The Status of Plasma Expanders in Open Heart Surgery*

David M. Long, Jr., Lt., MC, USNR**

Bethesda, Maryland

With the rapid growth of open heart surgery, blood banks have received demands for large volumes of fresh homologous blood. The task of typing and crossmatching five to 20 pints of donor blood for a single operation has imposed stringent requirements of perfection and timing on the personnel of the blood bank. Human errors can be disastrous and may be undetectable under such conditions. Furthermore, the likelihood of encountering still unknown problems in crossmatching of blood is also magnified. Hemorrhagic diatheses of unexplained etiology are a common occurrence after transfusions of large volumes of homologous blood. This latter fact is in itself sufficient justification for decreasing the requirements of whole blood. Other factors such as cost, procurement and transmission of infectious agents also enter the picture.

Several methods have been tried in the last three years to decrease the quantity of blood required in extracorporeal circuitry. Generally, these efforts have been designed to improve the results of cardiopulmonary bypass and only incidentally to decrease cost and technical requirements. Low molecular weight dextran
\(^1\) (Rheomacrodex),
\(^\dagger\) normal human serum albumin,\(^1\) 5 per cent dextrose in water\(^2\) and 0.9 per cent saline solution\(^3\) have been utilized as volume expanders. Oxygenators requiring little or no blood for priming have been designed for use at normal flow rates and at low flow rates. Methods for freezing and storing blood have finally reached a stage of clinical application so that even autologous blood can be collected and stored during the several months of advanced scheduling and used for priming the oxygenator.\(^4\)

Plasma Expanders

Recently, considerable interest in clinical application has been directed toward Rheomacrodex as a plasma expander. At least ten groups throughout this country have had significant clinical experience with this drug in extracorporeal circulation. However, the original reason for using Rheomacrodex was that this drug is the only known agent effective in countering intravascular aggregation of blood corpuscles and the resulting small vessel thrombosis. Therefore, it would seem appropriate to review intravascular aggregation and the significance of this phenomenon in cardiopulmonary bypass. Since extensive experimental and clinical observations have been obtained with Rheomacrodex, this story also serves as an example of what might be accomplished by additional studies with plasma expanders when used appropriately with the support of experimental evidence.

Microcirculation Studies: The capillary circulation is the focal point for the activity

---

*From the Department of Surgery, University of Minnesota, Minneapolis, and Naval Medical Research Institute, National Naval Medical Center, Bethesda. The opinions or assertions contained herein are the private ones of the author and are not to be construed as official or reflecting the view of the Navy Department or Naval service at large.

**Special Research Fellow, National Heart Institute, United States Public Health Service. Present address: Naval Medical Research Institute, National Naval Medical Center, Bethesda, Maryland.

\(^1\)Low molecular weight dextran (Rheomacrodex\(^\circ\)) is a dextran preparation with an average molecular weight of about 40,000. Pharmacia Laboratories, Inc., New York, N. Y.
of all components of the circulatory system. Consequently, this important phase of the circulation was examined during extracorporeal maintenance with artificial pumps and oxygenators. Severe aberrations in microcirculation were found to appear after approximately 90 minutes of total cardiopulmonary bypass in canine experiments. The principal cause of the focal interruption of the microcirculation at normothermia and mild hypothermia was found to be intravascular aggregation. The intravascular aggregation could be prevented or even reversed at early stages by the administration of therapeutic doses of Rheomacrodex. These observations have been confirmed by several investigators.

The pathophysiologic relevance of intravascular aggregation has been disputed for years. This dispute will probably continue as long as our methods for evaluating function are so gross and imprecise for organs with a large functional reserve. Furthermore, there are no methods for quantitating the magnitude of intravascular aggregation of blood corpuscles. In the meantime, the microcirculation remains impressed when large aggregates of corpuscles occlude arterioles and venules preventing capillary circulation to focal areas. In this regard, the work of Gelin was particularly stimulating in demonstrating the reversal of intravascular aggregation and the prevention of the anemia of injury and of microinfarctions with the use of Rheomacrodex in burns, fractures, soft tissue trauma and hypothermia. We have been able to demonstrate similar diffuse, renal, hepatic and myocardial microinfarctions in dogs undergoing three hours of total cardiopulmonary bypass. The development of such lesions was prevented or minimized by adding Rheomacrodex to the priming blood of the oxygenator in a dosage of 20 to 30 ml. of a 10 per cent solution in 0.9 per cent saline per kg. of body weight. The morphologic counterproof of the significance of intravascular aggregation was convincing. However, it should be added that no physiologic correlation has been produced as yet except for ECG and EEG abnormalities under certain experimental conditions.

The etiology of intravascular aggregation in extracorporeal circulation and in many forms of disease and trauma is probably not as simple as was once supposed. Lee demonstrated a film of denatured protein on erythrocytes and attributed the cohesiveness of the cells to this factor. The denaturation of the proteins was reversed with Rheomacrodex and the film disappeared. Denaturation of plasma proteins was far less with membrane type oxygenators than with any other type, but mild intravascular aggregation of red corpuscles still occurred. The factors controlling the electrochemical charge density on the corpuscles seem to be important also and are now being studied.

Clinical Studies: An attempt was made to correlate the observations in canine experiments with those of clinical cases of extracorporeal circulation. The two situations contrasted in several ways. First of all, intravascular aggregation was not found preoperatively in normal dogs, but was frequently present in cardiac patients, particularly those with cardiac decompensation and the more severe forms of heart disease. When intravascular aggregation was present preoperatively, it always became more severe during cardiopulmonary bypass. Secondly, most intracardiac operative procedures required less than 90 minutes of cardiopulmonary bypass so that intravascular aggregation was usually not observed in good risk patients. When intravascular aggregation was found clinically, it occurred early and was usually associated with additional complicating factors such as lesions technically difficult to correct and a poor myocardial, hepatic and renal reserve. Such associated and possibly related problems made it difficult to place a value on the importance of intravascular aggregation in open heart surgery in humans. The microcirculation in patients receiving Rheomacrodex was compared with those not receiving the drug in a blind control series, and
the patients were followed closely during the postoperative period. As a result of these studies, it was estimated that intravascular aggregation severe enough to cause mortality was present in no more than 5 per cent of the patients. However, this 5 per cent may represent from 15 to 20 per cent of the mortality in open heart surgery.

The efficacy of the plasma expanders Rheomacrodex and 5 per cent normal human serum albumin (Albumisol) was determined in a blind control study in human patients. Both Rheomacrodex and Albumisol decreased the requirements for whole blood by a quantity approximately equal to that of the plasma expander used. In the patients receiving Rheomacrodex, there was a statistically significant decrease in the amount of free plasma hemoglobin produced and in the drop of platelet counts. In these respects Rheomacrodex appeared to be superior to either Albumisol or, in the control series of patients, whole blood in larger quantities. Changes in the spectrum of coagulation studies observed were the same in the patients receiving Rheomacrodex or Albumisol as they were in the control series of patients. No evidence of increased bleeding or blood loss was found with Rheomacrodex or Albumisol. Only a mild temporary hemodilution was observed when plasma expanders were used.

Two additional advantages of Rheomacrodex have become apparent. First of all, Rheomacrodex was found to inhibit cold agglutination in vitro in blood specimens from patients having cold agglutinins. At this time, one can only speculate on the importance of cold agglutination in patients subjected to extracorporeal circulation and hypothermia. Circulating cold agglutinins may not be significant under such circumstances. Without such evidence, however, it seems safer to use the Rheomacrodex to prevent the cold agglutination. Finally, because of the molecular size and concentration of Rheomacrodex, the administration of this drug increases the colloidal osmotic pressure of the blood.

In patients with cardiac decompensation who do not have toxic injury and increased permeability of the alveolar membrane, pulmonary edema results when the hydrostatic pressure in the pulmonary capillaries exceeds the colloidal osmotic pressure of the plasma. Increasing the colloidal osmotic pressure of the blood can therefore be an effective temporary expedient in the therapy of pulmonary edema. In some postoperative patients, this method of therapy has been safer and more effective than induced hypovolemia.

The recommended therapeutic blood level for Rheomacrodex is 1.2 to 1.5 gm. per cent. Rheomacrodex is excreted rapidly by the kidney, and some of this substance enters the lymphatic and interstitial spaces. Adequate blood levels can be achieved and will be sustained for several hours by using a dosage of 10 to 15 ml. of a 10 per cent solution of Rheomacrodex per kg. body weight. In open heart surgery, the extracorporeal circuit usually contains a volume of blood roughly equal to that of the patient's own volume. To compensate for the increased blood volume, a dosage of 20 to 30 ml. of 10 per cent Rheomacrodex per kg. of body weight has been recommended for use in open heart surgery. Due to the relatively small molecular size of Rheomacrodex, the drug is excreted by the kidneys over a six to ten hour period and the blood level drops rapidly. When therapeutic blood levels are desired during the postoperative period, additional Rheomacrodex should be added by continuous intravenous infusion replacing part of the normal fluid requirements.

Rheomacrodex was used in place of the customary clinical Macrodex because of the bleeding tendencies reported with large quantities of Macrodex. In experimental canine studies when dosages of Rheomacrodex greater than 4 to 6 gm. per kg. of body weight were used, prolongation of the bleeding time was usually encountered. With these large doses, the effect of Rheomacrodex was reversed and transient intravascular aggregation was produced.
Concentrated human serum albumin has been used in small quantities by a number of groups. The purpose in using concentrated albumin has been to compensate for the decreased colloidal osmotic pressure of donor blood due to the added aqueous solution of anticoagulants. In this capacity, the albumin did not serve as a plasma expander per se. In the studies noted above, 5 per cent Albumisol was used in quantities of 20 to 30 ml. per kg. of body weight. With these larger quantities, Albumisol was found to be a safe effective plasma expander in open heart surgery.

Electrolyte solutions and crystalloid solutions have also been used in extracorporeal circuits to decrease blood requirements. Normal saline solution was used effectively due to its lesser density and tendency to layer out on top of the blood. Pumping was done primarily with blood with the volume of saline available in case of a fall in the reservoir volume. Five per cent glucose solutions have been used as priming agents with a modification of the helix reservoir of the bubble oxygenator. Electrolyte and crystalloid solutions have been used extensively as volume expanders in emergency situations of blood loss and a great deal of information has been procured on their efficacy. In extracorporeal circulation, glucose solutions apparently remained in the intravascular space for longer periods of time when low flow rates and moderate hypothermia were used resulting in a decreased hydrostatic pressure for filtration. When cardiopulmonary bypass was performed with flow rates equal to normal cardiac output in other experiments, the electrolyte and crystalloid solutions left the intravascular space more rapidly and were therefore less useful as plasma expanders.

Summary and Conclusions

In terms of the safety achieved, we were probably justified in the use of almost extravagant quantities of homologous whole blood in the initial years of open heart surgery. Our knowledge of the physiologic and mechanical problems of open heart surgery has advanced rapidly during the last seven years. Certainly not all of the problems have been solved. At least two minor problems, that of intravascular aggregation and protein denaturation have been solved, however, by the use of Rho-macrodex. There are no apparent reasons why plasma expanders should not be used as partial blood substitutes in open heart surgery. Theoretically, it should be possible to avoid the use of homologous blood entirely. Blood loss due to hemorrhagic diatheses has been greater in patients subjected to open heart surgery than in closed heart surgery. Only with the use of better apparatus and less homologous blood will it be ascertained whether or not this bleeding is related to massive transfusion. With the hemodilution of the patient’s blood and the prevention of aggregation, damage to corpuscular elements is proportionately decreased.

References


