

Extracorporeal Circulation Combined with Hypothermia and Hemodilution Technique

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(Received for publication, November, 20, 1963)

ABSTRACT

A hypothermic, low flow perfusion, using 5% dextrose in water as the priming fluid in the pump-oxygenator, was carried out to observe oxygen consumption, blood pH changes, and CO₂ tension during the bypass period.

A low oxygen consumption which was approximately one third of the preperfusion value, was observed during the total by-pass period. This is believed to be due to the effect of low flow rates employed, hypothermia and low CO₂ tension observed in these animals.

The pH of the arterial blood and the partition of the total CO₂ remained within a fairly normal range. There was a marked reduction in CO₂ tension during the bypass period. Its harmful effect on the oxyhemoglobin dissociation curve and cerebral circulation was discussed.

The hemodilution attendant to the use of 5% dextrose in water as the priming fluid is considered insignificant.

INTRODUCTION

A combination of hypothermia and extracorporeal circulation for cardiovascular surgery offers many advantages which are not available when either method alone is used. When properly combined, these modalities tend to supplement each other and make the whole procedure much simpler. One of the major items in the performance of open heart surgery utilizing a cardiopulmonary bypass is the procurement of large quantities of heparinized blood to prime the heart-lung machine.

It is in this area where hypothermic perfusion is considered quite useful because of the lower flow rates, which are adequate to supply the diminished metabolic demands of the hypothermic tissue, and enable one to reduce the priming volume in the oxygenator. Peirce et al. (1958) and Sealy et al. (1959) have shown that this combined technic is a practical method of reduction of the flow rates in extracorporeal circulation without significant derangements in tissue function. Recently, Zuhdi et al. (1961) introduced the technic of using 5% dextrose in water as the priming fluid in hypothermic perfusion, further reducing the amount of blood required in open heart surgery.

The "optimal" flow rates in this hypothermic range of 25 to 30°C has not been clearly defined. Zuhdi et al. (1961) recommended a flow rate of 20 ml/kg/min in moderate hypothermic perfusion and reported favorable clinical outcomes. However, DeWall et al. (1962) who used the same technic reported finding hematuria in some of their patients perfused at this low flow and recommended higher flow rates of 30 ml/kg/min for such perfusions. On the other hand, Sealy et al. (1959) who used a slightly different type of hypothermic perfusion recommended flow rates of 40 to 60 ml/kg/min for patients weighing less than 30 kg, and 20 to 40 ml/kg/min for patients weighing more.

The following experiments were carried out to observe several physiological parameters in low flow, hypothermic perfusions and to determine

their possible clinical implications.

METHODS

Twenty-two adult mongrel dogs of either sex, weighing from 11.5 to 23.6 kgm were used. These were anesthetized with 30 mg/kg of Secobarbital Sodium intravenously, intubated with a cuffed endotracheal tube and connected to a mechanical ventilator (Jefferson type) with a positive and negative phase control. The animal was then placed on a water mattress which was used to cool and warm the animal before and after the bypass procedure. The animal's esophageal temperature usually dropped between 2 to 4°C on this mattress before the initiation of the internal cooling.

A bubble dispersion type of a pump-oxygenator was used. This was either a Zuhdi modification (1961) of the DeWall oxygenator, incorporating a stainless steel coil as the heat exchanger, or a disposable plastic bag oxygenator of our own design with a stainless steel heat exchanger in the oxygenating system. In both units, the heat exchanger served the dual function of transferring heat and reducing the priming volume in the oxygenator. The system was primed with 20 ml/kg of 5% dextrose in water, and during the bypass, only small amounts of the same fluids were added to maintain the blood level in the oxygenator. The superior vena cava was cannulated through the azygos vein and the inferior vena cava through the atrial wall and the venous return was oxygenated and returned through the right femoral artery. The left femoral artery and vein were cannulated to monitor the arterial and venous pressures with a mercury and a saline manometer, respectively. Flow rates were calculated from the formula proposed by Melrose (1961) in normothermic perfusions and one third of those flow rates were used in these experiments.

After the cannulations were completed, a partial bypass was instituted until the esophageal temperature reached about 30°C; then the cooling was stopped and a total bypass carried out. During the total bypass, the esophageal temperature tended to vary between 26 to 31°C. After 20 to 40 minutes of total bypass, the tapes on the vena cavae were

released, resuming a partial bypass with warming until the temperature reached 33 to 35°C. The animals usually regained spontaneous respiration at this temperature range and were allowed to warm further on the warm water mattress. The control of heat exchange in these animals was isothermic in that both external and internal heat exchange occurred during the cooling and the warming process. One hundred per cent oxygen was used to oxygenate the blood. The coolant was ice water of about 4°C and the warming solution was kept between 43 and 45°C.

Blood samples were taken anaerobically in heparinized syringes at appropriate intervals for gas analysis and pH determination. The oxygen and carbon dioxide contents of the arterial and venous blood were determined by the Van Slyke and Neill method (1924). The pH of the blood was measured with a Beckman G pH meter at room temperature and the values were corrected to the animal temperature at the time the samples were taken by Rosenthal factor (1948). The pO_2 was calculated from a Severinghaus nomogram (1958), and pCO_2 from the total CO_2 and pH by the method of Van Slyke and Sendroy (1928). The oxygen consumption before and after the bypass was measured with a Douglas bag and a Scholander microgas analyzer, and during the bypass, from the flow rates and the arterial and venous oxygen contents. The hemoglobin values were calculated from the oxygen capacity of the blood. Although survival of the animals was not a primary consideration, efforts were made to resuscitate them after the experiments.

RESULTS

All animals regained spontaneous respiration at the end of the perfusion period but those which survived did not fully recover from the anesthetic effects until the next morning. None of the surviving animals showed evidence of neurological damage.

Cooling and warming rates: These animals were cooled at 0.3–0.9°C per minute and warmed somewhat more slowly. The rectal temperature

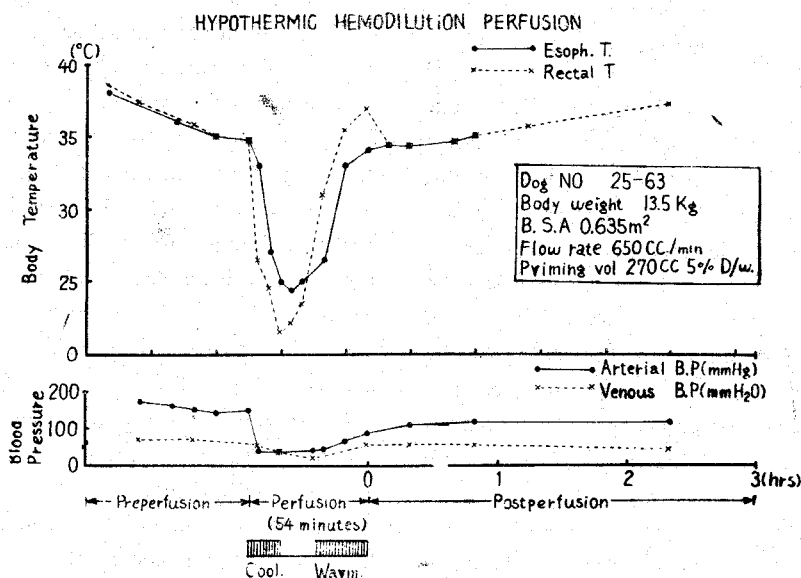


Fig. 1. Body temperature and blood pressure changes in hypothermic, hemodilution perfusion.

responded to temperature changes more promptly than the esophageal temperature, probably because of the inflow of the oxygenated blood through the femoral artery; but the temperature gradient was not too great, probably because both internal and external heat exchanges were used in these animals. The heat transfer rate was not considered too rapid which may have been due to the fact that the greater part of the heat exchange occurred during the partial bypass period, and the fact that the area of blood in contact with the heat exchanger was relatively small (Fig. 1).

Oxygen Consumption rate: The oxygen consumption of these animals during bypass is shown in Table 1. The average oxygen consumption under anesthesia was 7.4 ml/kg/min which is comparable

Table 1. Oxygen consumption in low flow hypothermic perfusion

	O ₂ Consump. (ml/kg/min)	% Preperf. value	No. Obs.
Preperfusion	7.40±1.82		4
Perfusion			
(26~28°C)	2.24±0.29	30.2±3.84	6
(29~31°C)	2.64±0.19	35.6±2.99	11
Postperfusion	11.40±0.57	154.6±9.50	5

to the figures reported by Clowes et al(1958), Hagnauer and D'Amato (1954) and Spurr et al (1954). The oxygen consumption during total bypass was 2.64 ml/kg/min at 29-31°C, and 2.24 ml/kg/min at 26-28°C temperature range. These represented 35.6% and 30.2% respectively of the preperfusion values under anesthesia. The average oxygen consumption increased to 11.4 ml/kg/min during the immediate postperfusion period which represents a 154% increase from the preperfusion value.

Oxygen consumption during the total bypass was related to flow rates as shown in Table 2. In the

Table 2. Relationship between flow rate and oxygen consumption

Dog No.	Body Weight (kg)	Esophage- al Temp. (°C)	Flow Rate (cc/min)	O ₂ Consump. (cc/min)
22~63	15.9	29.5	560	43.3
		29.5	740	51.7
29~63	21.4	26.2	700	33.1
		26.2	940	42.7

two animals in which it was studied, there was a definite increase in oxygen consumption rate as the flow rates were increased, despite the fact that the arteriovenous oxygen difference grew smaller.

The arteriovenous oxygen difference remained

essentially the same during the preperfusion and perfusion periods, but was increased markedly during the postperfusion period with a concomitant decrease in venous oxygen saturation. The arteriovenous oxygen difference was related to the animal mortality. Thus, the surviving animals showed a lesser degree of A-V oxygen difference than the non-surviving group and this was particularly pronounced during the postperfusion period (Table 3).

Table 3. Mortality as Related to A-V O₂ Difference and Venous O₂ Saturation

	A-V O ₂ diff. (Vols%)		Venous O ₂ sat. (%)	
	Alive	Dead	Alive	Dead
preperfusion	6.0	6.9	66.7	58.3
Perfusion	5.3	7.3	64.0	50.0
Postperfusion	8.5	10.9	41.0	27.6

Blood pH and CO₂ tension: Arterial pH tended to be slightly alkalotic during the preperfusion period, a finding most likely due to the active elimination of CO₂ with a positive and negative phase ventilator. The pH showed a tendency to diminish slightly during the perfusion and the postperfusion periods, but, in general, remained within the normal range.

The arterial CO₂ tension showed a low value during the preperfusion period (Table 4). This was decreased further with the onset of the bypass.

Table 4. Blood pH and pCO₂ changes (mean±S.E.)

	Blood pH	pCO ₂ (mmHg)	No.Obs.
Preperfusion	7.46±0.02	21.8±2.16	7
Perfusion			
10 min.	7.42±0.02	18.3±1.14	9
20 min.	7.40±0.01	18.1±1.81	6
Postperfusion	7.38±0.01	25.0±2.05	8

This low value remained essentially unchanged during the bypass period. During the postperfusion period, there was a marked increase in CO₂ tension, superceeding that of the preperfusion period, probably because many of the animals were allowed to resume spontaneous respiration.

Carbonic acid and bicarbonate: Figure 2 shows the partition of the total CO₂ into a buffer base bicarbonate and carbonic acid, and the ratio between the two during the preperfusion, perfusion

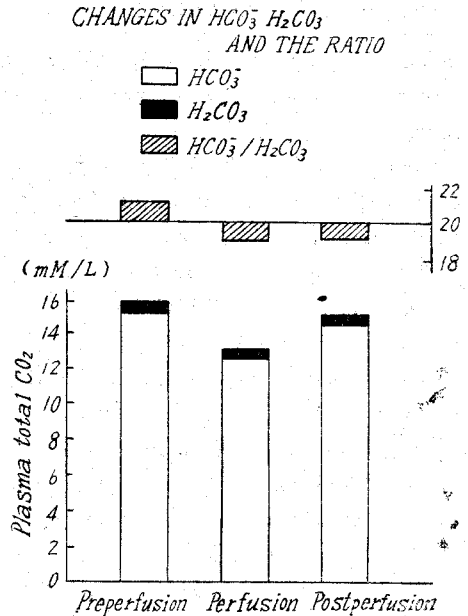


Fig. 2. Changes in bicarbonate, Carbonic acid and their ratio.

and the postperfusion intervals. In general, there was a marked decrease in total CO₂ with a proportionate decrease in bicarbonate and carbonic acid, maintaining the ratio within acceptable ranges. During perfusion, however, there was a more pronounced decrease in BHCO_3 in comparison with H_2CO_3 , throwing the ratio to 19.1. During the postperfusion period, this ratio remained essentially the same, although there was a marked increase in the total CO₂.

Hemodilution: The changes in the hemoglobin content of the blood during the perfusion are shown in Table 5. After the initiation of the bypass, there was a prompt and marked decrease in the hemoglobin concentration, amounting to 29.8% of the pre-perfusion value, which was due to intermixing of the 5% dextrose in water in the oxygenator with the animal blood. This was restored

Table 5. Changes in Hemoglobin Concentration
(mean±S.E.)

	Hemoglobin (gm%)	No. Obs.
Preperfusion	14.23±0.54	12
Perfusion	10.00±0.39	21
Postperfusion	13.30±0.58	12

to 13.3 Gm% or 92.0% of the preperfusion figure after the bypass when cell mass was returned to the animal.

These animals usually showed pooling of blood during the perfusion, lowering the blood level in the oxygenator, and often it was necessary to add small amounts of 5% dextrose in water to maintain the level. Usually most of the blood-fluid mixture in the oxygenator at the end of the perfusion had to be returned to the animal to maintain the arterial and venous pressures at adequate levels.

Blood pressure changes: There was a gradual fall of the arterial blood pressure during the initial mattress cooling phase. With the initiation of the bypass, however, the arterial pressure almost invariably decreased to a low level of 30 to 50 mmHg and remained at this level until end of the bypass. In some of the animals, the blood pressure showed a tendency to rise slightly toward the end of the perfusion, but this was an inconsistent finding. When the blood remaining in the oxygenator was returned to the animal at the end of the perfusion, the blood pressure also returned to a satisfactory level but did not quite reach the preperfusion value.

The venous pressure tended to remain low during the perfusion unless there was an obstruction to the venous drainage. This seemed to parallel the blood volume in the animal as indicated by the blood level in the oxygenator.

DISCUSSION

Under moderate hypothermia, the oxygen consumption seen in these animals during total bypass was approximately one third of the control value under anesthesia. This is considerably lower than the figures reported by Spurr et al. (1954) and Gordon et al. (1960) who stated that the oxygen

consumption rate at 29°C was approximately 50% of the control value under normothermia. This difference in oxygen consumption may be the result of different flow rates since either the cardiac output or the pump flow rate in their experiments was greater than that used in author's series. This assumption is supported by the fact that there was a definite increase in oxygen consumption when the flow rates were increased. Similar observations were reported by Kameya et al. (1960) who stated that, at all the temperature ranges studied, subbasal flow rates around 30 ml/kg/min allowed the organism to use about one half as much oxygen as was consumed at perfusion rates near 90 ml/kg/min. This may suggest the possibility that the tissue under these circumstances may not be using as much oxygen as it should for optimal function, although the arteriovenous oxygen difference and the venous oxygen saturation which were thought by Adolph (1956) to be reliable indicators of an adequate tissue oxygenation, remain at a reasonable level. This possibility is further strengthened by the fact that there was invariably an increase in oxygen consumption above the preperfusion value after the bypass which may indicate that the tissue is taking up extra oxygen to compensate for the debt incurred during the total bypass period.

The low oxygen consumption observed in these animals should be viewed, together with low flow rates, in light of other factors involved in hypothermic perfusion. One factor is the hypotension seen in these animals during total bypass which may have influenced the oxygen uptake of the tissues. The effect of hypothermia and of the slight alkalinity of the blood, both of which shift the oxy-hemoglobin dissociation curve to the left, also may have adversely affected the liberation of oxygen at the tissue levels in these animals. Again, the very low CO₂ tension seen in these animals during total bypass may have been instrumental in blocking the efficient release of oxygen from hemoglobin through the well-known Bohr effect. These are factors which should be carefully weighed in

evaluating the low oxygen consumption observed in this experiment.

Before the perfusion, there was a tendency for respiratory alkalosis which was due to hyperventilation with a positive and negative phase respirator. Although there was a tendency for it to diminish gradually, the pH of the arterial blood remained within a fairly normal range through the perfusion and the postperfusion periods. This may have been due to the fact that the blood pH was high at the beginning, and also to the fact that the bypass period was relatively short. Again, the use of external and internal cooling (isothermic) may have played a role. Wolfson et al. (1963) reported that there was a reduced production of excess fixed acids and a rapid return to normal pH after the bypass when the combined method was used.

Both buffer base bicarbonate and the carbonic acid were decreased, thus producing the low CO_2 values observed in these animals. Because of the greater decrease in the BHCO_3 fraction during the perfusion and the postperfusion periods, the $\text{BHCO}_3/\text{H}_2\text{CO}_3$ ratio was diminished somewhat during these periods, but still remained within a reasonable level, as reflected in the pH values of the arterial blood.

Perhaps more important is the low pCO_2 observed in these animals. The initial low value was decreased further when the blood came in direct contact with the oxygen bubbles. Although the low CO_2 values may not produce great changes in acid-base balance as indicated by the blood pH and the bicarbonate and the carbonic acid ratio, the low pCO_2 may not be as harmless as would seem on the surface. Besides its effect on the oxyhemoglobin dissociation curve, it may cause a reduction of the effective cerebral circulation through its known influence on cerebral vessels. Because of these, Osborn et al. (1961) advocates the adding of a small amount of hydrochloric acid to the perfusate during hypothermic perfusions.

During the bypass period, the hemodilution attendant to the introduction of 5% dextrose in water was only moderate and was considered to be insignificant as far as the oxygen carrying capacity of

the blood was concerned. The oxygen availability of diluted blood was studied by Tanaka et al. (1962) who stated that in hypothermia when blood was diluted with 5% dextrose in saline, the oxygen availability was as great or greater than that from the whole blood. Also, with more even perfusion, the temperature gradient between the tissues decreased. The hemoglobin value which was moderately low during bypass returned to a reasonable level, 92% of the preperfusion figure, after the bypass, indicating that most of the added fluid was not available to the circulation after the bypass when most of the blood remaining in the oxygenator was returned to the animal. The fate of the added electrolyte fluid in hypothermic perfusion was studied by Gollan et al. (1955). They reported in studies with RISA in dogs that, while all of the added Ringer's solution was available to the pump oxygenator during the perfusion, none of it remained available to the heart 15 minutes after the perfusion had been stopped. They further pointed out that the hemodilution technic is advantageous in reducing not only the degree of hemolysis, but also the doses of heparin required and the difficulties involved in defoaming.

SUMMARY AND CONCLUSIONS

1. A hypothermic perfusion, using a low flow rate and 5% dextrose in water as the priming fluid in the oxygenator, was carried out to determine changes in oxygen consumption, blood pH and CO_2 tension.
2. The findings indicated that the low oxygen consumption observed in these animals was related to the low flow rates employed in these experiments.
3. There were only slight changes in the blood pH, although the pCO_2 was diminished markedly during the total bypass. The possible harmful effect of the low pCO_2 was discussed.
4. The hemodilution attendant to the use of 5% dextrose in water is considered insignificant.
5. Although this method proved its value for procedures needing relatively short periods of bypass, further studies are needed to determine its

adequacy for longer bypass procedures.

Acknowledgment; The technical assistance of H.K. Park, B.S. of the Cardiopulmonary Laboratory in making the blood gas analyses is gratefully acknowledged.

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