May 12th, 12:30 PM - 12:45 PM

# Magnetic Resonance Image-Based Estimates of Hepatic Blood Flow In Children with and without Obesity; Implications For Physiologically-Based Pharmacokinetic Models

Yoon Cho
*Children's Mercy Kansas City*

Sherwin S. Chan
*Children's Mercy Hospital*

Chance S. Friesen
*Children's Mercy Hospital*

Valentina Shakhnovich
*Children's Mercy Hospital*

# MAGNETIC RESONANCE IMAGE-BASED ESTIMATES OF HEPATIC BLOOD FLOW IN CHILDREN WITH AND WITHOUT OBESITY; IMPLICATIONS FOR PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODELS

Cho,YY[1], Chan, SS[1,2], Friesen, C[1,3], Shakhnovich, V[1,2]

[1]Children's Mercy Kansas City; Kansas City, MO
[2]University of Missouri-Kansas City School of Medicine; Kansas City, MO
[3]University of Kansas School of Medicine; Kansas City, KS

# Background

- Drug development process is complex, lengthy and expensive
- Clinical trials for demonstrating pediatric effectiveness can be difficult
- Dose optimization is complicated in pediatrics due to the differences in physiological processes
- Physiologically-based pharmacokinetic models (PBPK) have become indispensable in drug development and personalized dosing

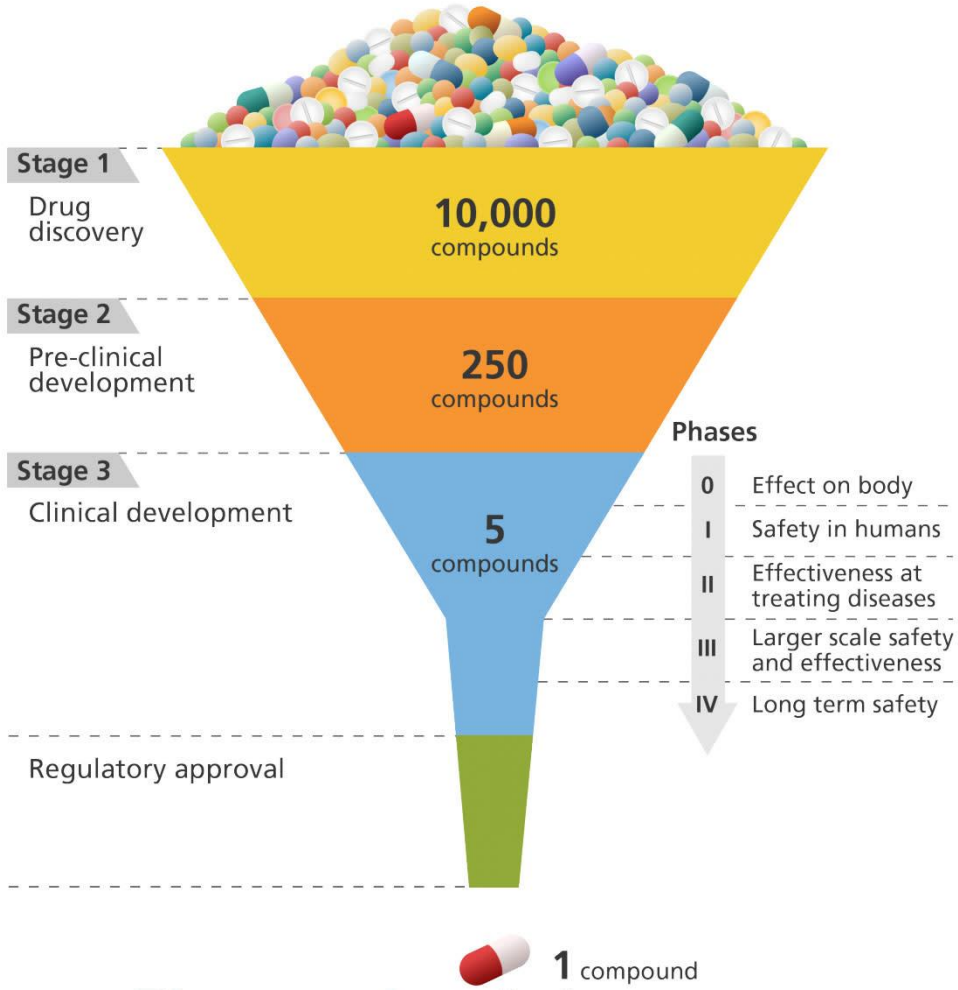


Image Credit: Genome Research Limited



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# Background

- Physiologically-based pharmacokinetic models (PBPK) is a mathematical modeling approach
- Enables you to conduct simulations in representative virtual populations
- PBPK can be a powerful tool in understudied or vulnerable populations
- To achieve this, PBPK models require accurate physiological variability data in demographic and biological components within relevant subpopulations

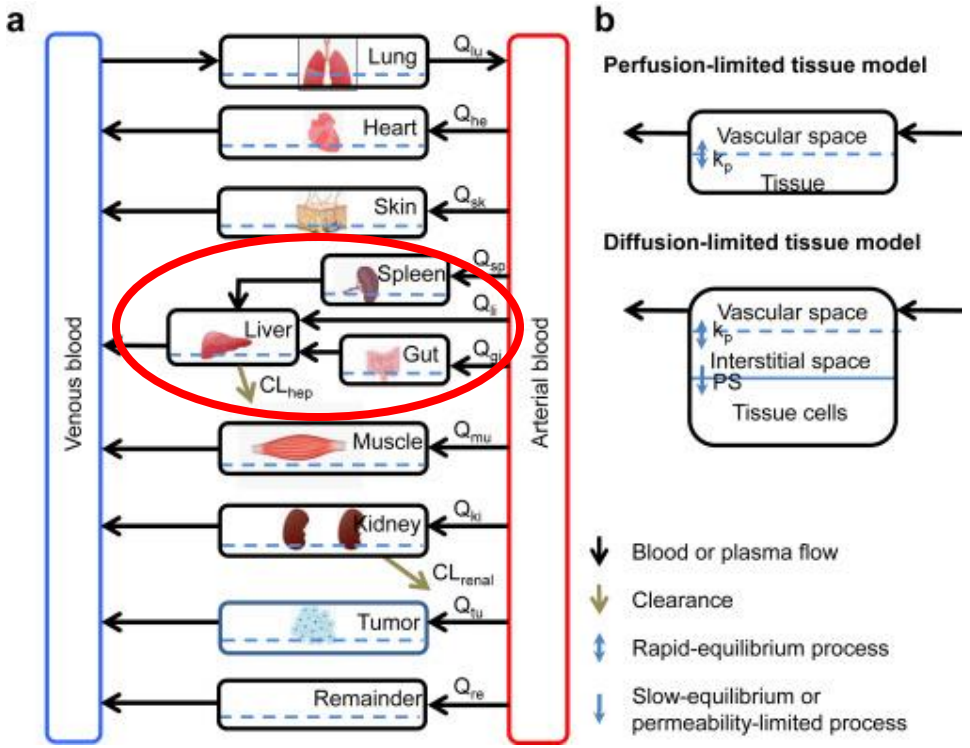


Image credit: https://jpharmsci.org/article/S0022-3549(18)30669-5/fulltext



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# Background

- Our focus was on the liver where a majority of the drugs are metabolized or processed
- Two-dimensional (2D) phase-contrast MRI is a widely available, rapid technique, and validated method for the noninvasive measure of large vessel flow


Image Credit: Siemens-healthineers.com



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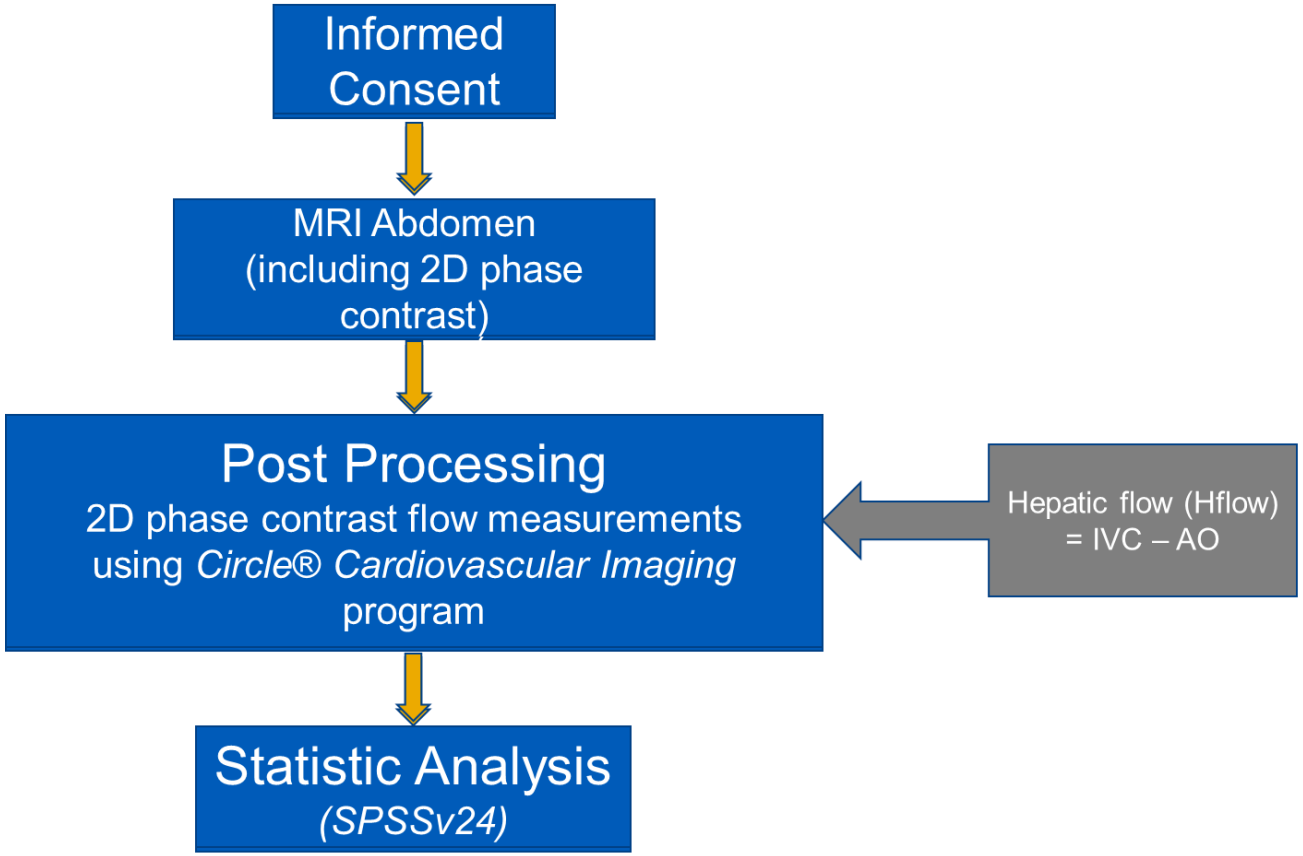
# Hypothesis

- Five anthropometric variables including age, height, weight, BMI-Z score, and liver volume can predict the hepatic blood flow.

# Methods

- A prospective study at a single institution from July 2018-May 2022
- Volunteers were recruited from obesity clinic at the Center for Healthy Living
- Volunteers both with and without obesity were enrolled (n=69)
- Those with known systemic disease, such as cirrhosis, were excluded



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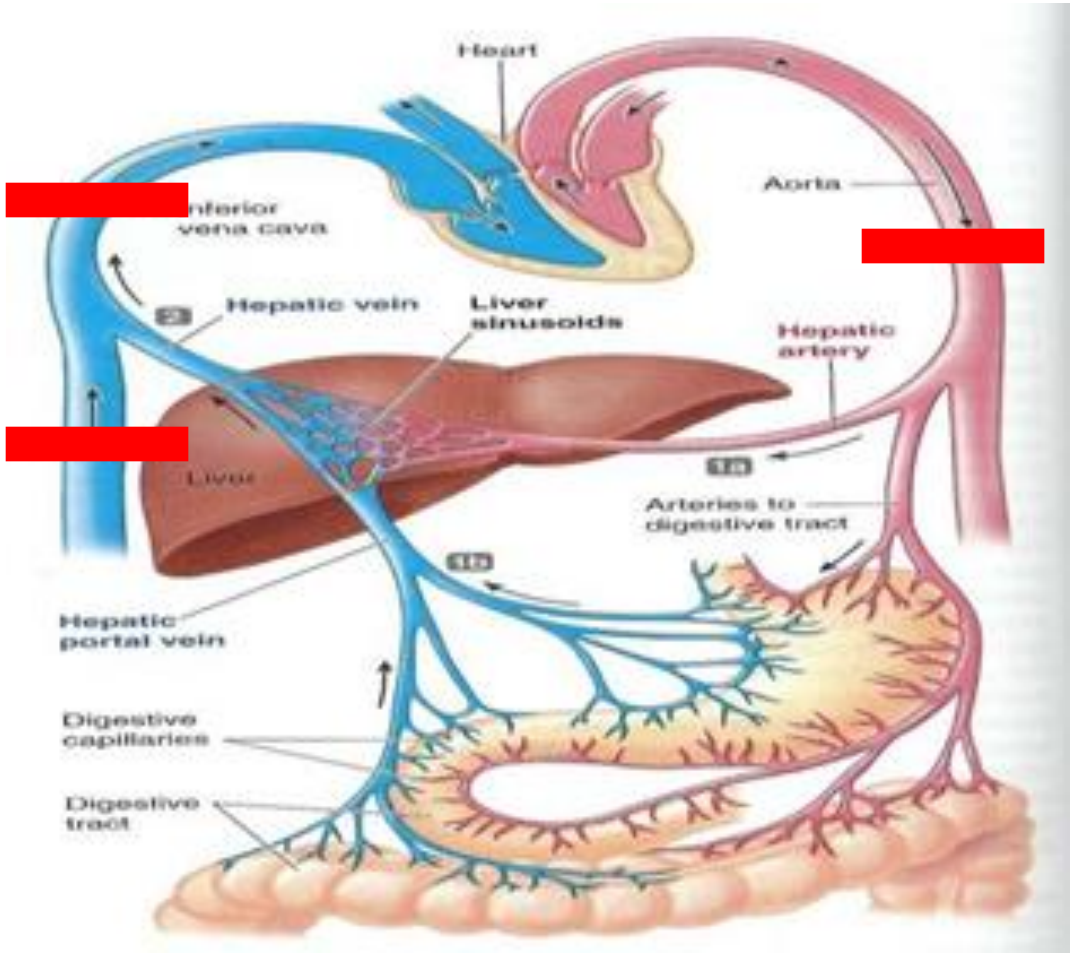
# Total Liver Blood Flow- Indirect Approach

Suprahepatic IVC

Infrahepatic IVC




Descending Aorta



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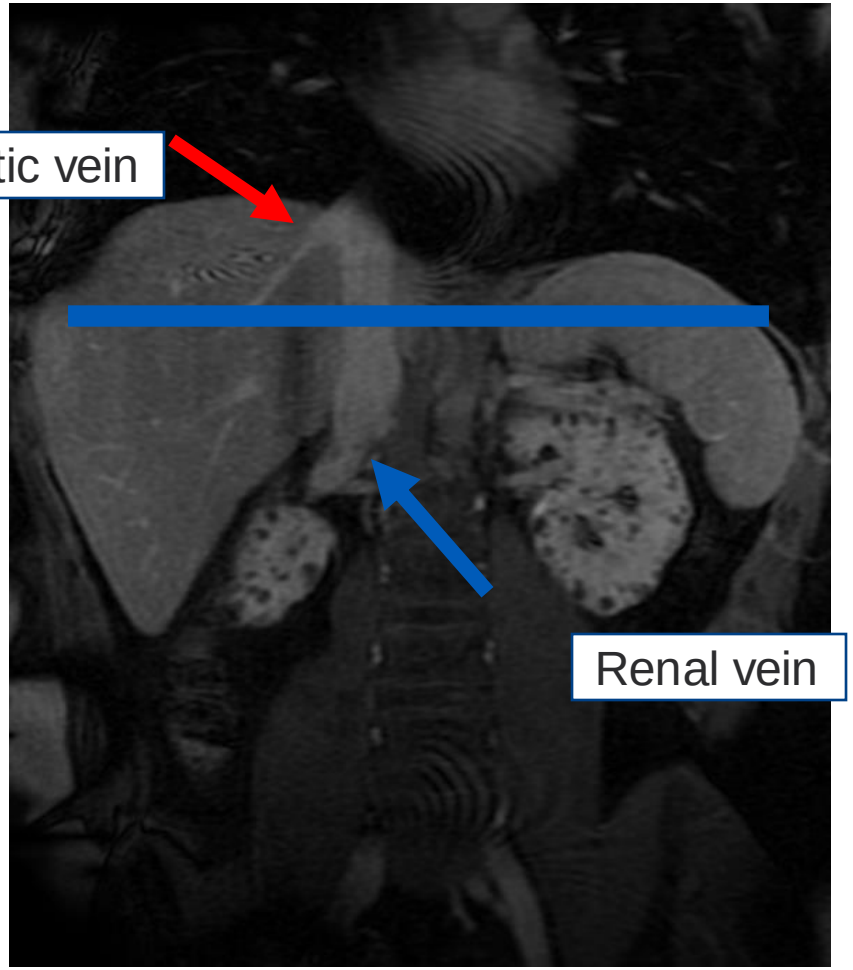
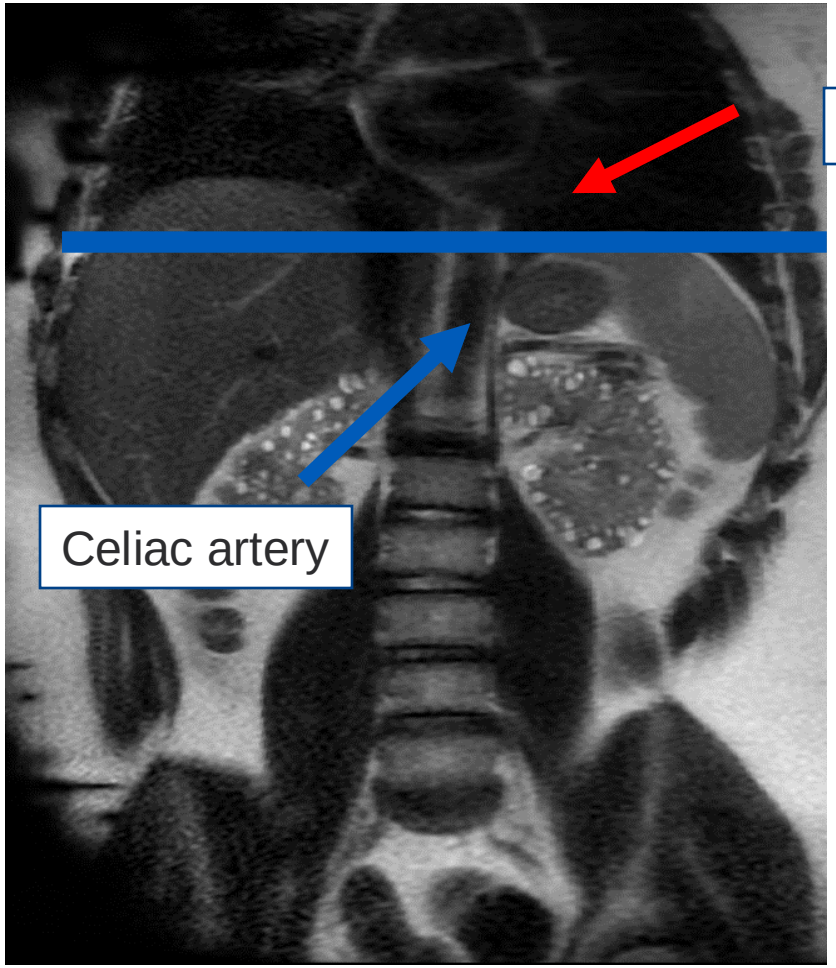
# Imaging Technique

## IVC Flow Measurement




## Descending Aorta Flow Measurement



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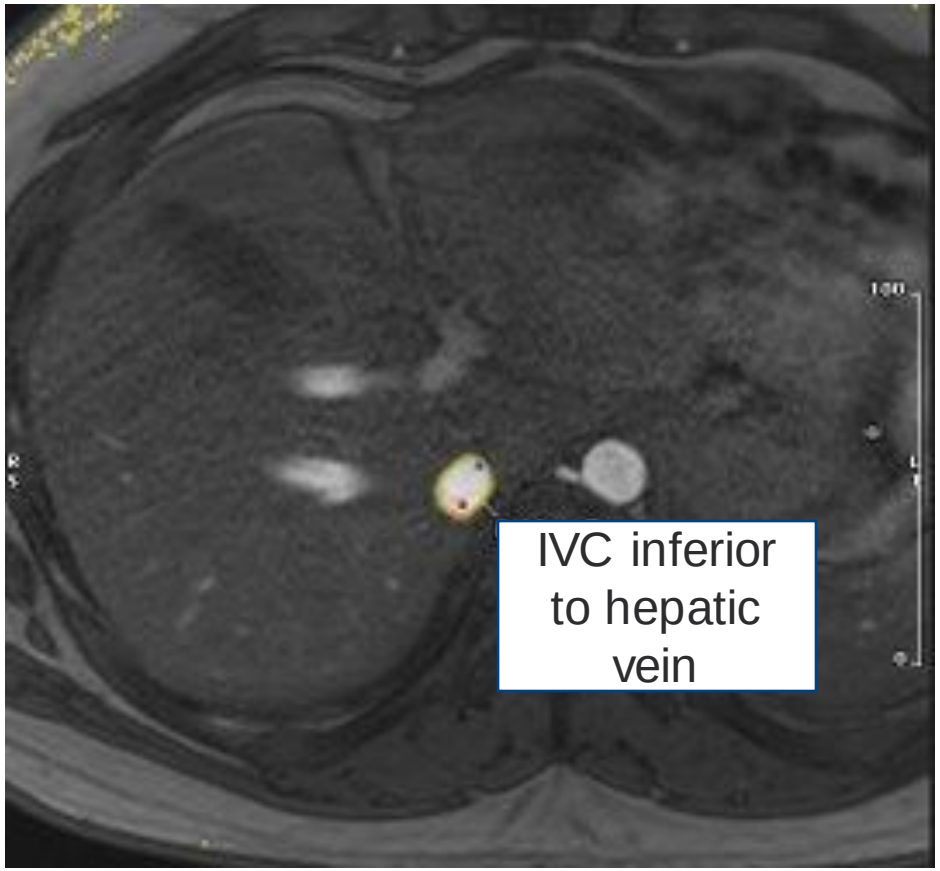
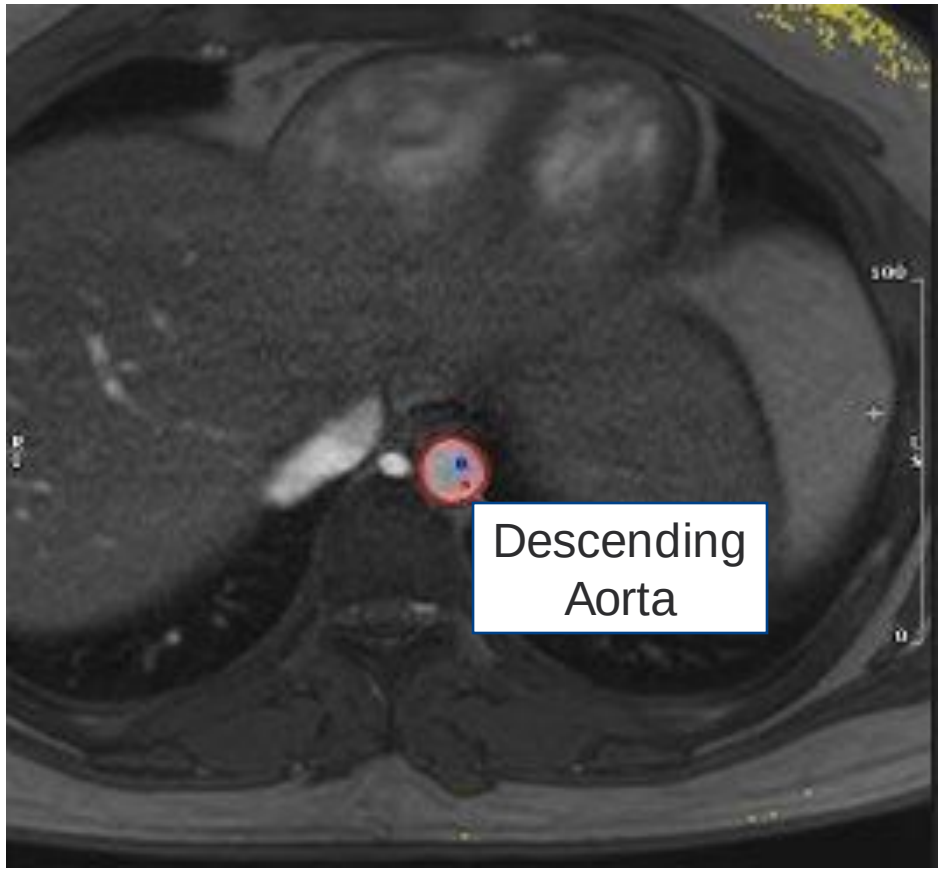
# Hepatic Blood Flow



# Results

| Median (Interquartile range) | |
|---|---|
| **Age** | 14 (12-16) |
| **Height (cm)** | 163.5 (155.1-172.0) |
| **Weight (kg)** | 71.4 (60.2-98.4) |
| **BMI-Z-score** | 1.8 (1.1-2.2) |

**Table 1. Patient Demographic Data**

| Weight class (n/%) | |
|---|---|
| **Normal** | 17 (25%) |
| **Overweight** | 23 (33%) |
| **Obese** | 29 (42%) |

**Table 2. Weight class**

# Nonparametric Correlation (Spearman Correlation)

| | | Age | Height | Weight | BMI-Z score | Liver Volume |
|---|---|---|---|---|---|---|
| **Blood Flow** | Correlation Coefficient | 0.204 | 0.431* | 0.430* | 0.229 | 0.408* |
| | Sig. (2 tailed) | 0.093 | 0.000 | 0.000 | 0.064 | 0.001 |

*Correlation is significant at the 0.01 level (2-tailed)

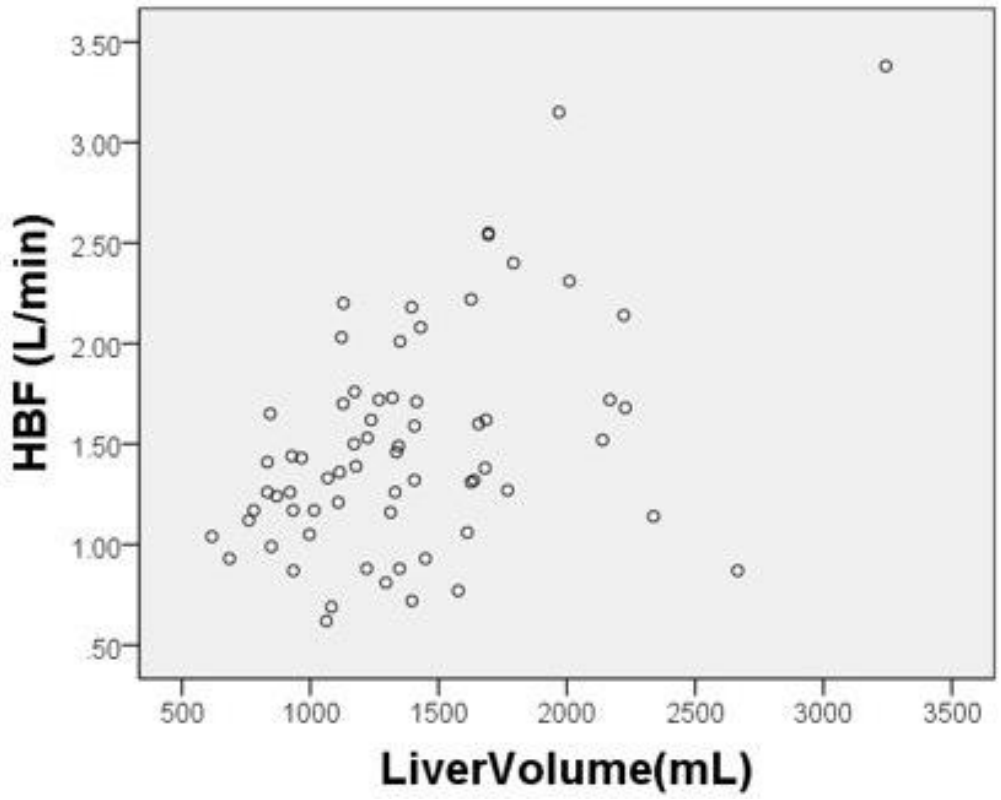
# Regression Coeficient for Predicting Hepatic Blood Flow

- Multivariable regression indicated about 30% of variability in Hepatic flow was explained by age, weight, height, and BMI Z score (r2 = 0.290)

| | Unstandardized coefficients | | Standardized coefficients | t | Sig |
|---|---|---|---|---|---|
| | B | Std. Error | Beta | | |
| AGE | -0.008 | 0.037 | -0.043 | -0.223 | 0.824 |
| HEIGHT | 0.010 | 0.009 | 0.215 | 1.118 | 0.268 |
| WEIGHT | -0.001 | 0.007 | -0.043 | -0.122 | 0.904 |
| BMI-Z score | 0.010 | 0.129 | 0.019 | 0.077 | 0.939 |
| Liver Volume | 0.000 | 0.000 | 0.420 | 2.236 | 0.029 |

# Results

- Liver volume displayed predictability of the Hepatic flow (p = 0.029; B= 0.42) while other variables remained constant



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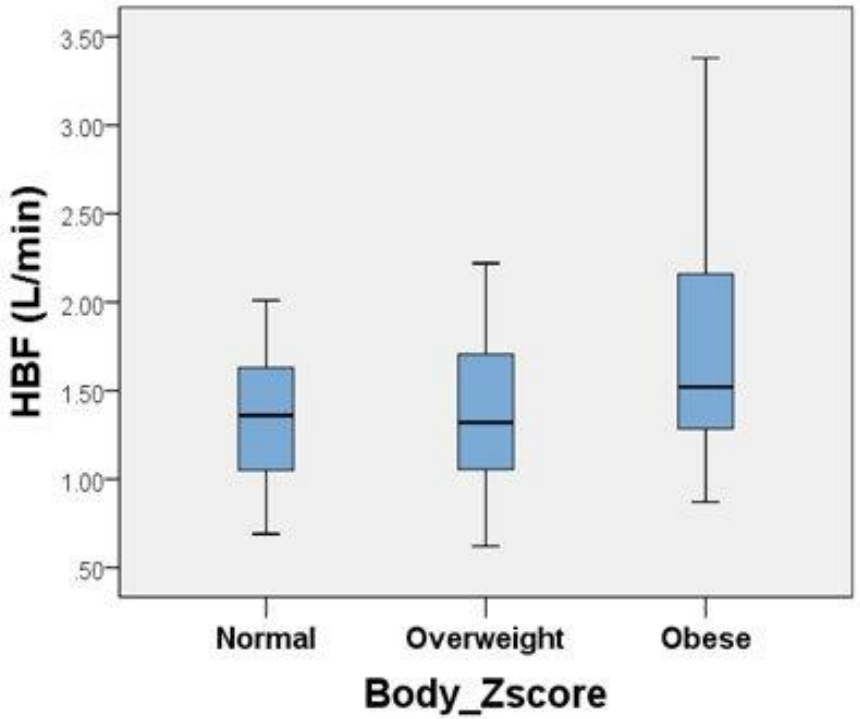
# HBF for BMI-Z score

- Independent sample T-test showed statistically significant difference in hepatic blood flow between normal and obese weight classes (F = 4.924, P = 0.032)



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# Conclusion

- Study showed differences in hepatic blood flow in patients with or without obesity
  - Ultimately suggests that availability of the drug systematically is also different
- Hepatic blood flow correlated with height, weight, and liver volume, but our study showed that due to weak correlation and high variability, more direct method to measure hepatic blood flow is needed, which can be provided by 2D-phase contrast MRI

# Future Considerations

- Focus on integrating the observed variability in hepatic blood flow into PBPK models for high extraction drugs (such as morphine, propofol, and verapamil), in order to assess net effect on accuracy of individual PK prediction
- Explore feasibility of MRI 2D blood flow data input into PBPK dashboard tool to predict precise individualized dosing

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