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

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Abstract−In this work the kinetics of volume changes of fluid spaces associated with infusion of Ringer's solution are analyzed by using the single-fluid space model. During infusion of Ringer's solution, the human body is assumed to be characterized by the single-fluid space model into which fluid is fed and from which fluid leaves. 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 single-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, Single-fluid Space, Parameter Estimation, Blood Hemoglobin, Maximum Dilution

INTRODUCTION

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 a 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, 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 an elementary mathematical model 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 has been 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 clear description on 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.

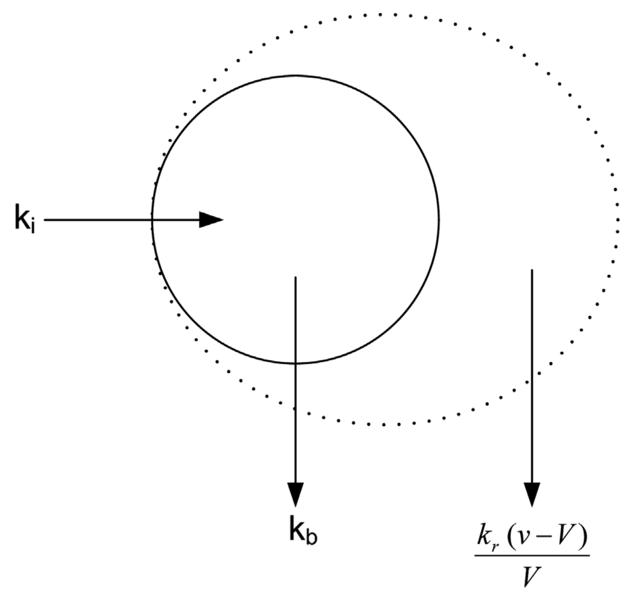

Fig. 1. Schematic diagram of the single-fluid space model.

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SINGLE-FLUID SPACE MODEL

The single-fluid space model can be considered as a balloon filled with water as shown in Fig. 1. During infusion, Ringer's solution enters an expandable fluid space of volume v at a rate k_i and is distributed in an expandable space. The functional form of k_i is dependent upon the type of infusion. Typically k_i can be block pulse, step, or impulse. The expandable fluid space has a target volume, V, which the human body strives to maintain. The time-dependent volume v changes due to the effluence of fluid from the fluid space by perspiration, basal diuresis and controlled efflux. The combined rate of fluid elimination due to perspiration and diuresis is represented as k_b. It is assumed that controlled efflux is proportional to the relative deviation of v from the target volume V with the proportional constant k_r.

The behavior of the expandable volume can be represented by the following simple differential equation.

$$\frac{dv}{dt} = k_i - k_b - \frac{k_r(v-V)}{V}, \quad v(0)=V \tag{1}$$

We assume that V and k_r are constant. We now introduce the dilution at time t as u=(v(t)−V)/V. Then we have u(0)=0, dv=Vdu. Eq. (1) can be rewritten as

$$\left(\frac{V}{k_r}\right)\frac{du}{dt} = \frac{k_i}{k_r} - \frac{k_b}{k_r} - u \tag{2}$$

From the basal fluid loss the parameter k_b can be estimated without much difficulty and the parameter k_i can be controlled experimentally. Therefore, these two parameters can be assumed to be known in the computation of model equations. Especially, the parameter k_i denotes the type of fluid infusion and we now consider three typical types as shown in Fig. 2: block pulse, step and impulse. Solutions of Eq. (2) for each infusion type are given in the 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

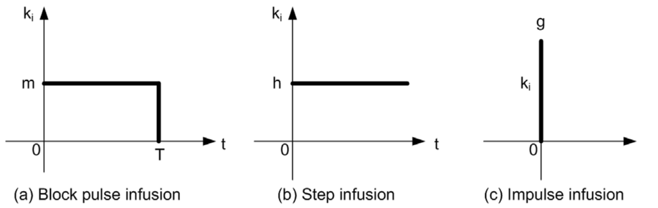

Fig. 2. Three types of infusion.

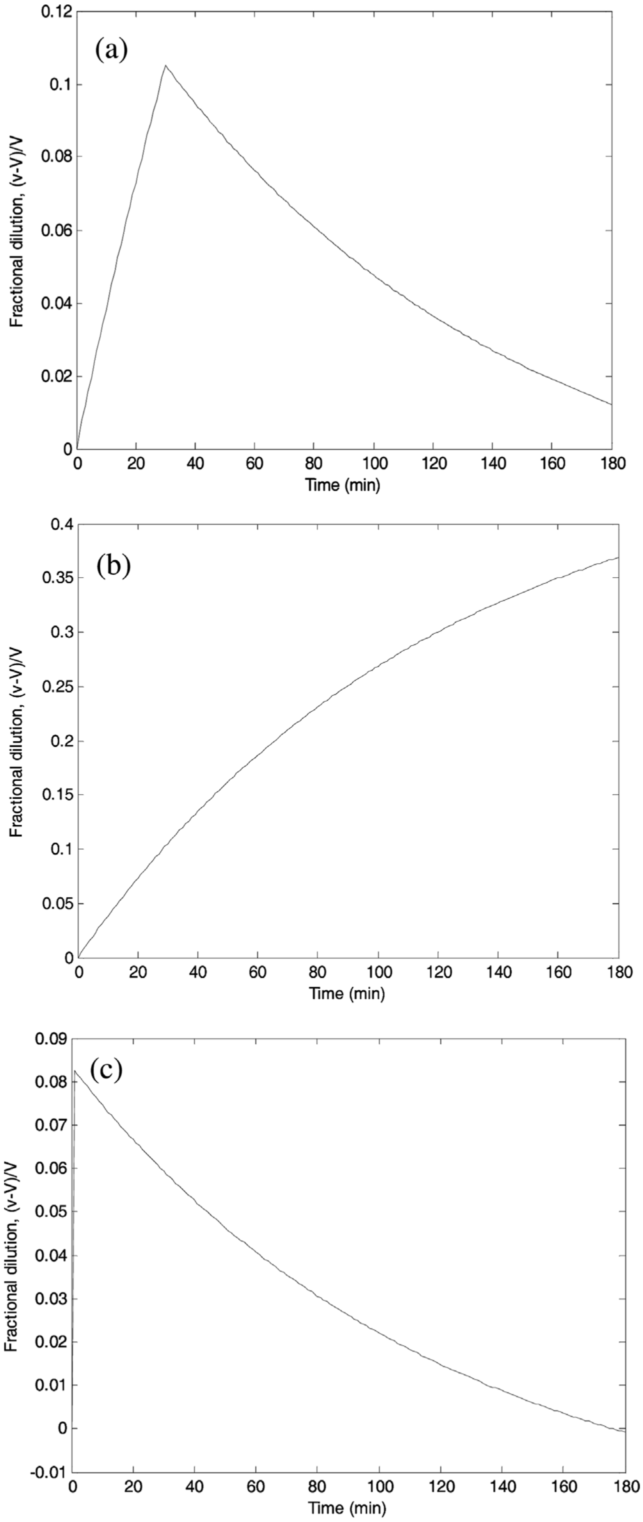

Fig. 3. Results of simulations for various infusion types.
(a) block pulse infusion, (b) step infusion, (c) impulse infusion

Table 1. Model parameters and volumes used in 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	1,000	100	200	4	8

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 four volunteers. 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. Ringer's 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 the 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 was drawn, 3 ml of Ringer's solution was injected to flush the cannula and one 2-ml sample to be discarded was drawn before each blood sampling to avoid undue hemodilution caused by this fluid. Before infusion of the fluid, one sample was drawn in duplicate and the mean value was used in the calculations. Table 2 shows experimental data represented as fractional dilutions obtained from infusion experiments.

Table 2. Changes of relative deviation in the block pulse infusion experiments (T=30 min, k_b=1.94 ml/min)

Time (min)	ID (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.

Dilution occurring during intravenous infusion of Ringer's solution can be assumed to indicate an increase in the volume of one or more expandable body fluid spaces. The volume of distribution is considered to be a constant. Similarly, the target volume of the single-volume model proposed in the present study is assumed to be constant, but the size of the fluid space expanded is changed. The size of a target volume can be found only by expanding the fluid space because it is the expandability that distinguishes this fluid space from other parts of the body water.

ESTIMATION OF MODEL PARAMETERS

The model parameters k_r, k_t and target volume V for the single-fluid space model can be estimated from the experimental data shown in Table 2. Dilution occurring during intravenous infusion of Ringer's solution can be assumed to exhibit an increase in the volume of the expandable fluid space. We define function f as follows:

$$f=u(t)-\frac{m-b}{k_r}(1-e^{-k_r t/V}) \qquad : 0\le t<T \qquad (3)$$

$$f=u(t)+\frac{b}{k_r}-\left[\frac{m}{k_r}e^{k_r T/V}-\frac{(m-b)}{k_r}\right]e^{-k_r t/V} \qquad : T\le t \qquad (4)$$

k_r and V can be estimated from the minimization of f based on experimental data given in Table 2. The least squares method can be used effectively and we can utilize many useful optimization functions implemented in MATLAB toolboxes (version 7.0, MathWorks Inc., USA). Table 3 shows results of estimation for single-fluid space model.

In order to validate the single-fluid space model, the estimated parameters were plug into the model and results of computations were compared with experimental data. Fig. 4 shows results of comparison between experimental values of fractional dilutions and computational results of models based on the estimated parameters for three volunteers. Certain volunteers show a little discrepancy between experimental results and simulation results, but we can say that the single-fluid model shows satisfactory tracking of overall trend of volume change for each volunteer. Characteristics of volunteers may be more distinguishable if we compare average values for volunteers. Fig. 5 shows results of comparison between average experimental fractional dilutions and computational results of models based on the estimated parameters using average experimental values.

STEADY-STATE DILUTION

For the block pulse infusion, in which duration time is T and k_b=

Table 3. Estimated values of the proportional parameter and volume for each volunteer

Volunteers (ID)	k_r (ml/min)	V (ml)
pch	74.9	6,315
lyj	114	11,821
pcw	213.5	8,666.5
ljy	125	10,481
Average	119.9	8,969

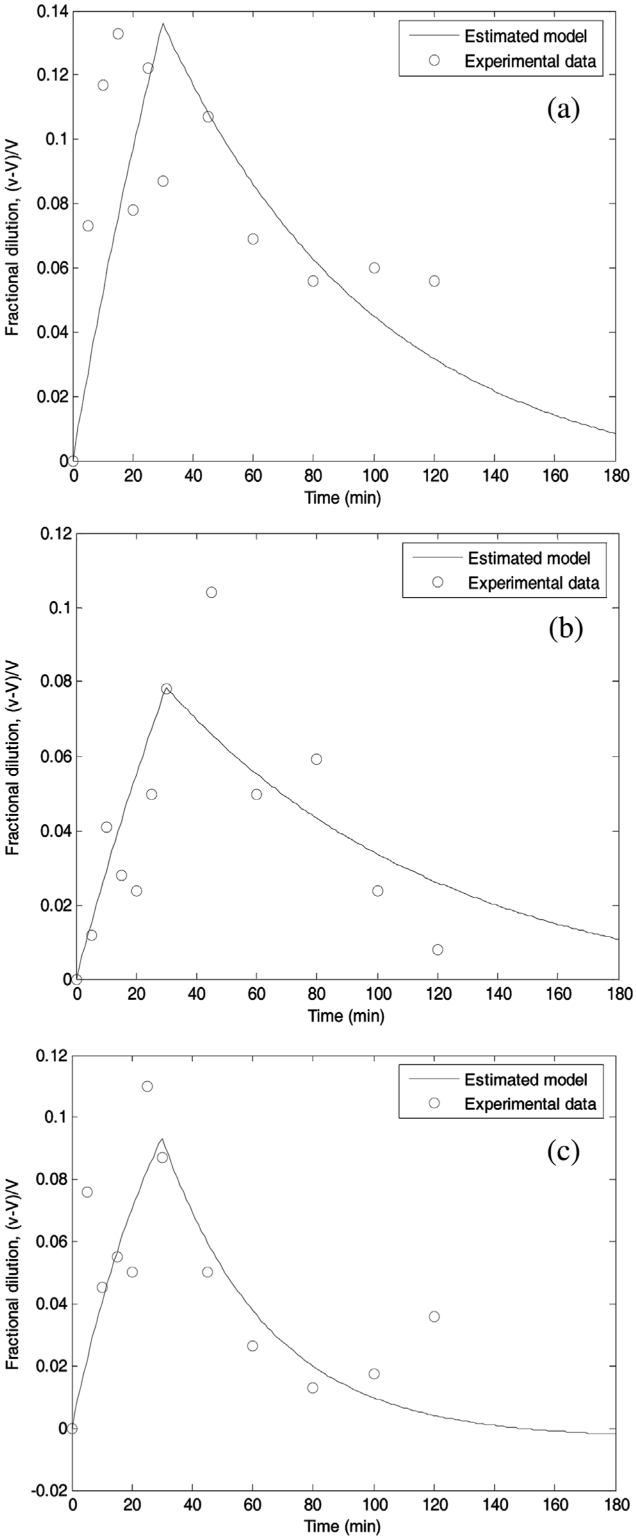

Fig. 4. Comparison between experimental values of fractional dilutions (Volunteers: (a) pch, (b) lyj, (c) pcw).

b=constant, the dilution is represented by Eq. (2). Fig. 6 shows a typical response for the block pulse infusion. For the case shown in Fig. 6, we can see that the maximum dilution is approximately 0.157 (i.e., 15.7%). In order to maintain the maximum dilution (i.e., steady-state with maximum dilution), a certain amount of fluid should be

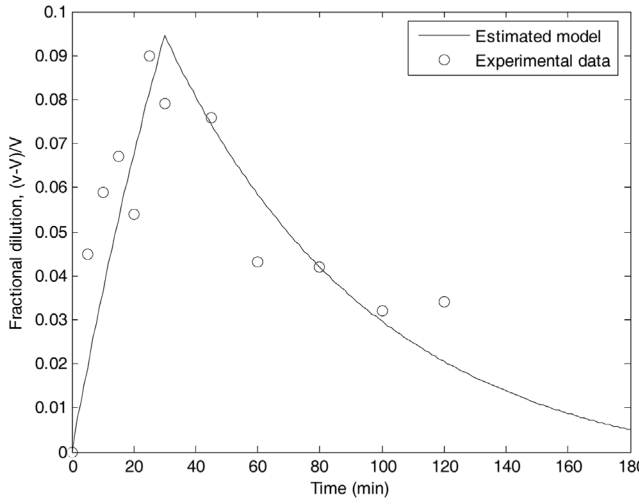

Fig. 5. Comparison between experimental values of fractional dilutions based on average values.

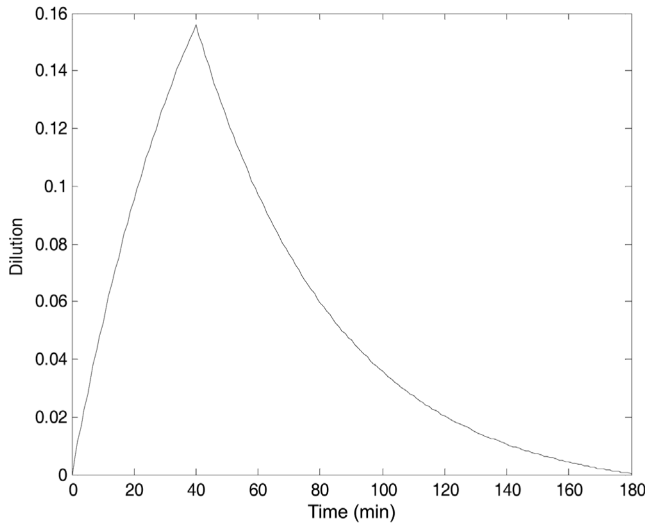

Fig. 6. Fractional dilution for a block infusion (V=6,610, k_r=148, b=k_b=1, m=k_i=40).

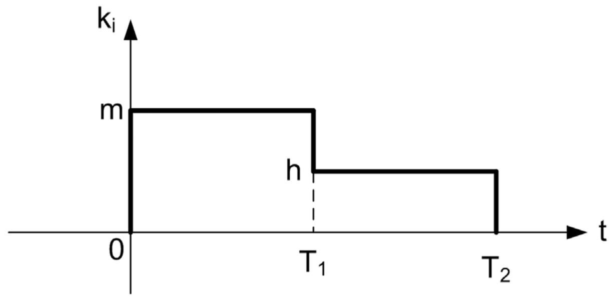

Fig. 7. Two-block infusion type.

administrated. Let the required infusion rate be h(ml/min) and suppose that h is maintained for T_2(min). Fig. 7 shows the infusion of two-block type with duration time of T_1(min) and T_2(min). The two-block infusion shown in Fig. 9 is represented by

$$k_i(t)=mu(t)-(m-h)u(t-T_1)-hu(t-T_2) \tag{5}$$

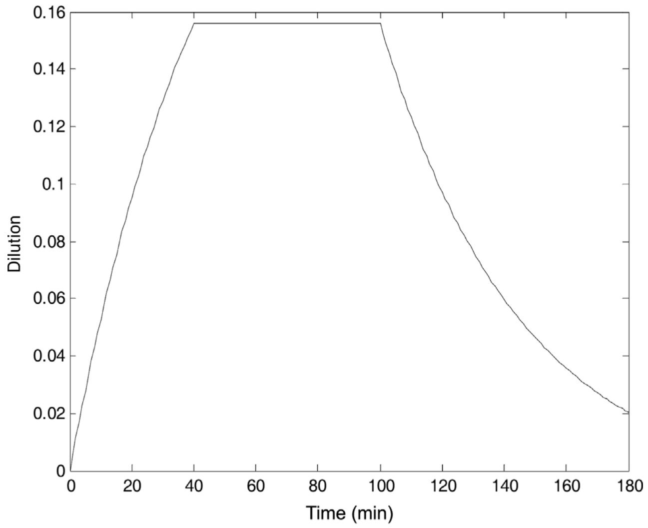

Fig. 8. Dilution change for two-block infusion.

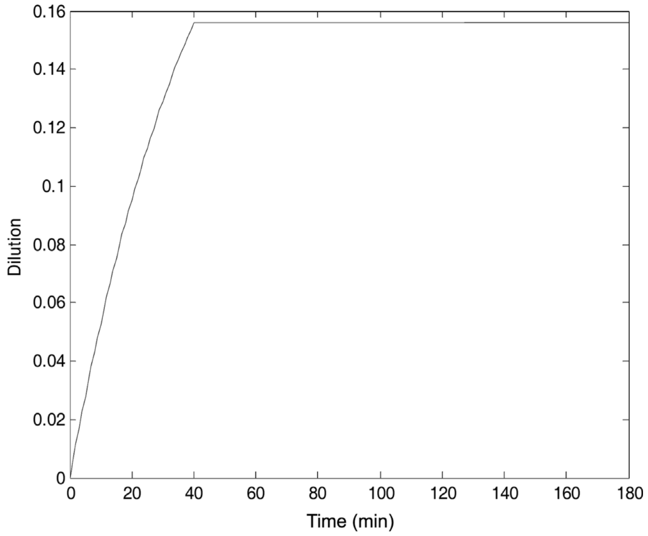

Fig. 9. Maximum steady-state dilution.

The computational procedure to find U(t) is shown in the Appendix. For V=6,610, k_r=148, b=k_b=1, and m=k_i=40, we can obtain h=24.0741. If we maintain this infusion rate for 60 minutes after the first infusion, we get the dilution shown in Fig. 8. Increasing T_2 up to the maximum permissible infusion time, we can get the dilution shown in Fig. 9.

The maximum dilution is achieved at t=T_1=T and is given by

$$U(T)=\frac{m-b}{k_r}(1-e^{-T/\tau}) \tag{6}$$

If the desired dilution is given by U_s, we have

$$m=k_i=b+\frac{U_s k_r}{1-e^{-T/\tau}}=b+\frac{U_s k_r}{1-e^{-k_r T/V}} \tag{7}$$

For various values of U_s (for example, U_s=2%, 5%, 10%, 15%, 20%, 25%), the relation between the infusion rate k_i and the infusion time T can be represented as in Fig. 10 for the case of V=6,610, k_r=148 and b=k_b=1. For a given maximum dilution U_s, the relation between

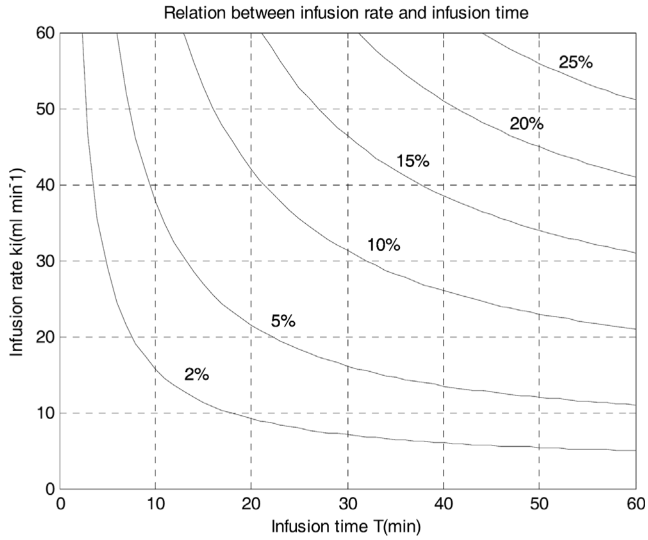

Fig. 10. Relation between the infusion rate and the infusion time.

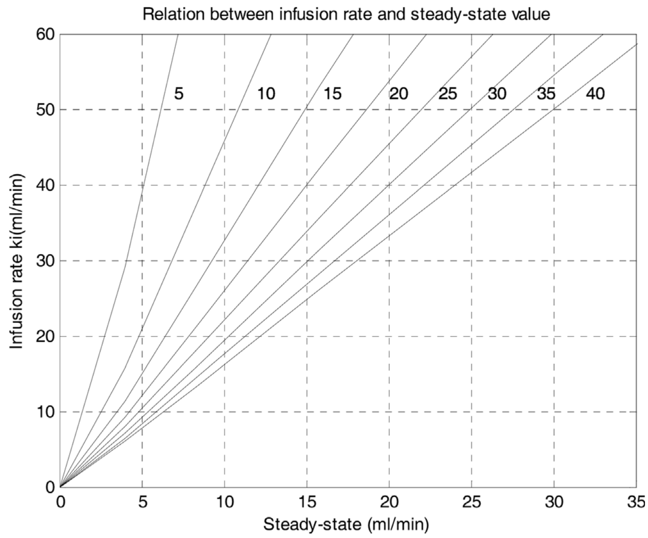

Fig. 11. Relation between the infusion rate and steady-state infusion rate for given dilutions.

the corresponding infusion rate k_i and steady-state infusion rate h can be represented as in Fig. 11 for the case of V=6,610, k_r=148 and b=k_b=1.

CONCLUSIONS

Characteristics of volume expansion effect during infusion of Ringer's solution were analyzed by using the single-fluid space model. During infusion of Ringer's solution, the human body is assumed to be characterized by the single-fluid space model into which fluid is fed and from which fluid leaves. 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 single-fluid space model was found to represent adequately the kinetics of human volume expansion during infusion of Ringer's solution. The steady-state analysis can serve as a simple guide for optimal infusion of Ringer's solution.

APPENDIX

1. Solution of Single Fluid Space Model

From the Laplace transformation of Eq. (2) we have

$$U(s)=\frac{1}{k_r}\frac{1}{\tau s+1}\{k_i(s)-k_b(s)\} \tag{8}$$

where

$$\tau=\frac{V}{k_r}$$

At steady-state,

$$u_s=\frac{k_{is}-k_{bs}}{k_r}=0$$

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). In this case $k_i(s)$ and $k_b(s)$ are given by

$$k_i(s)=\frac{m(1-e^{-Ts})}{s},\quad k_b(s)=\frac{b}{s}$$

Substitution of the above relation into Eq. (15) gives

$$U(s)=\frac{m-b}{k_r}\left(\frac{1}{s}-\frac{1}{s+1/\tau}\right)-\frac{m}{k_r}\left(\frac{1}{s}-\frac{1}{s+1/\tau}\right)e^{-Ts}$$

From the inverse Laplace transformation of the above relation and incorporation of steady-state relation $u_s=(k_{is}-k_{bs})/k_r=0$, we have

$$U(t)=u(t)=\frac{m-b}{k_r}(1-e^{-t/\tau})-\frac{m}{k_r}(1-e^{-(t-T)/\tau})u_s(t-T) \tag{9}$$

or

$$U(t)=u(t)=\frac{m-b}{k_r}(1-e^{-t/\tau}) \qquad : 0\le t<T$$

$$U(t)=u(t)=-\frac{b}{k_r}+\left[\frac{m}{k_r}e^{T/\tau}-\frac{(m-b)}{k_r}\right]e^{-t/\tau} \qquad : T\le t$$

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). In this case $k_i(s)$ and $k_b(s)$ are given by

$$k_i(s)=\frac{h}{s},\quad k_b(s)=\frac{b}{s}$$

Substitution of the above relation into Eq. (8) gives

$$U(s)=\frac{1}{k_r}\frac{h-b}{s(\tau s+1)}=\frac{h-b}{k_r}\left(\frac{1}{s}-\frac{1}{s+1/\tau}\right)$$

From the inverse Laplace transformation, we have

$$U(t)=u(t)=\frac{h-b}{k_r}(1-e^{-t/\tau}) \tag{10}$$

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). In this case $k_i(s)$ and $k_b(s)$ are given by

$$k_i(s)=g,\quad k_b(s)=\frac{b}{s}$$

Substitution of the above relation into Eq. (8) gives

$$U(s)=\frac{1}{k_r}\frac{1}{\tau s+1}\left(g-\frac{b}{s}\right)=\left(\frac{g}{k_r\tau}+\frac{b}{k_r}\right)\frac{1}{s+1/\tau}-\frac{b}{k_r}\frac{1}{s}$$

Again, from the inverse Laplace transformation, we have

$$U(t)=u(t)=\left(\frac{g}{k_r\tau}+\frac{b}{k_r}\right)e^{-t/\tau}-\frac{b}{k_r} \tag{11}$$

2. Two Block Infusion

From Laplace transformation and k_b gives

$$k_i(s)=\frac{m}{s}-\frac{m-h}{s}e^{-T_1s}-\frac{h}{s}e^{-T_2s},\quad k_b(s)=\frac{b}{s}$$

Substitution of the above relation into Eq. (8) gives

$$U(s)=\frac{1}{k_r}\frac{1}{s(\tau s+1)}\{m-(m-h)e^{-T_1s}-he^{-T_2s}-b\}$$

From the inverse Laplace transform we have

$$U(t)=\frac{m-b}{k_r}(1-e^{-t/\tau})-\frac{m-h}{k_r}(1-e^{-(t-T_1)/\tau})u_s(t-T_1)$$
$$-\frac{h}{k_r}(1-e^{-(t-T_2)/\tau})u_s(t-T_2) \tag{12}$$

or

$$U(t)=\frac{m-b}{k_r}(1-e^{-t/\tau}) \qquad : 0\le t<T_1$$

$$U(t)=\frac{h-b}{k_r}-\frac{1}{k_r}\{(m-b)-(m-h)e^{T_1/\tau}\}e^{-t/\tau} \qquad : T_1\le t<T_2$$

$$U(t)=-\frac{b}{k_r}-\frac{1}{k_r}\{(m-b)-(m-h)e^{T_1/\tau}-he^{T_2/\tau}\}e^{-t/\tau} \qquad : T_2\le t$$

In order for the steady-state to be maintained at the maximum dilution, the following relation should be satisfied for $T_1\le t$.

$$\frac{dU}{dt}=0=-\frac{1}{k_r\tau}\{m-b-(m-h)e^{T_1/\tau}\}e^{-t/\tau}$$

Rearrangement of the above relation gives

$$h=m+(b-m)e^{-T_1/\tau}=m+(b-m)e^{-k_rT_1/V} \tag{13}$$

NOMENCLATURE

A_i, 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 Letter

τ, τ_1, τ_2 : time constant [-]

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