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LETTER TO THE EDITOR

Comment on: "A Physiologically Based Pharmacokinetic Drug-Disease Model to Predict Carvedilol Exposure in Adult and Paediatric Heart Failure Patients by Incorporating Pathophysiological Changes in Hepatic and Renal Blood"

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Heart failure is associated with impaired cardiac output and tissue perfusion, thereby resulting in altered drug disposition and exposure [1–4]. In a recent issue of *Clinical Pharmacokinetics*, Rasool et al. [5] reported the worthwhile attempt to develop physiologically-based pharmacokinetic (PBPK) models for carvedilol in adult patients with chronic heart failure by incorporating pathophysiological alterations in hepatic and renal blood flows, and subsequently used the PBPK models to predict oral pharmacokinetics of carvedilol in pediatric patients by accounting for age-related physiological differences. The authors found that the incorporation of decreased hepatic and renal blood flows into their PBPK models resulted in a marked improvement in the predictive accuracy of the carvedilol PBPK models in adult patients with chronic heart failure. On the other hand, the authors noticed that incorporating known changes in hepatic and renal blood flows did not lead to any improvement in the predictive accuracy of the PBPK models for carvedilol in infants (aged 0.1–1 years) with chronic heart failure, and emphasized the knowledge gaps related to gastrointestinal physiology (namely 'gastric and intestinal pH, bile secretion, transporters and gut fluid dynamics') in infant populations which may influence the predictive performance of their PBPK models for infant patients. Ultimately, the authors concluded that their PBPK models "could be extended to other high-extraction drugs in heart failure patients".

Here, we would like to discuss some key considerations related to PBPK modeling for patients with chronic heart failure, which will promote good practice in the use of PBPK modeling to assess the impact of chronic heart failure on drug disposition and exposure. Additionally, we explore some specific details regarding modeling carvedilol absorption in adults and infants, which are well worth bringing to readers' attention.

1 Cardiac Output and Tissue Blood Flows in Heart Failure

Chronic heart failure has been shown to significantly reduce cardiac output and regional blood flow [6–8]. The decrease in regional blood flow to the hepatic, renal, mesenteric, and limb regions caused by chronic heart failure is proportional to the reduction in cardiac output [6, 7]. In a generic whole-body PBPK model, drug kinetics in each tissue compartment are characterized by a tissue-specific blood flow rate, volume, and partition coefficient [9–11]. From a PBPK perspective, diminished blood flow to the small intestine may lead to impaired drug absorption; declined blood flow to large or lipophilic tissues (such as muscle, skin, and adipose) may cause altered drug distribution; and decreased blood flow to the liver and kidneys

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may result in changed drug clearance. Unfortunately, only the reduction in hepatic and renal blood flows were taken into account by Rasool et al. [5] in the current models, which appeared to result in biased predictions in drug absorption and distribution.

To our knowledge, the first study regarding whole-body PBPK modeling for patients with chronic heart failure was reported by Carlton et al. [12] in 1996. Unlike Rasool et al. [5], heart-failure-associated changes in blood flow to the heart, gut, kidneys, liver, muscle, skin and adipose tissue had been incorporated in the earliest PBPK model for patients with chronic heart failure [12]. Nonetheless, we noticed that pathophysiological parameters (i.e. cardiac output and tissue blood flows) used in the earliest PBPK model [12] cannot be directly adopted in the current model by Rasool et al. [5] because of confounding by epoprostenol-induced alterations in blood flow and lack of pathophysiological data in relation to the severity of the disease.

Here, we summarize the pathophysiological changes in cardiac output and blood flow to individual tissues associated with different levels of heart failure (Table 1) through our comprehensive literature searches in the MEDLINE database. The physiological changes associated with heart failure are expressed as the ratios of mean reported values between the disease group and the healthy group. Because blood flowing into the limbs supplies skeletal muscle, bone, subcutaneous tissue, and skin [13], the decreases in blood flow to these tissues are identical to that in blood flow to the limbs (Table 1). Furthermore, because blood flow to individual tissues is computed as a percentage of cardiac output in dedicated software platforms for PBPK modeling, such as the Simcyp Simulator [14, 15] and PK-Sim [16, 17], changes in blood flow to the other tissues can be calculated by taking into consideration the alterations in cardiac index (cardiac output/body surface area) or cardiac output. Collectively, the pathophysiological parameters summarized in Table 1 are highly valuable for the improvement and future developmemt of PBPK modeling for patients with different degrees of chronic heart failure.

Table 1 Changes in cardiac output and blood flow to individual tissues associated with differing degrees of heart failure[a]

Study	Blood flow	Chronic heart failure		
		Mild	Moderate	Severe
Leithe et al. [6][b]	Cardiac index	0.80[d]	0.63[e]	0.50[f]
Leithe et al. [6][b]	Liver	0.76[d]	0.53[e]	0.47[f]
Leithe et al. [6][b]	Kidneys	0.78[d]	0.56[e]	0.63[f]
Leithe et al. [6][b]	Skeletal muscle[c]	0.67[d]	0.56[e]	0.45[f]
Leithe et al. [6][b]	Bone[c]	0.67[d]	0.56[e]	0.45[f]
Leithe et al. [6][b]	Skin[c]	0.67[d]	0.56[e]	0.45[f]
Leithe et al. [6][b]	Adipose[c]	0.67[d]	0.56[e]	0.45[f]
Sandek et al. [29]	Superior mesenteric artery	0.71[g]	0.42[h]	NA
Muller et al. [7]	Cardiac output	0.80[i]	NA	NA
Muller et al. [7]	Superior mesenteric artery	0.74[i]	NA	NA
Muller et al. [7]	Kidneys	0.70[i]	NA	NA
Gruhn et al. [30]	Brain	NA	NA	0.69[j]

NA not available, *NYHA* New York Heart Association

[a] Fractions of healthy control values

[b] Original data from the literature [6] were captured by computer digitization

[c] The reductions in blood flow to the skeletal muscle, bone, adipose, and skin are identical to that in blood flow to the limbs because blood flowing into the limbs supplies these tissues [13]

[d] From the 18 patients with mild chronic heart failure

[e] From the 20 patients with moderate chronic heart failure

[f] From the 26 patients with severe chronic heart failure

[g] From the 53 patients with non-cachectic chronic heart failure (mean NYHA class II)

[h] From the 12 patients with cachectic chronic heart failure (mean NYHA class III)

[i] From the patients (NYHA class II–III) at rest

[j] Fraction of the control value in the 12 patients with chronic heart failure (NYHA class III–IV) who had been evaluated for cardiac transplantation was identical to that of the 5 patients who underwent cardiac transplantation

2 Prediction of Intestinal First-Pass Metabolismin Heart Failure Patients

Oral bioavailability (F) can be considered as the continuous product of the fraction absorbed (f_a), the fraction of drug that escapes intestinal first-pass metabolism in the gut wall (F_G), and the fraction of drug that escapes hepatic first-pass metabolism and enters the systemic circulation (F_H) (see Eq. 1):

$$F = f_a \times F_G \times F_H \quad (1)$$

In Rasool et al.' models implemented in the Simcyp Simulator, F_G is estimated using the Q_{Gut} model, as shown in Eqs. (2) and (3) [18, 19]:

$$F_G = \frac{Q_{Gut}}{Q_{Gut} + fu_{Gut} \times CLu_{int,Gut}} \quad (2)$$

$$Q_{Gut} = \frac{Q_{villi} \times CL_{perm}}{Q_{villi} + CL_{perm}} \quad (3)$$

where Q_{Gut} is dependent on villous blood flow (Q_{villi}) and permeability through the enterocyte membrane (CL_{perm}), and fu_{Gut} and $CLu_{int,Gut}$ refer to the fraction of drug unbound in the enterocyte and the unbound intrinsic clearance in the gut, respectively.

Blood flow to the entire small intestine is provided by the superior mesenteric artery, and approximately 48 % of mesenteric blood flow supplies the epithelial cells of the villi [18, 20]. In other words, Q_{villi} is directly determined by the blood flow in the superior mesenteric artery. As shown in Table 1, impaired blood flow in the superior mesenteric artery resulting from heart failure definitely leads to significantly reduced Q_{villi}. In this regard, heart failure-associated declines in mesenteric blood flow have a remarkable impact on the prediction of intestinal first-pass metabolism and bioavailability (Eqs. 1–3). Hence, to extrapolate intestinal metabolism from in vitro data generated using human intestinal microsomes, incorporating the heart failure-related reductions in intestinal blood flow (mesenteric and Q_{villi}) is necessary.

On the other hand, mesenteric blood flow-dependent absorption has been observed in many drugs from animal studies [21–23]. Furthermore, the importance of intestinal blood flow on drug absorption and bioavailability has been identified by means of PBPK modeling for digoxin in heart failure patients [12]. All of this supports the overwhelming need to account for altered intestinal blood flow (mesenteric and Q_{villi}) in PBPK modeling for patients with heart failure.

3 Modeling Carvedilol Absorption in Infants

With regard to pediatric PBPK modeling, Rasool et al. noticed that their models "tended to generally overpredict the drug concentrations in those patients under 1 year of age" [5]. To interpret the inaccurate prediction of oral carvedilol pharmacokinetics in infants (aged 0.1–1 year), Rasool et al. highlighted the information gaps in terms of age-related gastrointestinal physiology (namely "gastric and intestinal pH, bile secretion, transporters, and gut fluid dynamics") in a pediatric adsorption model within the Simcyp Simulator, and stated that "the presented paediatric results must be judged in this context" [5]. This interpretation gives the impression that the differences in "gastric and intestinal pH, bile secretion, transporters, and gut fluid dynamics" between infants and adults that had not been incorporated in the Simcyp Simulator were partly responsible for the poor prediction of carvedilol pharmacokinetic profiles in infants, but that is not the case. First, the gastrointestinal pH in infants is similar to that in adults, which has been reviewed by the developers of the Simcyp Simulator [24], the current authors [25], and other researchers [26]. Second, intestinal bile salt concentrations under fasting conditions are comparable in infants and adults [26, 27]. Accordingly, it is reasonable to employ the 'adult' values of gastrointestinal pH and bile salt concentrations in pediatric absorption models, at least under fasting conditions. Furthermore, gastrointestinal pH and bile salt concentrations primarily affect drug solubility, but, surprisingly, no data on carvedilol solubility can be found in the development of models by Rasool et al. [5]. As such, even if there is any difference in gastrointestinal pH and bile salt concentrations between infants and adults, it is not expected to have any impact on the predictive proformance of carvedilol pediatric PBPK models, to say the least. Third, as mentioned by Rasool et al. [5], carvedilol is a poor substrate for P-glycoprotein (P-gp) or other tansporters, indicating that transporters have no effect on the accuracy of their model prediction. Lastly, as stated by Rasool et al. [5], "The fluid intake with the dose was not modified according to the age of the paediatric subjects; however, no relevant impact on the results from the four infants under 1 year of age was seen". Because gut fluid dynamics depends on fluid intake, fluid secretion, and reasorption in the Simcyp Simulator [20], fluid intake largely determines gut fluid dynamics when volume of fluid intake is highly greater than that of fluid secretion and reasorption. Hence, under the scenarios described by Rasool et al. [5], gut fluid dynamics should not be expected to have any significant influence on the predictive accuracy of carvedilol pediatric PBPK models.

4 Future Perspectives

As shown by Dr. Rasool et al. [5], incorporating altered hepatic and renal blood flows into PBPK models could improve the prediction of carvedilol pharmacokinetics in adult patients with chronic heart failure. Nonetheless, more information regarding heart-failure-associated changes in blood flow to individual organs should be incorporated in

PBPK models for patients with chronic heart failure. We believe the physiological parameters pertaining to changes in blood flow to individual tissues associated with differing levels of heart failure in Table 1 are highly valuable, not only for drug clearance prediction but also for the prediction of intestinal first-pass metabolism, drug absorption, and distribution. These physiological data pave the way for the implementation and future development of whole-body PBPK modeling for patients with different degrees of heart failure. Further investigations on PBPK modeling for this disease population using other representative drugs are warranted.

With respect to pediatric PBPK modeling for carvedilol, we support the call by Rasool et al. regarding the need for further improvement on pediatric absorption models. Moreover, understanding the similarities and differences in gastrointestinal physiology between infants and adults facilitates better practice in the application of pediatric PBPK modeling to evaluate oral drug exposure in infants [25]. On the other hand, parameter sensitivity analyses can help identify potential factors related to poor prediction in infants [28].

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Compliance with Ethical Standards

Conflicts of interest Guo-Fu Li, Xiao Gu, Guo Yu, Shui-Yu Zhao, and Qing-Shan Zheng have no conflicts of interest to declare that are directly relevant to the content of this letter.

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