Autologous and Homologous Fresh Human Plasma as a Volume Expander in Hypovolemic Subjects

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UNTIL RECENTLY, it was agreed that fresh human plasma is a good blood volume expander. According to Freedman [10] and Hutchison,[26, 27] however, this assumption must be questioned. These authors demonstrated that when deep-frozen homologous (non-autologous) plasma is infused into normovolemic volunteers, in half the subjects a large amount of plasma leaves the circulation rapidly. In some cases, this phenomenon is associated with urticarial reactions. We previously found that infusions of *human dried plasma* and *pasteurized plasma* solutions regularly lead to an expected volume increase.[16, 17, 19, 20, 22] Schneider *et al.*[38] and Ahnefeld and co-workers [1] confirmed these results, and recently Hillman [25] demonstrated that *stored, pooled human plasma* as used in the USA also is a reliable volume expander. No studies on the volume effect of *fresh* autologous and homologous plasma are available.

The incidence of transmission of viral hepatitis by fresh plasma transfusions being very low in Sweden,[34] this simple preparation is widely used in this as well as in several other countries, in instances when a colloid infusion is indicated. However, stored pooled human plasma, single donor dried plasma, or pasteurized plasma solutions are preferred in many other countries both in Europe [1, 17, 38] and in the United States.[8, 25]

Since fresh plasma corresponds to the plasma contained in ACD banked blood used all over the world, it seems of importance to know if such plasma exerts a volume expanding effect as do stored preparations. The following study was therefore carried out to compare blood volume expanding effect of homologous and autologous fresh plasma infused into moderately hypovolemic healthy volunteers.

Methods

Seventeen healthy men between 20 and 55 years of age volunteered for this study. None had a history of renal, cardiovascular or allergic disease, nor had any previously received blood or plasma transfusions. Two weeks before the experimental day, exactly 500 ml. blood from a cubital vein was collected in a 1-liter bottle containing 120 ml. of ACD solution. The same procedure was repeated a week later. After another week, a third bleeding of 500 ml. was carried out in an average of 7 minutes (min. 5, max. 11) and immediately replaced through the same large bore needle, by infusing 500 ml. autologous or homologous plasma. The infusion time took an average of 7 ($\pm$2) minutes. In those receiving homologous plasma,

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only plasma with the ABO-Rhesus-groups of the recipient was used. Volunteers did not take food nor fluids after midnight before the experiment and were kept in bed during the study the next morning.

Immediately prior to the third bleeding, baseline blood volume (BV_1) by means of the Volemetron-RI^{131} HSA technic [42] and hematocrit (Hct_1) were determined. At five minutes and at 2½ hours after the infusion, second (BV_2) and third (BV_3) determinations of blood volume—and hematocrit (Hct_2, Hct_4) were made. Also at one hour after the infusion, an additional hematocrit (Hct_3) was measured. Pulse, blood pressure and temperature were monitored throughout the study and repeated examinations were carried out for allergic reactions.

All samples for blood volumes and hematocrits were taken without a tourniquet; ten minutes' mixing time for RI^{131} HSA was allowed. All hematocrits were determined in triplicate by a micromethod and on blood from the postmix sample for blood volume determination. Hct_3 was done on blood obtained by fingertip puncture. Repeated checks in Wintrobe tube (centrifugation at 3,000 rpm for 30 min.) revealed no significant differences compared to microhematocrit determinations. Hematocrit, hemoglobin and all standard blood groups as well as the Rhesus genotype, Duffy, Kell and Lewis factor were determined at each blood collection. Sedimentation rate, Wassermann, Meinicke and Kline reactions were also checked. Blood was stored in a refrigerator at 4° C. until the plasma was removed the evening before use. The latter was again stored at 4° C. until 2 hours before use

Calculation of Blood Volume

By definition, the true blood volume (BV_{tr}) is the sum of red cell volume (RV) and plasma volume (PV):

$$BV_{tr} = RV + PV. \quad (1)$$

The plasma volume can be expressed as follows:

$$PV = (1 - Hct_c) \times BV_m, \quad (2)$$

where Hct_c is the observed hematocrit corrected for plasma trapping [5] and BV_m is the blood volume as measured by a plasma tag (RI^{131} HSA) in the Volemetron.

If Hct_{tb} represents the total body hematocrit

$$\left(\text{by definition } \frac{RV}{RV + PV}\right),$$

the red cell volume can be expressed as

$$RV = Hct_{tb} \times BV_{tr}. \quad (3)$$

By substituting (2) and (3) into equation (1), we find that

$$BV_{tr} = Hct_{tb} \times BV_{tr} + (1 - Hct_c) \times BV_m$$

which reduces to

$$BV_{tr} = \frac{1 - Hct_c}{1 - Hct_{tb}} \times BV_m. \quad (4)$$

TABLE 1. *Homologous Plasma Infusion. Changes of Hematocrit and Blood Volume (in l)*

	Baseline Values		5 Min. after Bleeding and Infusion		1 Hr. after End of Infusion	2½ Hr. after End of Infusion		Change of Blood Volume at End of Exp. in Ml.
Subject	Hct_1	BV_1	Hct_2	BV_2	Hct_3	Hct_4	BV_3	$BV_3 - BV_1$
F. A.	36.0	5.74	31.5	5.57	33.5	35.0	5.14	−600
P. Oe.	43.0	4.99	40.5	5.02	41.0	41.0	4.85	−140
W. B.	37.0	5.64	30.5	5.44	33.5	35.5	5.05	−590
J. Å.	38.5	5.32	35.0	5.59	33.5	34.5	5.37	+ 50
B. B.	38.0	4.27	34.5	4.02	33.0	35.0	4.31	+ 40
E. C.	40.0	5.51	37.0	5.45	36.0	38.5	5.40	−110
O. A.	42.5	4.99	37.5	4.86	37.0	38.5	4.75	−240
O. S.	42.0	4.33	36.5	4.36	36.5	37.0	4.15	−180
A. K.	34.5	5.56	30.5	5.64	32.5	31.5	5.60	+ 40

TABLE 2. *Autologous Plasma Infusion. Changes of Hematocrit and Blood Volume (in l)*

Subject	Baseline Values		5 Min. after Bleeding and Infusion		1 Hr. after End of Infusion	2½ Hr. after End of Infusion		Change of Blood Volume at End of Exp. in Ml.
	Hct_1	BV_1	Hct_2	BV_2	Hct_3	Hct_4	BV_3	$BV_3 - BV_1$
J. M.	38.5	4.68	32.5	4.91	33.0	32.0	4.60	− 80
B. C.	42.5	4.86	39.0	4.92	38.5	40.5	4.63	−230
S. B.	42.0	4.54	39.5	4.45	38.5	39.5	4.46	− 80
L. Th.	37.0	6.02	34.0	6.29	34.0	35.0	6.11	+ 90
O. B.	40.5	6.43	39.0	6.24	39.5	39.5	6.16	−270
B. A.	37.0	6.00	34.5	—	35.0	35.5	6.02	+ 20
O. H.	40.0	4.80	37.0	4.78	35.5	36.0	4.78	− 20
R. S.	38.0	4.84	33.5	—	34.0	34.5	4.91	+ 70

According to Chaplin et al.,[6] Hct_{tb} can be substituted in healthy persons by

$$Hct_{tb} = 0.91 \times Hct_c. \quad (5)$$

Therefore, equation (4) results in

$$BV_{tr} = \frac{1 - Hct_c}{1 - 0.91 \times Hct_c} \times BV_m. \quad (6)$$

All blood volume values tabulated were calculated according to equation (6) where Hct_c is always the average of three measurements, and BV_m is the result read on the Volemetron.

Results

Changes in hematocrit (not corrected for trapping) and blood volume (BV_{tr}) during the experimental period for the two groups receiving homologous (9 subjects) or autologous (8 subjects) plasma are shown in Tables 1 and 2.

Table 2 shows that the hematocrit drops ($Hct_1 - Hct_2$) immediately after substitution of blood by autologous plasma. After this, hematocrits (Hct_3, Hct_4) remain constant for the period of observation (Fig. 2).

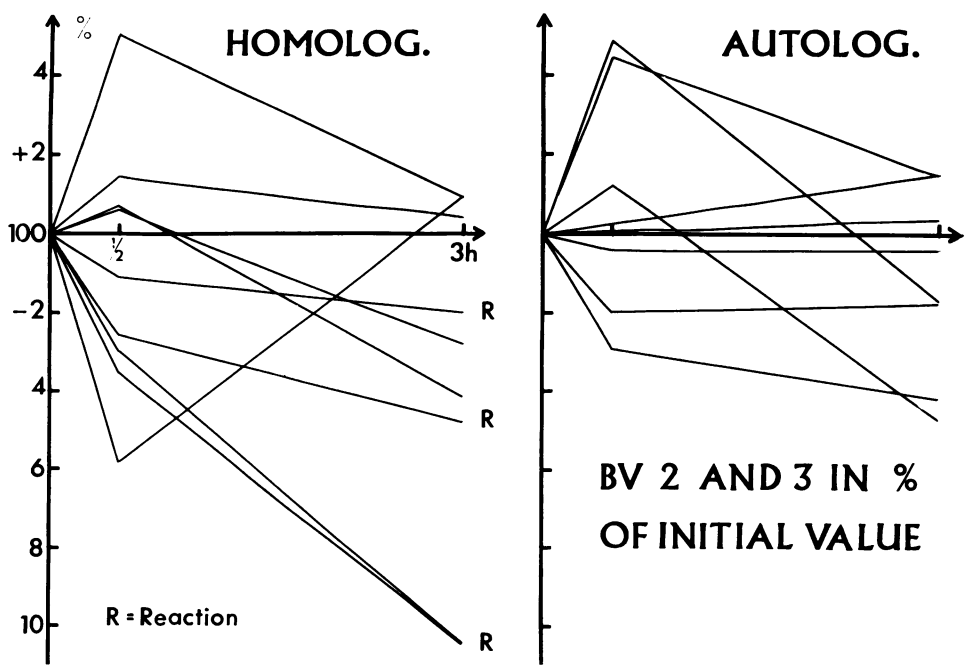

FIG. 1. Values for blood volume 2, i.e., after replacement of 500 ml, whole blood by homologous or autologous plasma, and for blood volume 3 (result read 3 hr. after initial blood volume) for both groups are plotted as % change of initial blood volume, taken as 100%.

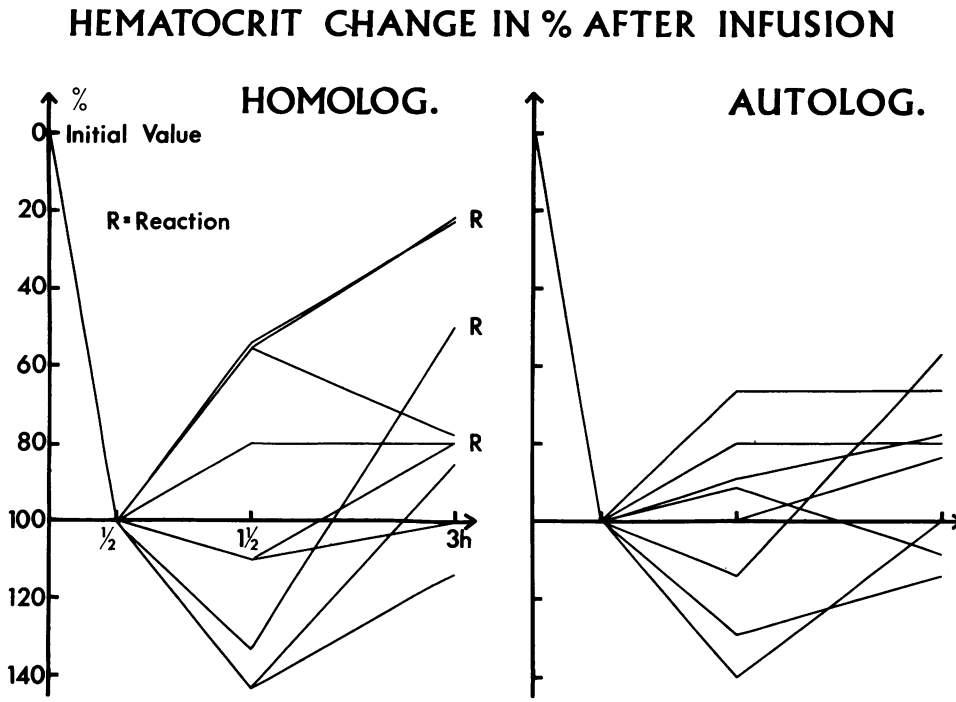

FIG. 2. Changes in hematocrit after plasma infusion for the two groups are indicated. The fall in hematocrit from the first to the second determination (immediately after bleeding and infusion) was taken as 100% for each individual. Hct_3 and Hct_4 (end of observation period) are plotted in % increase or decrease of this value. It is evident that the two individuals who showed a marked decrease in blood volume after homologous plasma administration also had a definite rise in hematocrit, proving that plasma was lost.

Blood volumes (BV_2) are practically unchanged at 5 minutes after the end of the plasma infusion. The variation of ±3–4% is an expression of the error of the method, BV_3, at the end of the experiment, averages 62 ml. lower than the initial value (Fig. 1). This is probably due to the fact that the plasma infused contained ACD solution which by this time left the intravenous space.

In those receiving homologous plasma (Table 1), seven of nine subjects followed the same pattern as with autologous plasma, both concerning changes in hematocrit (Fig. 2) and blood volume (Fig. 1). Two subjects (F. A. and W. B.), however, reacted differently. After an initial drop in hematocrit and a BV_2 unchanged compared to BV_1, hematocrit rose continuously accompanied by a decrease in blood volume (BV_3), thus indicating loss of plasma (600 and 590 ml.). This loss represents more than 10% of the total initial blood volume (BV_1), which is beyond the range of error of the method (Fig. 1).

In Tables 3 and 4, body weight, blood groups and clinical reactions are shown. Two individuals in the homologous group (W. B., E. C.) showed typical transient urticarial reactions, a third (O. A.) had chills. One urticarial reaction occurred in subject W. B. who showed a definitely lower BV_3. Subject F. A. also had a much lower BV_3, without a clinical reaction. No reactions occurred in the autologous group.

Discussion

According to Williams [42] and our own studies,[2, 15, 18] blood volume can be determined with the technic employed here with an accuracy of ±3%. Tempus and Hügli [39] found an over-all sigma of 2.5%, Kirchner [29]

TABLE 3. *Homologous Plasma Infusion. Body Weight, Blood Groups of Recipient and Donor, and Clinical Reactions*

Subject	Body Weight (Kg.)	Blood Groups	Blood Groups of Donor	Clinical Reaction
F. A.	86.0	A Rh+ R_1r (CDe/cde) K− Fy (a+)	A Rh+ R_2r (cDE/cde) K− Fy (a+) P. Oe.	—
P. Oe.	80.6	A Rh+ R_2r (cDE/cde) K− Fy (a+)	A Rh+ R_1r (CDe/cde) K− Fy (a+) F. A.	—
W. B.	74.2	AB Rh+ R_1R_1 (CDe/CDe) K− Fy (a−)	AB Rh+ R_1R_2 (CDe/cDE) K− Fy (a−) J. J.	Urticaria
J. Å.	73.1	A Rh+ R_1r (CDe/cde) K− Fy (a−)	A Rh+ R_1r (CDe/cde) K− Fy (a+) L. L.	—
B. B.	55.8	A Rh− rr (cde/cde) K− Fy (a+)	A Rh− rr (cde/cde) K− Fy (a+) C. O.	—
E. C.	84.9	O Rh+ R_1r (CDe/cde) K− Fy (a+)	O Rh+ R_1r (CDe/cde) K− Fy (a−) O. A.	Urticaria
O. A.	73.7	O Rh+ R_1r (CDe/cde) K− Fy (a−)	O Rh+ R_1r (CDe/cde) K− Fy (a+) E. C.	Chills
O. S.	74.0	A Rh+ R_1r (CDe/cde) K− Fy (a+)	A_1 Rh+ R_2r (cDE/cde) K− Fy (a+) A. K.	—
A. K.	75.2	A_1 Rh+ R_2r (cDE/cde) K− Fy (a+)	A Rh+ R_1r (CDe/cde) K− Fy (a+) O. S.	—

one of 2.24%, confirmed by Myhre and Rustad.[33] Thus, a decrease in blood volume of more than 500 ml. with an initial value of about 5,000 ml. seems significant. In contrast to Dagher and co-workers,[7] we (as others [1] have previously) measured the removal of about 200 ml. of erythrocytes, in each instance. The methodological aspects of this study will, however, be the subject of a separate paper.

We did not find the same incidence and degree of volume loss after homologous plasma infusate as did Hutchison *et al.*[26] (50%). Our results show that fresh homologous plasma is not always a reliable volume expander. It is possible that storage of plasma at 4° C. for 7 to 14 days, as in our experiments, contrasted to storage at −23° C. *for a few days* as in Hutchison's study, partly eliminates substances responsible for plasma leak, whereas storage for 6 months at 32° C., freeze-drying or heat-treating apparently destroys such factors completely, since preparations stored for 6 months are known to be good plasma expanders.[1, 21, 22, 25, 38]

The nature of the substance causing plasma loss is not known. Hässig [24] thinks that immunoglobulins at the cell surface, also suspected to be the cause of febrile transfusion reactions, increase capillary permeability. These immunoglobulins are destroyed in heat-treated preparations and possibly denaturated by storing. Melrose and co-workers [31] have evidence that viable leukocytes in fresh homologous blood may initiate a graft-versus-host reaction in the lung, followed by pneumonitis which might be associated with plasma loss. Thus, different numbers of viable leukocytes in various preparations could be responsible for the different results.

Gadboys *et al.*[13] attempted to isolate a dialyzable substance, the removal of which causes hypotension during exchange, with dialyzed homologous dog plasma. They previously showed [11] that homologous blood exchange with heart worm-free donors and

TABLE 4. *Autologous Plasma Infusion. Body Weight, Blood Groups and Clinical Reactions*

Subject	Body Weight (Kg.)	Blood Groups	Clinical Reaction
J. M.	66.2	A Rh+ R_1r (CDe/cde) K− Fy (a+)	—
B. C.	73.4	O Rh− rr (cde/cde) K− Fy (a+)	—
S. B.	75.8	O Rh+ R_1r (CDe/cde) K− Fy (a+)	—
L. Th.	80.1	A Rh+ R_1R_2 (CDe/cDE) K− Fy (a+)	—
O. B.	83.6	O Rh− rr (cde/cde) K− Fy (a−)	—
B. A.	103.5	A Rh+ R_2r (cD^uE/cde) K− Fy (a−)	—
O. H.	79.6	A Rh− rr (cde/cde) K− Fy (a+)	—
R. S.	74.7	A Rh+ R_1r (CDe/cde) K− Fy (a−)	—

recipients caused arterial hypotension, hepatic and pulmonary congestion and depressed renal functions. They reported plasma volume deficits and significant congestion in the lungs.[12]

Gliedman *et al.*[14] showed that infusion of homologous blood in dogs causes an increase in inferior vena cava pressure below the liver with fluid sequestration in the liver. Autologous blood, low molecular weight dextran and 5% dextrose did not cause these changes.

Evidence of rapid disappearance of fresh homologous plasma has been reported in rats (Pareira[36]), dogs[4, 23, 37, 40] and man.[28, 43]

Elias and co-workers,[8] however, did not find any difference in the effectiveness of homologous and autologous plasma as a plasma volume expander in dogs made severely oligemic by acute hemorrhage. They think that the reactions seen in normal dogs are suppressed in shock by catecholamines liberated in response to hypotension. Yet there are other differences which might explain the disagreement: They worked with splenectomized, anesthetized dogs and plasma was separated by centrifuging in a refrigerated centrifuge. Thus, leukocytes or other substances could have been removed, or the response might have been mitigated under anesthesia.

Another reason for the higher incidence and severity of plasma loss in Hutchison's study might be that plasma was infused into normovolemic subjects, though this would not explain differences between autologous and homologous plasma. Hillman[25] showed that the postinfusion hypervolemia initiates a compensatory renal water and electrolyte diuresis to maintain normovolemia. Homologous stored plasma infused into hypovolemic subjects prevented this diuretic response and lead to the expected volume increase. Since we replaced removed blood immediately by infusion of the same amount of plasma, volume regulating factors probably could not have played a major role. More important is that two individuals showed a marked decrease in blood volume after fresh homologous plasma transfusion.

The fresh plasma component of whole blood corresponds to the plasma used in this study, and it therefore seems important to realize that this plasma will not always stay in circulation as long as generally assumed. This is confirmed by clinical observations in which larger amounts of whole blood or fresh plasma are needed to cover exactly measured volume losses.[9]

Taking into account the sometimes unreliable volume effect, the threat of hepatitis virus transmission, transfusion reactions and possibly aggravation of decreased bacterial resistance in hypovolemic shock[35] by the administration of ACD banked blood, it seems justified to use other colloids free of these side effects in the initial treatment of hypovolemia,[41] as long as the red cell volume does not fall to a critical level. In view of these facts, the use of autologous blood in elective operations, as suggested by Milles[32] and Langston,[30] seems reasonable, but is, unfortunately, not practicable in emergencies.

Purified albumin and pasteurized plasma solutions contain the colloid-osmotic effective portion of plasma and are virtually free of side effects but use is limited by cost and availability. Human dried plasma is not free of hepatitis virus, nor is pooled plasma stored for 6 months (Personal Communication, A. G. Redeker), but good artificial plasma expanders, if needed in combination with packed red blood cells, do provide a reliable volume effect since the colloid-osmotic effect of proteins is important in initial shock treatment, and other specific functions have not been proved.

Summary

The reliability of an infusion of 500 ml. of fresh homologous and autologous human

plasma as contained in ACD banked blood as a volume expander was studied in 17 moderately hypovolemic subjects. Changes in blood volume were measured directly with Volemetron-RI^{131} HSA technic and indirectly from changes in hematocrit. Confirming previously reported volume losses after infusion of deep-frozen plasma into normovolemic subjects associated with allergic reactions, fresh homologous plasma, stored at 4° C., provided predictable expansion in only seven of nine subjects. Three had allergic manifestations, which in one was correlated with poor expansion of plasma volume. Volume loss in two subjects receiving homologous plasma was accompanied by a concomitant increase in hematocrit. Administration of autologous plasma always lead to the expected volume increase, with the expected hematocrit depression and without allergic phenomena. It is concluded that in clinical emergencies the sometimes unreliable volume expanding effect of fresh homologous plasma (and thus of ACD banked blood) and other known side effects of these preparations, should be considered in selecting the proper infusion solution.

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