Compartmental modeling enhances the reliability of the measurement of portal systemic shunting by the HepQuant SHUNT test

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Background

- HepQuant SHUNT test measures portal and systemic clearances simultaneously, involving:
  - IV dose of carbon-13-labeled cholate (13C-CA)
  - Oral dose of deuterium-labeled cholate (d4-CA)
  - 5 peripheral venous blood draws over 90 minutes
- Previously, a noncompartmental analysis (the Minimal Model) characterized IV clearance by exponential fits and oral clearance by cubic spline fits [1]
- Physiological-based compartmental models, described by distribution volumes and transfer rates between volumes, can estimate parameters not defined by noncompartmental analyses

Aims

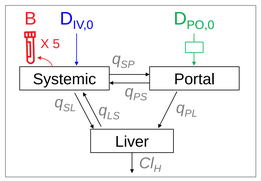
- Apply a Compartmental Model [2] to elucidate the underlying mechanisms of hepatic uptake of cholate and anatomic shunting
- Compare the Compartmental Model to the previously validated Minimal Model [1] in terms of reproducibility

Methods

- A Compartmental Model was evaluated using results from a study of HepQuant SHUNT test reproducibility [3].
  - N=16 controls, N=16 NASH, and N=16 HCV
  - 3 replicate SHUNT tests per subject on 3 separate days
- Reliability of 6 hepatic disease indices compared between Compartmental Model and Minimal Model methods:
  - DSI, HR, HFR_S, HFR_P, SHUNT, and STAT
- Intra-class correlation coefficients (ICC):
  - Single measurement, 2-way mixed effects model for absolute agreement
  - P value: 1-sided test for lower acceptable limit (ICC>0.7)

Compartmental Model

- Transfer between compartments was modeled by a system of 18 differential equations
- Assumptions from measured and literature-derived values
- Parameters estimated by nonlinear least-squares regression, for each subject, for oral and IV data simultaneously



$D_{PO,0}$ = oral dose of d4-CA at 0 min.

$D_{IV,0}$ = IV dose of 13C-CA at 0 min.

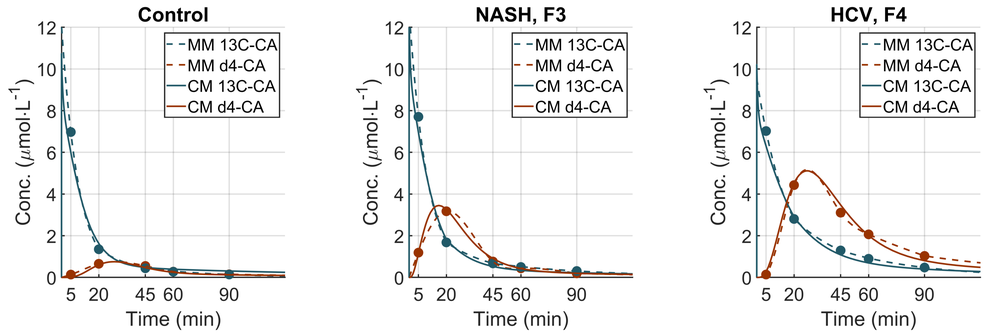
B = blood draws at 5, 20, 45, 60, 90 min.

q, Cl_H = flow rates and hepatic clearance

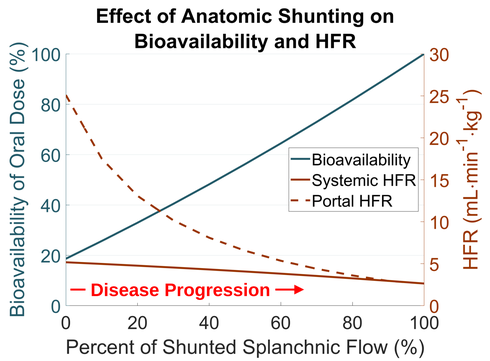
q_{PS} = anatomic shunting

Results

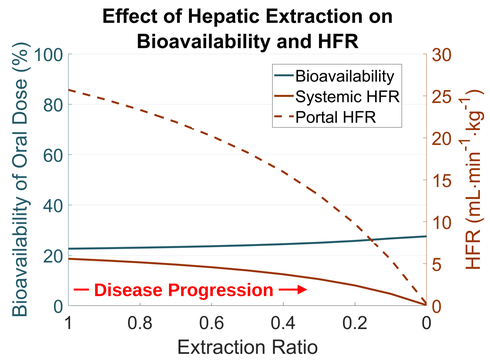
Compartmental Model accurately reproduced systemic and portal clearance curves.



Parameter scans of Compartmental Model demonstrated ability to differentiate effects of anatomic shunting and hepatocyte function.



Simulation of varying portal-systemic shunt flow (q_{PS}) while holding ER at 0.78



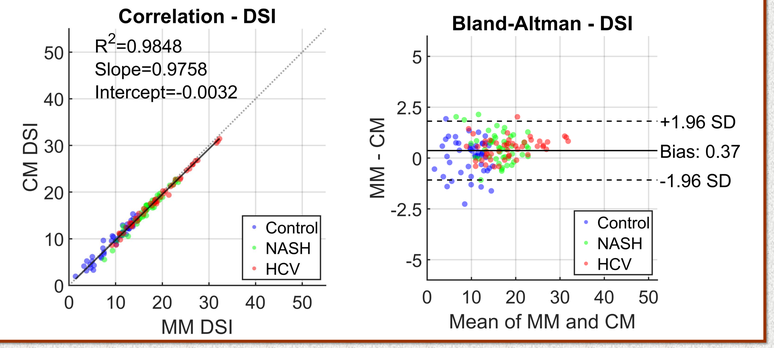
Simulation of varying hepatic extraction ratio (ER) while holding q_{PS} at 0 L/min

Compartmental Model improved within-individual reproducibility of SHUNT in terms of intra-class correlation coefficient (ICC) for all subjects (N=48).

Index	Minimal Model			Compartmental Model		
	ICC	*95% CI*	*P value*	*ICC*	*95% CI*	*P value*
DSI	0.94	(0.90–0.96)	<0.001	0.93	(0.88–0.95)	<0.001
HR	0.97	(0.94–0.98)	<0.001	0.96	(0.94–0.98)	<0.001
HFR_S	0.82	(0.73–0.89)	0.0080	0.88	(0.82–0.93)	<0.001
HFR_P	0.84	(0.75–0.90)	0.0017	0.80	(0.70–0.87)	0.0288
SHUNT	0.73	(0.60–0.83)	0.3095	**0.84**	**(0.76–0.90)**	**0.0012**
STAT	0.90	(0.84–0.94)	<0.001	0.90	(0.84–0.94)	<0.001

DSI = Disease Severity Index | HR = Hepatic Reserve | HFR_S = Systemic Hepatic Filtration Rate
HFR_P = Portal Hepatic Filtration Rate | SHUNT = Shunt Fraction | STAT = d4-CA concentration at 60 minutes

Compartmental Model demonstrated agreement with validated measure of liver function (DSI) in control, NASH, and HCV.



Conclusions

- **The Compartmental Model:**
  - **provided an excellent fit to systemic and portal clearance**
  - **allowed determination of anatomic shunt & hepatic extraction**
  - **improved within-individual reproducibility for SHUNT**
  - **correlated with the validated MM of hepatic disease/health**
- **The Compartmental Model of the SHUNT test addresses both hepatocellular dysfunction and anatomic shunting across the spectrum of liver disease**
- **The Compartmental Model of the SHUNT test could be used as a *precision liver diagnostic tool* by identifying the elements of liver function and physiology affected by treatments or interventions**

References

[1] Everson GT et al. Aliment. Pharmacol. Ther. 2007; 26:401-410.

[2] *McRae MP et al. Transl. Res. 2022; in press.

[3] Burton JR, Jr. et al. Transl. Res. 2021; 233:5-15.

***Note:** A portion of the work submitted in our original abstract is in press sooner than expected.

Disclosures

MPM is a paid consultant for HepQuant LLC. SMH and GTE are employees and equity members of HepQuant LLC. All authors have provisional patents pending. HepQuant tests are not FDA approved and are for investigational use only under FDA guidelines for investigational device exemption (IDE).

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