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Modeling of Change in Blood Volume and Extracellular Fluid Volume during Hemodialysis

Fansan Zhu, *Member, IEEE,* Franz Kappel, Edward F. Leonard, Peter Kotanko, Nathan W. Levin

***Abstract*— Knowledge of dynamics of shift of fluid volume between intra- and extravascular compartments during hemodialysis (HD) is important for managing HD treatment to help patients approach dry weight without hypotension. The Relative blood volume (RBV) monitor indicates change in plasma volume based on the difference between ultrafiltration rate (UFR) and plasma refilling rate (PRR) during HD. However, the absolute value of PRR cannot be obtained from RBV. The aim of this study was to investigate whether fluid transport from the interstitial to blood spaces can be quantitatively analyzed with a two compartments model. 14 patients (30 measurements) were studied. RBV using a blood volume monitor (BVM, Fresenius) and calf extracellular volumes (ECV) by calf bioimpedance device (Hydra 4200, Xitron) were continuously measured during HD. A mathematic model was established with unknown transport coefficients (k_1, k_2, α, β, γ, δ) and these coefficients were estimated using a Least Squares Optimization algorithm by fitting from experimental data. A high correlation (R^2>0.8) between experimental data and calculation by the model were observed in both RBV and ECV measurements. Coefficients k_1 and δ significantly differed with different degree of hydration. This model provides parameters which can used to understand relationships between degree of hydration and refilling rate.**

I. Introduction

Patients with end stage renal disease (ESRD) require dialysis to remove toxic substances and excess fluid volume from the body. In hemodialysis (HD) treatments, two major clinical problems exist which are achievements of optimal fluid status (dry weight) and prevention of hypotension during HD. An appropriate prescription of ultrafiltration volume (UFV) required in an individual HD treatment is facilitated by two factors: 1) accurate assessment of dry weight and 2) use of an acceptable ultrafiltration rate (UFR) because hypotension might occur when the UFR is greater than the tolerance of hypovolemia in the intravascular compartment. Therefore, both blood volume (BV) and interstitial fluid volume play an important role in understanding fluid dynamics during HD [1]. Relative blood volume (RBV) is used to monitor change in plasma volume during HD [2]. However, change in RBV reflects the difference between UFR and plasma refilling rate so that this change cannot represent the actual plasma refilling rate. On the other hand, static extracellular fluid volume (ECV) measurement in the whole body or segments technique provides fluid status but cannot indicate dynamic information of change in blood volume during ultrafiltration [3]. Many clinical studies have been performed to try to understand the dynamic relationship of fluid shift between blood and interstitial fluid compartments in order to adjust UFR or UFV [4]-[6]. A recent study reported that change in fluid distribution in segments of the body during HD is an important factor influencing stability of hemodynamics [7]. Measurement of fluid change in the leg or the calf may represent total fluid removal in the body during HD [8]. The aim of this study was to investigate whether fluid transport from the interstitial to blood spaces can be quantitatively analyzed with a two compartment model.

F. Zhu is with the Renal Research Institute New York, NY 10128 USA (corresponding author to provide phone: 212-870-9245; fax: 212-870-9767; e-mail: fzhu@rriny.com).

F. Kappel is with Institute for Mathematics and Scientific Computing, University of Graz, Austria (e-mail: franz.kappel@uni-graz.at)

E. F. Leonard is with the Dept. of Chemical Engineering, Columbia University, New York, NY 10027 USA.(e-mail: leonard@columbia.edu).

P. Kotanko is with the Renal Research Institute New York, NY 10128 USA (e-mail: pkotanko@rriny.com).

N.W. Levin is with the Renal Research Institute New York, NY 10128 USA (e-mail: nlevin@rriny.com).

II. Methods and Materials

A. Principle of physiology during hemodialysis

First, excess fluid volume (plasma) is removed from the blood compartment by ultrafiltration; secondly, if major fluid accumulation is present in the interstitial space, excess fluid must be transferred from the intestinal tissue to the blood compartment. This process can be described with a simple two compartments model shown in Figure 1. In addition, since change of plasma volume in the calf ECV is small, we assume that the change in V_E is only from reduction of interstitial fluid volume [9].

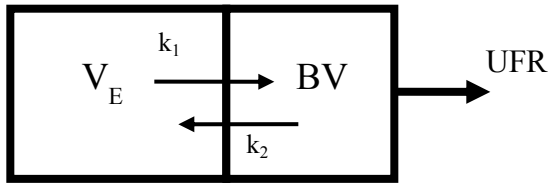

Figure 1. Block diagram of the model during ultrafiltration

B. Mathematic model

According to the two compartments model of Figure 1 the change in blood volume dBV/dt and the change in interstitial fluid volume dV_E/dt can be written as

$$\frac{dBV}{dt} = k_1 V_E - k_2 BV - UFR, \quad (1)$$

$$\frac{dV_E}{dt} = -k_1 V_E + k_2 BV, \quad (2)$$

where BV and V_E represent blood volume and ECV in interstitial fluid in the calf respectively; $\boldsymbol{k_1}$ and $\boldsymbol{k_2}$ represent transfer coefficient from ECV to BV and BV to ECV respectively. Since absolute BV cannot be measured in f clinical practice, relative blood volume *RBV(t) =BV(t)/BV(0)* has been widely used in clinical studies. Accordingly, the relative change (*RVE(t)=VE(t))/VE(0)* in ECV can be represented by the ratio $R_E(0)/R_E(t)$ of the extracellular resistance because we have $V_E(t) = \rho L^2/R_E(t),\ t \geq 0,$ where the constants ρ and *L* are the resistivity and the length of the segment being measured, respectively. In order to get differential equations for RBV and RV_E we divide equation (1) by $BV(0)$ and equation (2) by $V_E(0)$. After some computations we get

$$\frac{dRBV}{dt} = \alpha RV_E + \frac{\alpha\delta}{\gamma} RBV - \beta, \tag{3}$$

$$\frac{dRV_E}{dt} = \gamma RV_E + \delta RBV, \tag{4}$$

where

$$\alpha = \frac{V_E(0)}{BV(0)} k_1, \tag{5}$$

$$\beta = \frac{UFR}{BV(0)}, \tag{6}$$

$$\gamma = -k_1, \tag{7}$$

$$\delta = k_2 \frac{BV(0)}{V_E(0)}. \tag{8}$$

The initial conditions for RBV and RV_E are given by $RBV(0) = 1 = RV_E(0)$. When necessary we indicate the dependence of the solutions to system (3), (4) on the parameter vector $\boldsymbol{b} = (\alpha, \beta, \gamma, \delta)$ by writing

$$RBV(t) = RBV(t; \boldsymbol{b}) \tag{9-1}$$

and

$$RV_E(t) = RV_E(t; \boldsymbol{b}). \tag{9-2}$$

C. Parameter identification

The unknown parameters of our model (3), (4) are α, β, γ and δ which are related to the unknown transfer rates k_1, k_2 and the unknown initial volumes $BV(0), V_E(0)$ by formulas (5) – (8). In order to determine the unknown parameters we use measurements available for $RBV(t)$ and $RV_E(t)$ available at sampling times $0 = t_1 < \cdots < t_N = T$,

$$\xi_j \approx RBV(t_j),\ \eta_j \approx RV_E(t_j),\ \ j = 1, \ldots, N,$$

where $t_{j+1} = t_j + 10$ min and T is the duration of the dialysis session. The parameter vector $\boldsymbol{b}$ is determined by a least squares approach, i.e., by minimizing the following quadratic (in the residuals) cost functional:

$$J(\boldsymbol{b}) = \sum_{j=1}^{N} \left(\left(\xi_j - RBV(t_j; \boldsymbol{b}) \right)^2 + \left(\eta_j - V_E(t_j; \boldsymbol{b}) \right)^2 \right).$$

In order to minimize $J(\boldsymbol{b})$ we used the MatLab routine fminsearch.

D. Subjects and study protocol

Stable HD patients were studied more than one with planned decrease in post HD weight in order to achieve a normal body hydration state. For this study, all UFR were kept at a constant value during the same HD treatment in order to simplify the process by modeling with two variables only.

E. Measurements

Body height, weight, UFR, UFV and calf circumference were recorded in each measurement. A blood volume monitor (BVM, Fresenius, Germany) was used to continuously measure relative change BV (RBV) from initial $BV(0)$. Calf bioimpedance spectroscopy (cBIS, Hydra4200, Xitron Technologies San Diego, CA) was used to continuously measure calf resistance and reactance every 20 seconds with range of frequency from 5 kHz to 1 MHz. Extracellular resistance (R_E) was calculated using a program based on the Cole model. Calf ECV (cECV) was calculated using a program provided by Xitron. Calf normalized resistivity (CNR) as a hydration indicator was computed according to resistance at 5 kHz and calf circumference [8].

F. Data analysis

Data are presented with mean ± SD. Data were divided into two groups as fluid overload (FO) and normal hydration (NH) according to the post HD CNR (CNR $\geq 18.58 \cdot 10^{-2}$ [$\Omega \cdot m^3/kg$] in males and $\geq 19.1 \cdot 10^{-2}$ [$\Omega \cdot m^3/kg$] in females). Experimental data were collected every 10 minutes for the fitting process. Nonlinear and linear regression analyses were performed to indicate: 1) goodness of fit between experimental data and calculation, 2) relationship of transfer coefficients (k_1, k_2, α, β, γ, δ) to UFR and CNR. Exclusion criteria were: 1) correlation coefficient (R^2) between RBV and $R_E(0)/R_E(t)$ less than 0.7 and square of root of sum of error less than 15.

III. Results

Fourteen HD patients (age 51.7±10.6 year, height 164.5±12 cm, dry weight 83.8±31.8 kg, Sex 7m, Race 11 AA) were studied with 30 measurements.

No significant difference in transfer coefficients with two groups divided into high UFR (UFR>1.0 L/h) and low UFR (UFR≤1.0 L/h) was observed (Table 1).

TABLE1. Comparison of different UFR groups

		High UFR (1.26±1.5, L/h) N=13	Low UFR (0.76±0.16, L/h) N=27	P value
k_1	L/min	0.032±0.06	0.33±0.94	ns
k_2	L/min	0.011±0.02	-0.31±0.94	ns
A	L/min	0.01±0.02	-0.31±0.94	ns
β		0.001 ±0.001	-0.0003±0.003	ns
γ	L/min	-12.4±44	-0.33±0.95	ns
δ	L/min	0.03±0.06	0.33±0.95	ns
UFV	L	4.35±0.95	2.71±0.62	<0.001
$R_E(0)/R_E(t)$	%	78±9.7	77.7±6.7	ns
Last RBV	%	82.4±5.1	86.3±5.1	<0.05
Pre HD Wt,	kg	87±20	70.5±15	<0.05
CNR	10^{-2} Ω·m^3/kg	15±2.9	13.6±2.1	ns

Table 1 shows comparison of the change in $R_E(0)/R_E(t)$ and the change in RBV at the end of HD with a high UFR (H-UFR > 1.0 L/h) to low UFR (L-UFR ≤ 1.0 L/h). Pre HD body weight and last RBV was significant decrease with H-UFR but either $R_E(0)/R_E(t)$ or CNR did not differ significantly between different UFR.

However, the transfer coefficients (k_1 and δ) in the patients with fluid overload identified by CNR < $18.5\cdot10^{-2}$ [Ω·m^3/kg] differed significantly from those whose CNR ≥ $18.5\cdot10^{-2}$ [Ω·m^3/kg] (see Table 2).

TABLE 2 shows comparison of two CNR groups

		CNR ≥18.5 10^{-2} Ω·m^3/kg N=11	CNR < 18.5 10^{-2} Ω·m^3/kg N=19	p
k_1	L/min	0.0057±0.02	0.314±0.9	<0.01
k_2	L/min	0.0062±0.018	-0.27±0.9	ns
α	L/min	0.005±0.014	-0.272±0.89	ns
β		0.0003±0.004	0.0007±0.0009	ns
γ	L/min	-14.7±48.6	-0.314±0.9	ns
δ	L/min	0.0037±0.022	0.314±0.9	<0.01
UFR	L/h	1.1±0.26	0.9±0.27	=0.05
UFV	L	3.70±0.84	3.27±1.2	ns

In the fluid overload group (CNR<$18.5\cdot10^{-2}$ [Ω·m^3/kg]) α and β were less but γ and δ were larger than in the normal hydration group respectively. γ is the fluid volume transfer coefficient from interstitial space to blood volume so that fluid transfer rate is quicker in fluid overload patients.

A high correlation (R^2 > 0.8) between experimental data and curve of calculation by the model were observed in both RBV and ECV measurements. The average of root mean square error (RMSE) is 7.7±2.8 % for all treatments. Figure 2 shows an example of data fitting by the model. In this case, the experimental data were presented every 10 minutes for both RBV and $R_E(0)/R_E(t)$. The solid lines in the red and in blue are the curves calculated by the model for both RBV and RV_E respectively.

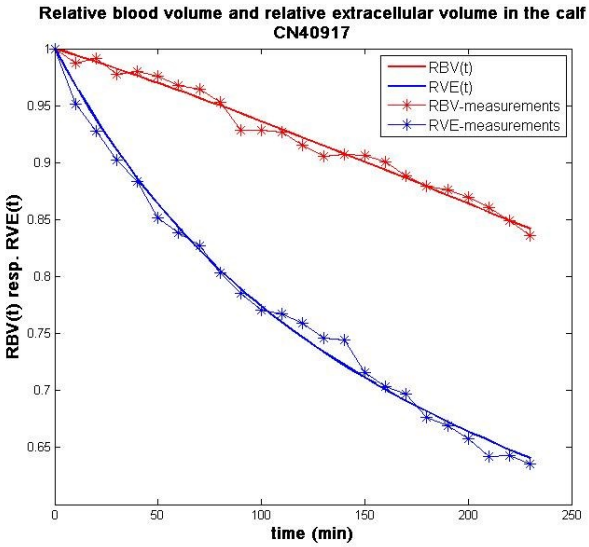

Figure 2. This is a typical treatment in a patient in whom 3.32 L excess fluid were removed using 0.9 L/h UFR in about 230 minutes. The red line represents RBV and blue line represents $R_E(0)/R_E(t)$ respectively.

To understand the effect of UFR on the curves of RBV and $R_E(0)/R_E(t)$, two figures (Figure 3 and Figure 4) from the same patient with different UFRs are compared. It is not surprising to see that about a 7% decrease in RBV (Figure 3) and a more than 12% decrease in RBV (Figure 4) by the end of treatment when UFR was increased from 0.57 L/h to 0.75 L/h respectively. In contrast, decrease in $R_E(0)/R_E(t)$ was the same in both treatments.

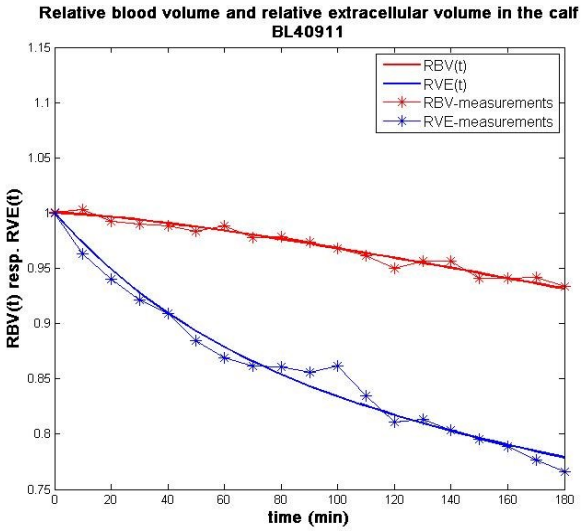

Figure 3. The patient with a lower UFR (0.57 L/h) during HD and UFV= 1.8 L in about 190 minutes. Change in RBV and $R_E(0)/R_E(t)$ were 7 % and 24 % respectively.

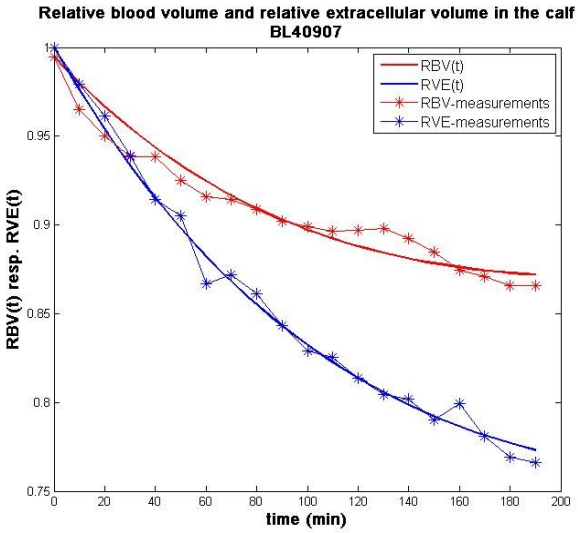

Figure 4. This Figure shows the same patient as in Figure 3 with a relative higher UFR (0.75 L/h) with UFV=2.5 L. Change in RBV and $R_E(0)/R_E(t)$ were 13 % and 23.5 % respectively.

IV. Discussions

A high correlation between experimental data and the curve by the model was observed (Fig. 2 – Fig. 4). This demonstrated that this mathematic model can quantitatively describe the behavior of plasma and interstitial fluid during ultrafiltration. This study provided a mathematical model and established an LSO algorithm to find the coefficients of differential equations.

A. Factors to determining RBV

Change in RBV was determined by two major variables: degree of UFR and plasma refilling rate $k_1 V_E$. The latter can be affected by two factors: 1) amount of ECV in the interstitial fluid volume V_E and 2) transfer coefficient k_1 which could be influenced by individual nervous system, the structure of the veins or change in body temperature. No difference in $\boldsymbol{k_1}$ was observed between high and low UFR groups. This suggests that the rate ($\boldsymbol{k_1}$) of fluid transfer from interstitial to blood space cannot equal to the speed of removal water from the blood by UFR.

B. Identification of the hydration

Measurement of extracellular fluid volume V_E provides information about the fluid status (hydration) and changes in V_E indicate changes in the degree of hydration. However, since measuring V_E alone cannot provide information of plasma refilling, a possible hypotension could not be protected according to decrease in V_E. To make appropriate prescription for the removal of excess fluid volume in individual patients, we have to quantitatively know the dynamics of fluid transport during HD.

C. Advantages and limitations

This study provides a simple method based on least squares optimization algorithm to obtain information about fluid transport during HD. The major advantage with this method is the calculation of differential equations without knowledge of absolute blood volume which is difficult to obtain in routine clinical practice. Transfer coefficients from the model might provide meaningful information to better understand how the rate of fluid transfers from interstitial to intravascular compartment is affected by different UFRs or at different state of hydration. In addition, this information is helpful to understand not only change in blood volume but also in initial blood volume. For example initial blood volume $BV(0)$ could be calculated (6). The study and especially confidence in the measurement should be improved by using an increased number of patients.

V. Conclusion

Using a LSO method to find transfer coefficients between intra and extravascular compartment improves current understanding of fluid dynamic systems in patients during HD. *RBV* provides information about difference between UFR and plasma refilling rate and plasma refilling is affected by degree of hydration. Further study is necessary to apply this model in clinical practice.

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