

# Plasma Protein Solution

for Cardiopulmonary Bypass

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## Introduction:

Blood substitutes for priming extracorporeal systems have ranged from the total whole blood circuit first employed in controlled cross circulation by Lillehei et al<sup>1</sup>, use of citrated banked blood<sup>2</sup>, to the concepts of hemodilution with dextran and albumin advanced by Long<sup>3 4 5 6</sup>, and DeWall<sup>7</sup>, to complete hemodilution with electrolyte solutions as proposed by DeWall<sup>8 9</sup>, Zuhdi<sup>10</sup> and Cooley<sup>11</sup>. Many of these techniques have been abandoned or modified. Many modifications have resulted in well designed but very complex solutions. Our interest was in a solution which could approximate the desirable characteristics of whole blood without the dangers of reactions or the ever present potential of serum hepatitis.

Pasteurized plasma protein solution (PPS) has been used for volume replacement in hypovolemic states since 1959<sup>12</sup>. More recently it has been used as a perfusate for renal preservation<sup>13</sup>. One of the authors\* has had experience with the use of this agent for treatment of shock and hypovolemia resulting from traumatic injuries in military combat. The use of this solution as a perfusate for experimental cardiopulmonary bypass was recently reported by Vasko et al<sup>14</sup>. As a result of these preliminary studies we have extended the use of American PPS● for routine cardiopulmonary bypass procedures in the operating room and for assisted circulation.

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Table I

This table illustrates the blood loss-replacement in mixed priming solution. In the blood loss column no numbers are given because all blood during bypass was returned to the extracorporeal circuit.

PRIMING SOLUTION D = 5% DEXTROSE IN WATER  
P = PLASMANATE

PT--SEX--AGE	WT (KG)	PRIMING SOLUTION (ML)	OTHER FLUIDS (ML)	TYPE OF SURGERY	DURATION PERFUSION (MIN)	BLOOD GIVEN (ML)	BLOOD LOSS (ML)	URINE OUT (ML)
RC--M--46	97.3	D 1000 P 500	2000	CABPG	98	1750		495
LH--M--56	80	D 1000 P 500	1000	AORTIC V.	96	3000		225
CA--M--54	67.3	D 570 P 500	1000	CABPG	205	3500		440
BH--M--63	68.2	D 600 P 500	1000	MIT. ANNU.	131	4000		500
S--F--5	23.7	D 500 P 125	250	ASD	42			110
FR--M--51	93.2	D 1000 P 500	1000	CABPG	86	4500		890

## Method and Materials:

American PPS is a 5% solution containing 88% albumin, 7% alpha globulin, 5% beta globulin in a solution containing Na<sup>+</sup> (110 mEq/L), K<sup>+</sup> (2.0 mEq/L) and Cl<sup>-</sup> (50 mEq/L). It is pasteurized by exposure to a temperature of 60° C for 10 hours. It has been demonstrated and reported that this procedure inactivates the hepatitis virus<sup>15</sup>. Canine studies were carried out using a similar solution+ prepared from canine plasma.

## Surgical Procedures:

All dogs were quarantined, immunized against canine distemper, infectious canine hepatitis and Leptospirosis (L. Canicola and L. Icterohemorrhagica), and treated with anti-parasitic agents when indicated to assure uniform healthy experimental preparations. The surgical procedure was carried out aseptically though these were acute experiments. The dogs were clipped, shaved, and bathed with Phisohex 24 hours preoperatively. Anesthesia was induced and maintained with methoxyflurane. A median sternotomy was performed and a single cannula placed in the right ventricular outflow tract into the right ventricle for venous return. The aortic root was cannulated for arterial infusion. The extracorporeal circuit was venous return from the right ventricle through a conventional bubble oxygenator† and reinfusion to the root of the aorta. Total bypass was achieved by cross-clamping the pulmonary artery.

†Temprol, Bentley Laboratories, Santa Ana, California

Table II

In this table the volume stability of PPS is apparent since the "blood loss" column represents that which was discarded in the vacuum unit and not returned to the patient.

PRIMING SOLUTION ----- PLASMANATE

PT--SEX--AGE	WT (KG)	PRIMING SOLUTION (ML)	OTHER FLUIDS (ML)	TYPE OF SURGERY	DURATION PERFUSION (MIN)	BLOOD GIVEN (ML)	BLOOD LOSS (ML)	URINE OUT (ML)
PL--M--64	77.3	1500	250	AO. ANEUR.	31	4500	3800	6
GB--M--58	67	1000	500	PERICARD.	96	500	350	55
NB--F--60	63	1000	800	AO. ANEUR.	33	1500	1200	26
LC--M--51	76.3	1250	500	CABPG	144	2000	1900	620
ME--F--64	73.1	1000	300	ASD	19	1000	575	0
RM--M--54	79	1500	800	CABPG	199	3000	2500	500
WB--F--64	73	1000	500	AORTIC V.	102	2500	2200	410
EB--M--10	25	1000	250	VSD	29	500	100	NO CATH
CD--M--57	85	1000	500	CABPG	159	2500	2350	410
BP--F--18	46.5	1000	1000	AORTIC V.	98	2000	2300	745
JR--M--64	82.2	1500	1500	CABPG	195	3500	3000	1020
FR--M--54	73.3	1500	700	CABPG	133	2500	2200	221
RF--M--60	83	1000	600	CABPG	65	2500	1900	745
DF--F--21	66	1250		ASD	28	250	350	95
WD--M--15	89.5	1000		PUL. STEN.	19	250	259	NO CATH

**Table III**

This table is representative of the cases in which all blood was returned to the extracorporeal circuit (no numbers in blood loss column) and the relatively large quantities of blood which were added in spite of this.

PT-SEX-AGE	WT (KG)	PRIMING SOLUTION (ML)	OTHER FLUIDS (ML)	TYPE OF SURGERY	DURATION PERFUSSION (MIN)	BLOOD GIVEN (ML)	BLOOD LOSS (ML)	URINE OUT (ML)
MB--M--46	88.2	1100	1000	MIT. & AO. VALVE REP. AORTIC V.	175	2000		1420
CB--M--50	75	1200	3000		160	3000		300
NM--M--63	63.6	1050	1000	CABPG	89	3500		210
EP--M--48	72.7	1200	1500	CABPG	124	4500		890
MF--M--56	91	1500	1500	CABPG	157	3500		760
CM--M--55	72.7	1150	2000	CABPG	179	3000		895
HMcC--M--51	72.7	1150	2000	CABPG	145	4500		465
MA--M--48	64.1	1050	1500	CABPG	70	3000		380
NW--M--38	80.9	1300	1500	MITRAL V.	108	3000		645

Initial studies on the disappearance of three solutions (5% dextrose in water, balanced electrolyte solution and PPS) from the extracorporeal circuit were performed on fifteen dogs. In each case the extracorporeal flow was maintained at a constant rate of perfusion until the reservoir volume decreased to 50% of initial level ( $V^{50}$ ). Following this each of the solutions was readded to the system in quantities sufficient to restore initial reservoir level in the extracorporeal circuit, while maintaining the same flow.

The clinical study is composed of two groups. Group I was composed of patients in which the priming volume consisted of part PPS and part 5% dextrose in water. The proportions varied due to difference in priming volume but were between 40 and 60% PPS. Group II was composed of patients who were perfused with priming solution composed entirely of PPS. The data regarding age, sex, weight, operation, volume of fluids, length of perfusion, blood loss and replacement is seen in Tables 1, 2.

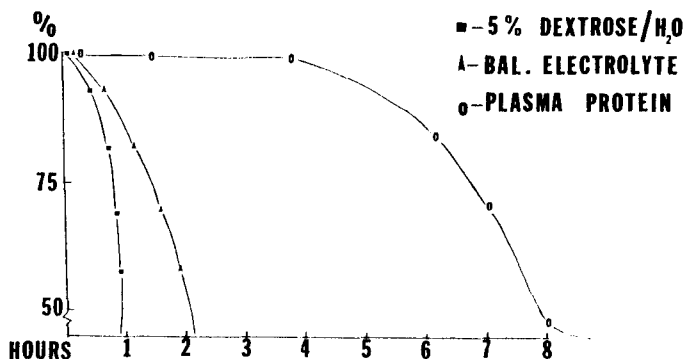
These two groups were compared to a third group of patients selected on the basis of similarity of disease and surgical operation, but in which the priming volume was entirely 5% dextrose in water (Table 3). All three groups were perfused utilizing a bubble oxygenator and the same perfusion technique of normothermia, normotension and "high flow". The details of this perfusion technique have been described elsewhere by Vasko and DeWall<sup>16</sup>.

In all patients presented in this study, measurements were made of arterial and venous pH,  $pCO_2$ , and calculated buffer base deficit or excess by the method of Severinghaus<sup>17</sup> or using a composite acid-base diagram<sup>18</sup>.

□ Radiometer, Copenhagen, Denmark

**Figure 1**

Represents the observed disappearance both in time and duration of the three solutions tested.



**Results:**

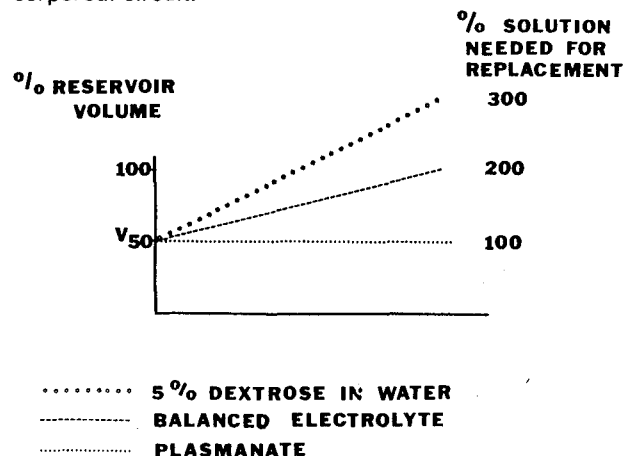
In the experimental study using dogs there were several notable findings. First the disappearance of the three solutions studied is quite different and the time period which transpired to reach  $V^{50}$  is dramatic especially in the PPS group (Figure 1). Note that the mean time for 5% dextrose in water is 50 minutes. The balanced electrolyte solution had disappeared to  $V^{50}$  in a mean time of 125 minutes while PPS had a curve in which  $V^{50}$  was reached after 8 hours. Another, and perhaps more interesting and important finding is that the volume remained virtually unchanged in the PPS perfused dogs up to 3 hours and 50 minutes.

A second finding was the additional volume required to restore the initial reservoir level (Figure 2). PPS was equal-volumetric while it required twice the volume of balanced electrolyte solution and up to three times the quantity of 5% dextrose in water to achieve the same result.

Three other points of interest were the relatively stable electrolytes especially  $K^+$ , in the PPS group compared to either the balanced electrolyte or D<sup>5</sup>W groups. The possible reasons and significance of this will be discussed later. Comparing the blood gases in the three groups those in the PPS group were more uniform but there were no statistically significant differences. A reduction in the gas flow/blood flow ratios was noted and was highest in the total PPS primed group. *(concluded on page 24)*

**Figure 2**

This figure illustrates the disparity in quantity of fluid required to restore initial reservoir volume in the extracorporeal circuit.



In the patients studied the most striking result was volume stability which resulted in dramatic reductions in the amount of whole blood required in the pre-perfusion and perfusion consistent with stable arterial and venous patient pressures. The only instances in which reinfusion was required were either the occurrence of a negative blood loss-replacement situation or in those cases where mixed priming solution was utilized and urinary output and/or blood loss not adequately compensated. For a comparison of the three groups with regard to priming solution, blood loss and blood replacement refer to Table I. It should be noted that in those cases in which D<sup>5</sup>W alone was used that the blood replacement represents a much greater volume loss because in those cases all blood during perfusion was returned to the extracorporeal circuit while recently in the total PPS prime group almost all blood is being discarded as it was found by Riley et al<sup>19</sup> in this laboratory that the greatest source of hemolysis is in pericardial and thoracic cavity blood which accumulates during the surgical procedure.

#### Discussion:

The disappearance time of the various solutions in experimental procedures is not surprising for although the two non-protein solutions are isotonic, they do not share the property of PPS in being iso-oncotic with plasma. These terms express constitutive relationships and though convenient are not totally sound because of the dynamic state of the species of molecular components involved.

The five percent dextrose solution and the balanced electrolyte solution probably exit to the interstitial fluid due to factors such as the Gibbs-Donnan equilibrium and other less well defined characteristics such as the binding of some divalent cations to plasma proteins. Further loss to the supporting tissues, in which exchange is said to be slow<sup>18</sup>, and to the transcellular (secretory) fluids must provide loss of the more dilute solutions. PPS on the other hand probably remains in the intravascular space for longer periods because of the same phenomena.

The replacement volumes required to restore original reservoir volume are probably explained on the same basis of transport phenomena. Other phenomena such as the relative stability of electrolytes is probably due to both the oncotic characteristic of PPS but also the slower transfer rate which should naturally occur with the co-existence of electrolytes in the solution.

Reduction of the gas flow/blood flow ratio in the extracorporeal circuit may be due to multiple factors including the increased stability of acid-base balance which would favor optimal loading and unloading of oxygen and carbon dioxide. The most important factor however, is the physical solubility and diffusion of oxygen in plasma as compared to electrolyte solutions as it is said to be relatively low in electrolyte solutions.

The diffusion coefficient of plasma is four to five times greater than in erythrocytes, therefore the attainment of a greater physical concentration should enhance transfer to red cells. All of the above can probably be clearly defined when one assumes that the solubility coefficient of a gas is equal to the physical solubility and the chemical combining power.

#### Conclusions:

A laboratory and clinical study of PPS has been described in which the findings of greater volume stability (less whole blood needed), electrolyte stability and lower gas flow/blood flow ratios were consistently noted. The positive results which accrue have led us to use of PPS in all clinical cardiopulmonary bypass procedures. Although the quantities of blood used have been large in certain cases it is only to replace that which is now being discarded rather than returned to the extracorporeal circuit.

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