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)

• 5-10% of nonalcoholic fatty liver disease patients develop NASH

• Diagnostic hallmark of NASH is **liver inflammation** in the setting of steatosis
### Disease Characteristics

<table>
<thead>
<tr>
<th>Disease Characteristics</th>
<th>Clinical Imaging</th>
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<tbody>
<tr>
<td>Liver Steatosis</td>
<td>Magnetic Resonance Proton Density Fat Fraction (MR-PDFF) or Computed Tomography (CT)</td>
</tr>
<tr>
<td>Liver Inflammation</td>
<td>?</td>
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<tr>
<td>Liver Fibrosis</td>
<td>Magnetic Resonance Elastography (MRE), Ultrasound Elastography</td>
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Development and Translation of PET Methods for NASH Imaging

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

- Sarkar S, MD
- Wang GB, PhD
- Corwin M, MD
- Badadwi RD, PhD
- Matsukuma K, MD
- Chen S, PhD
- Lyo V, MD
- Spencer BA, PhD
- Medici V, MD
- 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

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

\[
K_i = \frac{K_1 k_3}{k_2 + k_3}
\]

- 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

- 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.,

\[ h(t) = \kappa e^{-\kappa a t} \]

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:
    
    $$h(t) = t^{P_0}(P_1 e^{-P_2t} + P_3 e^{-P_4t})$$
  
  - Winterdahl et al 2010:
    
    $$h(t) = \frac{\beta}{(t + \beta)^2}$$

- 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

Unknown parameters are jointly estimated by TAC fitting using numerical optimization

\[
C_D(t) = f_A C_A(t) + (1 - f_A) C_{PV}(t)
\]

\[
C_A(t)
\]

\[
C_{PV}(t)
\]

Tissue TAC

Artery input

Portal vein input

Chen et al. TNS 2008; Kudomi et al. EJNMMI 2009; Feng et al. TRPMS 2020;
Optimization-derived DBIF: Model for FDG

- 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)

Differential Equations:

$$\frac{d}{dt} \begin{bmatrix} C_f(t) \\ C_m(t) \\ C_{PV}(t) \end{bmatrix} = \begin{bmatrix} -(k_2 + k_3) & k_4 & K_1(1 - f_A) \\ k_3 & -k_4 & 0 \\ 0 & 0 & -k_a \end{bmatrix} \begin{bmatrix} C_f(t) \\ C_m(t) \\ C_{PV}(t) \end{bmatrix} + \begin{bmatrix} K_1f_A \\ 0 \\ k_a \end{bmatrix} C_A(t)$$

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

ml/min/mL

2.0

0.0
Demonstration of Liver Inflammation and FDG $K_1$

A. Inflammation Grade: 1
Liver $K_1$ = 1.29

B. Inflammation Grade: 3
Liver $K_1$ = 0.83

C. Inflammation Grade: 5
Liver $K_1$ = 0.60

Sarkar et al. AJR 2019
Liver Inflammation Was Associated with Decreased Glucose Transport

Liver glucose transport ($K_1$)

- Low: 1.2
- Medium: 1.0
- High: 0.8

$K_1$: 0.01

Glucose metabolism ($K_i$)

- Low: 0.014
- Medium: 0.016
- High: 0.018

$K_i$: all p values > 0.9

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

$R = 0.9903$
$p = 1.3e-18$
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
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