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Kinetics of volume expansion during infusion of Ringer's solution based on two volume model

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Abstract−In this work mathematical models were developed to represent the kinetics of volume changes of fluid spaces associated with infusion of Ringer's solution. During infusion of Ringer's solution, the human body is assumed to be characterized by the two-fluid space model which has second volume space in addition to the first volume so that fluid exchanges between these two spaces are possible. Various infusion types were tested to accommodate different medical situations. Volunteers were given Ringer's solution and the changes in blood hemoglobin were detected. From the comparison with experimental data, the two-fluid space model was found to represent adequately the kinetics of human volume expansion during infusion of Ringer's solution.

Key words: Volume Expansion, Ringer's Solution, Two-fluid Space, Parameter Estimation, Blood Hemoglobin

INTRODUCTION

Ringer's solution is an electrolyte solution similar to blood plasma. It is usually used to supply water and electrolyte during physical operation or when the human body is in the dehydration state. Ringer's solution consists of 130 milli-equivalent/liter of Na^+, 4 milli-equivalent/liter of K^+, 3 milli-equivalent/liter of Ca^{++}, 109 milli-equivalent/liter of Cl^- and 28 milli-equivalent/liter of lactate.

Infusion of Ringer's solution (or Hartman's solution) is an important part of patient care in surgery or trauma care. It is well known that the amount of Ringer's solution needed to restore normal blood volumes is thought to be three to five times the volume of blood lost. The fluid molecules infused within the human body have been assumed to be distributed within a fluid space of constant volume. But it is obvious that volumes of fluid spaces change when a considerable amount of fluid is added or removed from the body. The volume expansion effect of the administered fluid is believed to be the therapeutic goal. However, this volume effect is difficult to study. Major differences in volume expansion between infusion fluids are fairly well known, but there is a lack of methods that represent their dynamic properties [Dorbin and Hahn, 2002]. A water molecule entering the fluid space consisting of one expandable portion and one rigid portion can be found anywhere and therefore has a volume of distribution, being the sum of the two portions of the entire fluid space. But only the expandable portion of the fluid space is influenced by added water molecules. The volume effect of Ringer's solution has a time course that determines the optimal rate of infusion for the fluid. The blood volume is expanded most during and just after the infusion, but the expansion becomes less pronounced with time.

Recently, simple single and two fluid space volume models have been proposed and tested experimentally [Stahle et al., 1997; Drobin et al., 1999; Sjostrand et al., 2001]. Stahle et al. [1997] proposed elementary mathematical models to represent the changes in volume of fluid spaces associated with intravenous administration of a crystalloid solution. They employed experimental results to estimated model parameters but failed to show the effectiveness of the proposed models upon which our study is based. Svensen and Hahn [1997] analyzed volume kinetics of Ringer's solution, Dextran 70 and Hypertonic saline in male volunteers. They confirmed that the distribution of intravenous fluids can be analyzed by a kinetic model adapted for fluid spaces even with slightly different results depending on the marker used to indicate dilution of the primary fluid space. Volume kinetics of glucose solutions given by intravenous infusion were also analyzed by Sjostrand et al. [2001].

In all the volume expansion models proposed so far the infusion was assumed to be represented as a block pulse. But, in some critical situations such as emergent surgery, infusion of Ringer's solution can be represented as a step or an impulse function. The purpose of the present study is to develop a clear description of volume expansion caused by various types of infusion of Ringer's solution. In this study, we have worked with kinetic models that allow various types of infusion and can be applicable during and after volume loading.

TWO-FLUID SPACE MODEL

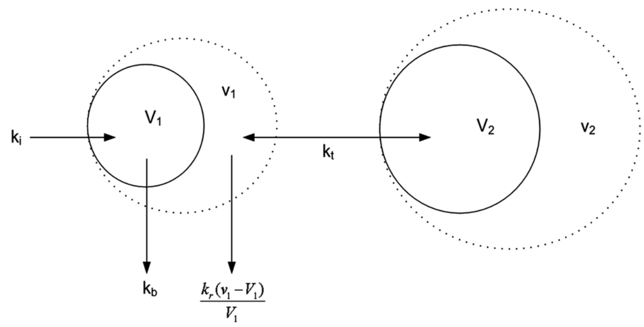

Fig. 1. Schematic diagram of the two-fluid space model.

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The two-fluid space model can be considered as two balloons filled with water and connected to each other as shown in Fig. 1. The primary fluid space communicates with a secondary fluid space. The net rate of fluid exchange between the expandable fluid spaces is proportional to the relative difference in deviation from the target volumes. The system strives to maintain the target volumes by acting on the controlled outflow mechanism in proportion to the relative deviation from the target volume of the primary fluid space.

During infusion, Ringer's solution enters an expandable fluid space of volume v_1 at a rate of k_i. As in the single-fluid space model, the functional form of k_i can be block pulse, step, or impulse. There is a secondary expandable fluid space of volume v_2 which exchanges fluid with the primary fluid space v_i. Both fluid spaces have target volumes V_1 and V_2, respectively. v_1 changes with time due to the effluence of fluid from the fluid space by perspiration, basal diuresis and controlled efflux and due to the fluid exchange with the secondary fluid space. v_2 is time dependent due to the fluid exchange with the primary fluid space. The rate of fluid change between the two fluid spaces is assumed to be proportional to the difference in relative deviations from the target volumes with the proportional constant of k_t. The combined rate of fluid effluence from v_1 due to perspiration and diuresis is represented as k_b. It is assumed that controlled efflux is proportional to the relative deviation of v_1 from the target volume V_1 with the proportional constant k_r. The behavior of the expandable volumes can be represented by the following differential equations.

$$\frac{dv_1}{dt} = k_i - k_b - \frac{k_r(v_1 - V_1)}{V_1} - k_t\left(\frac{v_1 - V_1}{V_1} - \frac{v_2 - V_2}{V_2}\right) \quad (1)$$

$$\frac{dv_2}{dt} = k_t\left(\frac{v_1 - V_1}{V_1} - \frac{v_2 - V_2}{V_2}\right) \quad (2)$$

$$v_1(0)=V_1,\ v_2(0)=V_2 \quad (3)$$

We assume that V_1, V_2, k_t and k_r are constant. As in the single-fluid space model, parameters k_b and k_i are considered to be known. We now consider three typical types as shown in Fig. 2: block pulse, step and impulse. Solutions of Eqs. (1) and (2) for these infusion types are given in Appendix.

In most cases the parameters k_b and k_i in model equations are known as stated before. u or u_1 is the measured dilution of blood and is available from experimental data. The remaining model parameters k_r, k_t and two target volumes V_1 and V_2 should be estimated from the experimental data. In order to check first the effectiveness of the model equations developed in the present study, we assume values of model parameters and target volumes as shown in Table 1 to perform numerical simulations. Simulations were performed using the MATLAB computing tool (version 7.0, MathWorks, U.S.A.). Fig. 3 shows results of simulations for block pulse infusion, step infusion and impulse infusion.

EXPERIMENTS

Ringer's lactate solution was given to six healthy volunteers (four males and two females). The ages and weights of volunteers are within the range of 28-34 years and 48-80 kg, respectively. The infusion experiments were approved by the Ethics Committee of Asan medical center in Seoul, Korea and each volunteer gave informed consent. Twelve hours before the experimental procedure, food and water were discontinued. Volunteers were placed comfortably on beds, and 20 minutes of equilibration was allowed before the fluid administration. Cannulae were placed into the antecubital vein and the radial artery. Ringers' lactate solution (Choong wae, Seoul, Korea), electrolyte contents of which were 130 mmol/*l* of Na, 4 mmol/*l* of K, 2 mmol/*l* of Ca, 1 mmol/*l* of Mg, 24 mmol/*l* of lactate 24 and 110 mmol/*l* of Cl. The Ringer's solution was infused into a vein at a constant rate of 15 ml/kg over 30 min with the aid of infusion pumps (IVAC 560, San Diego).

Samples (1 ml each) for measurement of blood hemoglobin concentration were obtained from the radial arterial cannula at 0, 5, 10, 15, 20, 25, 30, 45, 60, 80, 100 and 120 minutes after administration. After a blood sample is drawn, 3 ml of Ringer's solution is injected to flush the cannula and one 2-ml sample to be discarded is drawn before each blood sampling to avoid undue hemodilution caused by this fluid. Before infusion of the fluid, one sample is drawn

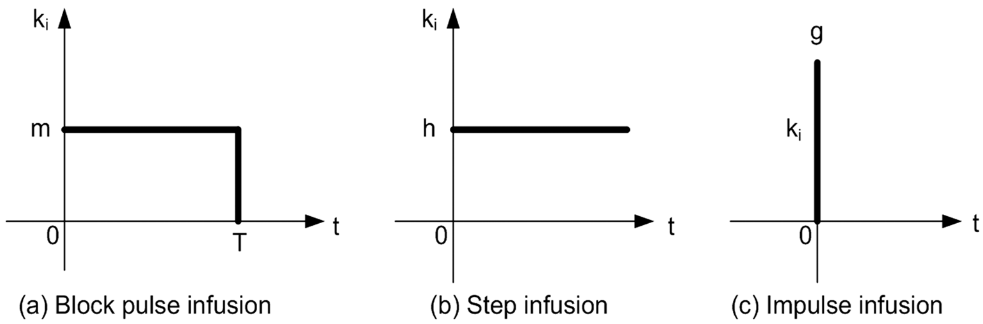

Fig. 2. Three types of infusion.

Table 1. Data for numerical simulations

Infusion type	T (min)	k_b (ml/min)	k_i (ml/min)	k_r (ml/min)	k_t (ml/min)	V_1 (liter)	V_2 (liter)
Block pulse	30	2.5	50	100	200	4	8
Step	-	2.5	50	100	200	4	8
Impulse	-	2.5	1000	100	200	4	8

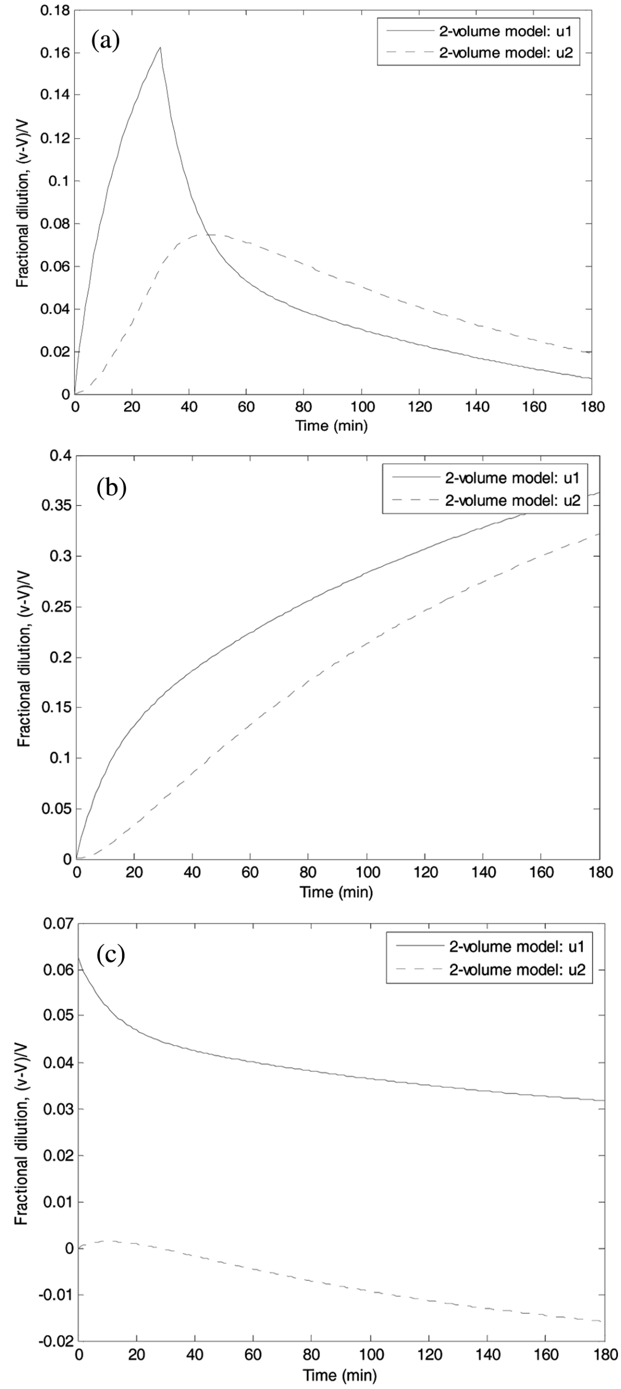

Fig. 3. Results of simulations for various infusion types ((a) block pulse infusion, (b) step infusion, (c) impulse infusion).

in duplicate and the mean value is used in the calculations.

It takes 4 hours to perform whole procedures on a volunteer. Basic apparatus required in experiments are Hartman's solution (1 liter), 4 infusion pumps, a pressure bag, an arterial pressure kit, an ear temperature probe and a syringe (2 ml). Blood sampling: through 3-way route connected to pressure bag, discard the first 1 ml, take the next 1 ml of blood as a sample and flush with 2-ml Hartman's solution connected to the pressure bag.

Fig. 4 shows a snapshot of experiments. Tables 2 and 3 show experimental data represented as fractional dilutions obtained from

Fig. 4. Infusion dynamics experiment.

Table 2. Results of block pulse infusion experiments for male volunteers (T=30 min, k_b=1.94 ml/min)

Time (min)	ID (Male volunteers)				Average
	pch	lyj	pcw	Ljy	
0	0.000	0.000	0.000	0.000	0.000
5	0.073	0.012	0.076	0.017	0.045
10	0.117	0.041	0.045	0.034	0.059
15	0.133	0.028	0.055	0.052	0.067
20	0.078	0.024	0.050	0.064	0.054
25	0.122	0.050	0.110	0.079	0.090
30	0.087	0.078	0.087	0.064	0.079
45	0.107	0.104	0.050	0.045	0.076
60	0.069	0.050	0.026	0.027	0.043
80	0.056	0.059	0.013	0.041	0.042
100	0.060	0.024	0.017	0.027	0.032
120	0.056	0.008	0.036	0.038	0.034
Parameters					
Weight (kg)	72	76	80	68	74
Urine (ml)*	750	400	600	190	485
k_b (ml/min)	1.94	1.94	1.94	1.94	1.94
T (min)	30	30	30	30	30
k_i (ml/min)	36	38	40	34	37

*: Amount of urine collected after 120 minutes of infusion.

infusion experiments for male and female volunteers, respectively.

ESTIMATION OF MODEL PARAMETERS

For the block pulse infusion, in which duration time is T and k_b= b=constant, the volume change characteristics are given in the Appendix. The experimental data in Table 2 exhibits characteristics of the first volume. Thus we can estimate parameters k_r, k_t, V_1, V_2 for the two volume model as follows:

$$f=u_1(t)-K(A_1+B_1e^{r_1t}+C_1e^{r_2t}) \qquad : 0\le t<T \qquad (4)$$

$$f=u_1(t)+\left(\frac{KA_1b}{m-b}\right)-KB_1e^{r_1t}\left\{1-\left(\frac{m}{m-b}\right)e^{-r_1T}\right\}$$

Table 3. Results of block pulse infusion experiments for female volunteers (T=30 min, k_b=1.51 ml/min)

Time (min)	ID (Female volunteers)		Average
	swj	ymo	
0	0.000	0.000	0.000
5	0.017	0.053	0.035
10	0.041	0.059	0.050
15	0.087	0.065	0.076
20	0.108	0.070	0.089
25	0.087	0.065	0.076
30	0.108	0.114	0.111
45	0.087	0.065	0.076
60	0.087	0.065	0.076
80	0.060	0.032	0.046
100	0.108	0.017	0.063
120	0.017	0.012	0.014
Parameters			
Weight (kg)	45	57	51
Urine (ml)*	280	200	240
k_b (ml/min)	1.51	1.51	1.51
T (min)	30	30	30
k_i (ml/min)	22.5	28.5	25.5

*: Amount of urine collected after 120 minutes of infusion.

Table 4. Results of estimation (two-volume model)

Volunteers		k_r (ml/min)	k_t (ml/min)	V_1 (ml)	V_2 (ml)
Male	pch	45.5	399.2	1,358.6	6,212.5
	lyj	126	67	7,745	10,079
	pcw	173.9	85.2	6,900.4	8,474.5
	ljy	64	286	6,654	12,973
	Average	98.1	305.7	6,493.5	3,651.2
Female	swj	38.8	309.1	3,692.8	2,338.7
	ymo	86.2	301.9	6,182.7	5,107.4
	Average	77.2	620.8	2,888.2	2,466.5

$$-KC_1 e^{r_2 t}\left\{1-\left(\frac{m}{m-b}\right)e^{-r_2 T}\right\} \qquad : T \le t \qquad (5)$$

Values of parameters that minimize the objective function f can easily be found as in the single-fluid model case. Table 4 shows results of estimation for the two-volume model.

In order to validate the two-volume model, the estimated parameters were plugged into the model and results of computations were compared with experimental data. Fig. 5 shows results of comparison between experimental values of fractional dilutions and computational results of models based on the estimated parameters for three male volunteers, and Fig. 6 shows those for two female volunteers. Characteristics of males and females may be more distinguishable if we compare average values for males and females. Fig. 7 shows results of comparison between average experimental fractional dilutions and computational results of models based on the estimated parameters using average experimental values.

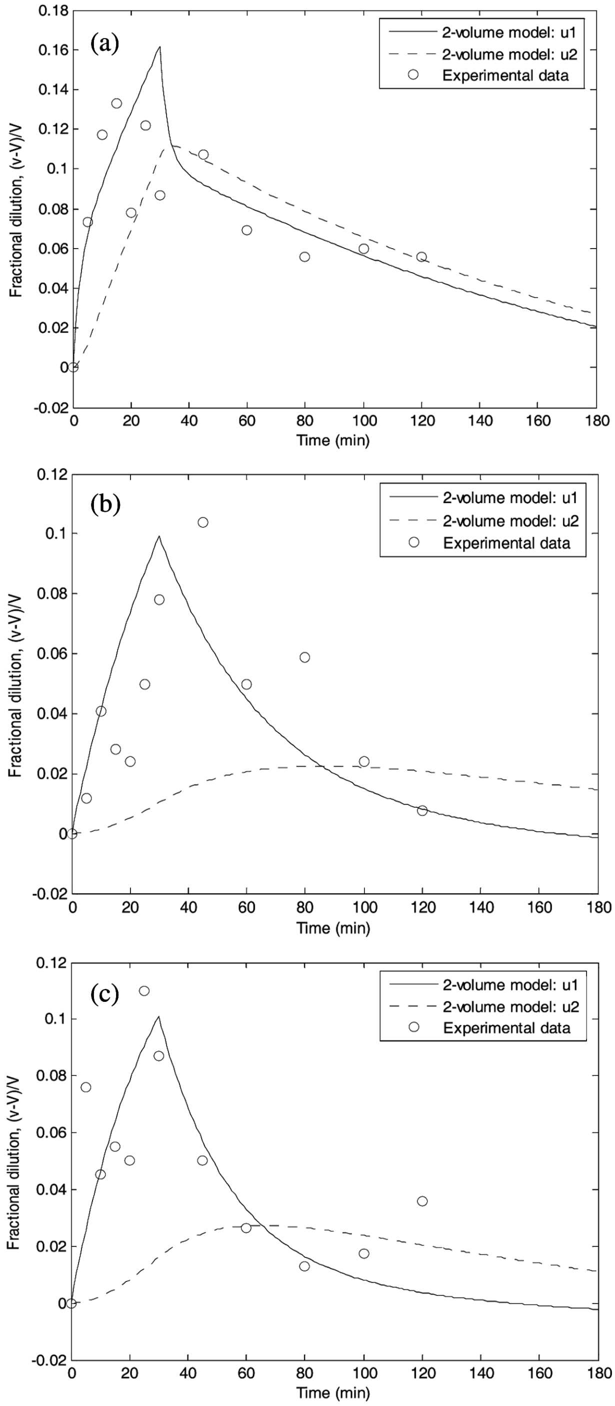

Fig. 5. Comparison between experimental values of fractional dilutions (Male volunteers: (a) pch, (b) lyj, (c) pcw).

CONCLUSIONS

Characteristics of the volume expansion effect during infusion of Ringer's solution were analyzed by using the two-fluid space model. During infusion of Ringer's solution, the human body is assumed to be characterized by the two-fluid space model into which fluid is fed and from which fluid leaves. The two-fluid space model has secondary volume space in addition to the first volume so that fluid exchanges between these two spaces are possible. Various infu-

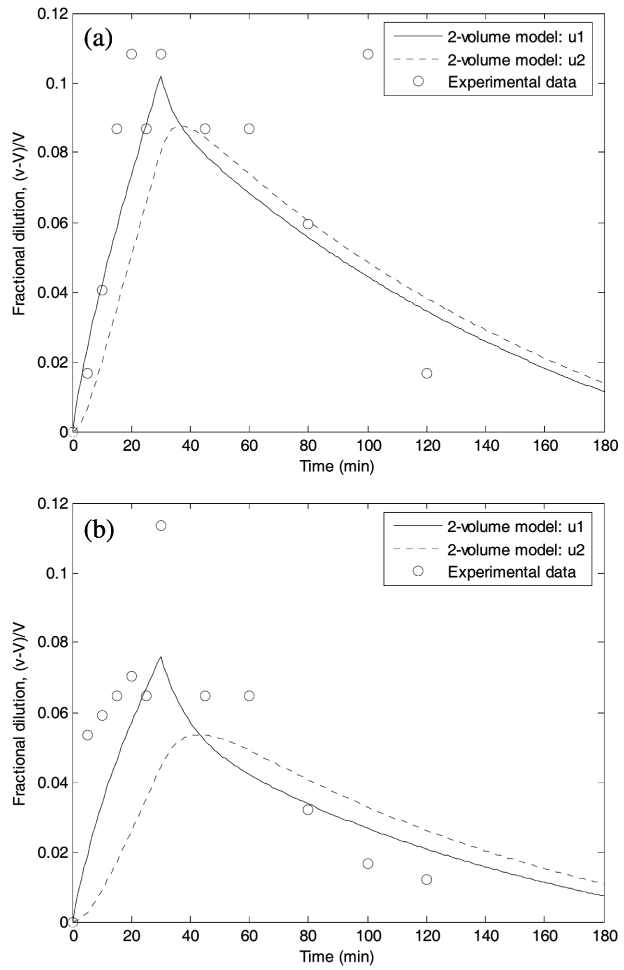

Fig. 6. Comparison between experimental values of fractional dilutions (Female volunteers: (a) swj, (b) ymo).

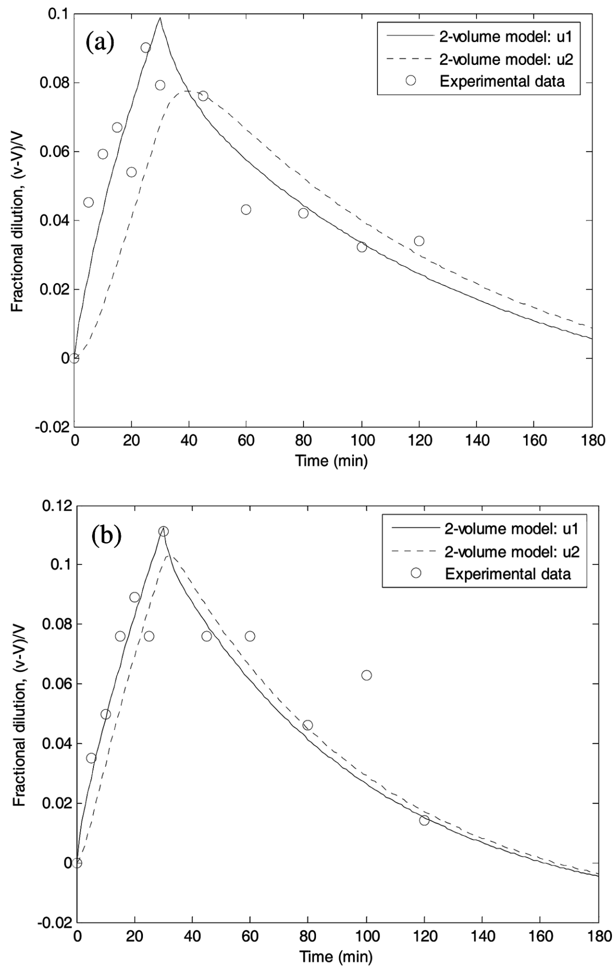

Fig. 7. Comparison between experimental values of fractional dilutions (Based on average values: (a) male, (b) female).

sion types were tested to accommodate different medical situations. Volunteers were given Ringer's solution and the changes in blood hemoglobin were detected. From the comparison with experimental data, the two-fluid space model was found to represent adequately the kinetics of human volume expansion during infusion of Ringer's solution.

APPENDIX

We now introduce $u_1=\dfrac{v_1-V_1}{V_1}$ and $u_2=\dfrac{v_2-V_2}{V_2}$. Then we have

$u_1(0)=u_2(0)=0$, $dv_1=V_1du_1$, $dv_2=V_2du_2$.

Eqs. (3) and (4) can be rewritten as

$$\left(\frac{V_1}{k_r+k_t}\right)\frac{du_1}{dt}=\frac{1}{k_r+k_t}(k_i-k_b)-u_1+\frac{k_t}{k_r+k_t}u_2$$

$$\left(\frac{V_2}{k_t}\right)\frac{du_2}{dt}=u_1-u_2$$

At steady-state we can see that $u_{1s}=u_{2s}=\dfrac{k_{is}-k_{bs}}{k_r}=0$. From the Laplace transform of above relations, we have after some rearrangement

$$U_1(s)=\frac{(\tau_2s+1)}{(k_r+k_t)(\tau_1s+1)(\tau_2s+1)-k_t}\{k_i(s)-k_b(s)\}$$

$$U_2(s)=\frac{1}{\tau_2s+1}U_1(s)=\frac{\{k_i(s)-k_b(s)\}}{(k_r+k_t)(\tau_1s+1)(\tau_2s+1)-k_t} \qquad (6)$$

where

$$\tau_1=\frac{V_1}{k_r+k_t},\quad \tau_2=\frac{V_2}{k_t}$$

Case I: k_b=b=constant and k_i=block pulse with magnitude of m and duration time T. This type of infusion can be represented as Fig. 2(a). Substitution of $k_i(s)$ and $k_b(s)$ into Eq. (6) gives after some rearrangement

$$U_1(s)=\frac{m-b}{\tau_1\tau_2(k_r+k_t)}\cdot\frac{(\tau_2s+1)\left\{1-\left(\dfrac{m}{m-b}\right)e^{-Ts}\right\}}{s\left\{s^2+\left(\dfrac{\tau_1+\tau_2}{\tau_1\tau_2}\right)s+\dfrac{1}{\tau_1\tau_2}\left(1-\dfrac{k_t}{k_r+k_t}\right)\right\}}$$

$$=\frac{m-b}{\tau_1\tau_2(k_r+k_t)}\left(\frac{A_1}{s}+\frac{B_1}{s-r_1}+\frac{C_1}{s-r_2}\right)\left\{1-\left(\frac{m}{m-b}\right)e^{-Ts}\right\}$$

$$U_2(s)=\frac{1}{\tau_2 s+1}U_1(s)$$

$$=\frac{m-b}{\tau_1\tau_2(k_r+k_t)}\left(\frac{A_2}{s}+\frac{B_2}{s-r_1}+\frac{C_2}{s-r_2}\right)\left\{1-\left(\frac{m}{m-b}\right)e^{-Ts}\right\}$$

where

$$r_1=\frac{1}{2}\left[-\left(\frac{\tau_1+\tau_2}{\tau_1\tau_2}\right)+\sqrt{\left(\frac{\tau_1+\tau_2}{\tau_1\tau_2}\right)^2-\frac{4}{\tau_1\tau_2}\left(1-\frac{k_t}{k_r+k_t}\right)}\right]$$

$$r_2=\frac{1}{2}\left[-\left(\frac{\tau_1+\tau_2}{\tau_1\tau_2}\right)-\sqrt{\left(\frac{\tau_1+\tau_2}{\tau_1\tau_2}\right)^2-\frac{4}{\tau_1\tau_2}\left(1-\frac{k_t}{k_r+k_t}\right)}\right]$$

$$A_1=\frac{1}{r_1r_2},\quad B_1=\frac{\tau_2r_1+1}{r_1(r_1-r_2)},\quad C_1=\frac{\tau_2r_2+1}{r_2(r_2-r_1)}$$

$$A_2=A_1=\frac{1}{r_1r_2},\quad B_2=\frac{1}{r_1(r_1-r_2)},\quad C_2=\frac{1}{r_2(r_2-r_1)}$$

From the inverse Laplace transformation we have

$$U_1(t)=u_1(t)=K(A_1+B_1e^{r_1t}+C_1e^{r_2t})$$
$$-K\left(\frac{m}{m-b}\right)\{A_1+B_1e^{r_1(t-T)}+C_1e^{r_2(t-T)}\}u_s(t-T) \qquad (7)$$

or

$$u_1(t)=K(A_1+B_1e^{r_1t}+C_1e^{r_2t}) \qquad :0\le t<T$$

$$u_1(t)=-\left(\frac{KA_1b}{m-b}\right)+KB_1e^{r_1t}\left\{1-\left(\frac{m}{m-b}\right)e^{-r_1T}\right\}$$
$$+KC_1e^{r_2t}\left\{1-\left(\frac{m}{m-b}\right)e^{-r_2T}\right\} \qquad :T\le t$$

Where

$$K=\frac{m-b}{\tau_1\tau_2(k_r+k_t)}=\frac{k_t(m-b)}{V_1V_2}$$

Similarly, from the inverse Laplace transformation of $U_2(s)$ gives

$$U_2(t)=u_2(t)=K(A_2+B_2e^{r_1t}+C_2e^{r_2t})$$
$$-K\left(\frac{m}{m-b}\right)\{A_2+B_2e^{r_1(t-T)}+C_2e^{r_2(t-T)}\}u_s(t-T) \qquad (8)$$

or

$$u_2(t)=K(A_2+B_2e^{r_1t}+C_2e^{r_2t}) \qquad :0\le t<T$$

$$u_2(t)=-\left(\frac{KA_2b}{m-b}\right)+KB_2e^{r_1t}\left\{1-\left(\frac{m}{m-b}\right)e^{-r_1T}\right\}$$
$$+KC_2e^{r_2t}\left\{1-\left(\frac{m}{m-b}\right)e^{-r_2T}\right\} \qquad :T\le t$$

Case II: k_b=b=constant and k_i=step with magnitude of h. This type of infusion can be depicted as Fig. 2(b). Substitution of $k_i(s)$ and $k_b(s)$ into Eq. (6) gives after some rearrangement

$$U_1(s)=\frac{h-b}{\tau_1\tau_2(k_r+k_t)}\cdot\frac{(\tau_2s+1)}{s\left\{s^2+\left(\frac{\tau_1+\tau_2}{\tau_1\tau_2}\right)s+\frac{1}{\tau_1\tau_2}\left(1-\frac{k_t}{k_r+k_t}\right)\right\}}$$

$$=\frac{h-b}{\tau_1\tau_2(k_r+k_t)}\left(\frac{A_1}{s}+\frac{B_1}{s-r_1}+\frac{C_1}{s-r_2}\right)$$

$$U_2(s)=\frac{1}{\tau_2s+1}U_1(s)=\frac{h-b}{\tau_1\tau_2(k_r+k_t)}\left(\frac{A_2}{s}+\frac{B_2}{s-r_1}+\frac{C_2}{s-r_2}\right)$$

From the inverse Laplace transformation we have

$$U_1(t)=u_1(t)=K_1(A_1+B_1e^{r_1t}+C_1e^{r_2t}) \qquad (9)$$

$$U_2(t)=u_2(t)=K_1(A_2+B_2e^{r_1t}+C_2e^{r_2t}) \qquad (10)$$

where

$$K_1=\frac{h-b}{\tau_1\tau_2(k_r+k_t)}=\frac{k_t(h-b)}{V_1V_2}$$

Case III: k_b=b=constant and k_i=impulse with magnitude of g. This type of infusion can be depicted as Fig. 2(c). Substitution of $k_i(s)$ and $k_b(s)$ into Eq. (6) gives after some rearrangement

$$U_1(s)=\frac{1}{\tau_1\tau_2(k_r+k_t)}\cdot\frac{(\tau_2s+1)(gs-b)}{s\left\{s^2+\left(\frac{\tau_1+\tau_2}{\tau_1\tau_2}\right)s+\frac{1}{\tau_1\tau_2}\left(1-\frac{k_t}{k_r+k_t}\right)\right\}}$$

$$=\frac{1}{\tau_1\tau_2(k_r+k_t)}\left(\frac{A_3}{s}+\frac{B_3}{s-r_1}+\frac{C_3}{s-r_2}\right)$$

$$U_2(s)=\frac{1}{\tau_2s+1}U_1(s)=\frac{1}{\tau_1\tau_2(k_r+k_t)}\left(\frac{A_4}{s}+\frac{B_4}{s-r_1}+\frac{C_4}{s-r_2}\right)$$

where

$$A_3=\frac{b}{r_1r_2},\quad B_3=\frac{(\tau_2r_1+1)(gr_1-b)}{r_1(r_1-r_2)},\quad C_3=\frac{(\tau_2r_2+1)(gr_2-b)}{r_2(r_2-r_1)}$$

$$A_4=-\frac{b}{r_1r_2},\quad B_4=\frac{(gr_1-b)}{r_1(r_1-r_2)},\quad C_4=\frac{(gr_2-b)}{r_2(r_2-r_1)}$$

From the inverse Laplace transformation of $U_1(s)$ and $U_2(s)$ we have

$$U_1(t)=u_1(t)=K_2(A_3+B_3e^{r_1t}+C_3e^{r_2t}) \qquad (11)$$

$$U_2(t)=u_2(t)=K_2(A_4+B_4e^{r_1t}+C_4e^{r_2t}) \qquad (12)$$

where

$$K_2=\frac{1}{\tau_1\tau_2(k_r+k_t)}$$

NOMENCLATURE

A-, B_i, C_i : parameters [-]
b : magnitude of base diuresis [ml/min]
g : magnitude of impulse infusion [ml/min]
h : magnitude of block infusion [ml/min]
K, K_1 : gain [-]
k_b : base diuresis rate [ml/min]
k_r : proportional constant for single fluid model [ml/min]
k_t : proportional constant for two fluid model [ml/min]
m : magnitude of block infusion [ml/min]
r_1, r_2 : constants [-]
t : time [min]
T, T_1, T_2 : infusion duration time [min]
u, u_1, u_2 : relative deviation from the target volume [-]
U, U_1, U_2 : relative deviation from the target volume [-]
u_s : unit step function [-]

v : volume [ml]
V, V_1, V_2 : target volume [ml]

Greek Letters

τ, τ_1, τ_2 : time constant [-]

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