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STUDY ON ALTERATIONS OF BLOOD FLOW AND BLOOD VISCOSITY UNDER HEMORRHAGIC SHOCK AND EFFECTS OF PLASMA EXPANDER

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ABSTRACT

Experiments were performed in 48 dogs subjected to a shock produced by hemorrhage after the modified Wiggers' method. Dogs were infused 90 minutes after hemorrhage with one of six test substances; shed blood, 5% glucose solution, or four kinds of dextran (mw. 75,000, 47,000, 29,000 and 12,000). Infusion of dextran with mw. 29,000 produced the most remarkable increase in femoral arterial blood flow above the prehemorrhagic level. This flow improvement was thought to be more attributable to reduction in blood viscosity than an increase in blood volume.

INTRODUCTION

The development of shock is a complicated phenomenon not necessarily causally related to any one factor. The shock may be resulted from a multiplicity of influences such as hormonal, neural, circulatory and so on[1].

Hemorrhage, if it is significant in amount, may cause irreversible responses of the circulatory system. Maintenance of blood volume and blood pressure is necessary, but there is no guarantee to restore capillary circulation even with an adequate blood replacement. The circulatory conditions after hemorrhage are accompanied by cellular aggregation or sludging, increased blood viscosity and venular stasis of cells[1)-4)]. Cellular aggregation, if uncorrected, may reduce nutritive capillary blood flow and result in hypoxic damages of the parenchymatous organs. A failure of capillary circulation is related to a principal cause of a fatal process. Reversal of cellular aggregation with return toward normal circulation is seen after the administration of low molecular weight dextran (LMWD)[2)5)-9)].

The hemodynamic changes induced by the LMWD administration have been studied, both in terms of acute plasma volume expansion and in terms of blood flow increase attributed to the viscosity altering effects[10)-13)]. Many studies[2)6)7)10)-12)] emphasize the relationship of viscosity alterations to the microcirculatory changes in the disturbed circulatory states and the usefulness of LMWD for

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improvement of the impaired capillary circulation.

The present study, therefore was undertaken first to investigate the alterlations of blood flow (femoral arterial flow) and blood viscosity in a series of dogs under a hemorrhagic shock. Secondly, the effects of four kinds of dextran (average molecular weight of 75,000, 47,000, 29,000 and 12,600) with narrow molecular weight distribution were studied on blood viscosity, blood flow and blood pressure. Finally, the blood volume expanding effect of shed blood, 5% glucose solution and two kinds of dextran (mw. 75,000 and 29,000) was studied.

MATERIALS AND METHODS

Experiments were performed in 48 dogs subjected to a shock produced by hemorrhage after the modified Wiggers' method. Dogs used in these experiments were healthy adult animals weighing from 10 to 17 kilograms.

All dogs were anesthetized lightly by thiamylal sodium administrated intravenously. Through short incisions, both femoral arteries, both femoral veins and one of the common carotid arteries were exposed. Four mg/kg of heparin was injected into the femoral vein prior to cannulation. Blood pressure was measured via a mercury manometer attached to a catheter in one femoral artery. A noncannulating flow prove was placed around the other femoral artery and flow was measured by an electromagnetic flow-meter connected to the flow prove. Viscosity determination was made by means of a cone in cone viscometer. Viscosity was determined at a constant temperature of 37°C for five different rates of shear, 1.2, 3.8, 7.8, 73 and 146 inverse seconds.

A summary of experimental plan is illustrated in Fig. 1. Determinations of control flow, blood pressure, hematocrit and blood viscosity were made prior to hemorrhage. A 15 gauge needle was inserted into the common carotid artery and connected to a graduated glass bottle into which shed blood was to flow. All dogs were bled rapidly into the bottle until the blood pressure of 35 mm of mercury was reached. The blood pressure was maintained for 90 minutes between 35 and 45 mm of mercury by removal or injection of a small amount of blood. At the end of this period, flow determination and sampling of blood were made. Arterial blood samples were with-drawn into a heparinized

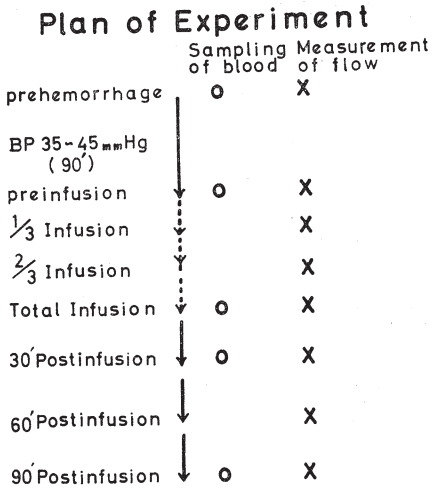


FIG. 1

syringe through a three way stopcock in the bleeding line. Thirty six dogs were then randomly divided into 6 groups and each gronp was infused with one of the six test substances.

In the first group (GI), 8 dogs were infused with their own shed blood into the femoral vein. In the second group (GII), 6 dogs were infused with 6% dextran with an average molecular weight of 75,000 in 5% glucose in water. In the third group (GIII), 5 dogs were infused with 6% dextran with an average mw. 47,000 in 5% glucose in water. In the fourth group (GIV), 7 dogs were infused with 6% dextran with an average mw. 29,000 in 5% glucose in water. In the fifth group (GV), 5 dogs were infused with 6% dextran with an average mw. 12,600 in 5% glucose in water. In the sixth group (GVI), 5 dogs were infused with 5% glucose in water. The test substances were infused intravenously at rates of 10 to 12 ml per minute. The amount of solution infused was equal to the amount of shed blood. Determinations of blood flow and blood pressure, and samplings of blood were made at 30 minute intervals for 90 minutes after infusion.

Hematocrit (Hct) was measured in a Wintrobe tube centrifuged at 3,000 r.p.m. for 30 minutes. Osmolality of four kinds of dextran was determined by the freezing point depression method with an osmometer. Blood volume determination was made with the use of I^{131} labelled albumin (RIHSA) according to the isotope dilution principle. RIHSA was injected into one femoral vein and blood samples were withdrawn from the other femoral vein after allowing 15 mintes to pass for mixing. Large vessel Hct was measured. Counting was made on 3 ml plasma in a glass tube. Blood volume was measured before and after infusion of shed blood. 5% glucose solution and two kinds of dextran (mw. 75,0000 and 29,000). An increase in blood volume was calculated as a percent change from the control value (infusion volume) by the following formula.

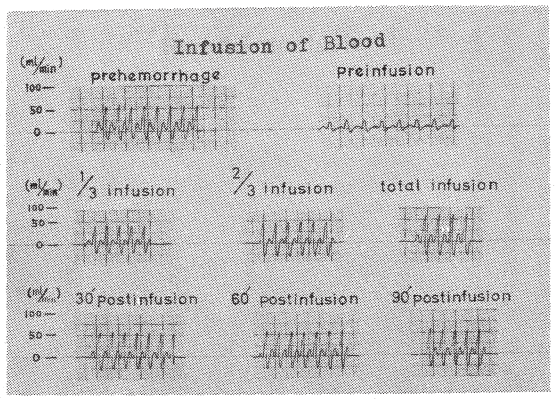
$$\frac{\text{Postinfusion Volume} - \text{Preinfusion Volume}}{\text{Infusion Volume}} \times 100$$

RESULTS

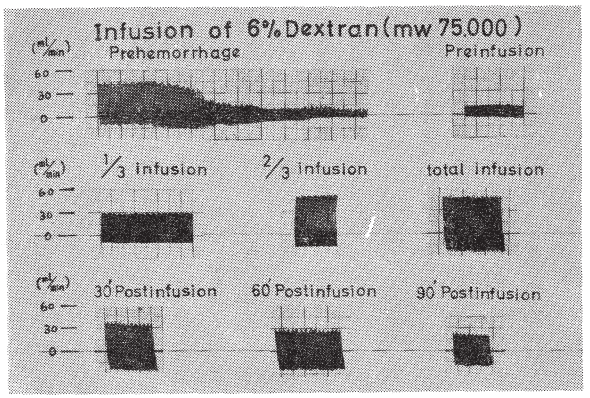
Thirty six of 48 dogs were used to study the alterations of blood flow, blood pressure (B.P.) and blood viscosity during the experiments. Twelve of 48 dogs were used to measure the blood volume changes after infusion of the test substances. The amount of shed blood in all dogs varied from 28 to 38 ml/kg of body weight (average 35 ml/kg).

Typical flow patterns and vicosity curves for each group are illustrated in Figs. 2, 3, 4, 5, 6 and 7.

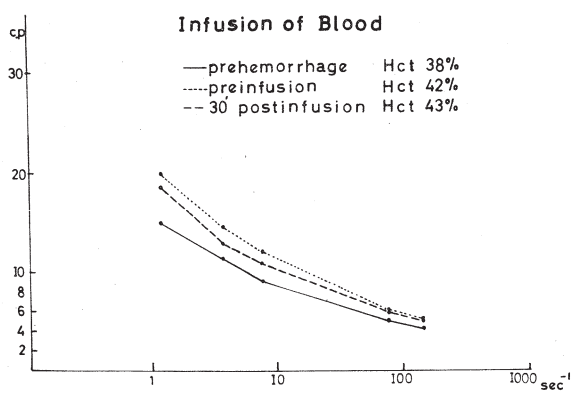
Hematocrit: Hct changes during experiments are shown in Fig. 8. After



Patterns of flow curves during the experiment. Flow was returned to the control level after infusion of blood.

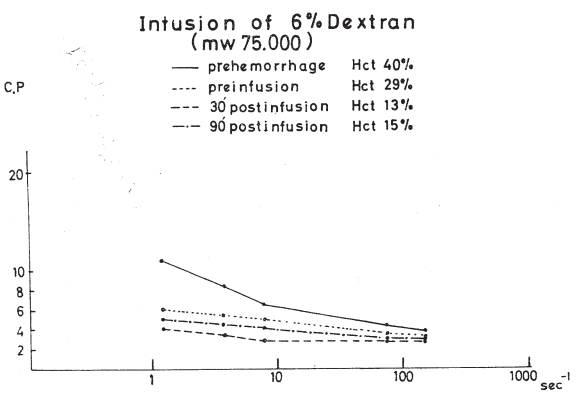


After infusion, flow was restored to the control level, but it, thereafter, fell gradually.



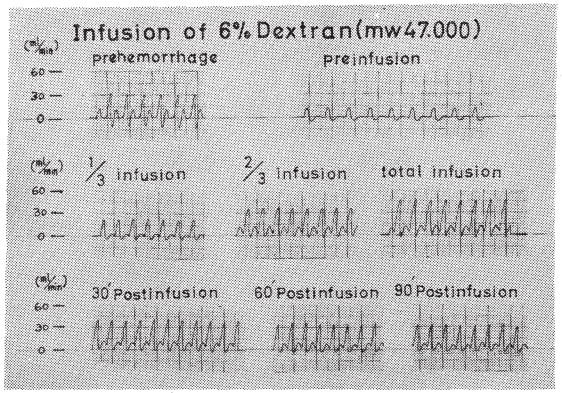
Viscosity curves. After infusion, the viscosity was elevated above the control level.

FIG. 2

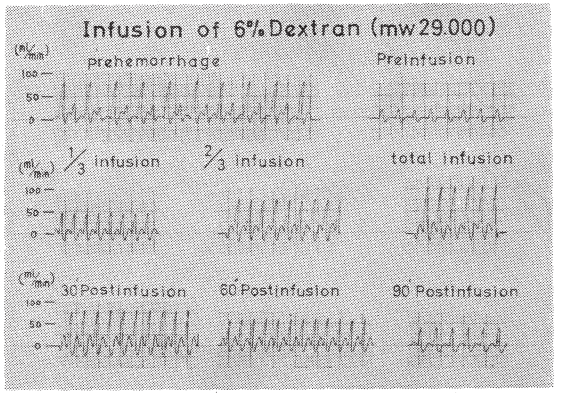


After infusion, viscosity was moderately reduced at low shear rates.

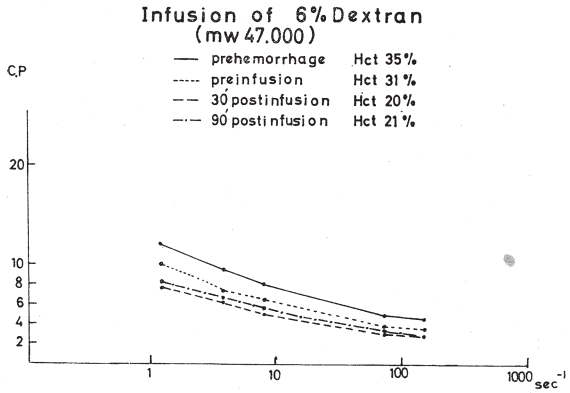
FIG. 3



At the end of infusion, flow was elevated significantly above the control level.

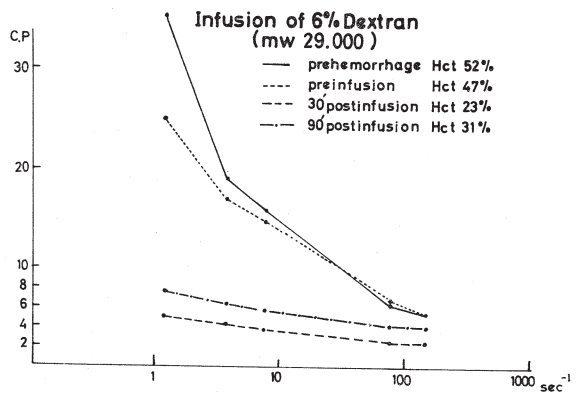


A significant recovery of flow was observed at the end of infusion.



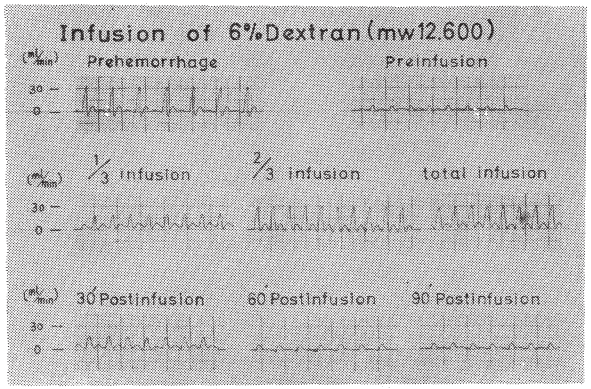
Marked change in viscosity was not seen after infusion.

FIG. 4

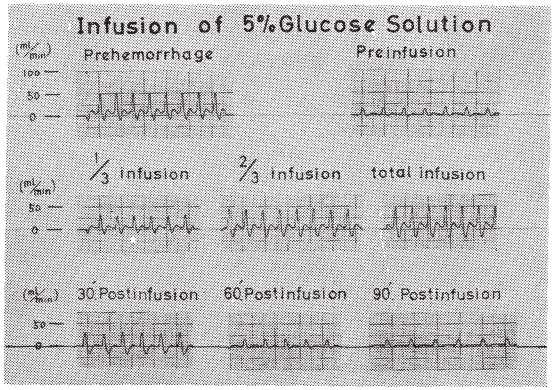


Viscosity was significantly reduced with infusion.

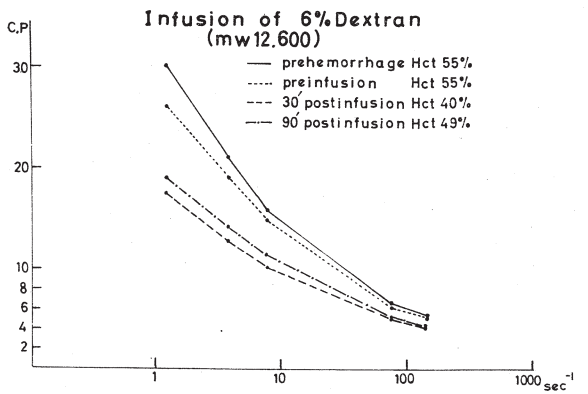
FIG. 5



Flow fell rapidly after infuaion.

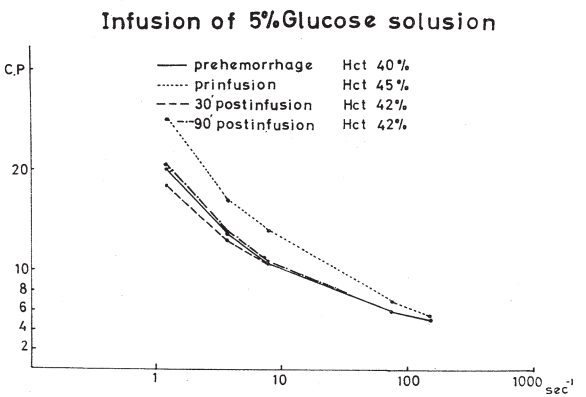


Flow patterns were similar to those shown in Fig. 6.



Viscosity moderately reduced after infusion.

FIG. 6



Marked change was not observed aftr infusion.

FIG. 7

hemorrhage, an increase in Hct was observed 9 dogs (average 12%), while 25 dogs exhibited a decrease in Hct (average 9%). However, no changes were seen in 2 dogs. Thirty minutes after infusion, Hct decreased remarkably in G II, G III, G IV, G V and G VI. On the contrary, 5 dogs in G I exhibited an increase. Ninety minutes after infusion, Hct reduction in G IV and G V was considerably less than that of 30 minutes after infusion.

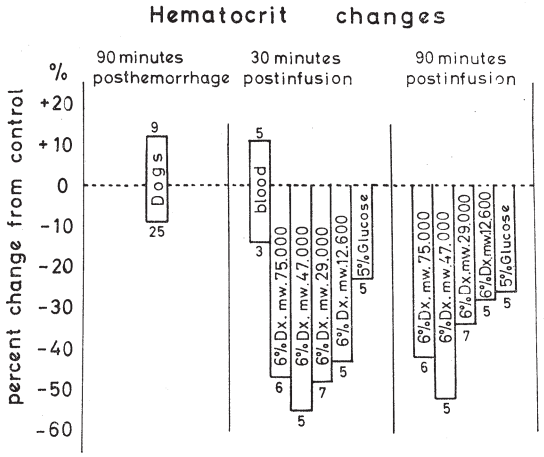


FIG. 8. Figure above each bar indicates the number of dogs.

Flow: Femoral arterial flow in 36 dogs after hemorrhage was reduced by between 54% and 74% of the control level (average 64%). Flow alterations after infusion in each group are shown in Fig. 9, expressed as the percent change from the control. Flow in G I returned to the near control level at the end of infusion, while flow in G III and G IV elevated 26% and 50% over the control. This effect remained for about 60 minutes until flow returned to the control level. In G V and G VI, flow elevated above the control, but the effect was rather transient and flow was immediately reduced below the control. In G II flow failed to elevate above the control.

Viscosity: After hemorrhage, in 9 dogs with Hct increase viscosity exhibited an elevation of 26% from the control level at a shear rate of 1.2 per second and 10% at a shear rate of 146 per second. In 25 dogs with a decrease in Hct, viscosity showed a reduction of 38% at 1.2 per second and 17% at 146 per second. Fig. 10 illustrates the viscosity changes 30 minutes after infusion of the substances. In G I, viscosity elevated at all shear rates, but a marked reduction in viscosity was seen after iniusion of dextran and the 5% glucose solution. The reduction in viscosity after infusion of dextran with mw. 29,000 was most remarkable, as compared with the other kinds of dextran. Fig. 11

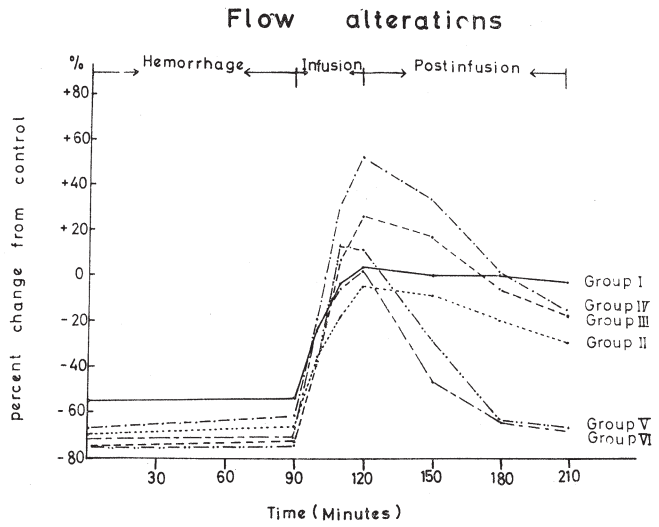


FIG. 9. Flow in G III, G IV and G V elevated above the control level.

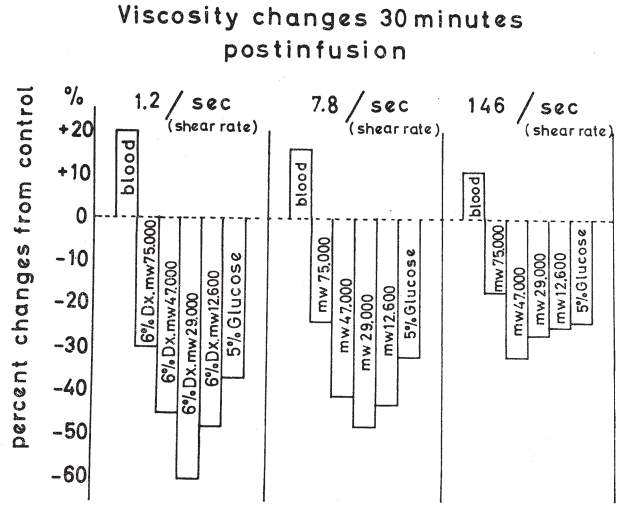


FIG. 10

shows the viscosity changes 90 minutes after infusion, infusion of the 5% glucose solution exhibited a relatively marked reduction in viscosity, as compared with the change 30 mintes after infusion. On the other hand, in groups infused with dextran, viscosity reduced slightly with time.

Blood pressure: Blood pressure alteration during experiments is illustrated in Fig. 12. A profound reduction of B.P. after hemorrhage was recovered to the near control level with infusion of blood and dextran with mw. 29,000,

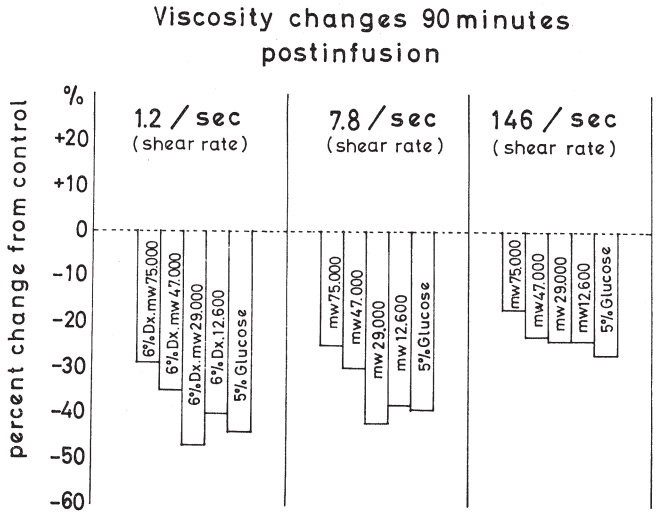


FIG. 11

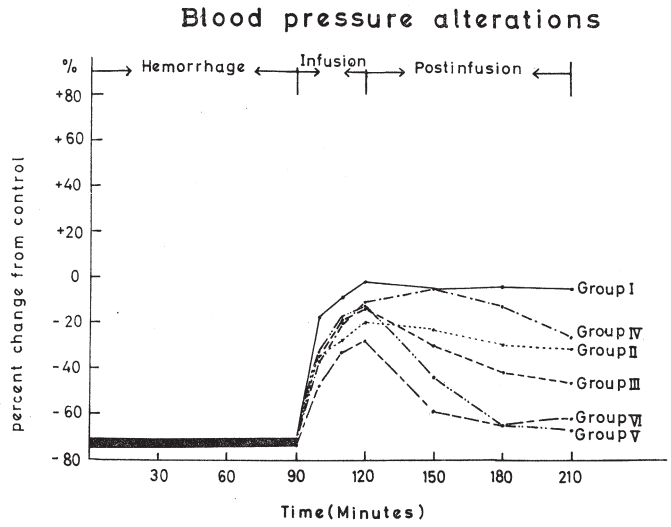


FIG. 12. B.P. in G I and G IV returned to the control level after infusion.

This dextran infusion lowered B.P. with the lapse of time, but blood transfusion maintained B.P. constant. After infusion of the 5% glucose solution and dextran with mw. 12,600, a transieat and incomplete recovery was observed. Afterwards B.P. fell rapidly toward the preinfusion level. Dextran with mw. 75,000 and 47,000 could not elevate B.P. to the control level.

Blood volume: Blood volume changes are shown in Fig. 13. Increases in blood volume after infusion of blood and dextran with mw. 75,000 were near

to the volume infused, but the infusion of the 5% glucose solution exhibited an increase of only 22% of the volume infused.

Viscosity of each dextran solution is illustrated in Fig. 14. Osmolality of each dextran solution is exhibited in Fig. 15.

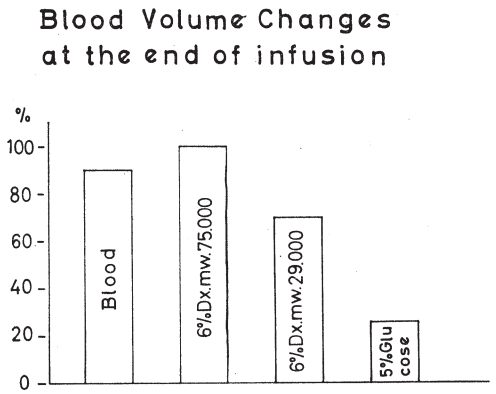


FIG. 13

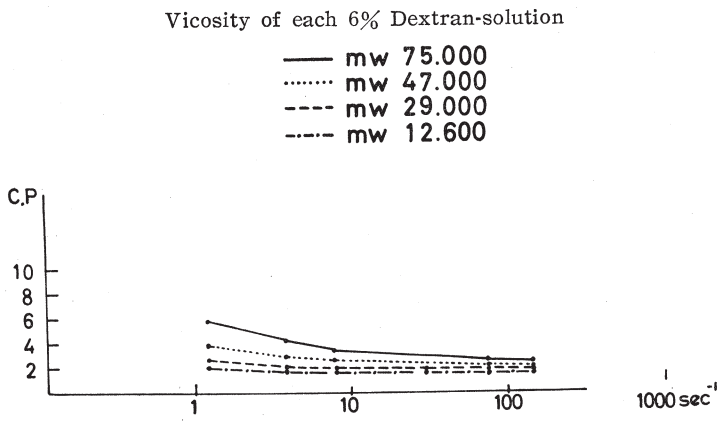


FIG. 14. Dextran with the laiger molecular weight shows the higher viscosity.

Osmolalty for each dextran solution

6% Dx.	mw. 75000	313 m. osmol
〃	mw. 47000	313 〃
〃	mw. 29000	310 〃
〃	mw. 12600	311 〃

FIG. 15

Survival rate after hemorrhagic shock: Two of 8 dogs in G I, 2 of 6 in G II, 3 of 5 in G III, 5 of 7 in G IV and 3 of 5 in G V were alive, but all dogs died in G VI. Dog was considered survival if alive 5 days after the completion of the experiment.

DISCUSSION

The purpose to use four kinds of dextran at the same concentration was to study the alterations in blood viscosity and blood flow induced by various fractions of dextran. These kinds of dextran had narrow molecular weight distributions. The ratios of weight average of molecular weight to number average of molecular weight in dextran, mw. 75,000, 47,000, 29,000 and 12,600 were 1.54, 1.41, 1.41 and 1.56 respectively.

Blood viscosity measurement: There are some difficult problems to solve concerning blood viscosity measurement, because blood viscosity is influenced by many factors as described later. Many of these factors are not directly measurable *in vivo*. When viscosity measurement is made *in vitro*, different values may be obtained by different methods. The method for viscosity measurement in the present study will not be discussed in this paper, because advantages and disadvantages of a cone in cone viscometer were described in detail by Iino[14] and Yamaguchi[15]. Although viscosity may be determined using heparinized blood samples withdrawn from the carotid artery, the anticoagulant is not thought to affect blood viscosity[16].

It is reasonable to expect that viscosity measurement of blood samples taken from a large vessel would tend to reflect both direction and magnitude of changes in various areas of vascular system.

Blood viscosity: In the rheological nomenclature, the blood is a non Newtonian fluid. Blood viscosity may be affected by velocity of blood flow, red cell concentration, temperature, concentration of various kinds of plasma protein, diameter of vessels, etc. Since blood viscosity varies as a function of velocity gradient or shear rate, the blood flowing from arteries to arterioles changes its viscosity continuously[17][18]. The shear rate in the aorta is estimated to be probably around 100 per second in a normal man at rest and in arterioles to be around 10 per second[19]. This is based on the formula that for a Newtonian fluid the shear rate at the tube wall is obtained from the value of $4V/r$ (V: flow velocity. r: radius of the tube). The aortic blood flow velocity of 35 cm/sec and a radius of 1.3 cm would result in the shear rate of 108 per second. If one assumes that an arteriole flow velocity is 0.11 cm/sec and a radius 10 μ, blood in this arteriole would have the shear rate of around 10 per second. This ten fold change in shear rate is presumed to approach the reduction in flow velocity as blood flow progresses from a large artery to the microcirculation[3][5],

Although the shear rate in capillary circulation is not conceivable, shear rate below 10 per second may have special significance in such a low flow state as the microcirculation or shock. Consequently, blood viscosity changes in this study were discussed at the shear rates of 1.2, 7.8 and 146 per second. However, it is widely accepted that, in vessels with small diameter, less than 400 μ, the blood no longer behaves as a mixture; plasma skimming phenomenon[19] occurs and blood viscosity depends upon the plasma[30]. The greatest change in viscosity after infusion of the test substances was observed at the lowest rate of shear, 1.2 per second. This result is in agreement with observations by Gelin[21] and others[3,11,17,34,35]. As Fig. 10 illustrates, blood transfusion exhibited 20% elevation in viscosity above the control level. Contrariwise, 60% reduction was seen after infusion of dextran with mw. 29,000. This reduction in viscosity is probably attributable to the Hct alteration which was most significant among the other test substances. The relationship of Hct to viscosity of blood has been extensively studied by Wells and Merrill[17]. Blood viscosity is greatly depend upon Hct. This fact seems to be proved from the results of the present study. Virgilio *et al.*[22] demonstrated that the viscosity-Hct relationships at a constant temperature showed a linear relationship between logarithm of viscosity and Hct. The effect of infused medium on Hct is thought to be depend on its plasma expanding effect. According to Reemtsma and Creech[23], 6% LMWD (mw. 40,000) was more viscous than the plasma. However, this solution may lower viscosity of the whole blood by lowering the Hct level[31]. The oncotic effect of dextran exerts in various body arreas with different permeability and causes water to enter the circulation from the surrounding tissues, so lowering viscosity. On infusion of dextran used in this study, the plasma expanding effect will be proportional to the amount of dextran in the plasma because of the similar waterbinding capacity of dextran with the similar osmolality. Gelin *et al.*[24] explained that the plasma expanding effect of dextran should be ascribed to the property and amount of colloid and not to the amount of the fluid infused. It is clear that the larger molecules of dextran will stay for longer duration in the circulation and will bring about the larger plasma volume expansion. Furthermore, the infused dextran can affect Hct by changing the degree of red cell aggregation. Shoemaker[9] and Gelin[25] reported that the administration of high viscosity dextran produced a non circulating red cell and decreased arterial Hct. From these investigators' considerations, dextran with mw. 75,000, the highest fraction in dextran, was expected to produce the largest reduction in Hct, but the largest reduction was shown by dextran with mw. 47,000.

Thorsen and Hint[26] demonstrated that dextran with a molecular weight of less than about 50,000 reduced red cell aggregation, whereas dextran with a high molecular weight promoted it. In almost all instances, red cell aggregation

seems to increase viscosity[19)27)].

Blood flow: It seems rational that systemic hemodynamic changes should be conjectured from a change in femoral arterial blood flow. Johnston *et al.*[10)] and Pearson[13)] *et al.* showed that Rheomacrodex (mw. 40,000) induced an augmentation in renal blood flow without increasing the renal fraction of the concomitantly rising cardiac outPut. The rise in renal flow occured on a systemic basis. Schenk *et al.*[28)] also proved such a fact as mentioned above with many regional flows (renal, splanchnic, somatic, abdominal, etc.).

Low molecular weight dextran has been widely used as a flow improver. Mechanisms of the flow improvement are thought as follows: first, reversal of cellular aggregation[6)7)9)] or antisludging action induced by change in surface charge of red cell membrane and phyicochemical property of protein envelope of the red cell; second, blood volume expansion by increasing the oncotic pressure of the plasma[12)28)]; third, lowering of blood viscosity by hemodilution[8)10)13)].

In clinical study, Carey *et al.*[12)] demonstrated that the marked rise in central venous pressure associated with increased cardiac output, diminished circulation time and diminished periperal resistance were observed in patients with shock after infusion of LMWD. These results suggested the improvement of flow in the microcirculation. Gelin and Ingelman[2)] observed in a patient with fracture through photograms that the occlusive aggregates in venules disappeared during and after infusion of Rheomacrodex. On the other hand, in experimental study, Lepley *et al.*[6)] considered that the administration of LMWD well maintained the microcirculation primarily by preventing cellular aggregation. Johnston *et al.*[10)] exhibited that cardiac output and renal flow were increased above the prehemorrhagic level after Rheomacrodex was infused to dogs in hemorrhagic hypotension. The similar experiment was carried out by Replogle *et al.*[11)] They concluded that the effect of LMWD on blood flow was achieved by either hemodilution or blood volume change. In this study, dextran with mw. 47,000 and 29,000 would seem to have a signiflcant effect on blood flow improvement, as compared with the blood, the 5% glucose solution and the other kinds of dextran. An increase in blood volume by the infusion of dextran with mw. 29,000 nearly disappeared by the time when the maximum femoral arterial flow was observed. At the end of infusion, the blood and dextran with mw. 75,000 produced more marked increase in volume than dextran with mw. 29,000, but flow improvement was not seen at this time. These findings were thought to support that blood flow promoting property was not greatly ascribed to an increase in blood volume. According to results of this study, flow promoting property of dextran appeared to be more attributable to lowering blood viscosity and reversal of celluar aggregation than to blood volume expansion.

Baker *et al.*[8] administrated LMWD to patients in surgical shock and concluded that the mechanism of action of LMWD would appear to be lowering blood viscosity in small vessels with subsequent improvement of flow and disaggregation of red cells. This conclusion is in agreement with the consideration on flow improvement delivered from this study. Furthermore, many investigators[10)24)29)] demonstrated that the plasma volume expansion by the infusion of Rheomacrodex was apparently gone by the time when the delayed and sustained flow promoting phenomena were observed. The postulated mechanisms which induced or sustained these flow phenomena were more likely those related to the viscosity altering effect of this drug.

The question arises as to whether the observed flow changes are due to alteration in viscosity or are a response to the lowered Hct and reduced oxygen carrying capacity of the blood. This question could not be explained by this study alone.

Blood volume: An increase in blood volume due to the dextran infusion is dependent on its colloid osmotic characteristics[7)24)32)33)]. These characteristics are a function of the molecular size of dextran, its concentration, and the membrane characteristics of the general capillary bed. Dextran molecules which can pass the capillary membrane will be transported out into the extravascular space. Molecules which are able to pass the glomerular membrane will be filtrated off into the urine. The smaller molecules will have a shorter survival in the circulation as compared with the larger ones. According to Arturson and Wallenius[30)], dextran with mw. 55,000 to 69,000 had an intravascular half-time of about 12 hrs. The half-time of dextran with mw. 28,000 to 36,000 was about 30 min. Therefore, the waterbinding capacity of dextran with mw. 75,000 is thought to be for longer duration than dextran witn mw. 29,000. Furthermore, the 5% glucose solution seems to disappear rapidly from the vascular system, since it is not a colloid solultion. Data in Fig. 13 are well explained by these results mentioned above. Gelin *et al.*[24)] demonstrated that Macrodex (mw. 75,000) was found to have a plasma volume expanding effect which corresponded to the volume infused, and a colloid free solution showed no significant increase in plasma volume when infusion was made at a rate of 500 ml in one hour.

Blood pressure: Infusion of dextran with mw. 29,000 and blood restored B.P. sufficiently to the control level, as compared with the other test substances, but B.P. in G IV fell with the elapse of time. In G I B.P. was maintained efficiently for 90 minutes after infusion. It was thought from these results that an elevation of B.P. with infusion was attributed to recovery of flow and maintenance of B.P. after the elevation was associated with an increase in blood volume and its duration.

Survival after comletion of experiment: The effect of LMWD on hemorrhagic shock was investigated by Lepley *et al.*[6] and survival rate was as follows: 2 of 10 dogs with blood transfusion and 5 of 10 dogs with infusion of dextran 80 (mw. 73,000) and 9 of 10 dogs with infusion of Rhomacrodex. In the present study, the best survival rate was obtained by infusion of dextran with mw. 29,000. This dextran preparation was thought to be one of the most beneficial plasma expanders for hemorrhagic shock.

SUMMARY

The amount bled in 48 dogs varied from 28 to 38 ml/kg of body weight. Dogs were infused 90 minutes after hemorrhage the equivalent volume of one of the six test substances. Serial determinations of femoral arterial blood flow. viscosity, Hct, B.P. and blood volume were made.

Results were summarized and discussed as follows: (1) Infusion of dextran with mw. 29,000 elevated flow most remarkable above the control level. Changes in B.P. and viscosity at low shear rates and survival rate were the maximum in these experiments. (2) Infusion of dextran with mw. 47,000 produced the maximum reduction in Hct. Alterations of flow, vicosity and B.P. were similar to the changes caused by dextran with mw. 29,000, but they were all below the levels induced by dextran with mw. 29,000. (3) Infusion of the 5% glucose solution and dextran with mw. 12,000 produced transient effects on flow and B.P, (4) Blood transfusion caused slight changes in flow, B.P. and blood volume, and induced a moderate increase in viscosity. (5) Infusion of dextran with mw. 75,000 entailed an increae of blood volume equal to the infused volume and caused less but prolonged effects on B.P., flow and viscosity.

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