



# Microvascular Dynamics and Hemodialysis Response of Patients With End-Stage Renal Disease

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### Specialty section:

This article was submitted to  
Biomechanics,  
a section of the journal  
Frontiers in Bioengineering and  
Biotechnology

**Received:** 16 December 2021

**Accepted:** 23 March 2022

**Published:** 18 May 2022

### Citation:

Lee J-S and Lee L-P (2022)  
Microvascular Dynamics and  
Hemodialysis Response of Patients  
With End-Stage Renal Disease.  
*Front. Bioeng. Biotechnol.* 10:836990.  
doi: 10.3389/fbioe.2022.836990

In our previous analysis of three sets of hemodialysis studies, we found that patients possessing higher hematocrit have a higher filtration coefficient  $K_{So}$  and more fluid being restituted from the tissue. A new dynamic analysis is developed to reveal how the plasma protein concentration, restitution volume, and plasma volume are changing over the time course of 240 min hemodialysis. For patients with the filtration coefficient  $K_{So}$  as 0.43 or 5.88 ml/min/mmHg, we find that the restitution rate would reach 50% of the extraction rate in 5.3 or 57.4 min, respectively. By the end of hemodialysis, the restitution rate of both patients asymptotically approaches a value of 0.93 ml/min which is slightly higher than the extraction rate of 9.03 ml/min. The plasma volume drops by 10% of the total plasma volume in 11 min for patients with low  $K_{So}$  and drops by 2.1% and turns around to an increasing trend in 5.6 min for patients with high  $K_{So}$ . These results suggest that the filtration coefficient acts like a facilitator in restituting more fluid from the tissue to compensate for the loss of plasma volume due to extraction. The hematocrit data of three sets of hemodialysis also indicate that significant microvascular blood volume is shifted from small veins toward the venous side of macrocirculation. A better understanding of how the factors examined here cause hypovolemia can be the basis for one to modify the hemodialysis process such that the development of hypovolemia can be avoided over the course of hemodialysis.

**Keywords:** blood volume, microcirculation, plasma protein concentration, hematocrit, hemodialysis

## 1 INTRODUCTION

Over the course of hemodialysis (HD), the continuous extraction of ultrafiltrate from the blood by the dialyzer will increase the plasma protein concentration (PPC) from  $C_p$  to  $C_p'$ . For three groups of patients with normal, anemic, and more anemic hematocrit, the PPC increment  $(C_p' - C_p)/C_p'$  is found as 11.7, 10.2, and 7.9%, respectively (Schneditz et al., 1992; Minutolo et al., 2003). The full circulation analysis (FCA) of these end-point protein data reveals that the large drop in the PPC increment is mainly due to the patients having these arterial hematocrits  $H_a$  ( $42.4 \pm 3.5\%$ ,  $33.5 \pm 2.4\%$ , and  $27.9 \pm 3.1\%$ , respectively) have these filtration coefficients  $K_{So}$  (0.43, 0.85, and 5.88 ml/min/mmHg, respectively, personal communication). A larger filtration coefficient is also shown by the FCA to associate with more fluid being restituted from the tissue and lesser reduction in the total plasma volume for patients with lower hematocrit. This impact of the filtration coefficient on plasma volume reduction suggests that the filtration coefficient acts like a factor facilitating the prevention of hypovolemia. In this article, we will expand the end-point analysis to one that can predict how these

variables, namely, PPC, restitution volume, plasma volume, microvascular blood pressure, and rate of the restitution are changing over the course of HD. A total of three sets of computations are made for patients having the three filtration coefficients mentioned previously. By comparing the temporal changes of the variables so calculated will help us better understand how and why that the filtration coefficient can be a facilitating factor for the patient to generate a fluid restitution to adequately compensate for the fluid extracted by the dialyzer and hence the prevention of the development of hypovolemia.

In the FCA, the full circulation is divided into three compartments: the macrocirculation, microcirculation, and the splenic microcirculation. The blood flowing in six groups of microvessels (the small arteries, arterioles, capillaries, post-capillaries, venules, and small veins) has a microvessel hematocrit in the range of 90–20% of  $H_a$  (Lipowsky et al., 1980). The blood pressure in the small arteries can be 100 mmHg, while that in the small veins is 2–4 mmHg. The organs in our body may have different filtration coefficients. In the FCA, the six groups are grouped into one microcirculation compartment with  $P_{mic}$  being its blood pressure,  $H_{mic}$  as its microvascular hematocrit of the microcirculation, and  $K_{So}$  as its filtration coefficient. Because the red blood cells (RBCs) in the splenic microcirculation are tethered by the microvessel wall, the hematocrit there can be 2.07 times of  $H_a$  (Gibson et al., 1946). Equations are formulated in our previous study to describe the transvascular fluid and protein movement between the microcirculation and the tissue. The equations are used to deduce from the measured PPC increment  $(C_p' - C_p)/C_p'$  and hematocrit increment  $(H_a' - H_a)/H_a'$ , the filtration coefficient  $K_{So}$ , the change in plasma volume  $\Delta V_p$ , and the reduction in microvascular blood volume  $\Delta V_{mic}$ . We will use the morphometric and hemodynamic characteristics of the microcirculation to deduce a value for  $P_{mic}$  and  $H_{mic}$  and to partition the calculated microvascular blood volume reduction to the six microvessel groups. The FCA simulates the transvascular protein movement as the transport of a fluid across the endothelia having  $\gamma C_p$  as its protein concentration. The constant  $\gamma$  is termed as the permeability fraction. A way to find the value of  $\gamma$  is described.

A hematocrit equation has been established in FCA to show how these three factors, namely, a change in plasma volume ( $\Delta V_p$ ), a change in microvascular blood volume ( $\Delta V_{mic}$ ), and a splenic RBC release change of the arterial hematocrit. Graphical results are generated to show how these three factors alter the arterial hematocrit over the course of HD. With known  $\Delta V_{mic}$ , we can calculate the change in macrovascular blood volume. The meaning of a change in microvascular blood volume and the impact of a change in macrovascular blood volume on cardiac filling are elaborated from the perspective of a 13-generation circulation model (Rothe 2011).

For many hypovolemia studies, the increase in hematocrit over the course of HD is used to determine the reduction in plasma volume over the course of HD (Schneditz et al., 1992; Calvacanti et al., 2006; Dasselaar et al., 2007; Booth et al., 2011). The Van Beaumont (1972) hematocrit equation

(VBHE) used in those studies can be derived from the hematocrit equation of the FCA under the assumption of no microvascular volume change and no splenic RBC release. In the study carried out by Schneditz et al. (1992), the blood volume change calculated from VBHE is used in their numerical procedure to determine the filtration coefficient of the more anemic patients. In FCA, we use the PPC data and the protein equation to determine the reduction in plasma volume and the filtration coefficient. The differences that are generated by these two computation procedures are examined.

## 2 ANALYSES, RESULTS, AND DISCUSSIONS

*The process on changing plasma protein concentration.* In this part of FCA, the plasma space in the entire circulation is treated as one compartment. Before HD, there is a constant filtration flux  $J_f(0)$  flowing out of the plasma compartment to the tissue. The 0 in the parenthesis identifies the quantity as one at the initiation of HD ( $t = 0$ ). This flux carries a protein concentration  $C_f$ . Meanwhile, there is a constant lymphatic return  $Q_{lym}$  which carries a protein concentration  $C_{lym}$ . As the plasma volume and the PPC are not likely to change before the initiation of HD, we have the following requirements:

$$Q_{lym} = J_f(0) \text{ and } Q_{lym} C_{lym} = J_f(0) C_f \quad (1)$$

As the interstitial space is being flushed by the filtration, these two equalities also indicate that the protein concentration in the interstitial fluid space  $C_t$  equals  $C_f$ . We regard that the transvascular fluid movement  $J_f(t)$  is governed by the Starling hypothesis, that is,

$$J_f(t) = K_{So} \{P_{mic}(t) - P_t - \sigma[\pi_p(t) - \pi_t]\} \quad (2)$$

where  $K_{So}$  is the filtration coefficient,  $P_{mic}(0)$  is a representative hydrostatic pressure of the microcirculation,  $P_t$  is the hydrostatic pressure on the tissue side,  $\sigma$  is the reflection coefficient,  $\pi_p(t)$  is the plasma colloidal osmotic pressure (COP) at time  $t$ , and  $\pi_t$  is the tissue COP. Over the course of HD, the total volume of the fluid restituted from the tissue is given by:

$$\Delta V_r = \int_0^{\Delta T} K_{So} [\sigma(\pi_p(t) - \pi_t) - (P_{mic}(t) - P_t)] dt + \Delta T \cdot Q_{lym} \quad (3)$$

We consider that the volume of fluid being restituted from the tissue to the circulation is much smaller than the fluid volume of the interstitial fluid space. Thus, we can assume that the interstitial fluid pressure and the tissue COP are not altered by HD. Thus, the replacement of  $Q_{lym}$  in Eq. 3 by  $J_f(0)$  converts Eq. 3 to the following form:

$$\Delta V_r = \int_0^{\Delta T} K_{So} \{ \sigma[\pi_p(t) - \pi_p(0)] - [P_{mic}(t) - P_{mic}(0)] \} dt \quad (4)$$

As derived later, Eq. 4 can be converted to the following algebraic equation:

$$\Delta V_r = k K_{So} [\sigma \Delta \pi_p - \Delta P_{mic}] \quad (5)$$

where  $\Delta \pi_p$  is  $\pi_p' - \pi_p$ ,  $\Delta P_{mic}$  is  $P_{mic}' - P_{mic}$ , and  $k$  is an integration constant (Eq. 8). From now on, quantity without ' is identified as one at  $t = 0$ , quantity with ' as one at  $t = \Delta T$ , and that with (t) as one at time  $t$ . Later on,  $P_{mic}$  is identified as a surface average of the blood pressure over the entire surface area of the microcirculation, and the pressure change  $\Delta P_{mic}$  can be calculated as:

$$\Delta P_{mic} = \zeta \Delta V_b / V_b \quad (6)$$

where  $\zeta$  is termed as the autonomous constant, and  $\Delta V_b$  is  $V_b' - V_b$ .

The volume of restitution subtracted by the extraction volume  $\Delta V_e$  is the change in plasma volume:

$$\Delta V_p \equiv V_p' - V_p = \Delta V_r - \Delta V_e \quad (7)$$

As we regard that the splenic RBC release does not change the blood volume of the splenic microvasculature, the change in total blood volume  $\Delta V_b$  is given by:

$$\Delta V_b = \Delta V_p \quad (8)$$

Let  $C_r$  be the protein concentration of the restituted fluid. Then, the protein mass added to the plasma compartment is  $C_r \Delta V_r$ . Thus, the increase in the protein mass over the course of HD is given by:

$$C_p' V_p' = C_p V_p + C_r \Delta V_r \quad (9a)$$

Eqs 7 and 9a can be combined to form the following equation:

$$\Delta C_p / C_p' = \Delta V_e / V_p - (\Delta V_r / V_p) (1 - C_r / C_p') \quad (9b)$$

where  $\Delta C_p$  is  $C_p' - C_p$ . As described later, we use the permeability fraction  $\gamma$  to characterize  $C_r$  as a fraction of  $C_p$ :

$$C_r = \gamma C_p \quad (10)$$

Termed the protein equation, Eq. 9b uses the change in PPC to calculate  $\Delta V_r / V_p$ . The first term  $\Delta C_p / C_p'$  in Eq. 9b is termed as the PPC increment (the increase in PPC induced by HD and then normalized by  $C_p'$ ), the second term  $\Delta V_e / V_p$  is termed as the extraction increment (the increment in PPC induced by the extraction), and the third term is the restitution dilution (the dilution of PPC by fluid restitution). As  $C_r$  is smaller than  $C_p$ , the value of restitution dilution is negative. The negativity makes us to name this third term as dilution.

Overall, we have six algebraic equations (Eqs. 5–10) to characterize the transvascular fluid and protein movements. The equations contain four modeling constants:  $K_{So}$ ,  $\sigma$ ,  $\gamma$ , and  $\zeta$ . Here,  $K_{So}$  is treated as an input parameter, while  $\sigma$  is taken as 1,  $\gamma$  as 0.09, and  $\zeta$  as 36.67 mmHg. The hemodialysis process is defined by two parameters:  $\Delta T$  and  $\Delta V_e$ . Once the initial values of plasma volume  $V_p$ , blood volume  $V_b$ , and PPC  $C_p$  are given, then we can use the equations to solve for these six end-values:  $C_p'$  or  $\Delta C_p$ ,  $C_r$ ,  $V_p'$  or  $\Delta V_p$ ,  $V_b'$  or  $\Delta V_b$ ,  $\Delta V_r$ , and  $\Delta P_{mic}$ . The value of  $\Delta \pi_p$  is derived from  $C_p$  and  $C_p'$  through the Landis and Pappenheimer (1963) equation (Eq. A6).

The two HD studies carried out by Minutolo et al. (2003) on patients with normal and anemic (N and A) hematocrit and the

high ultrafiltration experiment carried out by Schneditz et al. (1992) on patients with more anemic (MA) hematocrit are to be identified as N78%, A72%, and MA18%20 HD, respectively. The percentage defines the  $\Delta V_e / V_p$  imposed to the HD. The first two HDs have 240 min as  $\Delta T$ . The two digits 20 in the last HD is used to highlight that its HD time  $\Delta T$  is 20 min. These HD parameters,  $\Delta V_e$ ,  $\Delta T$ , and the initial value of  $C_p$ ,  $V_p$ , and  $V_b$  and the final PPC  $C_p'$ , can be found or derived from the publications. In our previous analysis, we used Eqs 5–10 and Eq. A6 to calculate these seven variables:  $C_r$ ,  $\Delta V_r$ ,  $\Delta V_p$ ,  $\Delta V_b$ ,  $\Delta \pi_p$ ,  $\Delta P_{mic}$ , and  $k K_{So}$ . Here, we use the equations in the Appendix to calculate the temporal changes of  $V_r(t)$ ,  $V_p(t)$ ,  $V_b(t)$ ,  $P_{mic}(t)$ ,  $\pi_p(t)$ , and the integration constant  $k$  and filtration coefficient  $K_{So}$ .

The second series of HDs will be identified as low  $K_{So}$ , medium  $K_{So}$ , and high  $K_{So}$  HD. They are to have these filtration coefficients: 0.43, 0.85, and 5.88 ml/min/mmHg, which are the filtration coefficients found for N78%, A72%, and MA18%20 HD, respectively. The initial conditions and the settings of  $\Delta V_e$  and  $\Delta T$  for this second series are those of N78% HD.

*Microvascular morphometry, hemodynamics, and hemodialysis.* In formulating FCA, two new modeling constants, the permeability fraction  $\gamma$  and the autonomous constant  $\zeta$ , and the microvascular blood pressure are introduced. In this section, a procedure based on the morphometry and hemodynamics of the microcirculation is presented to assess what likely values are to be set for the two constants and one pressure variable.

The morphometry data (generation number, vessel type, number of vessels, diameter, and length) of a central vascular tree model are reproduced in the first five columns of Table 1 (Rothe 2011). The surface areas and volumes of these vessels are listed in the 5th and 7th column of the table. With  $S_o$  and  $V_o$  being the total surface area and the total blood volume of the vascular tree, the surface and volume fractions ( $S_n/S_o$  and  $V_n/V_o$ ) of the 13-generations circulation are depicted in Figures 1A,B.

Through the relation between the *in vivo* microvascular hematocrit and vessel diameter (Lipowsky et al., 1980), we use the diameter reported in the table to set a value as the microvessel hematocrit  $H_{mic,n}$  of the  $n$ th generation and present it through this ratio  $\alpha_n (= H_{mic,n}/H_a)$  in the 9th column of Table 1. For the current investigations, the vessels of the 5th to 10th generation are categorized as microvessels, as their hematocrit ratios are all smaller than unity. Among these six generations, only the capillaries may be considered as rigid (Fung 1966), while other larger microvessels are distensible.

It is noted from Figure 1A that almost 99% of the surface area of the circulation resides in the microcirculation. All blood vessels are lined by endothelial cells, and the filtration and permeation characteristics of various microvessels may be similar to each other. Thus, the total surface area of the microcirculation should be taken as the  $S_o$  in Eq. 2. For this surface distribution, we form an S-axis (the 7th column) to mark the location of a point within the vascular network. As an example, the entrance of the microcirculation (i.e., the entrance of small arteries) is located at an S of 0.35%

**TABLE 1** | Morphometry and hemodynamics of a central vascular tree<sup>a</sup> (Rothe 2011).

<i>n</i>	Vessel type	Number $N_n$	Diameter $D_n$ , mm	Length $L_n$ , mm	Surface area $S_n$ , m <sup>2</sup>	S-axis (%)	Volume $V_n$ , mL	Ht <sub>n</sub> /Ha	$R_n$
1	Aorta	1	10	400	0.01	0.00	31.4	1	2.8
2	Large arteries	40	3	200	0.08	0.01	56.5	1	4.3
3	Main arterial branches	600	1	100	0.19	0.10	47.1	1	11.5
4	Terminal branches	1800	0.6	10	0.03	0.32	5.1	1	3.0
5	Small arteries	4.0E+07	0.019	3.5	8.36	0.35	39.7	0.52	25.1
6	Arterioles	4.0E+08	0.007	0.9	7.92	9.90	13.9	0.46	32.5
7	Capillaries	1.8E+09	0.0037	0.2	4.18	18.95	3.9	0.46	20.6
8	Post-capillary Venules	5.8E+09	0.0073	0.2	26.60	23.73	48.6	0.46	0.4
9	Venules	1.2E+09	0.021	0.1	7.92	54.12	41.6	0.48	0.0
10	Small veins	8.0E+07	0.037	3.4	31.62	63.17	292.5	0.59	0.9
11	Main venule branches	600	2.4	100	0.45	99.29	271.4	1	0.3
12	Large veins	40	6	200	0.15	99.81	226.2	1	0.3
13	Vena cava	1	12.5	400	0.02	99.98	49.1	1	1.1
	Total				87.5	100	1127		101.7

<sup>a</sup>By including the blood volume in the lungs and heart chambers, the total blood volume is 1376 ml. The cardiac output generating the pre-HD pressure is 1.376 L/min. The unit of resistance  $R_n$  is mmHg/(L/min).

which is the sum of the surface areas of all vessel upstream of the entrance divided by the total surface area (87.5 m<sup>2</sup>). Correspondently, the exit of the microcirculation is located at an S of 99.3%. The blood volumes tabulated in the 8th column indicate that 70% of the total blood volume resides in the 10th to 12th generation. We calculate the relative viscosity of blood  $\mu^*$  as  $13.2 \alpha_n^2 + 1.30 \alpha_n + 1.45$  and then take the resistance of the  $n$ th generation as  $A \cdot \mu^* L_n / (N_n \cdot D_n^4)$ . The resistance for each generation so calculated is shown in the last column of **Table 1**.

In the next five paragraphs, we will use the data in **Table 1** to determine what value should be set for  $\Delta P_{mic}$  in **Eq. 5**. Suppose the cardiac output for the central circulation of **Table 1** is set at 1.38 L/min, the arterial blood pressure at 140 mmHg, and the venous blood pressure at 0, then we can find a value for A to generate the distribution of blood pressure (the solid line) shown in **Figure 2A**. This distribution of blood pressure along the S-axis will be taken as that of the patient whose HD has been just initiated.

Based on the studies of Minutolo et al. (2003) and LaForte et al. (1994), the drop in the arterial blood pressure at the end of HD  $\Delta P_a$  is 20 mmHg while the drop in venous blood pressure  $\Delta P_v$  is -3 mmHg. By guessing the cardiac output as 1.21 L/min, setting  $P_v'$  as -3 mmHg, and using the resistance distribution shown in **Table 1** to do the pressure calculation, the distribution of blood pressure at the end of HD is shown as the solid line in **Figure 2B**. The pressure distribution shown in **Figure 2A** indicates that the pressure in the microcirculation to drop from 110 to 4 mmHg at the beginning of HD, while **Figure 2B** indicate that the drop is from 94 to 0.2 mmHg at the end of HD.

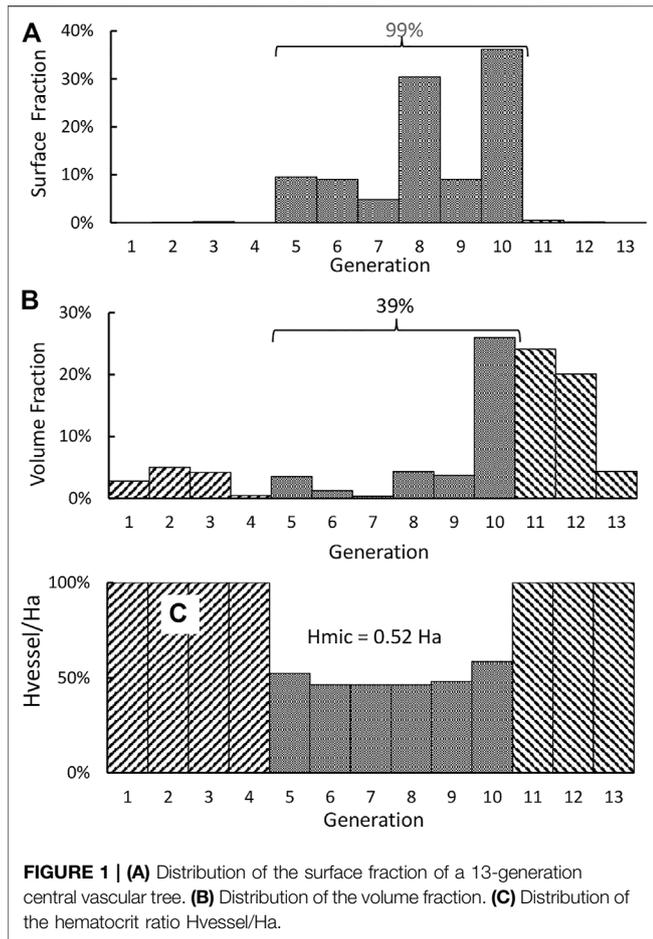
Let  $P_b$  be  $\sigma \pi p(0) + P_t - \sigma \pi t$ . These four pressures  $P_b$ ,  $\pi p$ ,  $P_t$ , and  $\pi t$  may be considered as constants as one moves along from the arterial end to the venous end of the microcirculation. The

fluid flux  $J_f$  in **Eq. 2** generated over the microvascular surface at time 0 is now calculated as:

$$J_f = \int_0^1 KSo (P - P_b) dS = KSo (P_{mic} - P_b) \quad (11)$$

If  $KSo$  is a constant, then the last equality of **Eq. 11** shows that  $P_{mic}$  is a surface average of the blood pressure in the microcirculation. The integration of the beginning pressure  $P$  shown in **Figure 2A** yields 19.2 mmHg as the value of  $P_{mic}$ . It is noted that  $P_b$  is used in **Eq. 11** to show that  $P - P_b$  is the net pressure driving the fluid flux  $J_f$ . The presence of  $P_b$  in **Eq. 11** has no effect on the determination of  $P_{mic}$ . With  $P_{mic}$  so determined, we plot the line  $P = P_{mic}$  as the dotted line in **Figure 2A**. The intercept between the dotted line and solid line as pointed by an arrow in **Figure 2A** corresponds to an S of 0.22, a location that is slightly downstream of the entrances of capillaries. We choose  $P_b$  as 17.2 mmHg so that there is a net driving pressure of 2 mmHg to produce the filtration flux before the initiation of HD (Patients with anemic hematocrit and a body weight of 54 Kg has the KS product as 0.85 ml/min/mmHg. This 2-mmHg pressure is chosen such that the fluid flows through the interstitial corresponding to a lymphatic flow of 1.7 L/day (= 2 mmHg · 0.85 ml/min/mmHg)). The line  $P = P_b$  is plotted as the broken line in **Figure 2A**. Then, the up arrows in **Figure 2A** originated from the broken line represent filtration for that portion of microcirculation, while the down arrows represent absorption.

We can add the resistances up to form a R-axis like the formation of the S-axis. Then, the plot of the blood pressure  $P$  against the R-axis will be a straight line with a negative slope. Let the total resistance be  $R_t$ . The intercept pointed at by the big

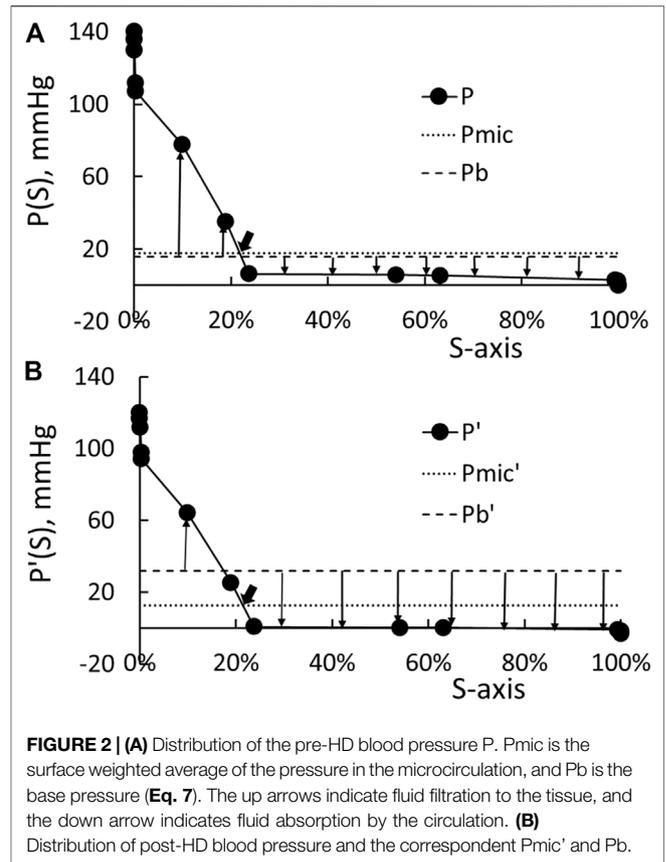


arrow in **Figure 2A** has  $f R_t$  as its resistance with the resistance fraction  $f$  taking 0.9 as its value. This is to say that the  $P_{mic}$  can be calculated as:

$$P_{mic} = (1 - f)P_a + fP_v \tag{12}$$

The computation of the area over the part of blood pressure covered by the up arrows yields the filtration flux  $Q_f$  as one driven by a pressure differential of 11.3 mmHg (i.e., the flux is 11.3 mmHg  $K_{So}$ ), while the absorption flux  $Q_a$  as one driven by  $-9.3$  mmHg. The sum of the filtration and absorption flux is the net flux which is driven by 2 mmHg.

By the end of HD, the arterial blood pressure drops by about 20 mmHg while the venous blood pressure by 3 mmHg (LaForte et al., 1994; Minutolo et al., 2003). We then guess a cardiac output, set the venous pressure at  $-3$  mmHg, and use the resistances listed in **Table 1** to calculate the pressure distribution such that the calculated arterial blood pressure will now be 120 mmHg. The distribution of  $P'$  so calculated is shown as the solid line in **Figure 2B**. The microvascular blood pressure  $P_{mic}'$  now takes 14 mmHg as its value. It is located at an  $S'$  of 0.215 and its correspondent resistance fraction  $f'$  takes 0.88 as its value. Because these  $S'$  and  $f'$  closely approximate the  $S$  and  $f$  derived from the blood pressure before the HD, we use the

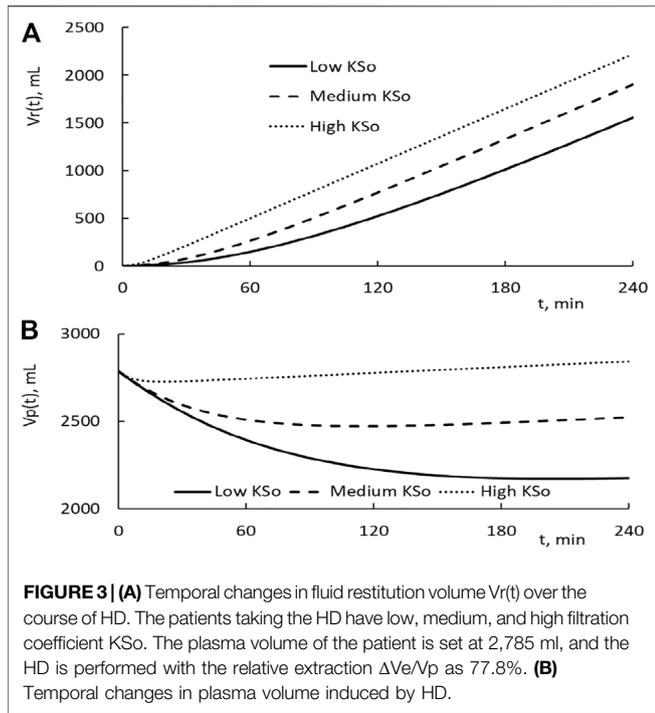


following formula to determine the change in microvascular blood pressure  $\Delta P_{mic}$ :

$$\Delta P_{mic} = (1 - f)\Delta P_a + f\Delta P_v \tag{13}$$

In the CHRE of LaForte et al. (1994), they found that the drops in arterial and venous blood pressure are linearly related to the reduction in blood volume. The substitution of the linear relations to **Eq. 13** yields **Eq. 6** given earlier. The value of  $\zeta$  is calculated as 36.7 mmHg for conscious rabbits and 23.7 mmHg for anesthetized rabbits. Because of the dependence on the consciousness of the rabbits, we term  $\zeta$  as an autonomous constant.

In the following three paragraphs, we describe how  $\Delta V_r$ ,  $Cr$ , and  $\gamma$  are related to the transvascular fluid and protein movement and what value should be used as  $\gamma$ . For patients with normal hematocrit, the HD induces the COP to increase by 16 mmHg ( $= \Delta \pi_r$ ). The new base pressure  $P_b' (= P_t + \pi_r' - \pi_t = P_b + \Delta \pi_r)$  is now set as 33.2 mmHg ( $= 17.2$  mmHg + 16 mmHg). The line  $P' = P_{mic}'$  and  $P' = P_b'$  are plotted as the dotted and broken line in **Figure 2B**, respectively. As one sees the filtration arrows in **Figure 2B** are shorter than those depicted in **Figure 2A**, while the absorption arrows in **Figure 2B** are longer than those in **Figure 2A**. The pressure producing the filtration flux  $Q_f'$ , absorption flux  $Q_a'$ , and net flux ( $= Q_f' - Q_a'$ ) are driven by these pressure differences 6.0,  $-25.2$ , and  $-19.2$  mmHg, respectively.



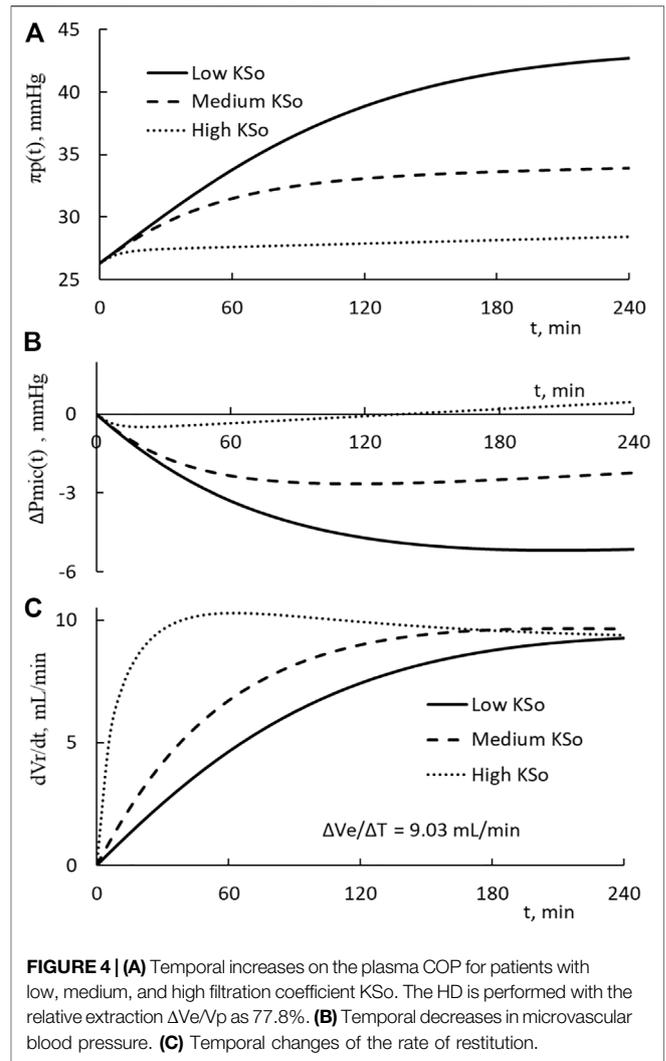
On the arterial side of the microcirculation, the fluid in the vascular side is being filtrated at the rate  $Q_f(t)$  from the circulation to the tissue. Let the protein concentration of the filtrated fluid be  $C_{r,f}$ . The semi-permeability of the endothelial lining may only allow a fraction of the protein in the plasma to filtrate to the tissue, i.e.  $C_{r,f}$  will be smaller than  $C_p$ . On the venous side, the fluid in the tissue is being absorbed to the circulation at a rate of  $Q_a$ . Let the protein concentration of the interstitial fluid be  $C_t$  and that of the absorbed or restituted fluid be  $C_{r,a}$  which is a fraction of  $C_t$ . The integration of these fluid and protein fluxes over the HD time yields the following two integrals:

$$\Delta V_r = \int_0^{\Delta T} [Q_a(t) - Q_f(t)] dt \quad (14)$$

$$\Delta V_r C_r = \int_0^{\Delta T} (Q_a(t)C_{r,a}(t) - Q_f(t)C_{r,f}(t)) dt = \Delta V_r \gamma C_p \quad (15)$$

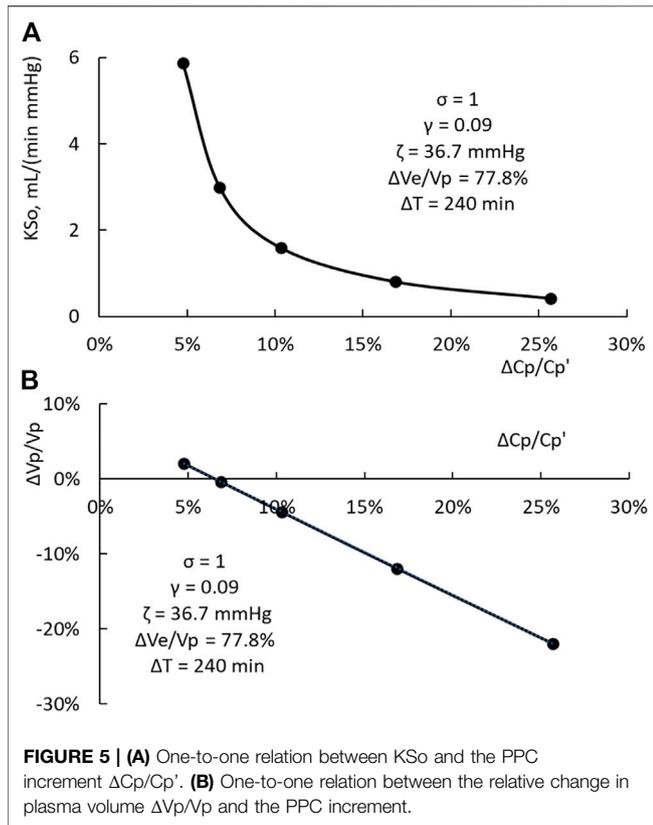
The permeability fraction:  $\gamma$  is the integral in **Eq. 15** divided by  $\Delta V_r C_p$ . Beyond the formula given by **Yuan and Rigor (2011)** on transvascular protein movement, more information on the quantities within the two integrals in **Eqs 14, 15** are required for calculating the value of  $\gamma$ .

As an alternative, we used in our previous analysis the following reasoning to deduce 0.09 as the value for  $\gamma$ . First, we set over the pre-HD time, the protein concentration of the filtration to the tissue  $C_{r,f}$  in this form  $\gamma^{1/2} C_p$ . As the interstitial fluid space is being flushed by this fluid for a long time, the protein concentration of the interstitial fluid  $C_t$  can take  $C_{r,f}$  as its value. Over the course of HD, the endothelia may allow



a similar fraction of protein to be restituted back to the circulation. Thus, we take the protein concentration of the restituted fluid as  $\gamma^{1/2} C_t$  which is also  $\gamma C_p$ . On their study of the composition of interstitial fluid, **Fogh-Andersen et al. (1995)** reported that the PPC of their subjects in supine position is 6.86 g/dl and the protein concentration of interstitial fluid is 2.06 g/dl. These two protein concentrations lead us to set the value of  $\gamma^{1/2}$  as 0.3 ( $\approx 2.06/6.86$ ). This selection is equivalent to set  $\gamma$  as 0.09. As a sensitivity check, some computations on  $\Delta V_p/V_p$  are made later on with 0.4 as the value of  $\gamma$ .

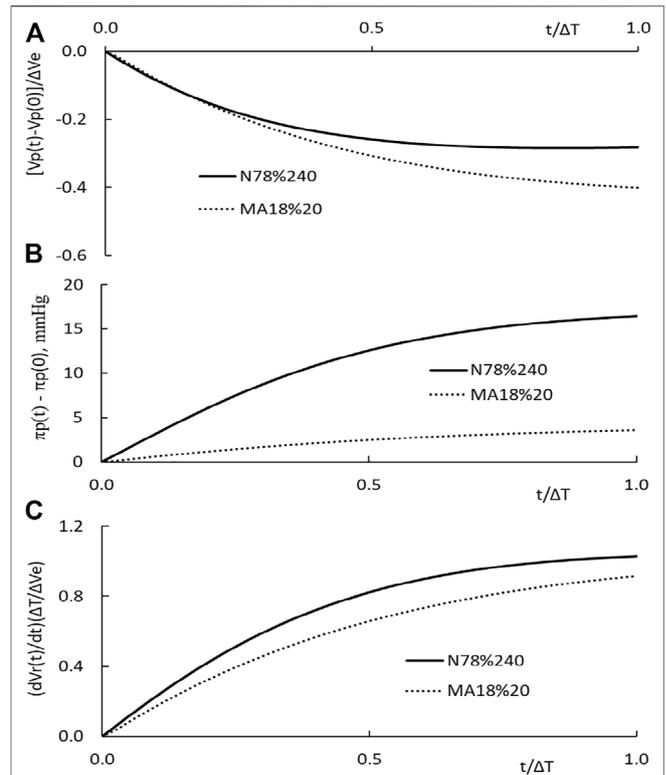
*Dynamics of transvascular fluid and protein movement.* The time courses of the restitution volume  $V_r(t)$  for the HD with low, medium, and high  $K_{So}$  are depicted as the solid, broken, and dotted line, respectively, in **Figure 3A**. As one can see that the initial rise in restitution volume is much higher for patients with higher  $K_{So}$ . Over the later time, the rate of increase in  $V_r$  becomes comparable for the three HDs. Because of their difference over the early stage of HD, more fluid is restituted from the tissue for patients with higher  $K_{So}$ .



The subtraction of the extraction from the restitution is the reduction in plasma volume. Its time courses for the three HDs are depicted in **Figure 3B**. As the HD is initiated, the plasma volume is in a decreasing trend. Around the time of 24, 114, and 210 min, the plasma volume of the high, medium, and low KSo HD turns to an increasing trend, respectively. An increasing trend means that the rate of fluid restitution at that time is higher than the extraction rate. The decrease in  $V_p$  at the end of HD is larger for patients with lower KSo.

The changes in plasma COP, microvascular blood pressure, and the rate of fluid restitution are shown in **Figures 4A–C**. The results on COP indicate that the PPC is in a monotonic increasing trend over the course of HD. The end COP is the largest for patients with the lowest KSo. The rate of restitution is shown to rise as the time progresses and then approaches asymptotically to about 9.3 ml/min which is slightly higher than the extraction rate of 9.03 ml/min.

The calculations presented in **Figures 3, 4** are made with the same initial conditions of  $V_p$ ,  $V_b$ , and  $C_p$ , the same modeling constant  $\gamma$ ,  $\zeta$  and the same HD parameters  $\Delta V_e$  and  $\Delta T$ . The differences among the three HDs shown in **Figures 3, 4** are the result that the filtration coefficient set for HD is different. However, there is one exception on the rate of restitution near the end of dialysis. At that time, the rates of the three HDs are about the same. **Eq. 9b** is made up of  $\Delta V_e/V_p$ , which describes how the extraction is to increase the PPC, and a term proportional to  $\Delta V_r(t)/V_p$ , which describes how the restitution is to dilute the PPC. Initially the increase in



**FIGURE 6 | (A)** Temporal changes in plasma volume of N78% HD carried out in patients with normal hematocrit (solid line) and that MA18%20 HD carried out in patients with more anemic hematocrit (dotted line). **(B)** Temporal changes in plasma COP  $\pi p(t)$  of the two HDs. **(C)** Temporal changes in the normalized rate of restitution  $dV_r(t)/dt$ .

restitution volume is small and the restitution dilution is low. The high initial increment in PPC ( $\Delta C_p(t)/C_p'(t)$ ) leads to a rapid increase in  $\pi p(t)$ ,  $V_r(t)$ , and restitution dilution. Then, the increase in restitution dilution as indicated by **Eq. 9b** will slow down the rise in PPC. As the rate of restitution rises to the rate extraction, the PPC will increase no more. The plateauing of the restitution rate to the extraction rate, as shown in **Figure 4C**, is a condition projected by **Eqs 5, 9b**.

We can calculate the total driving pressure and the pressure fraction,  $\Delta P_{mic}(t)/[(\Delta \pi p(t) - \Delta P_{mic}(t))]$ . At 1 h, the fractions of low, medium, and high KSo HD take these percentages 31, 32, and 23.6%, respectively. The correspondent values at the end of HD are 23.9%, 22.6%, and -28.9%. These percentages indicate that the reduction in microvascular blood pressure contributes about 30% of the driving pressure to reconstitute the fluid from the tissue.

For these three HDs, the filtration coefficient is the only variable being changed. The computation results indicate that KSo and  $\Delta V_p/V_p$ , as shown in **Figure 5**, have a one-to-one relation with the PPC increment  $\Delta C_p/C_p'$ . The data points in **Figure 5A**, computed from **Eqs 8, 9b**, can be matched by a straight line with a slope of 1.09 and a correlation coefficient ( $R^2$ ) of 0.9996. If 0.4 is set as  $\gamma$ , the relation between  $\Delta C_p/C_p'$  and  $\Delta V_p/V_p$  is slightly curvilinear. The slope of the straight line fit is

**TABLE 2** | Organ weights, volumes of minute vessels, microvascular hematocrit, and the organ KSn product of a normal dog<sup>a</sup>.

	OWN, g	Vmic,n, mL	Vmic,n/OWN mL/g	Vb,n, mL	Hmic,n/Ha	KSn/OWN	KSn
Spleen	72	36.7	0.510	47.5	2.07		
Liver	99	37.1	0.375	76.2	0.31	0.80	1.15
Lungs	252	29.9	0.119	65.2	0.78	4.55	0.15
Kidneys	58	4.7	0.081	25.7	0.21		
Heart	83	5.6	0.067	11.2	0.52		
Bowel	350	14.4	0.041	38.3	0.36		
Muscle	3540	57.1	0.016	130.4	0.45	0.14	0.50
Brain	62	2.0	0.032	6.6	0.21		

<sup>a</sup>The data in the 2nd to 6th column are derived from **Table 1** of Gibson et al. (1946). OWN stands for organ weight. The total blood volume Vb of the dog is 1,150 ml, and the dog weighs 11.9 kg. The units of KSn/OWN and KSn are mL/(min mmHg kg) and mL/min/mmHg, respectively.

1.47 and the  $R^2$  is 0.994. For a HD,  $\Delta C_p/C_p'$  can be measured readily. If the HD is done with a  $\Delta V_e$  and  $\Delta T$  similar to those used to derive the results shown in **Figure 5**, then the relations depicted in **Figure 5A** can be used to provide the first estimate of KSo and  $\Delta V_p/V_p$ .

The time course of the plasma volume, PPC, and the restitution rate of N78% and MA18%20 HD is depicted in **Figure 6**. The HD with patients of normal hematocrit has  $\Delta V_e/V_p$  as 77.8%, and  $\Delta T$  as 240 min. The  $\Delta V_e/V_p$  of the MA18%20 HD is 18.4%, and its  $\Delta T$  as 20 min. The filtration coefficients used in the computations are 0.43 and 5.88 ml/min/mmHg, respectively. Their rate of extraction  $\Delta V_e/\Delta T$  is 9.0 and 36.5 ml/min. To put these results for comparison, we normalize the time scale  $t$  of the figure by  $\Delta T$ , the plasma volume change by  $\Delta V_e$ , and the rate of restitution by  $\Delta V_e/\Delta T$ . A comparison of these results with those shown in **Figure 3** indicates that a change in  $\Delta V_e$  and  $\Delta T$  can significantly change the time courses of  $V_p(t)$  and  $dV_r(t)/dt$ .

**Multiple circulation system.** Gibson et al. (1946) obtain tissue samples cleared of visible blood vessels and used the tagged RBC and plasma protein methodology to measure the blood volume of minute vessels in eight organs and the hematocrit of blood in minute vessels. The organ weight, total microvascular blood volume, and total blood volume of the eight organs are given in **Table 2**. The distribution of microcirculation volume  $V_{mic,n}$  and the ratio of the microvascular hematocrit  $H_{mic,n}$  to  $H_a$  of the eight organs are listed in the 6th column of **Table 2**. In reference to the weight of the  $n$ th organ (OWN),  $V_{mic,n}/OWN$  for these eight organs is in the range of 0.016–0.77 ml/g. We also calculate the normalized total blood volume of the  $n$ th organ ( $V_{b,n}/OWN$ ) to highlight that the organ blood volume count is distributed over a wide range of 0.11–0.77 ml/g. The microvascular hematocrit of the spleen is 2.07 times of the arterial hematocrit. The other seven organs have a microvascular hematocrit in the range of 0.22–0.78 times of  $H_a$ . The volume weighted microvascular hematocrit for the seven organs (no spleen) is 0.47  $H_a$ .

Measured by the isogravimetric technique, the  $K_{Sn}/OWN$  of the liver (Bennett and Rothe 1981), lung lobe (Lee et al., 1996), and hindlimb (identified as the muscle, Michel 1984) are listed in the 8th column of **Table 2**. In view of the alveolar structure of the lung and the dense vasculature of the liver, the endothelial surface area of the lungs per unit lung weight ( $S_n/OWN$ ) may be the largest of the three organs and that of the muscle is the smallest.

The value of  $K_{Sn}/OWN$  and  $K_{Sn}$  are listed in the last two columns of **Table 2**.

The circulatory system is consisted of the vascular trees of various organs. From the perspective of the circulatory system, these trees can be viewed as multiple circulations arranged in parallel. Let the filtration coefficient of the  $n$ th circulation be  $K_{Sn}$  and its plasma volume be  $V_{p,n}$ . Then, we set the filtration coefficient KSo and the total plasma volume  $V_p$  of the circulatory system at:

$$K_{So} = \sum_{n=1}^m K_{Sn} \quad (16a)$$

$$V_p = \sum_{n=1}^m V_{p,n} \quad (16b)$$

For the given  $\Delta V_e$  and  $C_p$ , we can use the values of KSo and  $V_p$  so determined to calculate  $C_p'$ ,  $\Delta C_p/C_p'$ ,  $\Delta V_r$ ,  $\Delta V_p$ ,  $\Delta P_{mic}$ , and  $\Delta \pi_p$ .

Let us define the KS fraction  $\lambda_n$  of the  $n$ th circulation as:

$$\lambda_n = K_{Sn}/K_{So} \quad (17)$$

and assign  $\lambda_n \Delta V_e$  as the extraction imposed to the  $n$ th circulation,  $\lambda_n V_p$  as its plasma volume, and  $\lambda_n V_b$  as its blood volume.  $\lambda_n \Delta V_r$  will be set at the fluid volume restituted from the  $n$ th circulation. The substitution of these parameters into **Eqs 5–10** will reveal that all  $\lambda_n$  values are canceled out, and the five equations remain in the same forms. Remaining in the same form means that the values of  $C_p'$ ,  $\Delta C_p/C_p'$ ,  $\Delta P_{mic}$ , and  $\Delta \pi_p$  calculated for the  $n$ th circulation will be identical to those derived for the multiple circulation system. This identity justifies the use of **Eq. 16a** to derive the KSo of the entire circulatory system. The limited data on  $K_{Sn}$  shown in **Table 2** suggest that a significant fraction of the fluid restituted from the tissue through HD would be derived from the liver.

The plasma volume  $V_{p,n}$  set for the  $n$ th organ with the  $\lambda_n$  in **Eq. 17** may not be the true plasma volume of that organ. Thus, the PPC of the plasma coming out from the  $n$ th organ will be different from the one calculated for the multiple system. As the plasma is being mixed in the heart chambers, the mixed final PPC becomes the one predicted by the FCA for the multiple system.

The FCA of PPC increment induced by the HD of more anemic patients indicates that the value of  $K_{So}/BW$  is 0.11 ml/(min mmHg kg). If we apply this value to a dog of 11.9 Kg, then its KSo will be 1.33 ml/(min mmHg), which is smaller

than the sum of the three values given in the last column of **Table 2**.

*Microvessel hematocrit, whole body hematocrit, and Fcell ratio.* In FCA, the circulation (not including the splenic microcirculation) is divided into a microcirculation and a macrocirculation compartment. Their blood volumes are designated as  $V_{mic}$  and  $V_{mac}$ . The hematocrit of the blood in these two compartments are  $H_{mic}$  and  $H_a$ . We use the fractional numbers  $\alpha$  and  $\beta$  to describe the following relations:

$$H_{mic} = \alpha H_a \quad V_{mic} = \beta V_b \quad V_{mac} = (1 - \beta)V_b \quad (18)$$

The whole blood hematocrit  $H_w$ , the total RBC volume of the two compartments divided by the blood volume, and the  $F_{cell}$  ratio ( $=H_w/H_a$ ) of the two compartment circulation can be calculated as:

$$H_w = (H_a V_{mac} + H_{mic} V_{mic})/V_b = (1 - \beta)H_a + \alpha\beta H_a \quad (19a)$$

$$F_{cell} \equiv H_w/H_a = 1 - \beta + \alpha\beta \quad (19b)$$

**Eq. 19a** indicates that  $H_w$  is a volume weighted average hematocrit of the two compartments. We can form a full circulation by adding the pulmonary circulation and the four heart chambers to the central circulation shown in **Table 1**. The sum of the microvessel blood volumes in this full circulation yields a value of  $\beta$  close to 0.326. The volume weighted hematocrit of the full circulation yields a value of  $\alpha$  close to 0.54. The selection of 0.326 and 0.54 will make the  $F_{cell}$  defined in **Eq. 19b** to take 0.85 as its value. If we set the volume of splenic microcirculation that contains high hematocrit blood as 4.2% of  $V_b$  and its hematocrit as 2.07  $H_a$ , the  $F_{cell}$  for the micro- and macrocirculation and the splenic microcirculation will be increased to 0.90.

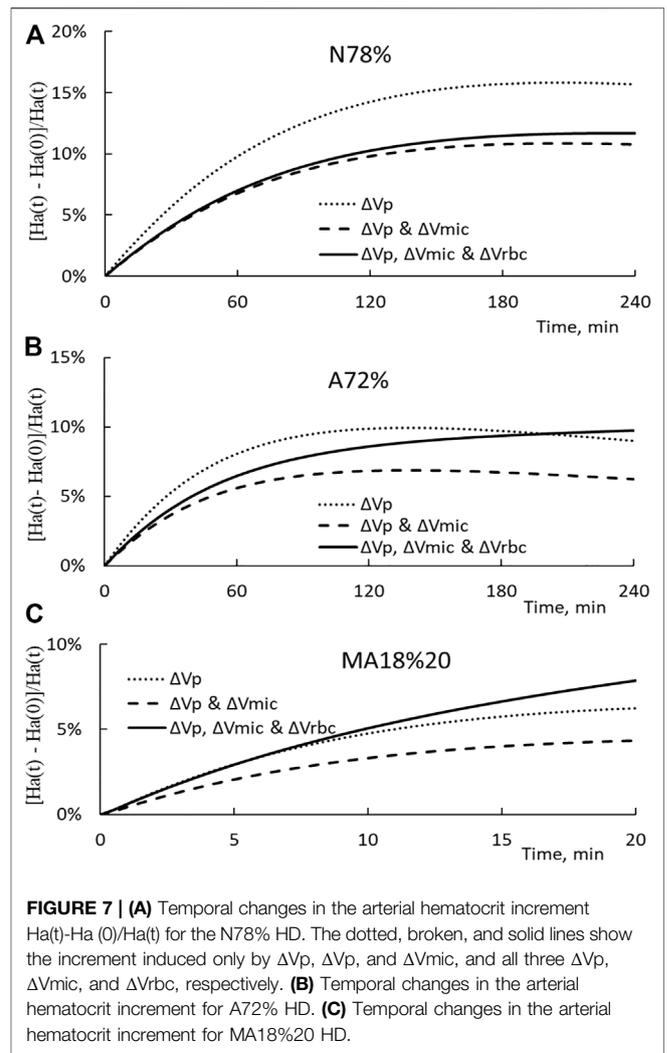
For comparison, *Dasselaar et al. (2007)* reported that the  $F_{cell}$  ratio measured for their HD patients is  $0.896 \pm 0.036$ . In their article, *Chien and Gregersen (1962)* point out that  $F_{cell}$  of subjects is 0.9 and that of subjects with no spleen is 0.85.

The initial value of  $\beta$  is 0.326. As the time progresses, the microvascular blood volume and the blood volume will be decreased by the HD. As calculated for N78% HD, the value of  $\beta$  derived from the FCA is reduced to 0.273 and the  $F_{cell}$  ratio is increased to 0.874. For calculations, we assume that the fractional constant  $\alpha$  is not altered by the change in microvascular blood volume.

*Factors changing the arterial hematocrit.* A change in plasma volume  $\Delta V_p$ , a change in microvascular blood volume  $\Delta V_{mic}$ , and a shift of the concentrated RBC from the spleen  $\Delta V_{rbc}$  to the circulation lead to the following change in the arterial hematocrit of blood circulating through the macrocirculation:

$$\Delta H_a/H_a' = [-\Delta V_p/V_b + (1 - \alpha)\Delta V_{mic}/V_b + (\Delta V_{rbc}/V_b)/H_a']/F_{cell} \quad (20)$$

This equation is derived from the conservation of RBC in the macrocirculation compartment and is termed as the hematocrit equation.



**FIGURE 7 | (A)** Temporal changes in the arterial hematocrit increment  $H_a(t)-H_a(0)/H_a(t)$  for the N78% HD. The dotted, broken, and solid lines show the increment induced only by  $\Delta V_p$ ,  $\Delta V_p$ , and  $\Delta V_{mic}$ , and all three  $\Delta V_p$ ,  $\Delta V_{mic}$ , and  $\Delta V_{rbc}$ , respectively. **(B)** Temporal changes in the arterial hematocrit increment for A72% HD. **(C)** Temporal changes in the arterial hematocrit increment for MA18%20 HD.

The results of CHRE indicate that the reduction in microcirculation blood volume due to hemorrhage is linearly related to the reduction in blood volume by the following equation:

$$\Delta V_{mic} = \eta \Delta V_b \quad (21)$$

The constant  $\eta$  takes 0.65 as its value (*LaForte et al., 1994*). In view of the large volume distributions in the small veins (**Table 1**), most of the  $\Delta V_{mic}$  could be originated from the volume reduction of small veins (the 10th generation).

In our previous analysis on the data of A72% and Ma18%20, if  $\Delta V_{rbc}$  is set as zero, the FCA projects that the microcirculation would be dilated by 3.3% $V_b$  and 2.5% $V_b$ , respectively. The arterioles are the only microvessel generation that could be induced by HD to dilate. As shown in **Table 1**, the arterioles contain only 1.2% of the blood volume. The large dilatation percentages estimated for  $\Delta V_{mic}/V_b$  indicate that the spleen is activated by the HD to release the concentrated RBC at these volumes ( $\Delta V_{rbc}^*$ ): 0.03% $V_b$  (N78%), 1.09% $V_b$  (A78%), and 0.91% $V_b$  (MA18%). These percentages are derived with  $\eta$  set

as 0.65. If we decrease  $\eta$  to 0.4 (i.e., the microcirculation is more rigid), the FCA projects that the spleen of patients of normal hematocrit is induced by N78% HD to retain 0.74% Vb of the concentrated RBC from the general circulation. The reduction in total radioactivity of the tagged RBC in the spleen found by Yu et al. suggests that the spleen is not likely to be activated by the HD to retain RBC from the central circulation.

To illustrate how splenic RBC release and microvascular volume reduction change arterial hematocrit over the course of HD, we set  $\Delta V_p/V_p$  as the one derived from Eq. 7,  $\Delta V_{mic}$  as the one derived from Eq. 21 with  $\eta$  set at 0.65, and  $\Delta V_{rbc}(t)$  computed from the following linear function of t:

$$\Delta V_{rbc}(t) = \Delta V_{rbc}^* \cdot \frac{t}{\Delta T} \quad (22)$$

The arterial hematocrit  $Ha(t)$  is calculated first with  $\Delta V_p$  only (the dotted line), then  $\Delta V_p$  and  $\Delta V_{mic}$  (the broken line), and finally with  $\Delta V_p$ ,  $\Delta V_{mic}$ , and  $\Delta V_{rbc}$  (the solid line). The hematocrit changes for N78%, A72%, and MA18%20 HD are presented in Figures 7A–C respectively. It is noted that the end point of the solid line corresponds to the hematocrit  $Ha'$  measured in the experiments. The results shown in the figure indicate that the reduction in the microvascular blood volume will reduce the hematocrit from that induced by the plasma volume change. In the opposite direction and as expected, splenic RBC releases will lead to an increase in the arterial hematocrit.

If HD does not induce the spleen to release its highly concentrated blood to the circulation (i.e.  $\Delta V_{rbc} = 0$ ) and the microcirculation is rigid so that  $\Delta V_{mic} = 0$ , then Eq. 20 is simplified to the following form:

$$\Delta Ha/Ha' = -\Delta Vb/Vb/F_{cell} \quad (23)$$

If we set  $F_{cell}$  at unity and replace  $\Delta V_p$  by  $\Delta V_b$  (Eq. 8), then Eq. 23 is further simplified to VBHE, which is widely used to determine the relative change in the blood volume (RCBV and  $\Delta V_b/V_b$ ) induced by HD. For the N78%, A72%, and MA18%20 HD, the VBHE projects that the patients would have RCBV as -11.7%, -10.2%, and -7.9%, respectively. The correspondent changes derived from the previous FCA are -14.5%, -8.3%, and -5.6%.

The RCBV measured by a tagging technology is assessed as -17.3% and that calculated by VBHE is -8.2% (Dasselaar et al., 2007). They conclude that the VBHE underestimates RCBV for patients with normal hematocrit and overestimates for patients with anemic hematocrit. The hematocrit of their patients is about 40% which is slightly below the normal hematocrit (42.4%) referred in this article. Their conclusion is compatible to our finding that the RCBV derived from the VBHE for patients with normal hematocrit is smaller than the RCBV derived from the FCA.

**Reduction in macrovascular blood volume.** Since the sum of macro- and microvascular blood volume is the total blood volume, we have the change in macrovascular blood volume as:

$$\Delta V_{mac} = \Delta V_b - \Delta V_{mic} \quad (24)$$

In view of the large volume fractions of the venous macrocirculation (Table 1), most of the  $\Delta V_{mac}$  could be originated from the venous macrocirculation. For N78%, A72%, and MA18% HD, the FCA projects the macrovascular volume reduction values ( $\Delta V_{mac}/V_b$ ) are -4.9%, -2.9%, and -2.0, respectively.

The venous macrocirculation has been regarded as a volume reservoir that can be used to improve venous return and cardiac filling. Because the right atrium resides downstream of the venous macrocirculation, it is likely that the macrovascular blood volume reduction derived from the FCA can be used as an index in characterizing whether the cardiac filling is being reduced by the HD.

**Comparisons with other experimentations and analyses.** LaForte et al. (1994) carried out their hemorrhage (5, 10, and 15% of the blood volume) in 2 min and then reinfusion in the next 2 minutes. Over this short period, the volume of the fluid restituted from the tissue will be much smaller than that of HD performed over 4 h. Similar changes in the hematocrit are also found for rabbits with their spleen removed (LaForte et al., 1992). Thus, the hematocrit decreases over the 2-min hemorrhage is generated mostly by a reduction in the microvascular volume. For 10% hemorrhage experiments, they found that the PPC is reduced by  $0.027 \pm 0.008$  g/dl and the hematocrit by  $1.20 \pm 0.04\%$ . The correspondent PPC increment  $\Delta Cp/Cp'$  is 0.5%, and the hematocrit increment  $\Delta Ha/Ha'$  is 3.6%. The analysis of the protein and hematocrit data yields these estimations:

- (i) The splenic RBC release is minimally induced by CHRE, and the rabbit's microcirculation functions like a passive elastic system.
- (ii) The hemorrhage volume of 7% is derived from the fluid being restituted from the tissue over 2 min, 60% from the reduction in microvascular blood volume (=  $\Delta V_{mic}$ ), and 33% from the reduction in macrocirculation blood volume (=  $\Delta V_{mac}$ ),
- (iii) The filtration coefficient of rabbit as projected by FCA is 0.21 ml/(min mmHg kg). The correspondent estimate derived from FCA of three HDs has the filtration coefficient in the range of 0.008–0.085 ml/(min mmHg kg).
- (iv) If the VBHE is used to compute  $\Delta V_b$  and Eq. 7 to calculate  $\Delta V_r$ , then the calculation by Eq. 5 will yield 1.08 ml/(min mmHg kg) as the filtration coefficient of the rabbit, which is almost 5 times larger than the one estimated by the FCA.

For the HDs analyzed here, the dialysis is done over a long period of time, the fluid volume restituted from the tissue can be significantly larger than that generated from the CHRE of rabbits. As a result, the PPC and hematocrit increments found for the three HDs analyzed here have comparable values. The difference between these two increments indicates that the HD does induce significant change in microvascular blood volume and cause the spleen to release RBC to the circulation.

On the MA18%20 HD, Schneditz et al. (1992) used a protein analysis to derive the RCBV. Then the matching of the RCBV with that derived from the hematocrit data leads to a projection that the filtration coefficient of the more anemic patients is 5.6 ml/(min mmHg 50 Kg). This is equivalent to set the value

of KSo as 7.74 ml/min/mmHg (= 69.1 Kg (BW) X 5.6 ml/(min mmHg 50 Kg)). In our FCA, we match the projected Cp' with the measured one and deduced KSo as 5.9 ml/min/mmHg. The difference in data matching (hematocrit vs PPC) may be the reason that the estimate of Schneditz et al. (1992) on KSo is different from our estimate.

### 3 CONCLUDING REMARKS

In this article, we use the FCA to determine from the protein data of the three HD studies, namely, the restitution volume, the change in plasma volume, and the filtration coefficient of patients with normal, anemic, and more anemic hematocrit. To further verify FCA and the modeling of the circulation, we recommend that the following experiments be performed:

- (i) The making of hourly PPC measurements over the course of HD. The measurements will verify whether the FCA projected the temporal changes in PPC correctly.
- (ii) A total of two HDs with two different relative extractions (i.e., at two  $\Delta V_e/V_p$ ) deriving the filtration coefficients from the protein data of these two HDs should have the same value. In cases that they do not, a different guess on the filtration coefficient and permeability fraction may lead FCA to generate results that can match the two measured PPC increments.
- (iii) The performance of the tagged protein and RBC experiments of Dasselaar et al. (2007) and the use of their procedure projected the reduction in plasma volume. With the PPC also measured in these experiments, then we can examine whether the reduction in plasma volume projected by FCA matches that by the tagging technology.
- (iv) The performance of the CHRE for the determination of  $\eta$  so that Eq. 20 can be used to determine the splenic RBC release.
- (v) Yu et al. (1997) found that the splanchnic radioactivity decreases to 90% of the baseline value after 2 h of the accelerated fluid removal during dialysis. The volume reduction of the splanchnic macrocirculation can cause a

decrease in radioactivity. If this radioactive technology can be shown to measure the splenic RBC release, then we have an independent way to verify the splenic RBC release projected by FCA.

The analysis of HD data with patients grouped according to their hematocrits leads to the recognition that patients having higher hematocrits are to have a smaller filtration coefficient and the suggestion that the filtration coefficient is a facilitator to generate more fluid restitution. As a result, we have a better compensation to the fluid extraction by the dialyzer and a lesser reduction in plasma volume for patients with lower hematocrit. It will be of interest to group patients according to their frequency of having intradialytic hypotension and/or their blood pressure variability (Flythe and Brunelli 2014) so that we can better understand what other factors can also be a limiting factor on having more fluid restitution. Through these experiments and data comparison, a better understanding of the factors inducing hypovolemia for patients taking HD can be the basis for one to modify the HD process such that the development of hypovolemia can be avoided over the course of HD.

### DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

### AUTHOR CONTRIBUTIONS

These authors J-SL and L-PL have contributed equally to this work and share first authorship.

### FUNDING

The funding for this research was provided by Global Monitors, Inc.

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**Conflict of Interest:** The authors JS. Lee and LP. Lee are the owners of Global Monitors Inc. and are employed by Global Monitor Inc. Funding for this research was provided by Global Monitors, Inc.

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## 4 APPENDIX: EQUATIONS AND COMPUTATION PROCEDURE

The entire HD period is divided into  $M$  segments. For each segment  $[i \cdot dt$  to  $(i + 1)dt]$ , the volume of fluid extracted by the dialyzer is  $dVe$  ( $= \Delta Ve/M$ ). The initial value  $Cp(0)$ ,  $Vp(0)$ , and  $Vb(0)$  are correspondent to the one set for  $Cp$ ,  $Vp$ , and  $Vb$  in **Eqs 3–5**. In addition, we also have  $Vr(0)$  as zero. To start the calculations, we will set a value as  $KSo$ . Then, we guess the PPC increment for the  $i$ th segment as  $dCp$ . The values of various variables are computed by the following equations:

$$Cp(i + 1) = Cp(i) + dCp \quad (A1)$$

$$Vr(i + 1) = Vr(i) + [dVe - dCp Vp(0)/Cp(i + 1)] / (1 - \gamma Cp(0)/Cp(i + 1)) \quad (A2)$$

$$Vp(i + 1) = Vp(i) + Vr(i + 1) - Vr(i) - dVe \quad (A3)$$

$$Vb(i + 1) = Vb(i) + Vp(i + 1) - Vp(i) \quad (A4)$$

$$Pmic(i + 1) = Pmic(0) + \zeta [Vb(i + 1) - Vb(0)] / Vb(0) \quad (A5)$$

$$\pi p(i + 1) = 2.1Cp(i + 1) + 0.16Cp(i + 1)^2 + 0.009Cp(i + 1)^3 \quad (A6)$$

$$KS1 = 2[Vr(i + 1) - Vr(i)] / dt / \{ \sigma[\pi p(i + 1) + \pi p(i) - 2\pi p(0)] - Pmic(i + 1) - Pmic(i) + 2Pmic(0) \} \quad (A7)$$

The value of  $dCp$  is changed until the value of  $KS1$  takes the value of  $KSo$ . Then, similar computations are performed for the next segment. The value of  $Cp(M)$ ,  $Vr(M)$ , and  $Vp(M) - Vp(0)$  is taken as  $Cp'$ ,  $\Delta Vr$ , and  $\Delta Vp$ , respectively. The value of  $k$  in **Eq. 4** is computed as

$$(\sigma \Delta \pi p - \Delta Pmic)k = \left[ \int_0^{\Delta T} \{ \sigma \pi p(t) - \sigma \pi p(0) - Pmic(t) + Pmic(0) \} dt \right] \quad (A8)$$

Experimentally, the value of  $Cp'$  is reported. Then, we can use **Figure 5** to set a likely value for  $KSo$ . Iterations will be performed until the resulting  $Cp'$  takes the experimentally measured value. The final value found for  $KS_i$  is taken as  $KSo$  of that patient.

## GLOSSARY

**(t)** Quantity without ' is that at beginning time 0 and with ' that at the end time  $\Delta T$ . For temporal calculations, (t) is added to the quantity.

**BW** Body weight in kg.

**CHRE** Cyclic hemorrhage and reinfusion experiment.

**COP** Colloidal osmotic pressure.

**Cr** The protein concentration in fluid restituted from the tissue to the circulation, Eqs 9, 10.

**FCA** Full circulation analysis. The full circulation is represented by a macrocirculation, a microcirculation, and a splenic microcirculation.

**Fcell** The ratio of the whole body hematocrit to the arterial hematocrit, Eq. 19b.

**HD** Hemodialysis.

**Hw** Whole body hematocrit, Eq. 19a.

**k** Constant in Eq. 5 and Eq. A8.

**KSo** Filtration coefficient with  $S_o$  representing the surface available for filtration

**Pa** Arterial blood pressure.

**Pb** Base pressure which is  $\pi_p - \pi_t - P_t$ . See Eq. 11.

**Pmic** Microvascular blood pressure. See Eqs. 2, 11, 12.

**PPC** Plasma protein concentration.

**Pv** Venous blood pressure.

**RBC** Red blood cell.

**RCBV** Relative change in blood volume.

**Rn** Flow resistance of the  $n$ th generation

**S-axis** Summation of the surface areas upstream of the point in the vasculature divided by  $S_o$ .

**Vb** Blood volume which is the sum of  $V_{mac}$  and  $V_{mic}$ .

**VBHE** van Beaumont hematocrit equation, Eq. 23 with  $F_{cell}$  set at 1.

**Vmac** Macrocirculation volume =  $(1-\beta) V_b$ .

**Vmic** Microcirculation volume =  $\beta V_b$ .

**Vp** Plasma volume =  $(1-H_w) V_b$ .

**Vr** Restitution volume.

$\alpha$  =  $H_{mic}/H_a$ .

$\beta$  =  $V_{mic}/V_b$ . The value of  $\beta$  can change over the course of HD.

$\gamma$  Permeability fraction, Eq. 10.  $\gamma C_p$  is taken as the protein concentration  $C_r$  in the fluid being restituted from the tissue to the circulation.

$\Delta P_{mic}$  Change in microvascular blood pressure =  $P_{mic}' - P_{mic}$ . Eqs 5, 6.

$\Delta T$  HD time.

$\Delta V_e$  Extraction volume or volume of ultrafiltrate being extracted by the dialyzer.

$\Delta V_p$  Change in plasma volume =  $V_p' - V_p$ .

$\Delta V_r$  Restitution volume or the total volume of the fluid restituted from the tissue.

$\Delta \pi_p$  Change in plasma COP =  $\pi_p' - \pi_p$ . Eq. 5.

$\zeta$  Autonomous constant which defines how the autonomous control changes the relation between  $\Delta P_{mic}$  and  $\Delta V_b$ . Eq. 6

$\eta$  Fraction constant relating the change in microvascular blood volume to the change in total blood volume, See Eq. 21.

$\lambda_n$  =  $K_{Sn}/K_{So}$ , where  $K_{Sn}$  is the filtration coefficient of the  $n$ th organ and  $K_{So}$  is that of the microcirculation. Eq. 17.

$\pi_p$  Plasma COP.

$\pi_t$  Tissue COP.

$\sigma$  Reflection coefficient, Eq. 2.