Low Molecular Weight Dextran and Cardiopulmonary Bypass in the BOS Experimental Subject

John M. Binford, B.S.
Diane Clark, B.S., C.C.P.
Terry N. Crane, B.S., C.C.P.
Charles C. Reed, B.S., C.C.P.

Dextran is a branched polysaccharide composed of about 200,000 glucose units. The glucose units in the main chain are bound together by 1:6 glucosidic linkages. A special strain of lactobacilli (lenconostoc Mesenteroides) converts sucrose to a highly linear dextran molecule which has a molecular weight of approximately 40 million. By means of partial acid hydrolysis and subsequent differential fractionation, this native dextran can be converted to polysaccharides of any desired range of molecular weights. The dextrans produced for clinical use are always polymolecular and are therefore defined by average molecular weight.

During World War II there was a great need for an "artificial plasma" or more specifically a plasma volume expander; thus the development of high molecular weight dextran (Dextran 70, Macrodex). Dextran 70 has an average molecular weight of 70,000. In 1950, Thorsen and Hilt14 demonstrated that dextran with a mean molecular weight greater than 60,000 caused a sharp increase in erythrocyte aggregation. They stated that "theoretically it should be possible to eliminate intravascular aggregation by the infusion of suitable low molecular weight colloids;" soon followed the development of low molecular weight dextran (Dextran 40, Rheomacrodex). Dextran 40 has an average molecular weight of 40,000 with 90% of the molecules being within the range of 10,000 to 80,000. Commercially, Dextran 40 is available as a 10% solution in .9% saline or as a 10% solution in 5% Dextrose and water.

Dextran 40, when indicated for use in pump oxygenators, has many advantages and few proven disadvantages. Dextran 40 enhances flow and capillary perfusion. This is accomplished by rapid blood volume expansion, anti-sludging, and reduction of blood viscosity. Blood volume expansion occurs due to the strong hypertonicity of the solution. It increases the oncotic pressure of plasma thereby mobilizing interstitial fluid and reducing intravascular fluid loss. A Dextran concentration of 4 Gm % exerts a colloid osmotic pressure equivalent to that of normal plasma. Expressed another way, 1 Gm of Dextran will "bind" approximately 25 ml of water. Generally, plasma volume is increased by 1 to 2 times the volume of Dextran 40 infused. The extent and duration of volume expansion produced is dependent upon the patient's degree of hydration and pre-existing blood volume, the rapidity of infusion, and the rate of Dextran clearance by the kidney. In normally hydrated patients with adequate renal perfusion, the urine specific gravity seldom exceeds 1.040. Poorly hydrated patients...
will exhibit high urine specific gravities following Dextran 40 infusion. The rate of
infusion is an important factor. During the first 90 minutes following infusion, the
plasma concentration falls rapidly which is mainly due to renal excretion of the smaller
molecular fraction. Clearance of molecules with molecular weights of greater than
50,000 is essentially zero. Wallineous\textsuperscript{15} demonstrated that following an infusion of 500
ml of Rheomacrodex approximately 60\% is excreted within 6 hours. The higher
molecular weight dextran molecules not excreted pass into the extravascular
compartment. A small amount of the molecules subsequently are returned to the
vascular system via the lymphatics. The remainder are removed by the
reticuloendothelial system where they are degraded by dextranase to glucose.

Sludging and erythrocyte aggregation directly affect flow through capillary beds.
In 1956, Gelin\textsuperscript{5} suggested that blood sludging is a biophysical response to various types
of trauma. In describing the “anemia of injury” he demonstrated that trauma caused a
reduction in circulating erythrocytes greater than could be explained by actual blood
loss. Further investigation showed that this decrease in circulating erythrocytes
resulted from a sequestration of red cells which removed them from the effective
circulating red cell mass. Gelin\textsuperscript{5} later demonstrated that this sequestration was due to
erthrocyte aggregation in the microvasculature and did not occur when low
molecular weight dextran was used. Long, et. al.,\textsuperscript{8} \textsuperscript{7}studied the microcirculation of the
ocular conjunctiva in both dogs and humans under normothermic and hypothermic
perfusion. When Dextran 40 was not used, Long observed the formation of
erthrocyte aggregates and concurrent obstruction of the microcirculation. When
Dextran 40 was used this phenomenon was not observed. To achieve complete
prophylaxis against aggregation, he determined that the minimum effective level of
Dextran 40 was 1,400 to 1,600 mg percent. 1.0 to 1.5 Gm/kilo Dextran 40 was
necessary to prevent aggregation as opposed to 2.5-3.0 Gm/kilo of albumin. In 1962,
Bernstein\textsuperscript{1} used a glass micro-electrophoresis chamber to demonstrate that low
molecular weight dextran increased the repulsive forces of red cells by increasing the
“zeta potential” (electronegativity).

Low molecular weight dextran increases flow and perfusion not only by
increasing blood volume and preventing sludging, but also by reducing viscosity. An
increase in cohesive forces causes an increase in peripheral resistance thereby reducing
flow. High viscosity in the microcirculation favors hypoxia by delaying passage of red
cells and also by decreasing the diffusibility of oxygen. Both Rand and Suzuki\textsuperscript{11} \textsuperscript{13}
demonstrated that blood and plasma viscosity is not appreciably effected by the
addition of heparin. Normal saline will reduce viscosity through dilution but the effects
are only transient due to rapid loss from vascular system.\textsuperscript{12}

The flow improving properties of Dextran 40 should make total body perfusion
more effective. Dextran 40 not only helps maintain adequate perfusion of vital organs,
but also increases urine output and reduces hemolysis. Arteriography\textsuperscript{4} has shown that
Dextran 40 helps to maintain normal distribution of blood flow in the kidney. Dextran
molecules with a molecular weight of less than 15,000 have the same renal clearance as
creatinine and are able to pass the glomerular membrane without restriction. The
active diuresis of the lower molecular weight component exerts significant protective
influence against the accumulation of nephrotoxic agents.

Rheomacrodex is the most effective nonhemic solution in the prevention of
hemolysis and thrombocytopenia. In a comparison of 5\% albumin, rheomacrodex,
and whole blood as priming fluids for human cardiopulmonary bypass, both Long and Mainardi found a direct relationship to hemolysis in the Dextran 40 group. With Dextran 40 there was a 42% decrease in plasma free hemoglobin per minute of bypass as opposed to only a 19% decrease with albumin. Brewer has reported a stenoplastic effect of dextrans on platelets. Platelets in the presence of Dextran 40 are more resistant to the disruptive effect of ultrasonic energy. This effect possibly explains why “Dextran coated” platelets do not readily lyse as a result of trauma.

In addition to the desirable attributes of increased flow and tissue perfusion, increased urine output, and reduced hemolysis, dextrans possess a few less desirable characteristics. Dextran is a potent antigen. In man the subcutaneous injection of only 1 mg maximum leads to the development of precipitins and cutaneous wheal reactions. Therefore, the antigenic activity of dextrans would seem to preclude its repeated use. However, when administered in the massive doses that are employed for infusion, antibody production does not occur. This is due presumably to the phenomenon of “immunological paralysis” and to the fact that Dextran has a very low degree of side chain branching.

In addition to rare antigenic effects, dextrans have been implicated in bleeding problems. However, a review of the literature reveals that serious hemostatic defects have been reported only when doses greater than 20 mg/kg have been administered. Long, Breckenridge, and Glass have demonstrated that reported bleeding problems were due to the large molecular weight fraction. When high molecular weight dextran was used in extracorporeal circulation, platelet counts and fibrinogen levels decreased and prothrombin times increased. When low molecular weight dextran was used these parameters were not appreciably effected and bleeding problems were not encountered.

In a recent study at the Texas Heart Institute, it was demonstrated that Dextran 40 is useful in the maintenance of satisfactory perfusion flow rates and in the reduction of tissue and pulmonary edema.

Total cardiopulmonary bypass of 120 minute durations permitted implantation of Total Artificial Heart Prostheses in 26 successive bovine calves. Calf weights ranged from 64 to 102 kg. Succinyl choline and halothane anesthetic were used to achieve desired anesthesia levels. Total heparinization was achieved using beef lung heparin (3 mg/kg) prior to cannulation. Arterial cannulation was to the left common carotid artery cephalically and the left femoral artery caudally. The inferior vena cava was cannulated through the right atrium, and superior vena cava cannulation was through the left jugular vein. The extracorporeal circuit was primed and total normothermic cardiopulmonary perfusion was initiated.

The first prime used in this series consisted of fresh donor blood and 5% Dextrose in Ringer's Lactate solution (D$_5$RL). Extreme hemodilution and decreased perfusion rates necessitated the addition of large amounts of citrate phosphate dextrose (CPD) blood and D$_5$RL (2000-6300cc). With regard to maintenance of adequate flow rate, this treatment proved either transiently effective or totally ineffective. The first 5 perfusions demonstrated severe intraoperative fluid shifts away from the intravascular compartment. Autopsies on calves sacrificed immediately following cardiopulmonary bypass demonstrated respiratory insufficiency of pulmonary edematous origin, severe ascites, and cerebral edema. Impaired or absent renal function and progressive metabolic acidosis resulted from grossly unusual

100 THE JOURNAL OF EXTRA-CORPOREAL TECHNOLOGY
vascular dynamics during cardiopulmonary perfusion. Platelet-leukocyte aggregation repeatedly occluded the extracorporeal microemboli filtering system.

Primary modifications were instituted in an attempt to rectify these problems. 1000 ml of fresh donor blood plus 1000 ml of D₃RL plus 500 ml of 10% low molecular weight dextran in normal saline (Dextran 40) was used to prime the circuit.

Normothermic extracorporeal perfusion was regulated primarily by the rate of perfusion flow with secondary regard to changes in mean arterial blood pressure. Flow rates between 45 and 55 ml/kg/min were considered optimal. Flow rates less than 40 ml/kg/min prompted fluid addition to the circulatory volume. A minimum hemoglobin concentration of 5 Gm % and a minimum hematocrit of 15% were values used as a regulation point in fluid balance and hemodilution. Flow rates were not sacrificed to correct increasing mean arterial blood pressures. During bypass attempts were made to pharmacologically maintain mean arterial pressure between 40 mmHg and 80 mmHg.

Table I summarizes the prime, weight, hemoglobin, pH and flow relationships. The 2500 ml Dextran 40-D₃RL-blood prime significantly improved maintenance of constant optimum flow rates without endangering oxygen capacities due to excessive hemodilution. These optimum arterial flow rates were easily obtainable during all cases which included the Dextran 40-D₃RL-blood priming solution. As seen in Table I, lower flow rates occurred when Dextran 40 was eliminated from the priming solution.

### TABLE I

<table>
<thead>
<tr>
<th>No. of Cases</th>
<th>Prime</th>
<th>Mean Wt</th>
<th>Mean Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Blood + D RL 1000 cc 1500 cc</td>
<td>82.6</td>
<td>37.6</td>
</tr>
<tr>
<td>21</td>
<td>Blood + D RL + Dextran 1000 cc 1000 cc 500 cc</td>
<td>83.6</td>
<td>54.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of Cases</th>
<th>Mean Hbg Low/End</th>
<th>Mean pCO</th>
<th>Mean pH Arterial</th>
<th>Urine cc</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>6.68/6.92</td>
<td>40.8</td>
<td>7.296</td>
<td>30</td>
</tr>
<tr>
<td>21</td>
<td>6.74/7.23</td>
<td>42.2</td>
<td>7.347</td>
<td>240</td>
</tr>
</tbody>
</table>

As shown in Table II, the addition of fluid following initiation of extracorporeal perfusion was unnecessary in one-half of the cases. In Group II, the entire group averaged only 233 ml added during bypass. Group I, in which Dextran 40 was omitted from the prime, averaged 1700 ml fluid added during bypass. Initial hemodilution resulted in hemoglobin concentrations of greater than 5.4 Gm % and rarely diluted concentrations below 6.2 Gm %. End hemoglobin concentration averaged 7.23 Gm %. The average urine output without Dextran 40 was 30 cc as opposed to 240 cc with Dextran 40. No diuretics were used during cardiopulmonary bypass and administration of alkalizing agents was not necessary.
**TABLE II**
Total Fluid Added During Bypass

<table>
<thead>
<tr>
<th>GROUP 1 Non-LMWD</th>
<th>GROUP 2 LMWD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-6300</td>
<td>11-0</td>
</tr>
<tr>
<td>1-1500</td>
<td>7-500</td>
</tr>
<tr>
<td>1-2000</td>
<td>2-200</td>
</tr>
<tr>
<td>1-500</td>
<td>1-1000</td>
</tr>
<tr>
<td>1-3000</td>
<td>Ave. = 2660</td>
</tr>
</tbody>
</table>

**REFERENCES**