
Concentration of Blood in the Extracorporeal Circuit Using Ultrafiltration

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Abstract

During cardiopulmonary bypass (CPB) the concentration of blood components is controlled by fluid administration and diuresis. However, diuresis is not always adequate and at the end of CPB the diluted pump blood, unless processed by expensive and cumbersome RBC saving techniques, is usually discarded. To control "diuresis" during CPB and to concentrate all blood components of the diluted pump blood post CPB, we evaluated ultrafiltration as a technique to extract plasma water from the extracorporeal circuit in 17 patients. At the end of each case, the blood left in the CPB circuit was circulated through a hollow fiber dialyzer (TriEx-3, Extracorporeal). At a transmembrane pressure of 430 torr, plasma water was extracted at 29 cc/min. Extracting plasma water decreased the initial pump volume by 50% causing the initial concentration of blood components to increase as follows: hemoglobin 80%, platelets 53%, fibrinogen 79%, total protein 75%,

and plasma hemoglobin 294%. Following concentration, the high activated partial thromboplastin, prothrombin and thrombin times obtained for the pump blood decreased towards normal. There were no clinically significant changes in the plasma concentration of electrolytes. The concentrated blood was transfused to the patient within 2 hours of collection without any adverse effects. As compared to the increase in hemoglobin, the smaller increase in platelets and larger increase in plasma hemoglobin indicates that the dialyser caused some platelet loss and red blood cell damage. However, the concentrated blood did provide whole blood for the patient without the risks associated with donor blood.

Introduction

Adjustments in fluid administration and diuresis are the most widely used methods to control hemodilution during open heart surgery. There are times during cardiopulmonary bypass (CPB), especially when large volumes of crystalloid cardioplegia is administered, that the rate of natural diuresis may not be sufficient. Although diuretics can enhance plasma water extraction, the rate is not easily controlled and may still be insufficient. At the end of bypass, the normovolemic and anemic patient requires an increase in the oxygen

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carrying capacity with little or no increase in the circulating volume. Consequently, administration of the diluted pump blood may not be possible. Discarding it is wasteful and its replacement with bank blood is expensive and carries the risk of hepatitis, acquired immune deficiency syndrome (AIDS) and transfusion reactions.

Presently used centrifugation processes (e.g., Cell Saver^a), although very efficient in collecting and concentrating red blood cells, discard blood components other than cells.¹ In contrast, ultrafiltration can concentrate blood cells and other components by removing the plasma water.

Principles of Ultrafiltration

In ultrafiltration, blood flowing along a porous membrane loses water, salts and some low molecular weight components through the membrane (Figure 1). The rate of water loss and the size of the molecules that pass through the membrane are determined by the number, "depth" and "diameter" of the pores as well as the transmembrane pressure and shear rate (i.e., rate of velocity change) of the blood at the membrane wall.² Unbound molecules smaller than the smallest pores will pass freely with the plasma water and their concentration will be equal on both sides of the membrane. Components larger than the largest pores cannot cross the membrane at all and concentrate in direct proportion to the volume of plasma water removed.

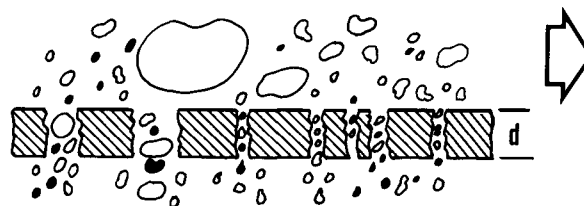
For any particular device, the rate of water extraction depends on the transmembrane pressure (TMP) and blood flow rate (which affects shear rate). The TMP is the pressure difference across the membrane driving the plasma water through the pores. It is defined as:

$$\text{TMP} = (\text{P}_i + \text{P}_o)/2 + \text{P}_u$$

where: P_i , P_o and $(\text{P}_i + \text{P}_o)/2$ are respectfully the inlet, outlet and mean pressure of the blood compartment and P_u is the absolute value of the negative pressure in the ultrafiltration compartment.

During ultrafiltration of blood, the retained components (e.g., proteins) concentrate along the porous membrane wall. Because of the higher concentration at the wall, there is also diffusion away

DYNAMICS OF ULTRAFILTRATION



- EXTRACTION RATE =**
- Number and Size of Pores
 - Depth of Pores
 - Transmembrane Pressures
 - Shear Rate

FIGURE 1. Dynamics of Ultrafiltration. A cross section of an ultrafiltration membrane indicating the selective passage of blood components according to the size of the pore in the membrane.

from the wall toward the center of the flow channel where the concentrations of retained solutes are lower. At any flow rate and transmembrane pressure, an equilibrium is established where the protein layer at the wall is maintained with diffusion away from the wall equal but opposite in direction to the build-up of concentration due to water extraction. When the protein concentration at the wall approaches saturation, the diffusion rate away from the wall is maximized. At saturation, as the transmembrane pressure increases, the protein layer thickness increases, increasing the resistance to water removal. When that resistance becomes significant relative to the resistance of the ultrafiltration membrane, then further increases in the transmembrane pressure increase the protein layer and prevent a corresponding increase in the extraction rate. Under these conditions, the extraction rate can be increased by reducing the protein barrier layer. This can be done by increasing the blood flow rate which enhances the diffusion of protein away from the membrane wall.

Until recently the use of ultrafiltration during open heart surgery has been sporadic and limited.³⁻⁸ The increased use of ultrafiltration makes it imperative that the effects of the devices on the blood and on the patient receiving the ultrafiltered blood be determined. Previous reported data on ultrafiltration during open heart has been collected during bypass and, therefore, the effects of the process on the blood and/or the patient were

^a Haemonetics, Corp., Braintree, MA 02184.

masked by the many variables accompanying CPB.^{3,5,8} It was the purpose of this study to determine the effects of ultrafiltration on pump blood as well as determine the effects of the transfusion of this blood on the patient.

Method

Seventeen patients undergoing coronary artery bypass surgery were studied. The CPB circuit included a Harvey 1000A oxygenator,^b Pall arterial filter^c and a Harvey 700F cardiotomy reservoir with filter.^b The circuit was primed with 2500 ml Plasmalyte,^d albumin (450 cc of 25 gm%),^e beef lung heparin (12,300 units),^f Keflin (1 gm),^g Lasix (20 mg.),^h Mannitol (12.5 gm.),ⁱ and sodium bicarbonate (66 mEq). The large prime volume was required for the blood cardioplegia administration method. In all cases, potassium blood cardioplegia (1000 ml initial bolus) was used in combination with systemic hypothermia (25 C). Before use, the ultrafiltration device (TriEx-3)^j was rinsed with a

separate 1,000 ml of plasmalyte flowing through it once and then discarded.

At the end of CPB, a blood sample (Pre-Conc) was taken from the arterial port of the oxygenator and then the blood was pumped from the coronary perfusion port of the oxygenator through the ultrafilter. The first 60 to 100 ml of solution to exit the ultrafilter were discarded. This allowed for most of the crystalloid priming solution to be discarded without losing blood. The outlet port was then connected to either the arterial drug administration port, or the quick prime port of the oxygenator (Figure 2), and the UF port connected to a vacuum source. The flow rate into the ultrafilter was 250–300 cc/min. The applied vacuum of –400 torr and the mean blood path pressure of 30 torr resulted in a transmembrane pressure of 430 torr. The blood was recirculated through the ultrafilter and the extracted plasma water collected in a graduated reservoir until the initial volume in the oxygenator was reduced by approximately 50%. Suction was discontinued, the blood flow stopped, the outlet port of the ultrafilter connected to the transfusion bag, the pump restarted and the blood pumped into the bag. During the collection, the ultrafilter was positioned with the blood outlet facing down assuring a more complete collection of the blood. The bag was weighed, mixed well and another blood sample taken (Post-Conc). Whenever the blood flow through the ultrafilter was stopped, the vacuum was first removed so that the ultrafilter was exposed to

^b Bard Cardiopulmonary, Santa Ana, CA 92705.

^c EC 3840, Pall Biomedical Products Corp., Glen Cove, NY 11542.

^d Travenol Laboratories, Deerfield, IL 60015.

^e Cutter Laboratories, Berkeley, CA 94710.

^f Upjohn Company, Kalamazoo, MI 49001.

^g Eli Lilly, Indianapolis, IN 46206.

^h Hoechst-Roussel, Somerville, NJ 08876.

ⁱ Merck Sharp and Dohme, West Point, PA 19486.

^j Extracorporeal Corporation Inc., King of Prussia, PA 19406.

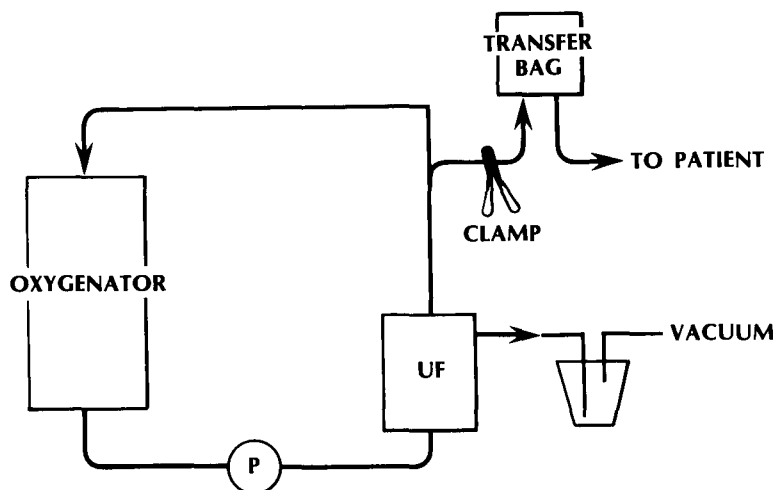


FIGURE 2. The ultrafiltration circuit incorporated into the cardiopulmonary bypass circuit. For this study, the blood was returned to the arterial drug administration port at the top of the oxygenator.

atmospheric pressure. This prevented over concentrating the blood which may cause blood damage and/or plug the capillaries of the ultrafilter.

Within 30 minutes after the patient arrived in the surgical intensive care unit, a control blood sample was taken from the patient (Pt-Cont) and the transfusion of the concentrated pump blood begun. Protamine, calculated from the heparin level obtained for the concentrated blood (Hepcon method), was given during transfusion of the pump blood. The blood was transfused within 60 minutes, and 30 minutes later another sample was taken (Pt-30). A final sample was taken the following morning (Pt-AM).

The following tests were performed on each sample: complete routine blood chemistries SNAC-20^k (glucose, chloride, CO₂, potassium, sodium, blood urea nitrogen, creatinine, uric acid, calcium, phosphorous, osmolality, total protein, albumin, cholesterol, total bilirubin, direct bilirubin, alkaline phosphatase, lactate dehydrogenase, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase and creatinine phosphokinase) complete blood cell count (Coulter-S Plus),^l prothrombin time, PT, (Electra 600),^m activated partial thromboplastin time, APTT,^m fibrinogen (Lancer Fibrinogen Analyzer),ⁿ heparin concentration (Hepcon),^o plasma hemoglobin and clotting factors (V, VII, VIII, and X). For all the clotting studies (9), except for the Hepcon, the heparin in the plasma of samples Pre Conc. and Post Conc. was neutralized with Hepabsorb^p (10). This allowed measurements of clotting parameters without the interference of heparin.

Analysis of Data

Using ultrafiltration to concentrate blood can cause changes in the total amount of recovered blood components in two ways. First, some blood can be retained in the ultrafiltration circuit and second, the ultrafiltration process can cause a loss of components (e.g., electrolytes) or gain of com-

ponents (e.g., free plasma hemoglobin if hemolysis occurs). To determine the net change of each blood component, the following equation was used:

$$\text{net change (\%)} = \frac{100 \times (V_i C_i - V_f C_f)}{V_i C_i} \quad \text{Eq. 1}$$

where V_i and V_f are the initial (pre-concentration) and final (post-concentration) blood volumes respectively and C_i and C_f are the initial and final concentrations in whole blood of any component of interest. V_i was the volume in the oxygenator and lines before concentration began and V_f was the volume of concentrated blood collected. (Both volumes were adjusted for volumes taken for samples).

The net change obtained in Equation 1 corresponds to the total changes due to both blood retained within the circuit and changes due to the ultrafiltration process itself. The two effects were separated by measuring the retained volume, V_r , from the ultrafiltration circuit removed at the end of the concentration period in three of the patients. In addition, the relative change in concentration between components due to ultrafiltration was determined by comparing the percent change in each component to the percent change in total hemoglobin. Total hemoglobin was chosen as a standard because it was thought to be unaffected by ultrafiltration. Thus, for components that do not cross the membrane the initial total amount of a component $C_i V_i$ should equal the final total amount of a component $C_f (V_f + V_r)$. That is

$$C_i \times V_i = C_f \times (V_f + V_r) \quad \text{Eq. 2}$$

or

$$C_f/C_i = V_i/(V_f + V_r) \quad \text{Eq. 3}$$

The ratio of C_f/C_i is determined from the measured initial and final concentration of the component of interest. It is referred to as the Measured Concentration Factor. A comparison between the Measured Concentration Factor of component A to that of B can serve as an indicator of changes caused by the ultrafiltration process in A relative to B independent of the volume change. The ratio of $V_i/(V_f + V_r)$ corresponds to the change in blood volume and is referred to as the Expected Concentration Factor. That is, if ultrafiltration reduces the blood volume by one half, then it is expected that the concentration of blood

^k Technicon Corp., Tarrytown, NY 10591.

^l Coulter Electronics, Hialeah, FL 33010.

^m Medical Laboratory Automation, Mt. Vernon, NY 10551.

ⁿ Sherwood Medical Industries, St. Louis, MO 63103.

^o HemoTec Inc., Englewood, CO 80112.

^p General Diagnostics, Morris Plains, NJ 07950.

components that do not cross the membrane would double.

The equations above require that all components whose concentration were measured in plasma be converted to concentration in whole blood, C-blood. The conversion was made by multiplying the plasma concentration, C-plasma, by the fraction of plasma in whole blood. Thus:

$$C\text{-blood} = C\text{-plasma} \times (100 - \text{hematocrit})/100$$

Eq. 4

The concentration of blood components measured in plasma were: all blood chemistries, plasma hemoglobin, fibrinogen and clotting factors.

In three cases the effects of 30 minutes of recirculation without ultrafiltration were studied by pumping the blood through the ultrafilter without applying vacuum or extracting any plasma water. Blood samples were taken before and 30 minutes after recirculation.

For the analysis of the data, Student's paired t-tests were performed using the statistical package for the social sciences (SPSS, 2nd edition, McGraw Hill, New York, N.Y.) on a Prime 850 computer. Groups were considered statistically different when the P value obtained from the paired t-test was less than 0.05 ($P < 0.05$). All values are given as mean \pm standard error of the mean.

Results

The mean volume of blood remaining in the pump was 1447 ± 27 ml (mean \pm standard error of the mean), the rate of water extraction was 29

± 1 ml/min, and the volume of concentrated blood collected was 709 ± 50 ml. In the three cases where the retained volume was measured, 75 cc of blood were forced out of the circuit and ultrafilter after "all" the blood was collected. This volume was not retrievable for patient transfusion. This resulted in an Expected Concentration Factor of $178 \pm 6\%$.

The data from the blood tests are summarized in tables I, II, III, and IV. All values are given as mean \pm standard error of the mean as a concentration in the solution in which they were measured. Thus, albumin is expressed as gram/100 ml of plasma whereas hemoglobin is expressed as gram/100 ml of whole blood. For parameters measured in plasma, the paired t-test was conducted for concentration in plasma and not concentration in whole blood.

Table I summarizes the values for blood chemistries, chloride, CO₂, potassium, sodium, blood urea nitrogen (BUN), creatinine, uric acid, calcium, phosphorous and osmolality. There were statistically significant differences between Pre-Conc and Post-Conc for all plasma values except sodium, creatinine and osmolality. The net loss ranged from $42 \pm 2\%$ for Calcium to $66 \pm 2\%$ for CO₂ with the net losses for most components being about 60%. Following transfusion, only CO₂ and uric acid were significantly different from Pt-Cont.

The data in table II indicates that after concentration there were statistically significant increases in the plasma concentration of total protein (3.8 ± 0.1 to 7.9 ± 0.4 gm%), albumin (2.8

TABLE I: BLOOD CHEMISTRIES

	Units	1		2		3		4		5		P < (t-test)				Net Loss *	
		Pre Conc	Post Conc	Post Conc	Pt-Cont	Pt-30	Pt-Am	2 vs 1	3 vs 1	3 vs 2	4 vs 3	%					
Glucose	mg%	207.00	24.00	179.00	24.00	199.00	14.00	191.00	10.00	192.00	8.00	.001	.001	.001	NS	65	2
Chloride	mEq/L	104.00	0.60	97.00	1.20	106.00	0.70	105.10	0.60	106.00	0.90	.001	.002	.001	NS	61	2
CO ₂	mEq/L	22.10	0.70	18.00	0.60	21.40	0.30	22.50	0.40	23.70	0.50	.001	—	.001	.046	66	2
Potassium	mEq/L	5.50	0.30	6.10	0.40	4.60	0.30	4.20	0.10	4.40	0.10	.006	.010	.006	NS	54	2
Sodium	mEq/L	139.70	0.50	140.50	0.70	140.50	0.60	141.50	0.70	140.10	0.70	NS	NS	NS	NS	57	2
BUN	mg%	16.80	1.80	15.20	1.60	16.60	2.00	21.40	5.70	17.20	2.10	.006	NS	.016	NS	63	2
Creatinine	mg%	1.28	0.10	1.25	0.10	1.32	0.11	1.27	0.11	1.36	0.13	NS	NS	.025	NS	59	2
Uric Acid	mg%	4.84	0.27	4.38	0.26	5.28	0.28	5.54	0.26	5.48	0.38	.001	.002	.001	.002	63	2
Calcium	mg%	7.66	0.29	10.52	0.48	9.87	0.28	10.02	0.30	8.75	0.13	.001	.001	NS	NS	42	2
Phosphorous	mg%	2.30	0.20	2.05	0.16	1.93	0.26	1.97	0.32	2.97	0.22	.001	.049	NS	NS	63	2
Osmolality	mOsm	277.10	1.21	276.5	1.24	277.90	1.46	279.10	1.53	276.70	1.89	NS	NS	.049	NS	—	—

All values are means \pm standard error of the mean. P values > 0.05 were considered non-significant (NS).

Abbreviations: Pre Conc, pre concentration; Post Conc, post concentration; Pt-Cont, patient before transfusion; Pt-30, patient 30 minutes after transfusion; Pt-Am, patient the morning after surgery; BUN, blood urea nitrogen.

* Whole blood concentration used for calculations.

± 0.1 to 5.5 ± 0.3 gm%), cholesterol (78 ± 4 to 169 ± 12 mg%), alkaline phosphatase (38 ± 2 to 74 ± 5 u/L), lactic dehydrogenase (LDH), (278 ± 21 to 720 ± 92 u/L), serum glutamic oxaloacetic transaminase (SGOT) (38 ± 4 to 84 ± 8 u/L), serum glutamic pyruvic transaminase (SGPT) (17 ± 6 to 32 ± 9 u/L) and creatinine phosphokinase (CPK) (144 ± 15 to 375 ± 44 u/L). Though not shown, the concentration in whole blood of the above parameters also increased by ultrafiltration but to a lesser degree. Also given in this table are the Measured Concentration Factors of the parameter measured (% Post/Pre). The loss of components expressed as a percent of initial amount was as follows: total protein ($8 \pm 2\%$), albumin ($7 \pm 2\%$), cholesterol ($7 \pm 3\%$), total bilirubin ($11 \pm 4\%$), and alkaline phosphatase ($16 \pm 2\%$).

Thirty minutes following transfusion (Pt-30), the concentration of all the parameters measured in plasma increased except SGOT and SGPT. The next morning there were small decreases in the plasma concentration of total protein, albumin, cholesterol, alkaline phosphatase and total bilirubin. There were no significant changes in the other parameters.

Table III summarizes the hematological values. Following ultrafiltration, there were statistically significant increases in WBC (6.8 ± 0.8 to $11.0 \pm 1.1 \times 10^3/\text{ul}$), RBC (2.01 ± 0.10 to $3.6 \pm 0.20 \times 10^6/\text{ul}$), Hgb (6.6 ± 0.2 to 12.0 ± 0.5 gr%) and platelets (117 ± 9 to $172 \pm 12 \times 10^3/\text{ul}$). Plasma hemoglobin increased from 50 ± 6 to 227 ± 32 mg%. These changes represent a net loss in WBC of $16 \pm 4\%$, RBC ($3.5 \pm 2\%$), Hgb ($6.9 \pm 2\%$) and platelets ($20 \pm 5\%$) and a net gain of $102 \pm 35\%$ in plasma hemoglobin. There was no difference in Mean Corpuscular Volume (MCV) but there was a small, statistically significant, decrease towards normal in Mean Corpuscular Hemoglobin (MCH) (33.2 ± 0.2 to 32.1 ± 0.3 ug). Following administration of the concentrated blood, there were increases in RBC (2.9 ± 1 to $3.3 \pm 0.2 \times 10^6/\text{ul}$), Hgb (9.4 ± 0.4 to 10.7 ± 0.5 gr%) and platelets (126 ± 12 to $136 \pm 12 \times 10^3/\text{ul}$). Plasma Hgb increased from 30 ± 5 to 41 ± 5 mg% but dropped to 5.0 ± 0.6 mg% the following morning. There were no differences in MCH before and after transfusion.

Table IV summarizes the values obtained for the clotting parameters. Prothrombin time (PT),

was used as an indicator of the extrinsic clotting mechanism (normal 10–13 sec), and activated partial thromboplastin time (APTT) as an indicator of the intrinsic clotting mechanism (normal 25–35 sec). Thrombin time (TT normal 3.5 ± 0.5 sec) was used as an indirect indicator of heparin absorption and as an indicator of clottable fibrinogen levels. The concentrated blood exhibited a significant decrease towards normal in PT (19.7 ± 1.6 to 15.3 ± 0.3 sec), APTT (50.7 ± 2.5 to 29.5 ± 0.5 sec), TT (8.0 ± 0.2 to 3.4 ± 0.2 sec), and an increase towards normal in fibrinogen (105 ± 11 to 211 ± 12 mg%). Of the clotting factors, only Factor V showed a statistically significant increase in percent activity (29.3 ± 5.2 to $40.3 \pm 7.6\%$). For Factors VII, VIII, and X, there were no significant changes in percent activity. There were no statistical differences in heparin levels (5.9 ± 0.1 vs 6.1 ± 0.2 units/ml of blood).

These changes correspond to a loss in Factor V ($43 \pm 11\%$), Factor VII ($47 \pm 10\%$), Factor VIII ($62 \pm 4\%$) Factor X ($59 \pm 2\%$) and heparin ($45 \pm 3\%$). Thirty minutes following transfusion of the concentrated blood, there was a decrease towards normal in PT (14.8 ± 0.3 to 13.0 ± 1 -sec), APTT (36.0 ± 1.7 to 32.0 ± 1.0 sec) and TT (4.8 ± 0.1 to 3.8 ± 0.2 sec) and an increase to normal in fibrinogen (148 ± 9 to 194 ± 14 mg%), but there were no significant differences in factor activities.

The comparison between the Measured Concentration Factor for total Hgb and other components showed that this ratio for Hgb ($180 \pm 5\%$) was not statistically different from the ratios obtained for albumin ($180 \pm 5\%$), cholesterol ($181 \pm 5\%$), LDH ($221 \pm 35\%$), SGOT ($185 \pm 10\%$), SGPT ($208 \pm 32\%$), CPK ($233 \pm 32\%$) and fibrinogen ($179 \pm 11\%$). The ratios were lower for WBC ($161 \pm 8\%$), platelets ($153 \pm 10\%$), for the clotting factors and for the small molecules (e.g., electrolytes). The ratio was higher for plasma Hgb ($394 \pm 61\%$), but was not significantly different from the Expected Concentration Factor (Figure 3).

Recirculating blood through the ultrafiltration circuit without extracting water did not alter the blood chemistries and hematological values.

Discussion

This study shows that ultrafiltration can be used to concentrate proteins, RBC, platelets and com-

TABLE II: LIVER FUNCTION TESTS

	Units	1		2		%*		3		4		5		P < (t-test)				Net Loss*	
		Pre Conc	Post Conc	Post/Pre	Pt-Cont	Pt-30	Pt-Am	2 vs 1	3 vs 1	3 vs 2	4 vs 3	%							
Total Protein	gm%	3.80	0.10	7.90	0.40	175	6	4.50	0.10	5.40	0.20	5.10	0.10	.001	.001	.001	.001	8	2
Albumin	gm%	2.80	0.08	5.50	0.27	180	5	3.30	0.08	4.10	0.13	3.70	0.09	.001	.001	.002	.001	7	2
Cholesterol	mg%	78.00	4.00	169.00	0.12	181	5	106.00	6.00	125.00	7.00	113.00	7.00	.001	.001	.001	.001	7	3
T Bilirubin	mg%	0.50	0.04	1.00	0.11	173	8	0.99	0.08	1.70	0.13	0.79	0.12	.001	.001	NS	.001	11	4
D Bilirubin	mg%	0.12	0.20	0.11	0.03	77	17	0.18	0.03	0.38	0.06	0.19	0.03	NS	NS	.021	.001	61	10
A Phosph	U/L	38.00	2.00	74.00	5.00	165	4	46.00	3.00	57.00	4.00	48.00	4.00	.001	.005	.001	.001	16	2
LDH	U/L	278.00	21.00	720.00	92.00	226	36	325.00	18.00	418.00	22.00	479.00	45.00	.002	NS	.002	.001	-11	17
SGOT	U/L	38.40	3.50	84.00	8.00	185	10	73.20	23.00	61.90	5.30	102.10	24.90	.001	NS	NS	NS	NS	NS
SGPT	U/L	16.80	5.50	32.00	8.60	208	32	23.70	6.00	27.50	7.00	37.00	8.00	.010	.001	NS	NS	NS	NS
CPK	U/L	144.00	15.00	375.00	44.00	233	32	224.00	20.00	313.00	34.00	661.00	167.00	.001	.006	.005	.001	-20	15

All values are means ± standard error of the mean. P values > 0.05 were considered non-significant (NS).

Abbreviations: Pre Conc, pre concentration; Post Conc, post concentration; Pt Cont, patient before transfusion; Pt-30, patient 30 minutes after transfusion; Pt-Am, patient the morning after surgery; T, total; D, direct; A Phosph, alkaline phosphatase; LDH, lactic dehydrogenase; SGOT, serum glutamic oxalacetic transaminase; SGPT, serum glutamic pyruvic transaminase; CPK, creatinine phospho kinase; U, units; L, liter. All concentrations are in plasma.

* Concentration in whole blood were used for calculation.

TABLE III: HEMATOLOGICAL VALUES

	Units	1		2		%*		3		4		5		P < (t-test)				Net Loss*	
		Pre Conc	Post Conc	Post/Pre	Pt-Cont	Pt-30	Pt-Am	2 vs 1	3 vs 1	3 vs 2	4 vs 3	%							
WBC	x10 ³	6.8	0.8	11.0	1.1	161.0	8.0	10.7	1.1	11.7	1.2	13.1	1.1	.001	.007	NS	NS	16	4
RBC	x10 ⁶	2.0	0.1	3.6	0.2	187.0	6.0	2.9	0.1	3.3	0.2	3.3	0.1	.001	.001	.002	.001	3.5	2
Hemoglobin	gr%	6.6	0.2	12.0	0.5	180.0	5.0	9.4	0.4	10.7	0.5	10.6	0.3	.001	.001	.002	.001	6.9	2
Hematocrit	%	18.0	0.5	33.0	1.5	187.0	7.0	26.0	1.0	30.0	1.0	30.0	1.0	.001	.001	.003	.001	3.5	2
MCV	um ³	91.0	0.1	91.0	0.1	100.0	0.2	91.0	1.0	91.0	1.0	91.0	1.0	NS	NS	NS	NS	—	—
MCH	ug	33.2	0.2	32.1	0.3	96.5	0.6	32.5	0.3	32.3	0.4	32.1	0.2	.001	.004	NS	NS	—	—
Platelets	x10 ³	117.0	9.0	172.0	12.0	153.0	10.0	126.0	12.0	136.0	12.0	115.0	11.0	.001	NS	.014	.042	20	5
Pl. Hgb	mg%	50.0	6.0	227.0	32.0	394.0*	61.0	30.0	5.0	41.0	5.0	5.0	0.6	.001	.012	.001	.010	-102	35

All values are means ± standard error of the mean. P values > 0.05 were considered non-significant (NS).

Abbreviations: Pre Conc, pre concentration; Post Conc, post concentration; Pt Cont, patient before transfusion; Pt-30, patient 30 minutes after transfusion; Pt-Am, patient the morning after surgery. E, expected concentration factor; C, calculated concentration factor; WBC, white blood cells; RBC, red blood cells; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; Pl. Hgb, plasma hemoglobin.

* Concentrations in whole blood were used for calculation.

TABLE IV: CLOTTING MECHANISM

	Units	1		2		%*		3		4		5		P < (t-test)				Net Loss*	
		Pre Conc	Post Conc	Post/Pre	Pt-Cont	Pt-30	Pt-Am	2 vs 1	3 vs 1	3 vs 2	4 vs 3	%							
Prothrombin time	sec	19.7	1.6	15.3	0.3	—	—	14.8	0.3	13.0	1.0	12.2	0.2	.002	.003	NS	NS	—	—
APTT	sec	50.7	2.5	29.5	0.5	—	—	36.0	1.7	32.0	1.0	29.0	0.4	.001	.002	.006	.036	—	—
Fibrinogen	mg%	105.0	11.0	211.0	12.0	179	11	148.0	9.0	194.0	14.0	287.0	12.0	.001	.001	.001	.001	12	5
Thrombin time	sec	8.0	0.2	3.4	0.2	—	—	4.8	0.1	3.8	0.2	3.3	0.1	.001	.001	.001	.001	—	—
Factor V	%	29.3	5.2	40.3	7.6	114	16	49.0	8.0	66.0	7.0	49.0	5.0	.044	.035	NS	NS	47	10
Factor VII	%	50.0	5.2	59.1	7.1	105	16	72.0	3.0	67.0	4.0	72.0	5.0	NS	NS	NS	NS	62	4
Factor VIII	%	94.4	8.6	88.1	8.5	78	7	80.0	9.0	79.0	7.0	71.0	6.0	NS	NS	NS	NS	59	4
Factor X	%	52.7	3.5	56.2	3.7	89	6	56.0	3.0	54.0	3.0	50.0	17.0	NS	NS	NS	NS	59	2
Heparin	u/ml	5.9	0.1	6.1	0.2	104	3	—	—	—	—	—	—	NS	—	—	—	45	3

All values are means ± standard error of the mean. P values > 0.05 were considered non-significant (NS).

Abbreviations: Pre Conc, pre concentration; Post Conc, post concentration; Pt Cont, patient before transfusion; Pt-30, patient 30 minutes after transfusion; Pt-Am, patient the morning after surgery. E, expected concentration factor; C, calculated concentration factor; APTT, Activated Partial Thromboplastin Time

* Concentration in whole blood were used for calculation.

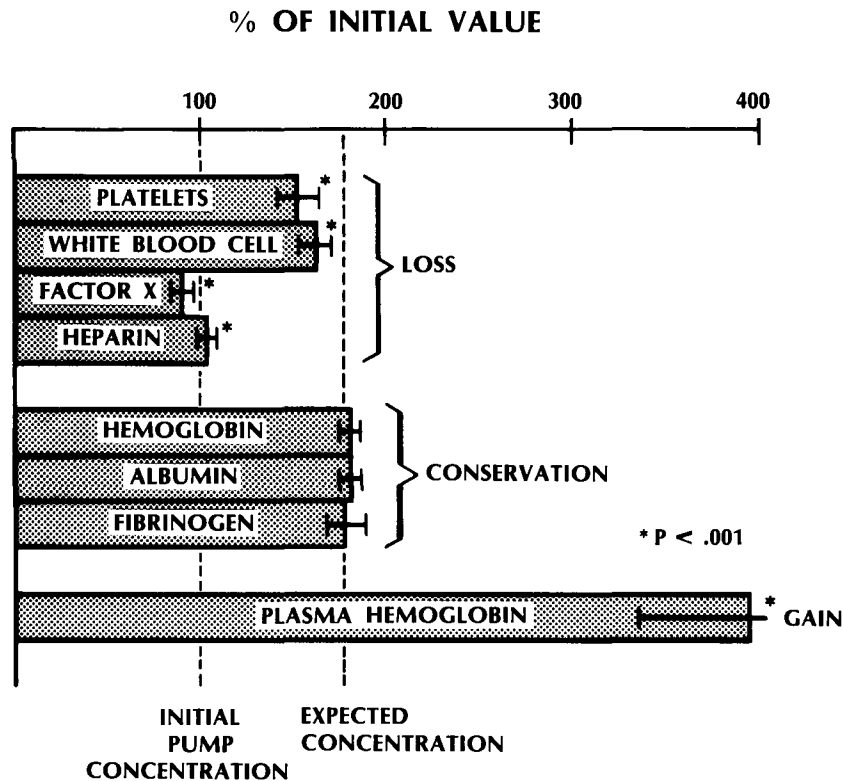


FIGURE 3. A comparison between the measured concentration of key blood components and the expected concentration, both expressed as percent of initial concentration. The lowered measured concentration for platelet, WBC, Factor X and heparin indicate loss. The measured concentration for hemoglobin, albumin and fibrinogen equalled the expected concentration indicating conservation. The measured concentration for plasma hemoglobin was higher than the expected concentration indicating a net gain of plasma hemoglobin.

ponents of the intrinsic and extrinsic clotting mechanism while maintaining the electrolyte concentrations within physiological ranges. The small changes in the concentration of the salts were accompanied by large net losses in the total amount of electrolytes. This was expected as they cross the ultrafilter membrane along with the extracted water. The lower loss in calcium was probably due to a portion of the calcium being protein bound. The net loss in components that do not cross the membrane such as total protein, albumin, WBC, hemoglobin, platelets, and fibrinogen may have been due to: 1) retention of blood in the circuit, 2) absorption and/or adsorption to the ultrafiltration membrane or 3) destruction by the process. Most of the losses were probably due to incomplete recovery of the blood from the ultrafiltration and its associated circuit. This was confirmed by the retention of 9.5% of the final collected blood volume in the ultrafiltration circuit. Additional

losses of WBC's¹¹ and platelets¹² can be explained by interaction with the ultrafiltration membrane. The smaller increase in Measured Concentration Factor of WBC and platelets relative to Hgb supports this conclusion.

The net gain in free plasma hemoglobin as well as the high Measured Concentration Factor for Plasma Hgb suggests hemolysis. The device used should have had a low hemolysis rate since its membrane has relatively small pores that retain protein. For ultrafiltration where the proteins are retained, a protein layer forms along the wall by the concentration process. Thus any cell that reaches the wall vicinity does not "see" the wall or its pores, only the protein layer. This lack of cell-wall contact should prevent hemolysis caused by the membrane. Furthermore the 30 cc/min water extraction rate, was low in relation to the shear rate rendered by the 250 cc/min blood flow rate.¹³ In three patients where the blood flowed

through the ultrafiltration device without suction applied (i.e. no water extracted) there were insignificant changes in cell count and plasma Hgb. Similar results were reported elsewhere.⁴ Therefore, even though the ultrafiltration conditions favored minimal blood damage, the increase in plasma hemoglobin could have been due to ultrafiltration.

Plasma Hgb increased approximately 4 times following concentration, twice as much as calculated from the Expected Concentration Factor, Figure 3. Although the percent increase was high, the plasma Hgb levels 30 minutes after transfusion were never higher than the levels at the end of bypass. The morning after surgery the levels decreased to 5.0 ± 0.6 mg%. The net increase in free plasma hemoglobin after 1500 ml of whole blood (Hct 20%) was circulated through the device at a flow of 300 ml/min for 20–30 minutes was 68 mg per 100 ml of blood. Under these conditions each red blood cell passed through the ultrafilter approximately 6 times. We would expect that during bypass when the total circulatory blood volume is larger, the increase in plasma free hemoglobin would be correspondingly lower. It should be pointed out that evaluation of other ultrafiltration devices did not produce significant hemolysis.^{14,15}

The recovery of clotting factors activity was low, with net losses being approximately 50%. Since the molecules responsible for clotting activity are very large,¹⁶ the loss in activity was probably due to the factors being very labile. The levels of clotting factors VII, VIII, X, still represent clinically significant activity. Expressed in terms of the activity found in fresh frozen plasma, ultrafiltered blood contained 84% Factor VII, 147% Factor VIII and 58% Factor X.¹⁷ Factor V activity did increase after concentration resulting in 43% of that found in fresh frozen plasma.¹⁷ The presence of significant clotting factor activity, along with normalization of the intrinsic and extrinsic clotting mechanism, the fibrinogen levels and platelet counts indicate enhanced potential clotting activity following concentration. Because the clotting reactions are concentration dependent, this enhancement was most likely the result of increases in the concentration of some of the components of the clotting system.

Thirty minutes following transfusion of the concentrated blood, there were increases in the platelet count, fibrinogen, RBC, Hgb, total protein as well as normalization of the extrinsic and intrinsic clotting system. Some of the changes may have been due to natural diuresis.

Conclusion

The ideal blood concentrator should concentrate cells, plasma protein and clotting factors while maintaining the salt concentration within clinically acceptable levels. The concentration process should preserve the quantity, function and viability of the blood components, operate on or off bypass in an intermittent or continuous manner and at an adjustable rate. The use of ultrafiltration may be a promising technique whereby a simple to operate, disposable device can closely fulfill the requirements of an ideal blood concentrator.

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