

# A CLINICAL REPORT OF THE USE OF LOW-MOLECULAR-WEIGHT DEXTRAN IN A ROTATING OXYGENATOR

BY

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Increasing use of heart-lung machines accentuates the desirability of reducing demands on blood donors by the addition of other priming fluids. Neptune, Bougas, and Panico (1960) described a machine requiring no priming blood, and Zuhdi, McCollough, Carey, Krieger, and Greer (1961) accepted haemodilution by 5% dextrose solution during hypothermic perfusion. Recently Long, Sanchez, Varco, and Lillehei (1961) have used low molecular weight dextran during perfusion, and demonstrate by elegant studies of the microcirculation that reduction in "sludging" of red cells results in improved peripheral circulation. Drake and Lewis (1961) are unable to confirm this effect but note the prevention of haemoconcentration during hypothermia as a benefit. Finsterbusch, Long, Sellers, Amplatz, and Lillehei (1961) found improved renal flow during perfusion using low molecular weight dextran.

All these studies used low flow perfusion rates. Unusual foaming characteristics when using dextrans in bubble oxygenators may be acceptable because of the debubbling methods already necessary but might provide special difficulties in the use of a rotating oxygenator, particularly at high flow rates. A clinical trial of these features has been successfully carried out.

## CASE MATERIAL AND METHOD

Twenty successive patients, 5 to 49 years old, requiring by-pass cardiac surgery have been perfused by the Melrose-N.E.P. heart-lung machine using volumes of low molecular weight dextran (Rheomacrodex). The immediately acceptable advantages did not justify the establishment of a "blind control" method of testing, but wherever possible comparison has been made with the maximum number of immediately preceding cases.

At the same time some investigation of the greatest tolerable haemodilution by low molecular weight dextran has been carried out in a limited series of dog perfusions.

High flow rates were used (2.4 to 2.8 l./sq.m. surface area) with hypothermia of 30 to 23° C., flow rates

at these temperatures never being reduced to less than 1.4 to 1.8 l./sq.m., for periods of 21 to 74 minutes, average 40 minutes.

The heart-lung machine is initially calibrated using normal saline and is then evacuated, leaving a residual volume which, with 90 mEq. of sodium bicarbonate added, leaves the circuit with 400 to 500 ml.; this diluting factor must be considered. Rheomacrodex (10% in normal saline) is then added (20 ml./kg.) and finally 48-hour-old blood in E.D.T.A., the volume of blood being 2 l. minus the volume of low molecular weight dextran.

At the end of perfusion some compensation for haemodilution is made by the transfusion of priming fluid from the machine. The amount given is a compromise between true balance and that volume theoretically necessary to restore cell volume to the patient. During the first 12 post-operative hours all patients had 5 ml./kg. 10% Rheomacrodex in 5% dextrose solution as part of their intravenous therapy.

Patients' weights ranged from 17 to 79 kg., surface areas from 0.72 to 2.05 sq.m., average 1.55 sq.m., and calculated blood volumes from 1,500 to 6,000 ml. Low molecular weight dextran, 340 to 1,250 ml., was used in the machine; on 10 occasions 1,000 ± 50 ml. was used.

## RESULTS

In all cases satisfactory perfusions with good arterio-venous oxygen saturations were obtained without technical difficulty. One patient developed transient hypotensive, hypoxic cardiac output with oliguria post-operatively and was omitted from the studies of urine flow. There was one death 24 hours post-operatively; the patient had an ostium primum defect with severe pulmonary hypertension. It was a well-supported but unproved clinical impression that peripheral circulation immediately after operation was improved in patients receiving low molecular weight dextran.

**HAEMODILUTION.**—The theoretical haemodilution was always calculated before confirming the addition of low molecular weight dextran. Allowing for the saline and bicarbonate already in the circuit, the dilution of the patient-machine

mixed blood volume was 80 to 84.3%, average 81.5%. This was detectable, but after the first patient no increase in the perfusion rate was made to compensate for the dilution of red cells.

Based on these figures, 20 ml./kg. of "machine fluid" should be added to the patient's blood volume at the end of perfusion to restore the erythrocyte count to 100%. In practice, 10 ml./kg., restoring haemodilution to 90%, was constantly given without cardiac embarrassment, and in the larger patients 15 ml./kg. above blood "balance" was acceptable.

During 30-minute perfusions of dogs, survivors for one week were obtained when perfusion haemodilution fell to 75% although there was evident anaemia and weakness. Complete anaesthetic recovery was not obtained in two dogs in which dilution fell to 70%.

FOAMING.—In one case the machine was primed too full at a high rate (4.5 l./min.) with rapid oxygenator revolutions (55/min.), resulting in a disturbing formation of foam. It is clear that, in this machine, bubbles in the arterial well are directly related to the product of these three functions. In all other cases foaming was definitely greater than without low molecular weight dextran but caused no worry during perfusion. It was not noted to increase with cooling.

PERIPHERAL RESISTANCE.—Although few estimations were made, there appeared to be no significant decrease or increase in peripheral resistance as indicated by central arterial pressure with a fully occlusive pump.

URINE FLOW.—It was not possible to carry out renal function tests during the series. However, urine flow was continuously measured and Table I sets out the results.

TABLE I  
URINE FLOW

	Eight Previous Cases	Low Molecular Weight Dextran Series*
During preliminary anaesthesia (ml./kg./hr.)	(In three cases less than 0.005) 0.24-1.29, average 0.57 (23 cases)	
During perfusion (ml./kg./hr.)	0.95-2.6, average 1.52	1.46-4.1, average 2.57
First 4 hr. following perfusion (ml./kg.)	2.04-5.0, average 2.53	2.82-5.48, average 3.95
First 12 hr. (ml./kg.)	5.46-14.7, average 10.45	7.35-15.5, average 11.71
24 hr.	14.00-32.5, average 20.15	13.6-37.5, average 21.12

\* Two patients were omitted: one had post-operative oliguria with hypotension; the other had an infarct-ventricular septal defect and aneurysm of the left ventricle and had been on extensive diuretics; his urinary flows at all times were severely below any others found.

BLOOD CLOTTING.—Heparin neutralization was achieved by the use of Polybrene, 1.5 ml./1,000 units heparin calculated in the mixed blood volume restored to the patient. After adequate heparin neutralization, confirmed in cases of doubt by the thrombin test of Rothnie and Kinmonth (1960), there was no instance of inadequate clotting at the end of perfusion, although in one patient it was described as "present but thin." No action was taken and no unusual loss of blood occurred.

BLOOD LOSS.—There was wide variation, 15.6 to 32.0 ml./kg. in 12 hours, average 23.1 ml., closely resembling that in the previous 20 patients, i.e., 14.8 to 34.0 ml./kg., average 24.0 ml.

HAEMOGLOBIN. — Haematocrits were not measured, but daily haemoglobin estimations were made. The pre-operative range was 12.9 to 16.0 g./100 ml. blood, and that on the first post-operative day 11.8 to 13.9 g., the maximum drop being 2.1 g. In four patients the haemoglobin increased. Figures on the second and fourth day were similar. No patient needed transfusion after the first 12 hours. These results were broadly similar to those previously obtained.

PLASMA HAEMOGLOBIN.—Only a few measurements were made in the first patients, the average increase of plasma haemoglobin during perfusion being 30 mg./100 ml. This is similar to whole-blood primings of the machine.

PLATELETS. — Considerable difficulty was experienced by the laboratory staff in obtaining reliable absolute counts; the normal and completely satisfactory method has been to report on the normality of the appearance of platelets and whether they are "plentiful," "diminished," or "scanty." On this basis there was only one adverse report on the first post-operative day, which was corrected within 24 hours. This was in one of 10 patients studied by absolute measurement, the pre-operative level being 202,000/ml., 55,000 on the first post-operative day, 186,000 the next, and 200,000 on the third. The patient presented no clinical problem. In the others, the pre-operative range was 200,000 to 325,000, on the first day 120,000 to 254,000, maximum drop 120,000. There were no significant falls in platelet level during the following seven days. All our patients before this trial had been reported as having "platelets plentiful and normal" on the first, second, fourth, and sixth post-operative days.

ACID-BASE STATUS.—Extensive studies were undertaken before, during, and after perfusion and

form the subject of more detailed study (Raison, 1962a). Two-day-old E.D.T.A. blood equilibrated with 97.5% O<sub>2</sub>/2.5% CO<sub>2</sub> has an average pH of 7.2, Pco<sub>2</sub> 51.3 mm. Hg, and standard bicarbonate level of 18.5 mEq./litre. It has been established previously that 90 mEq. sodium bicarbonate added to 2.5 l. priming blood in this state produced averages of pH 7.38, Pco<sub>2</sub> 60 mm. Hg, and standard bicarbonate 30.5 mEq., a satisfactory neutralization of the fixed acids present, the relatively high Pco<sub>2</sub> being rapidly eliminated during perfusion. Rheomacrodex, 10% in normal saline, has a pH of 5.1 and a buffer capacity of 1.5 ml. of 0.1 N NaOH/l., but measurements confirmed that no further addition of sodium bicarbonate was necessary when using low molecular weight dextran.

The incidence of both respiratory and metabolic acidoses bore no relation to the use of low molecular weight dextran.

MICROCIRCULATION.—It was not possible to make studies of this most interesting phenomenon of intravascular erythrocyte aggregation being reduced by low molecular weight dextran.

#### DISCUSSION

It is clear that low molecular weight dextran may safely be used in a rotating drum oxygenator at high flow rates. Inevitably haemodilution presents limiting factors. Long, Sanchez, Varco, and Lillehei (1961), in an addendum, state that satisfactory perfusions using 16 ml./kg. low molecular weight dextran in the machine have eliminated the need for priming blood. Such economy can only be achieved by low flow rates, which are unacceptable generally. Like many others, the Melrose machine has a minimum priming requirement of the order of 2 l. fluid in addition to 300 to 400 ml. saline already present and 100 ml. NaHCO<sub>3</sub>, if the technique described in this paper is followed. In these circumstances, 20 ml./kg. low molecular weight dextran substituted for an equal volume of blood is quite acceptable for perfusion. Clearly, if the machine is not initially washed through with saline, this volume can also be replaced by low molecular weight dextran, but this is hardly an economy.

The limitations of the volume/weight ratio for low molecular weight dextran would demand more donor blood for the machine for smaller patients; a smaller version of the Melrose oxygenator, with discs of special patterns allowing two different, smaller priming volumes, has been developed (Raison, 1962b), and this permits the use of the

same volume/weight addition of low molecular weight dextran. Theoretically it should be possible to use this smaller machine for adult patients, cooling whilst on partial perfusion, and using an increased volume of low molecular weight dextran within the limitation of a calculated ultimate haemodilution not significantly below 80%. This would permit the perfusion of a patient weighing 46 kg. at 2,300 ml./min. at 27° C., using the low priming oxygenator (1,250 ml.) containing no donor blood.

The increased urine flows during and immediately following perfusion are of interest. At present the particular effects of extracorporeal circulation, induced hypothermia, and anaesthesia have not been well separated. Habif, Papper, Fitzpatrick, Lowrance, Smythe, and Bradley (1951) showed significantly lower urine flows during anaesthesia, whilst Morales, Carbery, Morello, and Morales (1957), noting a 45% reduction at this time, state that it is reduced by only 25% during mild hypothermia. Beall, Cooley, Morris, and Moyer (1957) found that extracorporeal circulation reduced urine flow to 33%. In the present series the notable suppression during preliminary anaesthesia is followed by a marked increase during and following perfusion. Possibly the effect is in part the result of preservation of the extracellular fluid volume reported by Drake and Lewis (1961) and to that degree indicates the satisfactory effect of perfusion with low molecular weight dextran. It is notable, however, that so far as these patients are comparable with those not perfused with low molecular weight dextran, there is no marked alteration in the 24-hour urine flow, and the figures here closely correspond with those of Long *et al.* (1961). The initial urine flush therefore probably represents in part loss of the water load imposed by haemodilution. Whether the satisfactory elimination of this load is any indicator of the sufficiency of, or improvement in, renal flow is arguable. In any event, this fairly rapid compensation for the diluting factor of low molecular weight dextran is of assistance in restoring red cell and plasma volumes. If this excretion did not take place, 20 ml./kg. priming fluid would have to be added to the patient, *i.e.*, 20 to 25% of his blood volume. It is clear why 10 to 15 ml./kg., added without any upset to central vascular pressures, has been satisfactory and has not led to post-operative anaemia. A refinement of technique might be to withhold this compensation in patients with polycythaemic heart disease, but in practice these are among the patients who benefit from a slight increase in their post-

perfusion venous pressure. There is room for considerable study in this field of water balance and plasma/red cell volumes.

The prevention of intravascular sludging, if proven, would be of the greatest value in the maintenance of more physiological conditions during perfusions. It seems possible also that low molecular weight dextran, by the same physical actions, may prevent the encapsulation and inactivation of erythrocytes by denatured protein, described by Lee, Krumhaar, Fonkalsrud, Schjeide, and Maloney (1961).

Long *et al.* (1961) are impressed by the reduced demand for stored blood contributing a lesser "metabolic" factor to the acidotic bias of perfusion. But this may well be more important in the low-flow technique employed which they describe as generally resulting in a degree of metabolic acidosis. It has always been our practice to present the patient with chemically balanced donor blood from the machine, and with high flow rates no notable metabolic acidosis has existed which low molecular weight dextran might be expected to improve.

No special cross-matching arrangements have been made during the use of low molecular weight dextran, and no sensitivity reactions have been encountered.

#### SUMMARY

A brief clinical trial has confirmed the safety of Rheomacrodex, and that it can be used without undue foaming in rotating drum oxygenators at high flow rates. Further economies are discussed, the limiting factor being a haemodilution of 80%.

A very considerable saving in donor blood can be effected.

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