Dynamics of Plasma–Interstitial Fluid Distribution following Intravenous Infusions in Dogs

AN EXPERIMENTAL AND COMPUTER SIMULATION STUDY

By Joel I. Leonard and Peter H. Abbrecht

ABSTRACT

The dynamic distribution of intravenously infused solutions between the plasma and the interstitial compartments was studied. A mathematical model developed to simulate infusion experiments considered transcapillary fluid and protein exchange, lymph flow, interstitial compliance, capillary surface area, and peripheral vascular resistance. The experimental arterial and venous blood pressure responses and the infusion rate were used as forcing functions. A piecewise optimization procedure resulted in excellent agreement between the simulated and experimental plasma volume responses and provided reasonable time-varying behavior for the precapillary-postcapillary resistance ratio and the capillary surface area. The model was tested with experimental data collected by infusing isotonic Tyrode's or dextran solution into nephrectomized dogs. Blood volume was measured continuously by giving a single injection of $^{51}$Cr-labeled red cells and monitoring the blood radioactivity as it passed through an extracorporeal shunt. The model predicted qualitatively different responses for the precapillary-postcapillary resistance ratio depending on the type of solution infused and the value assumed for tissue compliance. Further analysis indicated that the assumption of a tissue space with overall high compliance (approximately 100 ml/kg mm Hg$^{-1}$) is more realistic than are the much lower compliances previously reported. Parametric studies revealed that the capillary surface area, the precapillary-postcapillary resistance ratio, and the tissue compliance, but not the lymph flow or the transcapillary protein movement, exert a strong influence on the short-term plasma retention of infused fluids.

KEY WORDS mathematical model transcapillary exchange
precapillary-postcapillary resistance ratio optimization blood volume
tissue compliance

It is becoming increasingly apparent that transcapillary fluid exchange plays an important role in both the short-term control of plasma volume (1) and the control of the entire extracellular fluid space (2). In situations such as hemorrhage, exercise, standing, fluid replacement therapy, or hemodialysis therapy, in which there are rapid adjustments in circulatory volume, the Starling fluid shift mechanism is the major short-term source of plasma volume control. Although considerable research has been done on plasma–interstitial fluid exchange following hemorrhage, there is relatively little information available on the reverse problem concerning fluid transport into the tissues during moderate infusions. This lack of information is especially true with regard to the short-term infusion response when many physiological variables may be changing rapidly. Also, there have been no previous attempts to determine quantitatively whether the Starling hypothesis of capillary exchange can adequately account for the whole body dynamics of plasma-Interstitial fluid exchange following infusion.

The theoretical factors governing transcapillary fluid exchange have been confirmed experimentally in careful investigations of small portions of the vascular bed (3-6). However, there has been correspondingly little attention paid to whole animal studies. Recently, several theoretical papers (7-9) have laid the groundwork for such an understanding of plasma–interstitial fluid exchange across the microcirculation as a whole. These authors (7-9) have suggested that the Starling fluid shift mechanism is only one of several important
factors in the regulation of extracellular fluid distribution. Using analog computer solutions of their mathematical models, they have shown that tissue compliance, lymph flow, protein exchange, and peripheral vascular resistance are also significantly involved in this process. However, these investigators did not examine their systems for short-term, non-steady-state phenomena, nor did they consider the problem of plasma expansion by infusion of fluids.

The objective of the present study was to use these models, with some modification, as a basis for simulating the short-term disappearance of infused fluids from the circulation. Infusion experiments performed on nephrectomized dogs were used to validate the model. By employing a suitable optimization procedure, the model was used to estimate the changes in the precapillary-postcapillary resistance ratio and the capillary surface area that occur during the infusion response. The effect of tissue compliance—a parameter whose value is presently under dispute (2)—was also examined. A unique feature of our simulation study was the use of experimentally determined blood pressures and infusion rates as time-varying forcing functions. To our knowledge there have been no previous efforts to quantitatively relate the retention of plasma expanders to the simultaneous increases in circulatory pressures.

Methods

PREPARATION

A total of 12 mongrel dogs, averaging 19.7 kg, were splenectomized and bilaterally nephrectomized under sodium pentobarbital anesthesia 1 day prior to the infusion experiments. In 6 dogs, the thoracic lymph duct was cannulated and a lymphovenous shunt was placed as described by Doemling and Steggerda (10). In 3 other dogs, catheters for cardiac output measurement were implanted in the jugular vein and the carotid artery. Care was taken to minimize blood loss by squeezing blood from the spleen before its removal. To make up for surgical losses and evaporation (1 ml/kg hour$^{-1}$ [11]) during the postsurgical period, lactated Ringer's solution (500 ml, iv) was administered during surgery. The dogs were not given any food after surgery. Drinking water was available during the recovery period, but the dogs consumed only negligible amounts.

Following the 18-hour recovery period, the dogs were anesthetized with Innovar-Vet (fentanyl-droperidol, McNeill Laboratories), an initial dose of 0.12 ml/kg was given, and the drug was administered later as needed at an average rate of 0.03 ml/kg hour$^{-1}$. Using local anesthesia, PE240 catheters were placed in the right femoral artery and vein for recording blood pressure, in the left femoral artery and vein for establishing an arteriovenous extracorporeal shunt, and in the right cephalic vein for giving infusions. With the dog placed on its side on a heating pad, the free end of the thoracic duct catheter was positioned level with the midpoint of the neck. Lymph was collected, measured, and infused into a vein. One-half hour after the catheters had been inserted, heparin was administered; 150 units/kg was given initially, and later the drug was administered as needed at an approximate rate of 35 units/kg hour$^{-1}$.

PROTOCOL

Prior to infusion, a period of at least 1 hour was allowed to ensure the equilibration of red cell tracer and to obtain control values for all measured variables: blood volume, mean arterial blood pressure, mean venous blood pressure, hematocrit, plasma protein concentrations, and, in some cases, lymph flow and cardiac output. All variables were measured for 2-3.5 hours following each infusion.

The dogs were divided into two groups according to the type of solution infused: group 1 included six dogs infused with Tyrode's solution and group 2 included six dogs infused with dextran dissolved in Tyrode's solution.

Two consecutive intravenous infusions were administered to each dog, the first at a rate of 15 ml/min and the second (2-3.5 hours later) at a rate of 100 ml/min. The total volume of each infusion was equal to 2.5% of the dog's weight. This volume would expand the blood volume approximately 35% if it were completely retained in the vascular compartment. All solutions were isotonic (300 mosmoles/liter). The concentration of the dextran ranged from 2.5% to 3.5% depending on its molecular weight. The exact amount of dextran added to the infusate was determined by adjusting its colloidal osmotic pressure (20 mm Hg) to be isotonic with dog's plasma. The colloidal osmotic pressure was determined with an osmometer similar to that described by Prather et al. (12).

Two different molecular size fractions of dextran were used; the molecular weight was 60,000-90,000 in three dogs and 200,000-300,000 in three others. A t-test revealed no significant difference in the blood volume response to these two fractions, and the results from these six dogs were pooled in group 2.

These solutions were chosen to minimize any net fluid exchange with the intracellular compartment following infusion and to enable the mathematical model to be tested over a wide range, since dextran and Tyrode's solutions leave the circulation at different rates.

SYMBOLS AND UNITS

A = Effective capillary surface area of body (cm$^2$).

$C_p$ = Plasma protein concentration (g/ml).

$C_i$ = Interstitial fluid protein concentration (g/ml).

$CO$ = Cardiac output (liter/min).

$COP$ = Colloid osmotic pressure (mm Hg).

$I_{tra}$ = Transcapillary protein diffusion rate (g/hour).

$I_{lymph}$ = Rate of protein removal via lymphatics (g/hour).

Circulation Research, Vol. XXXIII, December 1973
PLASMA—INTERSTITIAL FLUID DISTRIBUTION

\[ K_p = \text{Capillary protein transfer coefficient (ml/hr cm}^{-2}) \]
\[ K_w = \text{Capillary water transfer coefficient (ml/hr cm}^{-2} \text{ mm Hg}^{-1}) \]
\[ P_a = \text{Mean arterial blood pressure (mm Hg)} \]
\[ P_c = \text{Mean capillary hydrostatic pressure (mm Hg)} \]
\[ P_t = \text{Interstitial fluid hydrostatic pressure (mm Hg)} \]
\[ P_v = \text{Central venous blood pressure (mm Hg)} \]
\[ Q_{net} = \text{Net capillary ultrafiltration rate (ml/hr)} \]
\[ Q_{lymph} = \text{Rate of lymph flow (ml/hr)} \]
\[ R_p = \text{Precapillary-postcapillary resistance ratio (dimensionless)} \]
\[ R_a = \text{Precapillary resistance (mm Hg min/liter)} \]
\[ R_w = \text{Postcapillary resistance (mm Hg min/liter)} \]
\[ t = \text{Time (hours)} \]
\[ TPR = \text{Total peripheral resistance (mm Hg min/liter)} \]
\[ V_p = \text{Plasma volume (ml)} \]
\[ V_t = \text{Interstitial fluid volume (ml)} \]
\[ \gamma = \text{Compliance of interstitial fluid compartment (ml/kg mm Hg}^{-1}) \]
\[ \pi_p = \text{Colloid osmotic pressure of plasma (mm Hg)} \]
\[ \pi_t = \text{Colloid osmotic pressure of interstitial fluid (mm Hg)} \]

MEASUREMENTS AND ANALYSIS

Mean arterial and venous blood pressures were recorded continuously with strain-gauge transducers. Blood in the femoral arteriovenous shunt passed through a polyethylene coil inserted in a deep-well gamma counter (13). The shunt also contained fittings for blood sample removal, tracer injection, heparin administration, and lymph return and a drop chamber for measuring blood flow rate through the shunt. Blood flow through the shunt was maintained by arterial blood pressure at an average rate of 10 ml/min.

Cardiac output measurements were performed in three of the dogs in group 1. The carotid arterial catheter was connected to a densitometer, and a dye injection system was connected to the jugular catheter. Calculations were based on the dye-dilution technique using indocyanine indicator (14). Total peripheral resistance was calculated from the relationship:

\[ TPR = \frac{P_a - P_v}{CO} \]  (1)

Cardiac output, microhematocrit, and lymph and plasma protein concentrations were measured at 20-minute intervals. Protein concentrations were measured by both the biuret method with albumin standards (12, 15) and by the refractometric method (16).

Blood volume was monitored throughout the experiment by injecting approximately 100 \( \mu \)e of \(^{51}\text{Cr}\)-labeled erythrocytes (12, 17, 18) resuspended in Tyrode's solution to a hematocrit of 40 and continuously recording the blood radioactivity as it passed through the extracorporeal coil gamma-detector system. The amount of free \(^{51}\text{Cr}\) remaining in the supernatant fluid of this preparation was less than 0.5% of the total activity. A sample of the labeled blood mixture diluted 1:500 was pumped through the coil for calibration.

Blood radioactivity in the coil was recorded at 1-minute intervals by a scaler-analyzer equipped with a rapid digital printout. The effect of coil residence time (less than 1.5 minutes) was negligible except possibly early in the rapid infusion. All radioactivity counts were corrected for background radiation. The blood volume at any given time was calculated by dividing the amount of injected radioactivity by the blood activity and correcting for the effect of the whole body hematocrit-venous hematocrit ratio (\( F_{ctw} \) ratio).

Plasma volume measured during the control period with a dilution of Evan's blue dye was used to calculate the \( F_{ctw} \) ratio. This ratio was assumed to be constant for the rest of the experiment (19). It has been shown previously (18) and in the present experiment (Fig. 1) that a single dose of labeled red cells can remain in the vascular compartment following infusion.

Results

Figure 1 shows the effects of infusing 565 ml of dextran solution into a dog (22.5 kg): initially, the infusion rate was 15 ml/min and later it was 100 ml/min. Changes in the measured variables were consistently greater following the rapid infusion. The 24 separate infusions in 12 dogs were divided into four equal groups: slow infusions of Tyrode's solution, rapid infusions of Tyrode's solution, slow infusions of dextran solution, and rapid infusions of dextran solution. Figure 2 shows the average changes in plasma volume and blood pressures for these groups. The plasma volume response is presented in terms of the fraction of the infused volume retained in the circulation after the end of the infusion. Blood volume and pressure data were averaged at 1-minute intervals for the period immediately following each infusion and at 5-minute intervals thereafter.

In all experiments in which cardiac output and peripheral resistance were measured (Tyrode's infusions only), there was an initial increase in cardiac output and a decrease in peripheral resistance (Fig. 3). In five of the six infusion experiments, the total peripheral resistance increased, sometimes dramatically, after the initial fall. Our observations agree with those of other investigators (20) who have observed that the transient rise in cardiac output is damped considerably if the infusions are given slowly.

Neither lymph flow nor protein concentration changed appreciably when dextran solution was administered (ten experiments) regardless of the infusion rate. Lymph was collected only during three of the infusions of Tyrode's solution. In one slow infusion of Tyrode's solution there was little change in either lymph flow or protein concentration. However, during two rapid infusions of...
Results of a typical experiment showing the responses of a 22-kg dog to two consecutive infusions (565 ml each) of dextran solution (molecular weight 70,000-90,000). Measured variables are blood volume (BV), mean arterial pressure (MAP), mean venous pressure (MVP), hematocrit (HCT), plasma protein concentration ([Pr]), plasma colloidal osmotic pressure (COP), and red cell volume (RCV). Broken lines indicate the blood volumes which would result if the infusates were completely retained in the circulation.

Tyrode's solution the lymph flow rose transiently to almost three times its control value, but lymph protein concentration decreased steadily to as much as 50% below control values after 3 hours. A more detailed analysis of the experimental results has been reported elsewhere (21).

MATHEMATICAL MODEL

The extracellular space is considered to be divided into two distinct and well-mixed compartments—the plasma compartment and the interstitial compartment—separated by a capillary membrane of surface area A. Each compartment is characterized by certain state variables: a fluid volume, a protein concentration, and a hydrostatic pressure. Other variables and relationships considered in the model are the precapillary resistance, the mean arterial blood pressure, the mean venous blood pressure, the mean capillary pressure, the transcapillary ultrafiltration rate governed by the Starling-Landis relationship, the...
restricted colloid diffusion rate, a tissue pressure that is a function of tissue compliance, the interstitial volume, and a variable lymph flow rate that depends on the interstitial volume.

Electrolytes and smaller organic molecules are transported rapidly between compartments in relation to colloid movement and, therefore, do not contribute significantly to the transcapillary osmotic gradient (22). Additionally, this model does not consider regional differences in such parameters as capillary permeability, tissue compliance, and lymph flow. Instead, average values are assumed for the entire body. This simplification is necessary because data are not available to formulate a distributed-parameter model.

The mathematical relationships describing plasma—interstitial fluid exchange dynamics are depicted in the flow diagram of Figure 4. Each block can be described by a mathematical input-output function. Empirical relationships are represented by a box containing the particular function graph. In the following description, reference can be made to Figure 4 for functional relationships.

Fluid enters the extracellular compartment by intravenous infusion of isotonic solutions at a predetermined rate (block 1). The total volume infused \(V_{\text{INF}}\) is determined by integrating the infusion rate pulse function over time (block 2) and adding this volume to the existing extracellular volume (block 3). If the infused solution contains colloids, they are accounted for by adding them to the existing pool of extracellular colloids (blocks 4 and 5).

During and after infusion the pressures in the cardiovascular system increase (blocks 6 and 7). At present it is not possible to predict accurately their response following infusion. For this reason the values of \(P_a(t)\) and \(P_v(t)\) that were needed in the analysis came directly from our infusion experiments. These pressures were used to estimate changes in capillary pressure using the relationship first derived by Pappenheimer and Soto-Rivera (5) (blocks 8-10):

\[
P_a(t) = \frac{1}{1 + R} P_d(t) + \frac{R}{1 + R} P_v(t),
\]

where \(R\) is the precapillary-postcapillary resistance ratio, \(R_{pa}/R_{cv}\).

The dynamic changes in interstitial volume that occur when the normal fluid balance is altered are

---

**FIGURE 4**

Block diagram showing the functional relationships used in the mathematical model for plasma—interstitial fluid exchange. See text for explanation and abbreviations.

*Circulation Research, Vol. XXXIII, December 1973*
governed by the instantaneous rates of net transcapillary ultrafiltration and lymph flow (block 11).

\[
d\frac{V_t}{dt} = Q_{filt} - Q_{lymph}. \tag{3}
\]

Net ultrafiltration, as expressed by the Starling-Landis relationship, is proportional to the filtration conductivity coefficient \(K_wA\) and the difference between the hydrostatic pressures \(P_c - P_t\) and the colloidal osmotic pressures \(\pi_p - \pi_i\) of the two compartments, assuming a reflection coefficient for the plasma colloids equal to unity (blocks 12 and 13).

\[
Q_{filt} = K_wA(P_c - P_t + \pi_t - \pi_p). \tag{4}
\]

Since there have been no correlations that would accurately predict the dynamics of lymph flow, we have used an empirical correlation between lymph flow and interstitial volume derived from our experimental data (block 14 and Fig. 5).

The pressure in the tissue compartment \(P_t\) is a function of the compliance, \(\gamma\), of that compartment and the volume of fluid filling the compartment \(V_t\). Whether the normal tissue pressure is negative as first proposed by Guyton (23) is not fully settled. In the present analysis, the changes in tissue pressure are more important than are the absolute values. Although the absolute value of tissue pressure affects capillary pressure and other predicted variables, the trend of changes in these quantities, which form the basis of our conclusions, is not changed. However, the absolute value of compliance is a critical factor. There has been some dispute over the value of tissue compliance. Wiederhielm (8) considered the interstitial space to have a constant compliance \((\gamma = 96 \text{ ml/kg mm Hg}^{-1})\) and to be far less rigid at rest than did Guyton (24) \((\gamma = 4 \text{ ml/kg mm Hg}^{-1})\), who suggested that compliance increases as the tissue becomes edematous \((\gamma = 96 \text{ ml/kg mm Hg}^{-1})\). In the present computer analysis it was assumed that tissue compliance remained constant over the range of interstitial volumes studied. The effects of either a high \((96 \text{ ml/kg mm Hg}^{-1})\) or a low \((4 \text{ ml/kg mm Hg}^{-1})\) tissue compliance were examined (block 15).

The interstitial volume can be obtained by integration of the time derivative (block 16). The plasma volume is obtained by subtracting interstitial volume from extracellular volume (block 17).

The movement of colloids between the two extracellular compartments is considered to occur by restricted diffusion across the capillaries (blocks 18 and 19),

\[
h_{fil} = K_pA(C_{pl} - C_t), \tag{5}
\]

and by simple bulk flow through the lymphatics (block 20),

\[
J_{lymph} = Q_{lymph} \times C_t. \tag{6}
\]

In this last expression, the concentration of colloids in the lymph is considered to be identical to that in the interstitium, an assumption commonly used by other investigators (7, 8, 25). The material balance describing the rates of inflow and outflow of protein via the capillaries and lymphatics is given in block 21.

The amount of colloid in the interstitial compartment at any time is obtained by integrating the rate at which colloidal mass changes. This value is used to obtain the tissue and the plasma colloidal concentration (blocks 22-25). In simulating the infusion of dextran solution a distinction was made between exogenous and endogenous colloids by solving blocks 18-24 for both dextran and colloids. This procedure permitted the comparison of experimental and simulated protein concentration responses to infusions of dextran solution.

Block 26 represents an empirical relationship (22) for estimating the colloidal osmotic pressure.
TABLE 1

Experimentally Determined Initial Values for Simulation Studies

<table>
<thead>
<tr>
<th>Infusion group</th>
<th>Dog weight (kg)</th>
<th>$V_{ip0}$ (ml)</th>
<th>$C_{pl0}$ (g/100 ml)</th>
<th>$P_{pl0}$ (mm Hg)</th>
<th>$P_{ip0}$ (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow Tyrode's</td>
<td>19.4</td>
<td>488</td>
<td>986</td>
<td>6.15</td>
<td>67.0</td>
</tr>
<tr>
<td>Rapid Tyrode's</td>
<td>19.3</td>
<td>485</td>
<td>1198</td>
<td>5.14</td>
<td>62.0</td>
</tr>
<tr>
<td>Slow dextran</td>
<td>20.1</td>
<td>502</td>
<td>950</td>
<td>5.98</td>
<td>61.5</td>
</tr>
<tr>
<td>Rapid dextran</td>
<td>20.3</td>
<td>506</td>
<td>1295</td>
<td>5.18</td>
<td>58.4</td>
</tr>
</tbody>
</table>

See text for abbreviations.

\[
\pi = 2.1C + 0.16C^2 + 0.009C^3. \tag{7}
\]

Initial Conditions and Constants.—The initial values of variables required by the model (Fig. 4) were calculated from a steady-state analysis of the dynamic system already described. This analysis was accomplished by using experimentally obtained control values for $V_{pl0}$, $C_{pl0}$, $P_{pl0}$, and $P_{ip0}$ ($V_{pl}$ at time zero, etc.) and by assuming that the following quantities equaled zero at time zero: $dV_{pl}/dt$, $dM_{pl}/dt$, and $V_{inf}$. $V_{ip0}$ was 3.6 times the plasma volume (26). Resting lymph flow was 2 ml/kg hour$^{-1}$ (27). Table 1 summarizes the experimentally determined initial conditions. Average values of $K_{mA0}$, $K_{pA0}$, $A_{0}$, and $R_{0}$ used in the above steady-state analysis were taken from the literature and are shown in Table 2. Initial values for capillary pressure derived from Eq. 2 are shown in Fig. 6 at time zero. The average value of control tissue pressure ($P_{t0}$) obtained from the model was -0.61 mm Hg.

Simulation Procedure.—Four different situations were simulated paralleling the four experimental infusion groups listed in Table 1. Particular solutions of the equations describing the model were obtained using an IBM 360/67 digital computer and the IBM CSMP program. Input to the model consisted of the initial conditions and constants, the infusion rates, and the time-varying experimental blood pressures. Two parameters, $R$ and $A$, were optimized to obtain the best least-squares fit (28) between the simulated and the experimental plasma volume responses. The optimization subroutine consisted of a direct pattern search and steepest ascent method (29).

Three types of simulation studies were performed. The first type consisted of a series of parametric studies in which the sensitivity of the dynamic behavior of the simulated system to changes in certain important parameters was examined. Parameter optimization was not used in this phase of the analysis, since no attempt was made to obtain agreement with the experimental data. Two series of studies were then performed to determine optimal parameter values. In the constant parameter optimization studies, constant values of $R$ and $A$ were obtained over the entire simulated run using the optimization subroutine. Although this method produced fair agreement with the experimental results, it was felt that a more physiologically meaningful result could be obtained by treating the optimizing parameters as time-varying quantities. Therefore, in the piecewise optimization studies, the time courses of the experiments were divided into six segments and the entire run was optimized in a piecewise fashion using the optimized results of one segment as initial conditions for the next segment. This analysis resulted not only in a more rigorous fit between observed and simulated results but also in the production of a time profile

| Table 2

Assumed Values for Initial Constants (30-kg Dog)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capillary filtration coefficient ($K_{mA}$) (ml/mm Hg hour$^{-1}$)</td>
<td>100</td>
<td>22, 43, 44</td>
</tr>
<tr>
<td>Protein permeability coefficient ($K_{pA}$) (ml/hour)</td>
<td>25</td>
<td>22, 45</td>
</tr>
<tr>
<td>Capillary surface area ($A_{0}$) (cm$^2$)</td>
<td>$10 \times 10^4$</td>
<td>38, 44, 45</td>
</tr>
<tr>
<td>Precapillary-postcapillary resistance ratio ($R_{0}$)</td>
<td>4.0</td>
<td>38</td>
</tr>
</tbody>
</table>

*Assumes resting skeletal muscle has an area of 25 cm$^2$/g and that the 55% of body mass which is nonmuscular has three times more open capillaries at rest than does skeletal muscle.
Comparison of piecewise optimized simulation results and experimental data for plasma volume (PV), plasma protein concentration, and plasma protein mass following infusion of Tyrode's solution. Also shown are the model predictions for capillary pressure, precapillary-postcapillary resistance ratio \( R_p/R_v \), and capillary surface area.

The simulation results were evaluated by comparing the experimental responses with the theoretical responses and by determining whether the optimum values of the adjustable parameters were biologically plausible.

SIMULATION RESULTS

Parametric Studies.—In these studies the following parameters were examined: precapillary-postcapillary resistance ratio, capillary surface area, capillary filtration coefficient \( K_cA \), capillary protein permeability \( K_pA \), lymph flow, and tissue compliance. Results of a rapid infusion of Tyrode's solution are illustrated in Figure 7. The other infusions were also simulated, and results will be mentioned where appropriate.

The parametric study showed the following. (1) The parameters \( R \) and \( A \) greatly affect both the behavior and the absolute values of the plasma volume response (Fig. 7A and B). Variations in \( R \) have their most direct effect on the capillary pressure (Eq. 2). The effect of increasing \( A \) is an increase in both the net filtration and the colloid diffusion rates and thereby a decrease in the retention of infusate in the plasma. (2) The effects of varying the filtration coefficient are much greater than those of varying protein permeability, especially during the first hour after infusion (Fig. 7C). With protein leakage, water tends to enter the tissues because of osmotic gradients. Thus higher protein permeabilities increase the filtration rate and decrease the plasma volume retention. However, this effect is relatively small compared with the effects of changes in \( R \) or \( A \); therefore \( K_c \) would be a poor choice as a parameter to be optimized.

(3) The effects of two extreme values of tissue compliance were investigated (Fig. 7D), and the resultant plasma volume responses were quite different for the two cases. For a low-compliance tissue \( (\gamma = 4 \text{ ml/kg mm Hg}^{-1}) \), a given increase in capillary pressure that enhances filtration is quickly counteracted by a relatively high increase in the tissue pressure. This process results in a much lower net filtration rate and a greater retention of the infusate in the circulation than those observed for a tissue that is more compliant \( (\gamma = 96 \text{ ml/kg mm Hg}^{-1}) \).
During a typical simulation experiment, a rise in tissue pressure of 2 mm Hg was predicted when the tissue compliance was low; the predicted rise was about 0.1 mm Hg when the tissue compliance was high. Unless otherwise noted, the results presented were obtained by assuming a highly compliant tissue. In general, the simulation results indicate that the effect of lymph flow on the plasma volume response is minimal with infusion of Tyrode's solution and almost negligible with infusion of dextran solution. This finding is true even if the values for maximum lymph flow reported by Wasserman and Mayerson (30) and shown in the top curve in Figure 5 are used in the simulation instead of the lower values for lymph flow obtained in our experiments.

**Constant-Parameter Optimization Studies.**—In these studies, we tried to approximate the observed plasma volume response by finding constant optimum values of $R$ and $A$ over the entire infusion-response period. As noted above, these optimizing parameters exert a particularly sensitive influence on the response of our model. Figure 8 illustrates the results of this analysis by comparing the simulation of a rapid infusion of Tyrode's solution with that of dextran solution. Also shown are the predicted responses of filtration and lymph flow rates and the pressure factors that influence transcapillary filtration.

Changes in both capillary pressure and plasma colloid osmotic pressure are much greater than changes in the tissue compartment reflected by the tissue pressure and the interstitial colloidal osmotic pressure. During the initial stages of infusions of Tyrode's solution, capillary pressure increases and plasma colloid osmotic pressure decreases, thus enhancing filtration. After infusion, however, the capillary pressure and the tissue fluid colloid osmotic pressure decrease while plasma colloid osmotic pressure and tissue pressure increase, all tending to counteract the initial effect. This behavior is in agreement with the principles set down by Starling more than 70 years ago.

With infusion of dextran solution, plasma colloid osmotic pressure initially increases, and the resulting net driving force for filtration is about one-half that predicted during infusion of Tyrode's solution. The slow but steady disappearance of fluid from the circulation following infusions of dextran solution could not be accurately simulated by assuming any reasonable value of colloidal permeability. The simulated plasma volume either reached a steady-state plateau or turned upward as shown in Figure 8.

It is apparent from this study that, of the two fluid pathways that connect the plasma and the interstitial compartments, transcapillary filtration plays a much more important role than does lymph flow during brief infusions, at least during the major portion of the experiment. However, near the end of the experiment, the filtration rate declined to values approximately equal to that of the lymph and, in fact, decreased below lymph flow as shown. This process resulted in a net flow of fluid into the plasma compartment with a resulting increase in plasma volume; such behavior was observed in several experiments.

**Piecewise Optimization Studies.**—The system's dynamic characteristics can be observed most clearly from the results of the piecewise optimization studies. Simulation results for the four groups are shown in Figs. 6 and 9. The responses of six time-varying quantities have been selected for study: plasma volume, plasma protein concentration, and plasma protein mass are compared with the averaged experimental results, but capillary pressure, precapillary-postcapillary resistance ratio, and capillary surface area are purely predicted.
responses with no comparable experimental data. The time course of each experiment was divided into six segments, as indicated by the step changes in $R$ and $A$; each segment was optimized independently. Some of the more important results are as follows. (1) The simulation predicts that in the postinfusion period the resistance ratio is higher with infusion of Tyrode's solution than it is with infusion of dextran solution, but the opposite effect is true for the capillary surface area. There is a dramatic contrast between the capillary area response to the slow infusion of Tyrode's solution and the slow infusion of dextran solution. In both cases the area returns to near normal at the end of the experiment, but the transient response is always below control level for infusion of Tyrode's solution and above control level for infusion of dextran solution. Overall it appears that the behavior of these parameters is exaggerated at the higher infusion rates. The simulation predicts that the most dramatic changes in the resistance ratio response will occur in the later stages of infusion of dextran solution and not immediately after the initial infusion period as is true with infusion of Tyrode's solution. (2) The simulated capillary pressure wave form is derived directly from the optimized response of the resistance ratio and the experimental arterial and venous blood pressure responses (Eq. 2). The capillary pressure declines rapidly after both slow and rapid infusions of Tyrode's solution until it is just slightly below control. However, following dextran infusion, the capillary pressure is prevented from returning to control levels by the lowered resistance ratio. (3) The experimental results show that the increase in plasma protein mass is much larger following the slow infusion of dextran solution (as much as 25% above control) than it is for the three other groups (less than 7%). Simulation predicts that native plasma protein mass increases at the expense of interstitial protein mass after infusion and that the increase is less than 2% for all groups. Thus, the agreement between observed and simulated plasma protein responses is reasonable except during the slow infusion of dextran solution. There is poor agreement early in the simulation during rapid infusions of both dextran and Tyrode's solutions most likely because of inadequate mixing of the proteins in the plasma compartment during the minutes following infusion.

Effect of Tissue Compliance.—Compliance of the interstitial space exerted a profound influence on the dynamic behavior of the model. Figure 10
(bottom) compares the simulated results of a rapid infusion of Tyrode's solution, assuming either a high (96 ml/kg mm Hg$^{-1}$) or a low (4 ml/kg mm Hg$^{-1}$) tissue compliance. The graphs for high tissue compliance were reproduced from Figure 6. The results for low tissue compliance were obtained using the same piecewise optimization procedure previously described. The agreement with the experimental plasma volume response, although not shown, was equally good with both high and low tissue compliances. A similar analysis, not shown, was performed for a rapid infusion of dextran solution.

For a tissue space of low compliance, the resistance ratio was predicted to decrease well below the values found for high tissue compliance for infusions of both Tyrode's solution and dextran solution, causing the capillary pressure to increase. This increase in capillary pressure was necessary to counteract the effect of increased tissue pressure while maintaining the required filtration rate. With infusion of Tyrode's solution there was a major qualitative difference in the resistance ratio response. A high-compliance tissue caused an increase above control levels, but a low-compliance tissue caused a decrease below control levels. On the other hand, with infusion of dextran solution the resistance ratio decreased below control for both values of tissue compliance examined.

Discussion

The initial state of hydration is an important factor in the response to infusion. Although we do not have direct measurements of control interstitial fluid volumes, the findings that the average control plasma volume (4.8% of body weight) was within the normal range for the dog (31) and that the average control thoracic duct lymph flow rate (0.55 ml/min) was in the range of normal basal flow (27) are consistent with a grossly normal state of hydration.

ACCURACY OF THE SIMULATION ANALYSIS

The model used in this study considered a lumped-parameter rather than a distributed-parameter system. We neglected regional differences that exist in lymph flow, capillary permeability, precapillary-postcapillary resistance ratio, and tissue compliance. For example, the vascular resistance in muscle responds to blood pressure changes quite differently than does that in the intestinal vasculature. The lumped-parameter model is not capable of predicting local responses but is capable of predicting an integrated response of all the elements involved. Mellander (1) and Oberg (32) have suggested that the major portion of any acute plasma fluid shift occurs in muscle. Since muscle comprises a large portion of the body mass, the results we obtained for microcirculatory variables are probably most representative of what happens in that tissue.

Although a distributed-parameter model might permit a more detailed analysis of system responses, sufficient data on the variation in parameters for different vascular beds are not available to permit formulation of such a model at present. Furthermore, until experimental evidence regarding these predictions becomes available, it is not possible to state a priori that a model with additional compartments would change the nature of the whole body response that we have observed in our simpler model.

Although there is no direct evidence to support the simulated dynamic behavior of the precapillary-postcapillary resistance ratio, the capillary surface area, or the capillary pressure obtained during the piecewise optimization studies, there is indirect evidence that the results are reasonable. First, the degree to which these variables changed during any experiment is well within physiological limits. Mellander (1) has shown that during stressful situations such as hemorrhage, exercise, hypoxia, etc., the capillary pressure can vary ±15 mm Hg from normal, the capillary surface area can vary from 0.2 to 4 times normal, and the resistance ratio can vary from 1.7 to 18. In our studies, the capillary pressure varied from 7 to —3 mm Hg from normal, the capillary surface area varied from 0.5 to 1.8 times normal, and the resistance ratio varied from 2.8 to 4.8. Thus we can see that the model we have constructed is capable of predicting plausible values for quantities that could not be obtained explicitly. Second, not only the magnitude but also the direction of these changes can be interpreted to be compatible with current concepts of microcirculatory control.

ROLE OF TISSUE COMPLIANCE

An important result of the simulation study was the finding that the predicted peripheral resistance response was quite different depending on which solution was infused and which value of interstitial compliance was assumed. If this prediction is at all meaningful, then two questions should be asked. Why is there such a difference between the response to different solutions? Which of the
assumed values of compliance are more reasonable?

The answers would be simpler if data were available which showed the experimental dynamic response of the precapillary-postcapillary resistance ratio to infusions. Unfortunately, such data do not exist. However, although it would have been difficult to experimentally measure resistance ratio changes, it was possible to measure the total peripheral resistance, \( R_P = R_a + R_v \).

Fig. 10 presents the averaged results of three experiments in which Tyrode's solution was infused rapidly (data from Fig. 3). The dramatic and sustained increase in total peripheral resistance has been observed previously following infusions (33) and has been postulated by Guyton et al. (34) to be due entirely to autoregulation.

If, as is generally assumed, changes in total peripheral resistance are primarily due to changes in precapillary resistance rather than to changes in postcapillary resistance, then the values of total peripheral resistance may be assumed to vary in the same direction as the precapillary-postcapillary resistance ratio. Comparison of the simulated and experimental responses in Fig. 10 shows that the assumption of an overall highly compliant tissue appears more realistic than does one of low compliance. This conclusion is also confirmed for infusion of dextran solution but for different reasons. In that case, the predicted change in the precapillary-postcapillary resistance ratio when tissue compliance is low is well below the known physiological range previously observed for this variable under extreme conditions (1).

Our results supporting a fairly high-compliance tissue space do not necessarily invalidate the concept of a normally low-compliance tissue space (24). Guyton (24) has suggested that animals which are anesthetized for several hours tend to accumulate tissue fluid due to reduced lymph flow and osmotic forces. In the present study, the dogs were anesthetized several hours prior to the first infusion and then for several more hours during the infusion-response period. If tissue fluid progressively accumulated during this period it is possible that the tissue compliance would increase, as Guyton (24) has suggested. Although the volume of fluid of each infusion was below that required to produce the high-compliance condition associated with edema in conscious animals, the anesthetized state and the double infusions might have caused this state to develop more readily.

**ROLE OF PRECAPILLARY-POSTCAPILLARY RESISTANCE AND TRANSCAPILLARY FILTRATION**

In contrast to the results obtained with the infusion of Tyrode's solution, the simulation predicts that the precapillary-postcapillary resistance ratio will decrease following infusion of dextran solution, especially late in the experimental period, for both high and low tissue compliance. This finding suggests that certain control mechanisms with a delayed response may be invoked by the hypervolemic stress associated with dextran infusion but not with Tyrode's infusion. Although data on dynamic changes in precapillary-postcapillary resistance ratio are not available, Conway (14) has measured an increase in total peripheral resistance following infusion of dextran solution that is delayed more than 1 hour. In another study Prather et al. (18) have shown that stress relaxation (a delayed vasodilation reflex following blood volume expansion) following infusion of Tyrode's solution is minimal compared with that following infusion of dextran solution. Although neither of these observations appears to explain the simulation response mentioned above, it is certainly possible that they may be related. It is also probable that dramatic and delayed decreases in the precapillary-postcapillary resistance ratio involve the integration of both the resistance and the capacitance functions of the veins and the dynamic distribution of blood within the systemic circulation. Little information about these mechanisms (35, 36) is presently available and, if nothing else, the simulation results suggest that these areas are worthy of more study.

The precapillary and postcapillary resistances and the sphincter elements of the peripheral circulation play a crucial role in controlling changes in capillary pressure, capillary surface area, blood flow and distribution, and transcapillary fluid exchange. The simulation analysis suggests that adjustments in the microcirculation following infusions can be very effective in adjusting transcapillary filtration as a means of controlling total blood volume. The importance of the precapillary-postcapillary resistance ratio and the capillary surface area in autoregulating transcapillary filtration and fluid balance during exercise, standing, and hemorrhage has previously been discussed by Lundvall et al. (37) and others (1, 38). The present analysis suggests a similar kind of autoregulation during the hypervolemic response to infusions.

**PLASMA PROTEIN RESPONSE**

Although the large increase in plasma proteins following the first infusion of dextran solution was
not accounted for by the model, other investigators (30, 39-41) have reported similar changes of the same magnitude for infusion of both dextran and saline. Moore et al. (40) have suggested that it is unlikely that thoracic duct lymph proteins can account for the largest increases that they observed. The present experiments support this view. Lymphovenous shunts other than the thoracic duct, such as hepatosplenic lymphatics, might be involved in releasing a store of preformed proteins. It has recently been suggested (42) that interstitial protein can enter the circulation through pathways other than the lymphatics, namely through sites in the capillaries that are anatomically separate from those involved with filtration. The fact that a large protein release was observed for the first but not the second infusion of dextran solution in the same dogs suggests that the postulated store of preformed proteins became depleted from the stress of the first infusion.

Our objective was to validate a model describing the dynamics of plasma—interstitial fluid exchange. We found that the model was capable of accurately simulating the dynamic plasma response to infusion and at the same time could predict the time-varying behavior of certain microcirculatory parameters. These predicted changes are consistent with previously postulated mechanisms with which the circulatory system can protect itself against hypervolemic stress. The simulation suggests that changes in lymph flow and transcapillary protein movement do not play important roles in determining the short-term plasma retention of infused fluids. However, changes in the capillary filtration surface area, the precapillary-postcapillary resistance ratio, and the tissue compliance appear to exert a major influence on this process. Our results emphasize the need to study further the characteristics of tissue compliance, the integration of capacitance and resistance functions of the veins, and the distribution of blood following intravenous fluid loading.

Acknowledgment

We wish to acknowledge sincerely the fine technical assistance of Miklos Gellai during the experimental phase of this study.

References


Dynamics of Plasma-Interstitial Fluid Distribution following Intravenous Infusions in Dogs: An Experimental and Computer Simulation Study
JOEL I. LEONARD and PETER H. ABBRECHR

Circ Res. 1973;33:735-748
doi: 10.1161/01.RES.33.6.735

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1973 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/33/6/735

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/