport Hypothesis for Liver Inflammation

- Glucose is transported by glucose transporters (GLUTs)

- Chronic liver inflammation involves programmed cell deaths and may associate with low GLUTs expression

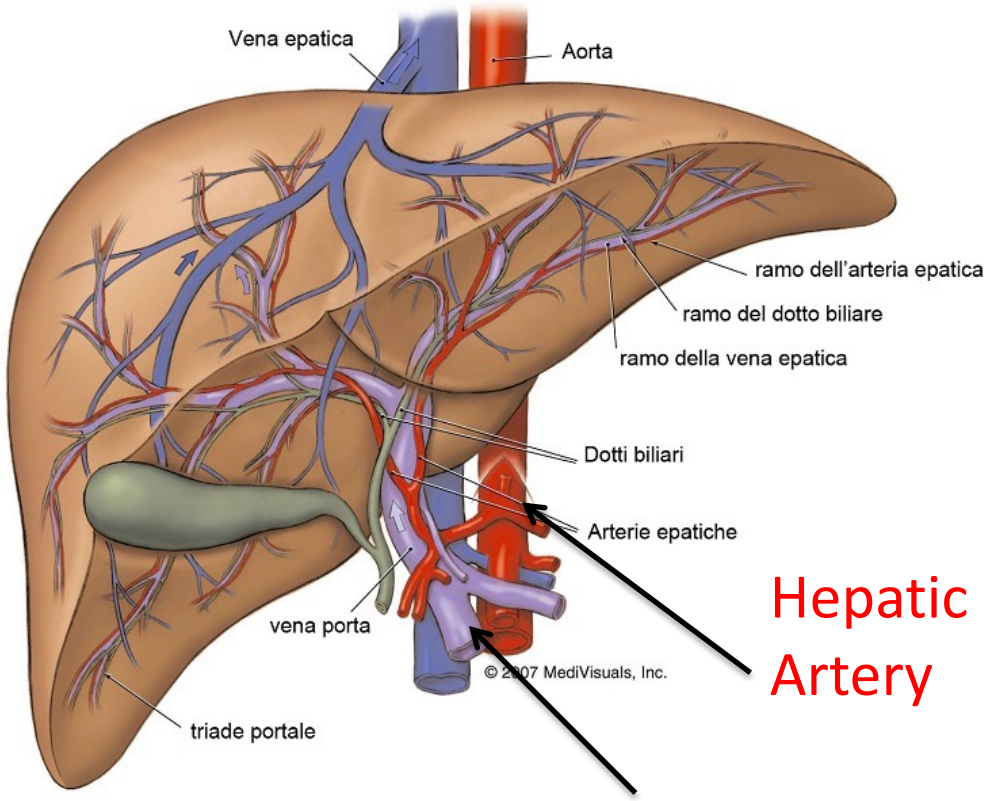


- Our hypothesis:

liver inflammation is associated with decreased glucose transport rate (measured by FDG K_1)

Challenge with Kinetic Quantification in the Liver

- Liver has two blood supplies: hepatic artery and portal vein
- Dual-blood input function is required for accurate kinetic modeling



S. Keiding, JNM 2012; Monk *et al,* JNM 2001

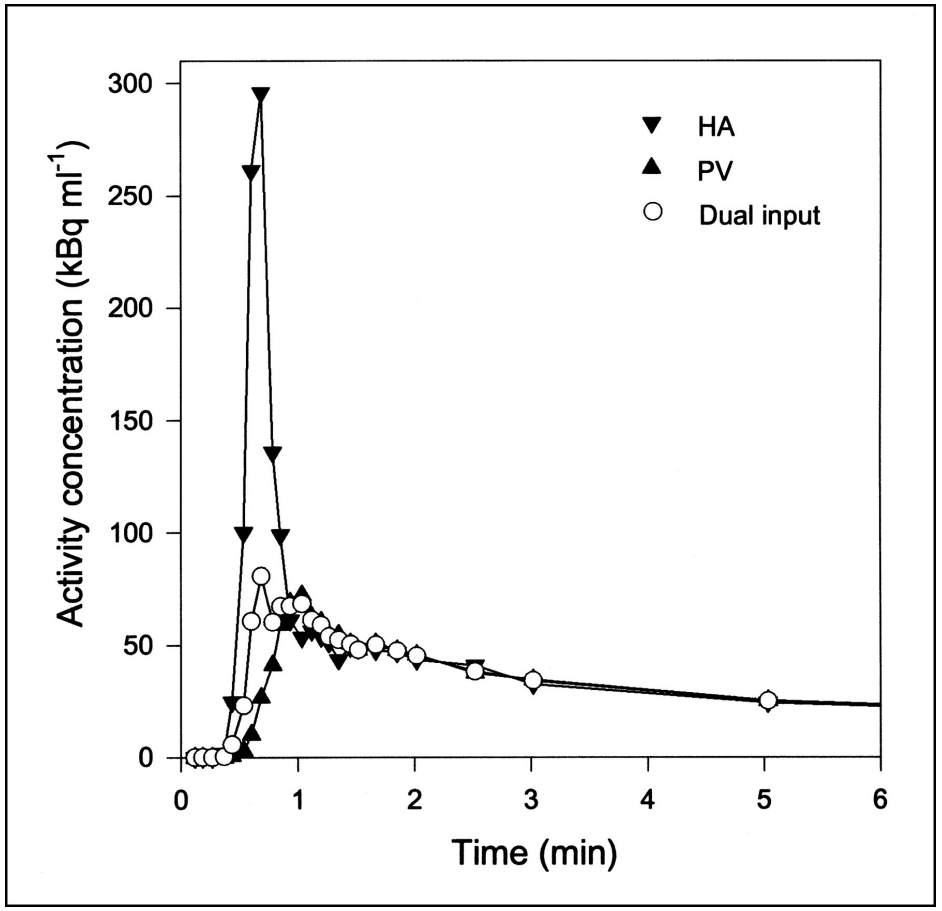
http://www.fragmenthealth.com/

Dual-blood Input Function (DBIF)

- Flow-weighted DBIF model

$$C_p(t) = f_A C_A(t) + f_{PV} C_{PV}(t)$$

- Typical weights measured with blood sampling in foxhounds
  - f_A: 20%
  - f_{PV}: 80%
- However, portal vein input can not be measured accurately from PET images



Monk *et al,* JNM 2001

Population-based DBIF: The Mathematical Model

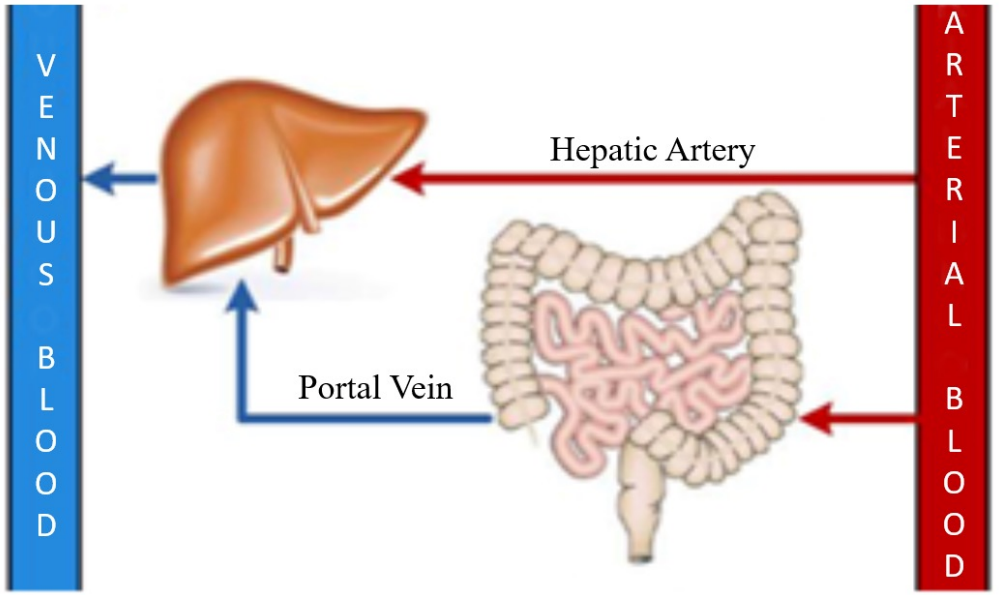


Image taken from Feng *et al* TRPMS 2020

- Describe $C_{PV}(t)$ as a convolutional model of $C_A(t)$

$$C_{PV}(t) = C_A(t) \otimes h(t;\theta)$$

- $h(t)$ is a dispersion function, accounting for the effect of tracer passing through the gastrointestinal tract, e.g.,

$$h(t) = k_a e^{-k_a t}$$

Brix *et al,* JNM 2001; Chen et al, 2008;

Population-based DBIF: Determination from Animal Data

- More examples of the dispersion model $h(t)$:
  - Brix *et al* 2001:

$$h(t) = t^{P_0}(P_1 e^{-P_2 t} + P_3 e^{-P_4 t})$$

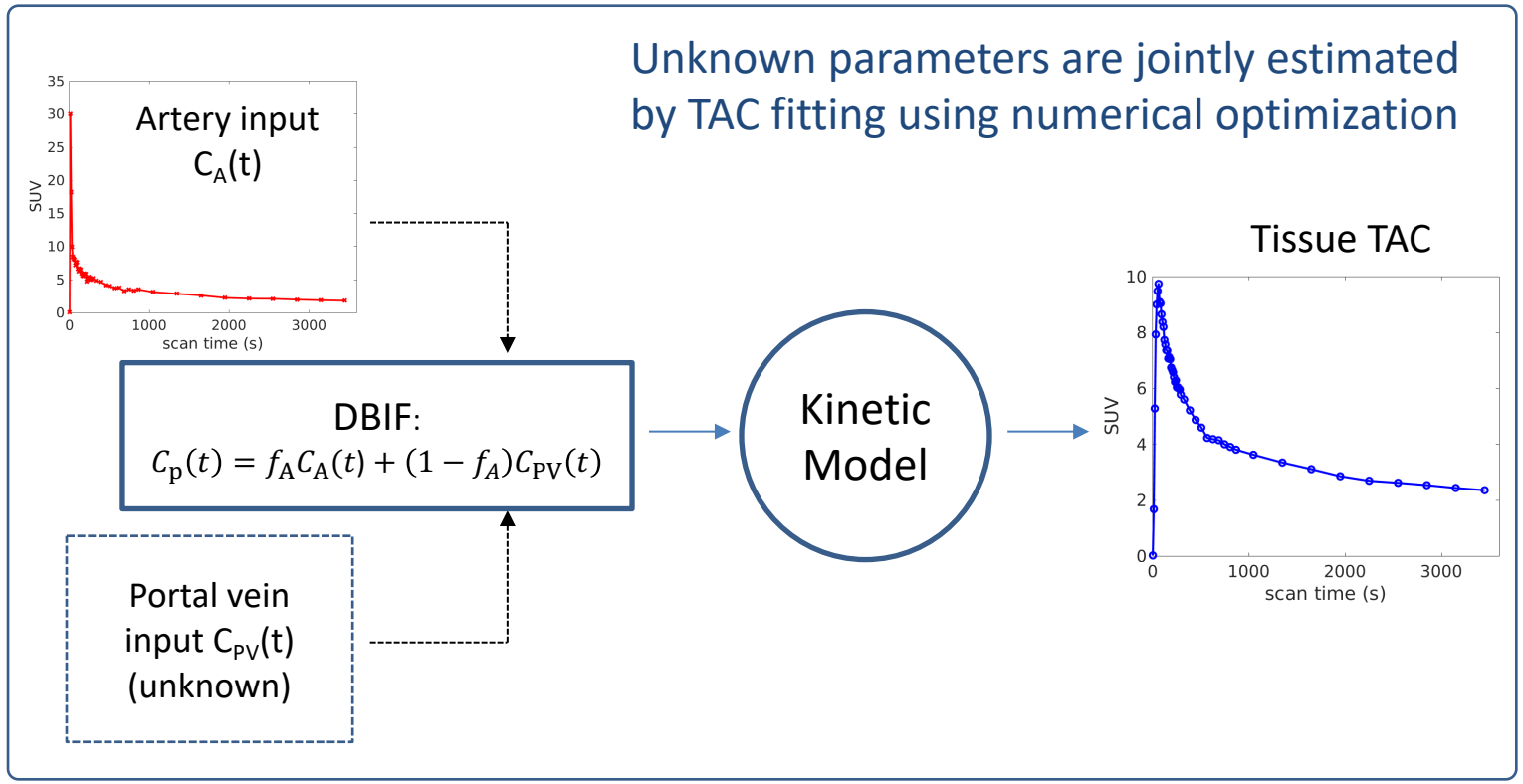
  - Winterdahl *et al* 2010:

$$h(t) = \beta/(t+\beta)^2$$

- Model parameters are determined from *animal* studies with blood sampling and then applied to *human* studies

Brix *et al,* JNM 2001; Winterdahl *et al*, EJNMMI 2010;

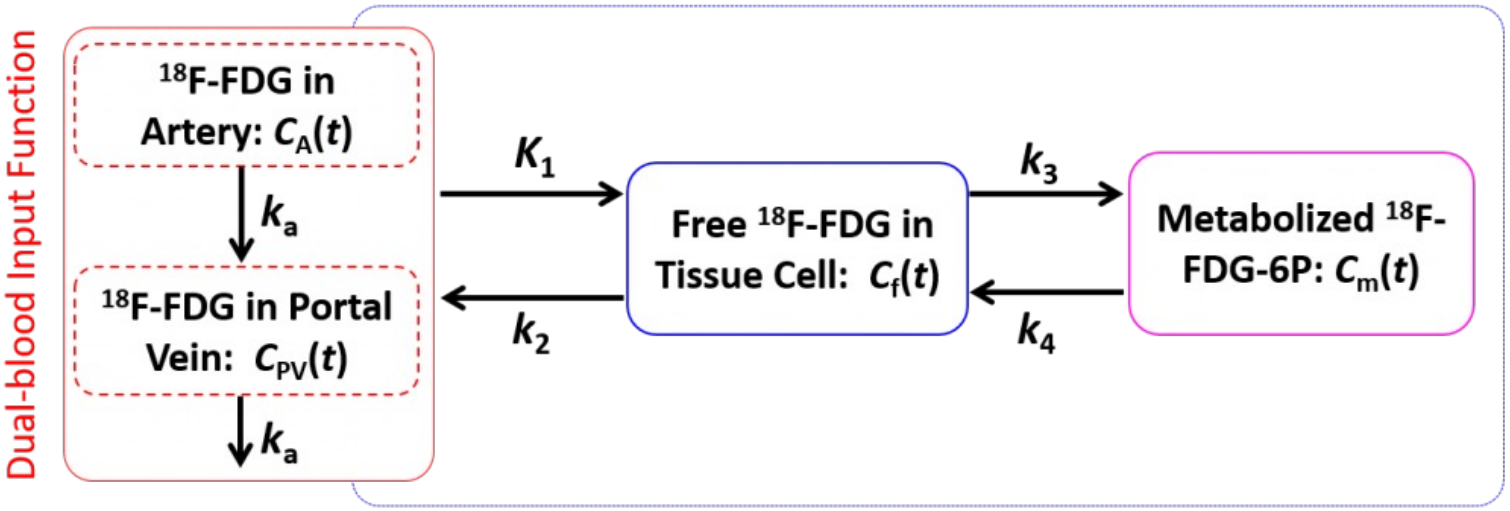
Optimization-derived DBIF: General Concept



- No blood sampling is required
- Directly applicable to human data

Chen *et al* TNS 2008; Kudomi *et al* EJNMMI 2009; Feng *et al* TRPMS 2020;

Optimization-derived DBIF: Model for FDG



Differential Equations:

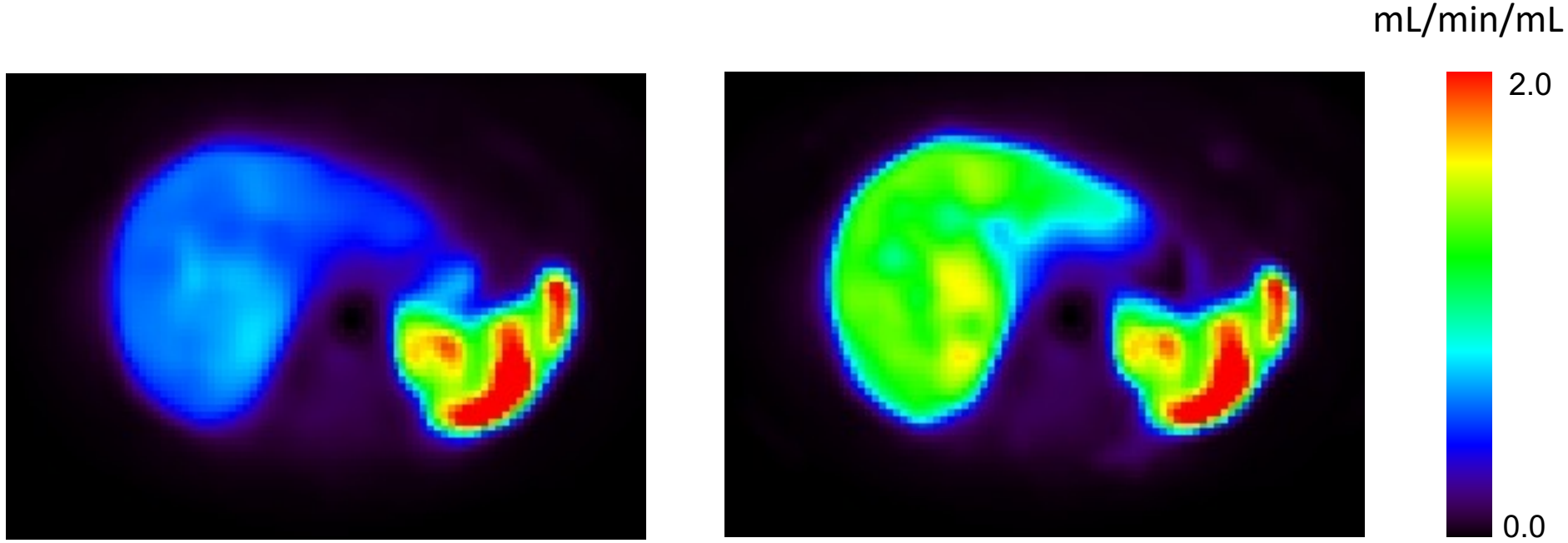
$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{bmatrix} C_f(t) \\ C_m(t) \\ C_{PV}(t) \end{bmatrix} = \begin{bmatrix} -(k_2+k_3) & k_4 & K_1(1-f_A) \\ k_3 & -k_4 & 0 \\ 0 & 0 & -k_a \end{bmatrix}\begin{bmatrix} C_f(t) \\ C_m(t) \\ C_{PV}(t) \end{bmatrix} + \begin{bmatrix} K_1 f_A \\ 0 \\ k_a \end{bmatrix} C_A(t)$$

- All model parameters are structurally identifiable, though subject to local solutions
- Estimates of K_1 and influx rate K_i are stable (low bias and variance)

Wang *et al*. PMB 2018; Zuo *et al* PMB 2019;

Impact of Liver DBIF on Parametric Imaging

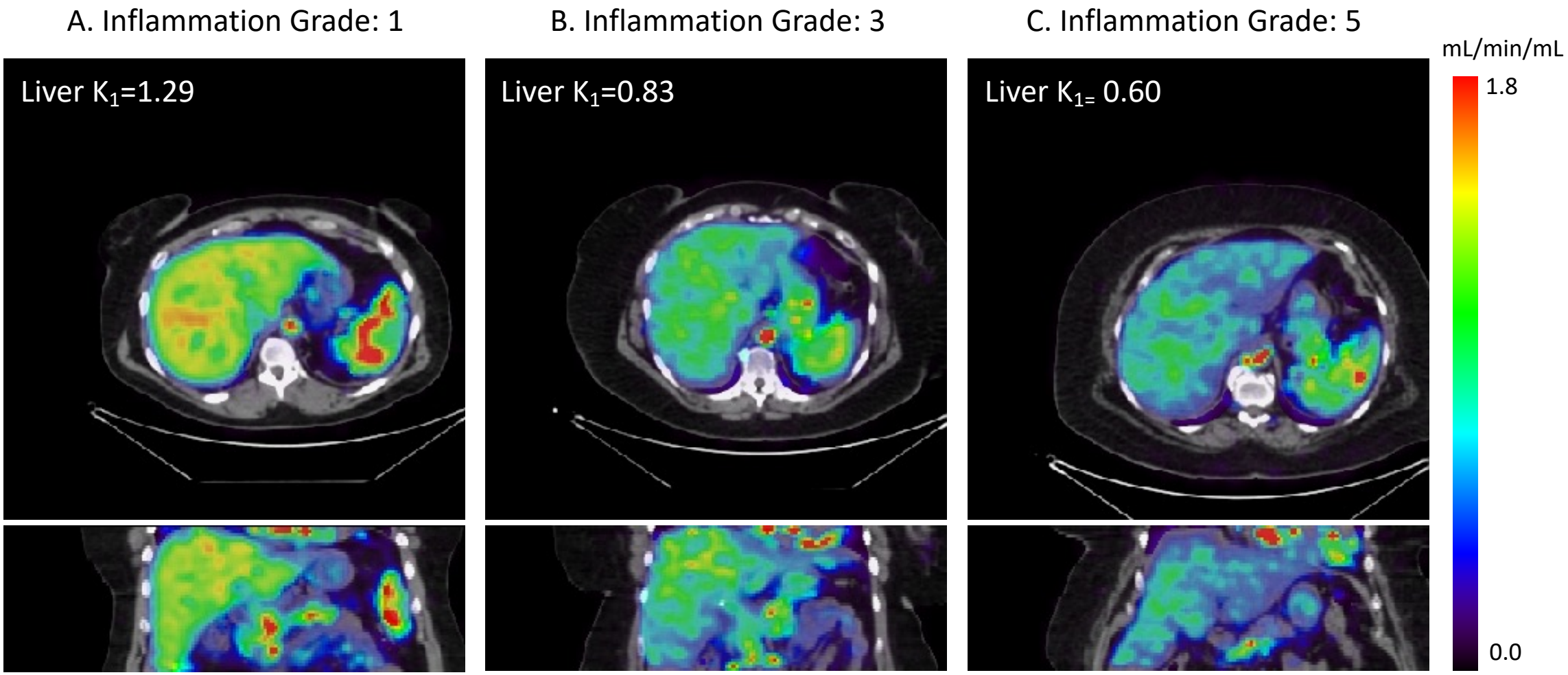
Parametric images of FDG K_1



(a) w/o DBIF

(b) with DBIF

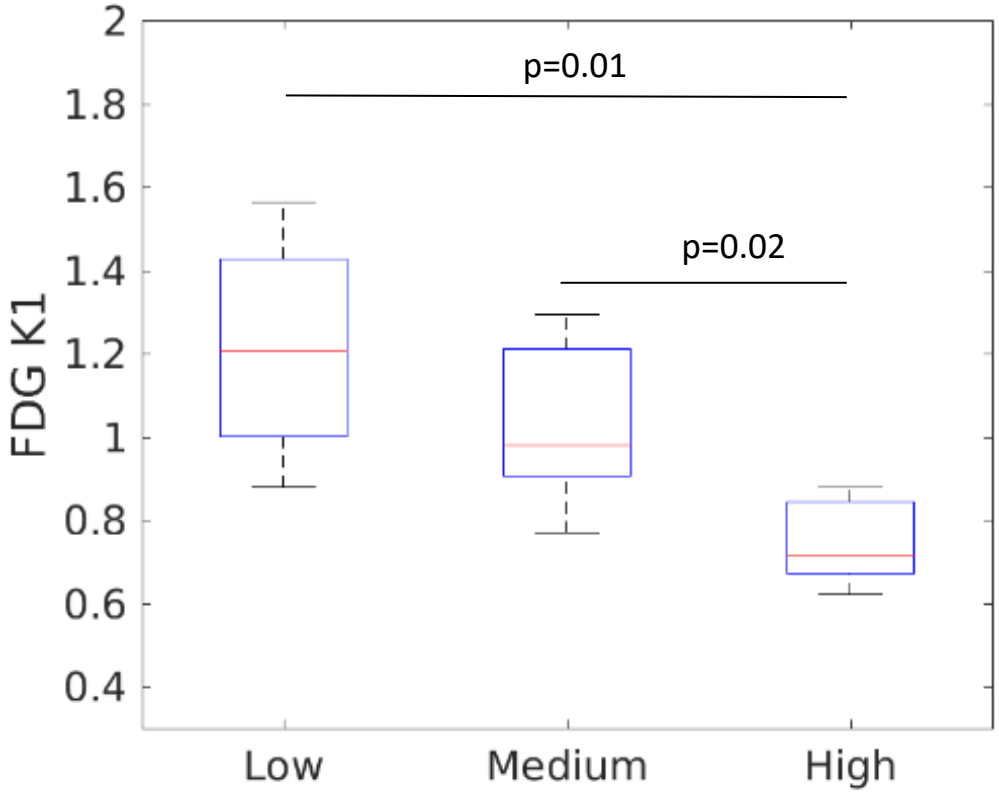
Demonstration of Liver Inflammation and FDG K_1



Sarkar *et al*. AJR 2019

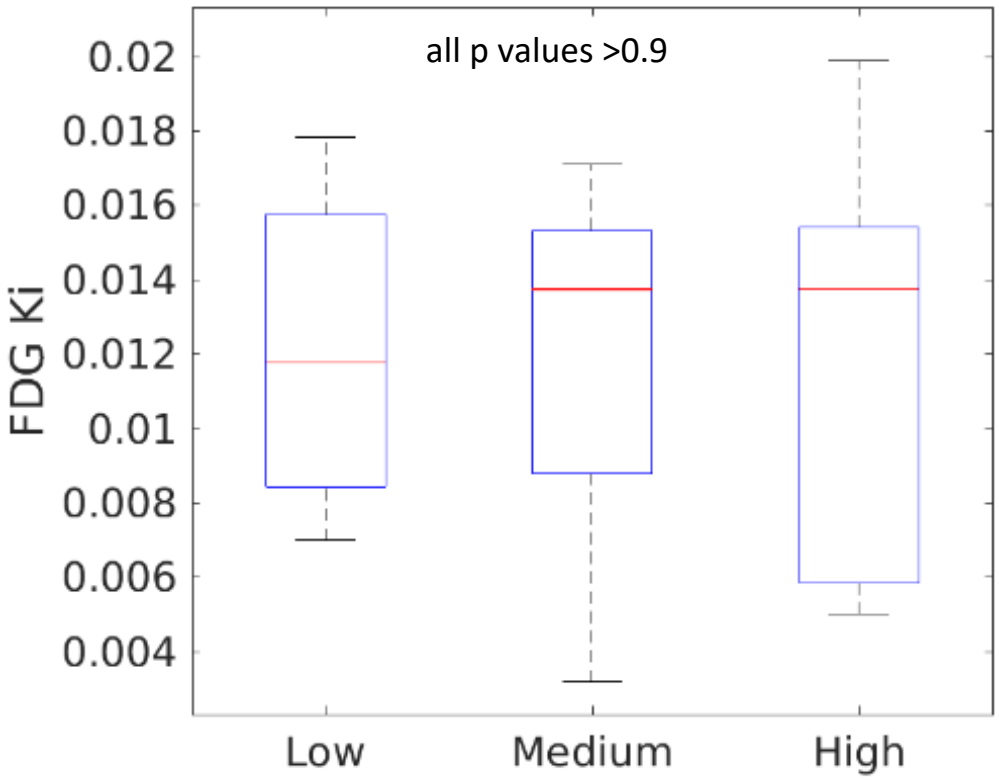
Liver Inflammation Was Associated with Decreased Glucose Transport

Liver glucose transport (K_1)



Liver inflammation grade by biopsy

Glucose metabolism (K_i)

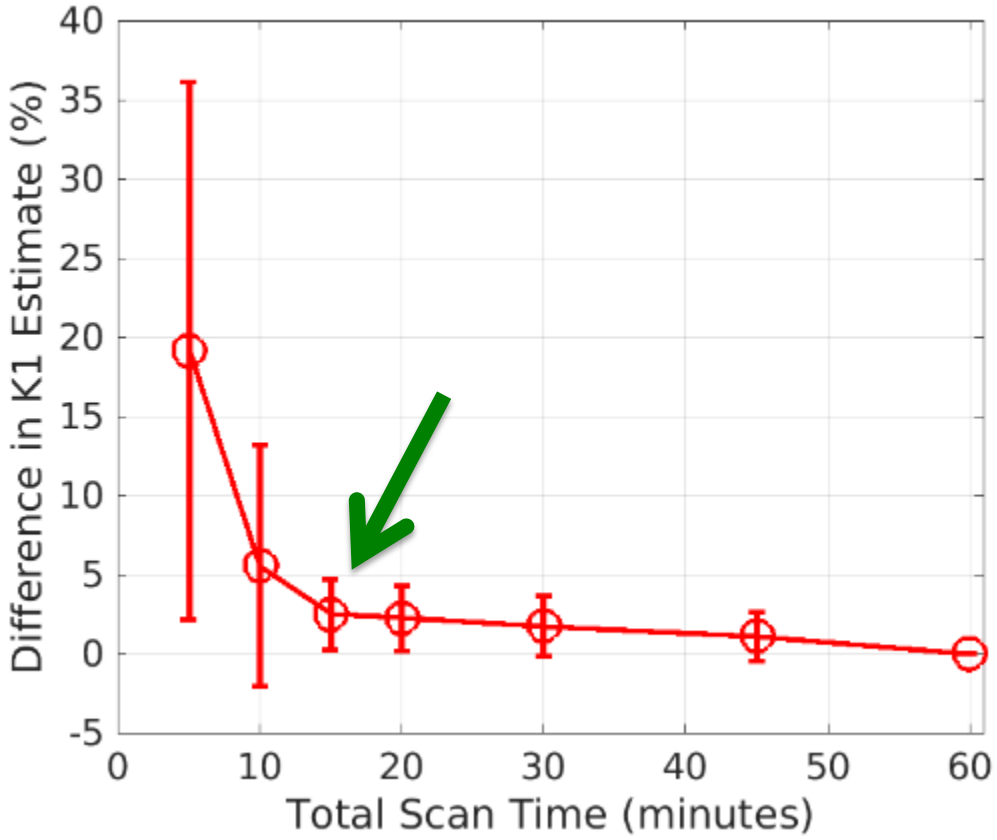


Liver inflammation grade by biopsy

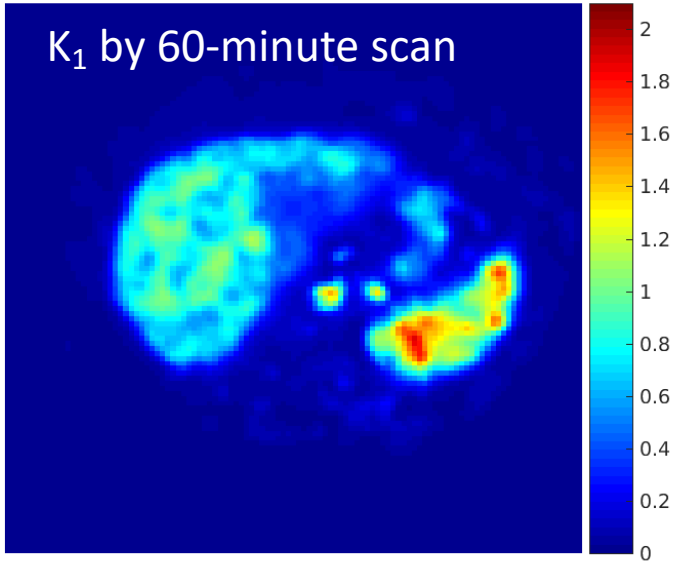
Sarkar *et al*. AJR 2019; CGH 2021

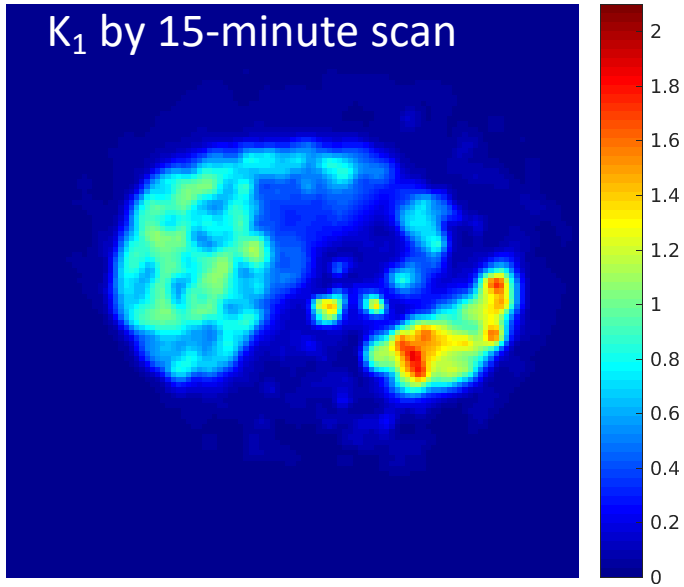
Can the Scan Duration Be Shortened?

- A 15-minute scan has a <5% difference in liver FDG-K_1 compared to the 60-min reference

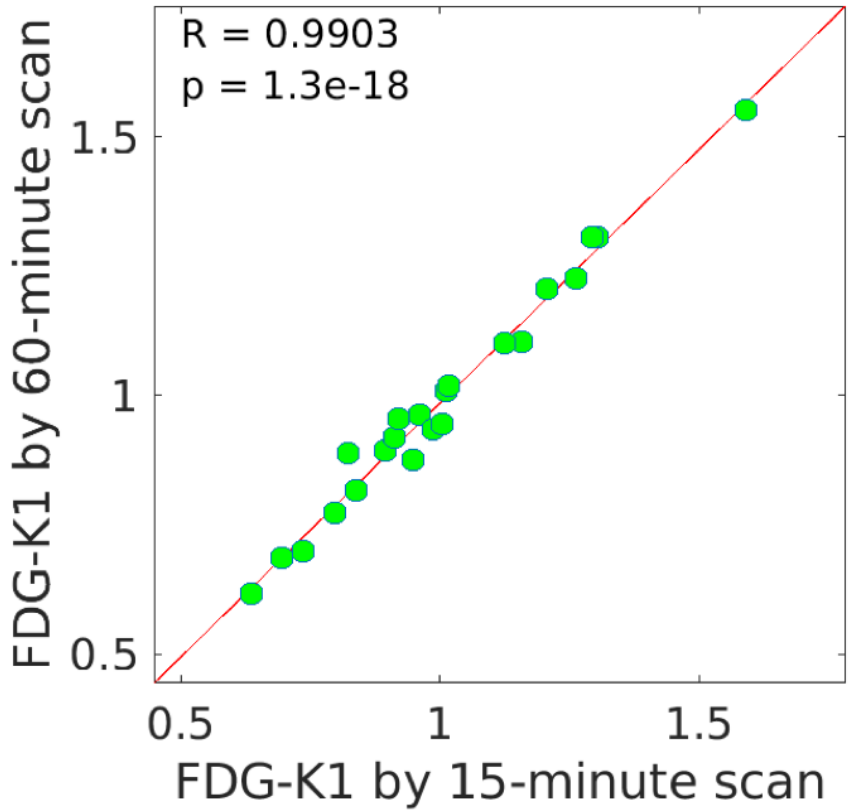


Feasibility of a 15-minute Scan Protocol





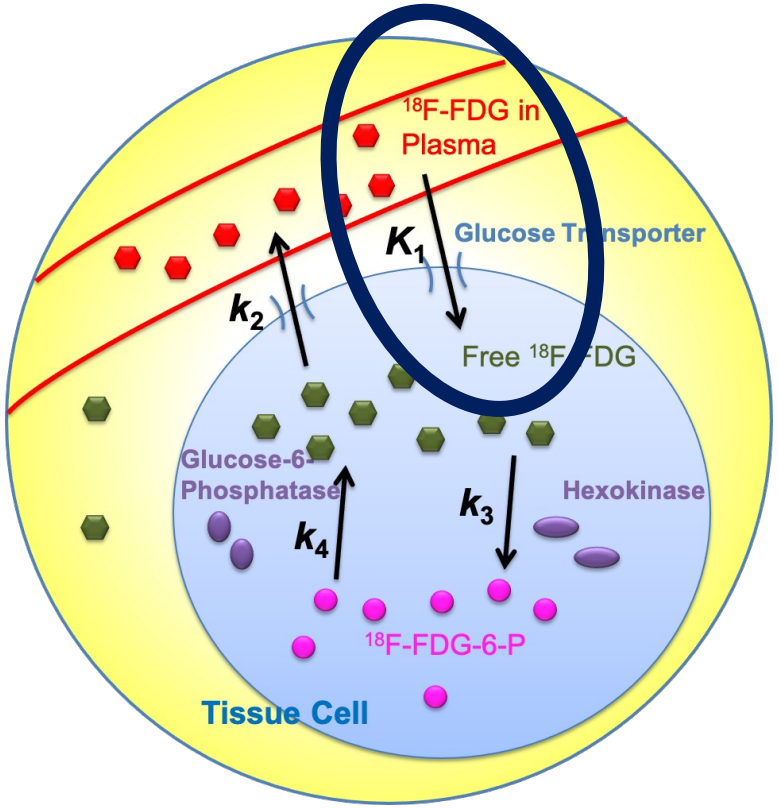
Correlation of liver FDG K_1 in 22 patients



What is FDG K_1 in the Liver?

- FDG K_1 represents the overall delivery rate of FDG from blood to liver tissue cells

- It is a mix of
  - Blood flow
  - Glucose-specific transport (from blood to the interstitial space and then to the intracellular space)



Opportunities Open Up by High-performance Scanners

- Recent sensitivity **boost** on commercial PET scanners

4-40x

- High-temporal resolution (HTR, e.g., 1-2s/frame) may become feasible for dynamic PET imaging
- HTR potentially enables separation of the transport processes to measure

blood flow and *tracer-specific transport* rates

from a single-tracer dynamic scan

UIH uEXPLORER

194 cm

Siemens Quadra

106 cm

Acknowledgments

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Dr. Victoria Lyo
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Dr. Kristin Olson
Dr. Souvik Sarkar

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Heather Hunt
Mike Nguyen
Michael Rusnak