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AN EXPERIMENTAL STUDY ON HYPOTHERMIC CARDIOPULMONARY BYPASS WITH HEMODILUTION TECHNIQUE

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ABSTRACT

Twenty-six adult mongrel dogs were subjected to a study on hypothermic cardiopulmonary bypass with hemodilution technique. The extracorporeal system used consisted of a rotating disc oxygenator, two roller pumps and two heat exchangers designed specially for this series of experiments. Five percent dextrose in water was the principal diluent. Saving the blood, keeping an adequate microcirculation and preventing possible homologous blood syndrome were the main purposes of hemodilution.

A lowered efficiency of the oxygenator due to the reduction in size was covered by inducing hypothermic perfusion at a low flow rate.

The efficiency of the heat exchanger was excellent enough to accomplish this perfusion technique satisfactorily. The model change of the heat exchanger resulted in the exclusion of the bubble trap and the reservoir from the extracorporeal system.

Complete bypass was achieved at an average rectal temperature of 25.1°C (esophageal 27.2°C) for 30 min at an average flow rate of 30 ml/kg/min.

The lowest hematocrit averaged 70% of the control value. Entering rewarming after complete bypass, changes in hematocrit, oxrygen content, blood pressure, EEG and ECG caused by the perfusion began to disappear progressively. The lowered pH and pCO_2 were thought to be corrected by using sodium bicarbonate, THAM or CO_2.

Fifteen animals out of 26 tolerated the procedure well, and the result of the clinical application of this perfusion technique was excellent.

INTRODUCTION

At the First Department of Surgery, University of Nagoya, School of Medicine, many patients had successfully been operated on open heart surgery with the aid of either simple hypothermia[1)2)3)] or normothermic cardiopulmonary bypass[4)5)6)7)]. In simple hypothermia, however, a long time is needed to cool and rewarm the patient: the duration of circulatory arrest available is obviously limited and short; and, the heart tends to develop ventricular fibrillation. The application of coronary perfusion[8)] or intrathoracic rewarming[9)10)] may cover

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these disadvantages, but only partly. It is apparent that cardiopulmonary bypass is needed to perform open heart surgery for more complicated cardiac lesions safely. In normothermic cardiopulmonary bypass, however, a large amount of blood is necessary to prime the apparatus. The use of a large amount of blood may induce a high incidence of homologous blood syndrome[11)12)] or serum hepatitis[13)], and collection of blood has become gradually difficult. Moreover, an heart-lung machine for such a method is expensive.

In order to economige the blood necessary for cardiopulmonary bypass, reducition of size of the apparatus, or applicatfon of hemodilution with non-blood perfusate, either alone or in combination, has been reported by many investigators[14)15)16)17)18)19)20)]. In 1961, Zuhdi *et al.*[21)] attempted nonhemic perfusion with 5% dextrose in water using a bubble oxygenator.

Saving of blood has been obtained also by reducing the flow rate at a state of lowered metabolic rate under hypothermia, as seen in many of the above reports.

This study proposes to investigate the physiological changes during hypothermic cardiopnlmonary bypass at a low flow rate using a newly deviced heart-lung machine consisting of a small rotating disc oxygenator, two roller pumps and heat exchangers, and to evaluate the possible availability of clinical application of this technique.

APPARATUS

1. Pump-oxygenator

A small rotating disc oxygenator was used. The discs were made of stainless steel, 130 mm in diameter and 0.5 mm thick, mounted 3 mm apart by means

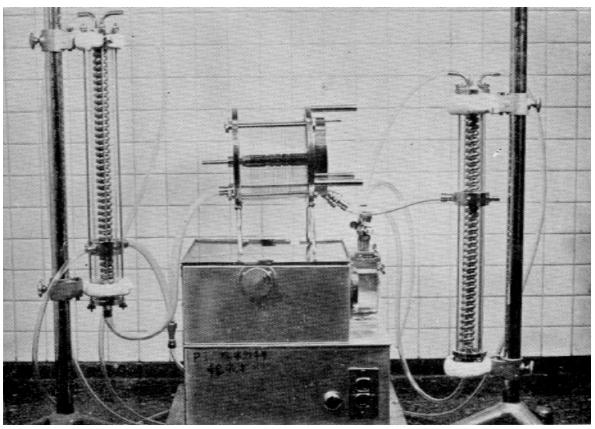

FIG. 1. Pump-oxygenator consisting of twin roller rotary pump, disc oxygenator and two helical heat exchangers.

of spacers on a central shaft. The disc assembly was held horizontally within a pylex cylinder in eccentric fashion. The oxygenator took an average of 1.39 ml/disc/min of oxygen at a flow rate of 1.81 to 2.79 l/min. at 37°C[7]. Three kinds of oxygenator having 20, 30 and 40 discs were prepared. Two twin roller pumps of the DeBakey type having a latex pump chamber, 12 mm in inner diameter, were used; one for arterial inflow and the other for coronary suction. The flow rate was adjustable from 0 to 2000 ml/min. Vinyl tubes, 8 mm in inner diameter, were used as connecting lines (Fig. 1)

2. Heat exchanger

The heat exchanger was designed for two purposes; one as a reservoir and the other as a heat exchanging apparatus itself. A helical stainless steel tube was placed vertically in a pylex cylinder, 500 mm long and 40 mm in diameter. The temperature of the blood outside of the helix was controlled by the water circulating within. Its cleaning, sterilization and assembling were very simple. Since a blood inlet was settled at the top of the heat exchanger and an outlet at the bottom at first (Fig. 2 and 3), the blood level in the heat exchanger has to be lower than that in the oxygenator on the arterial side at all times. With such an arrangement, some difficulties in blood level controlling were encountered. This disadvantage, however, was avoided by changing the design of the heat exchanger; that is, a stainless steel ring with a blood inlet was placed at the middle portion of the pylex cylinder in such a fashion as to divide the pylex into two parts, of 400 mm and 100 mm or 300 mm and 200 mm (Fig. 4 and 5).

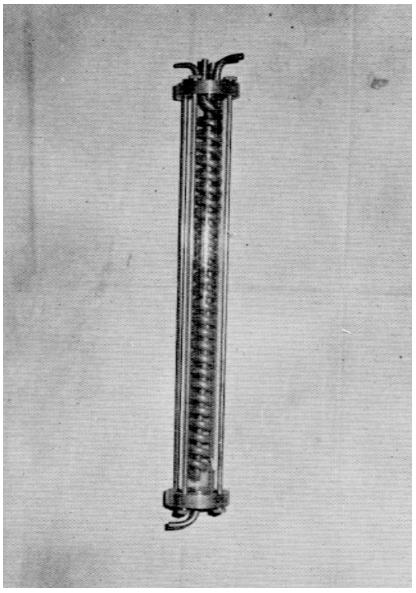

FIG. 2. Helical heat exchanger (before changing the design).

This model change possessed various advantages, as follows. (1) Since the blood level in the heat exchanger became the same as that in the oxygenator, this apparatus served as heat exchanger and a blood reservoir, simultaneously. (2) Since the top of the apparatus was open to the air, the bubble trap was excluded. (3) Since the stainless steel rings having a blood inlet were set at 100, 200, 300 and 400 mm apart from the bottom of the apparatus, priming volume was adjusted according to the body weight.

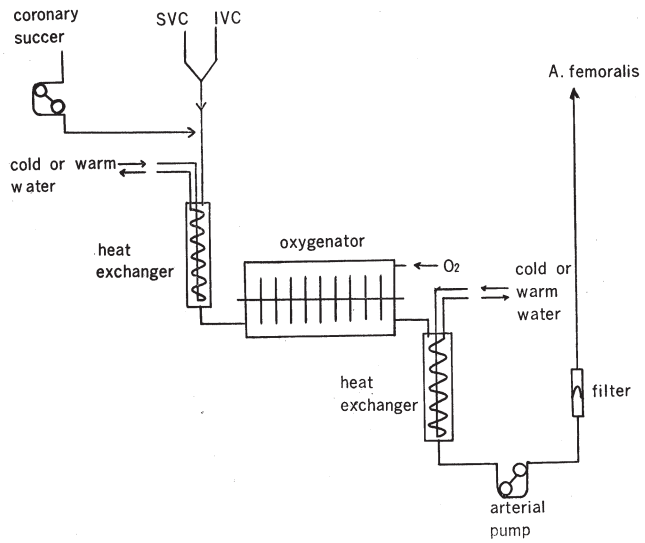

FIG. 3. The circuit, using the heat exchanger before changing the design.

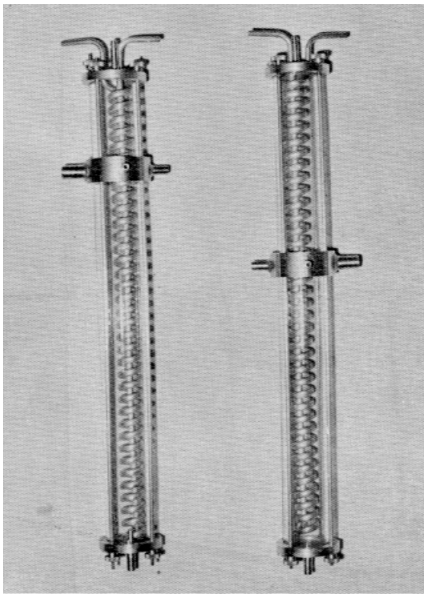

FIG. 4. Helical heat exchanger (after changing the design).

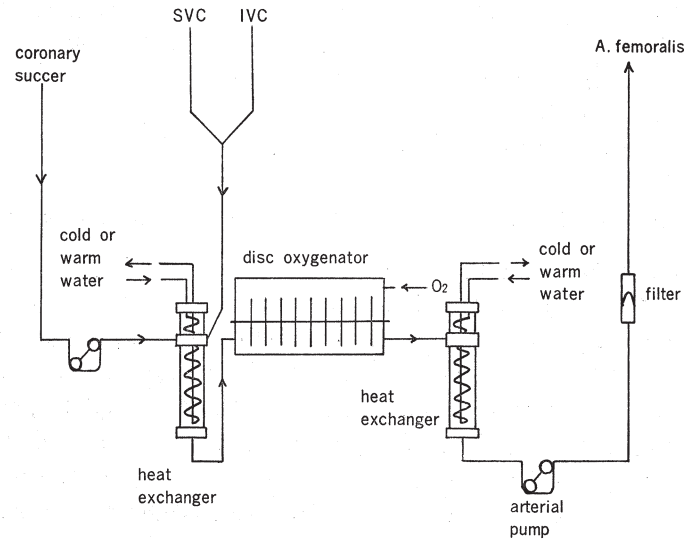

FIG. 5. The circuit, using the helical heat exchanger after changing the design.

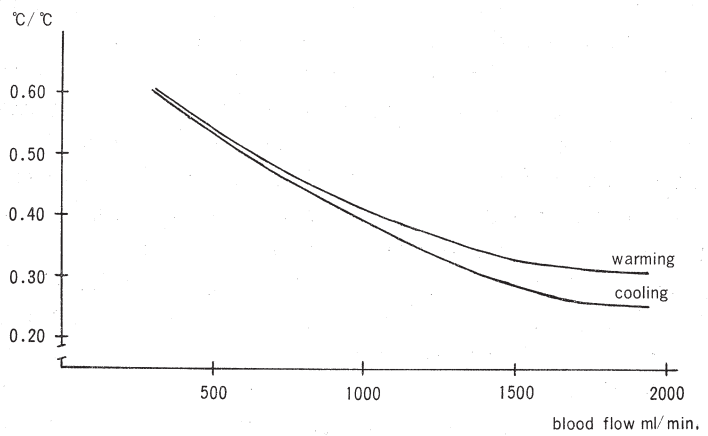

FIG. 6. Heat exchanging efficiency curve of the helical heat exchanger (after changing the design).

As seen inFig. 6, this apparatus showed excellent heat sxchanging facility. The efficiencies during cooling and rewarming were 0.38°C/°C and 0.41°C/°C, respectively, at the blood flow rate of 1000 ml/min and the water flow rate of 2500 ml/min with water temperature of 6°C during cooling and 45°C during rewarming.

METHODS

The system was primed with a 16 ml/kg of body weight of 5% dextrose

in water according to Zuhdi's method[21]. An additional amount of fluid, one fourth with 5% dextrose in water and three fourths with heparinized blood, was used to complete adequate priming, if necessary. Therefore,

$$\text{Amount of } 5\%\ D/W(\text{ml}) = B + \frac{A-B}{4}, \text{ and}$$

$$\text{Amount of heparinized blood (ml)} = \frac{3}{4}(A-B),$$ where A is priming volume in ml and B is 16 ml/kg of body weight.

Twenty-six mongrel dogs weighing between 10 and 23 kg (average, 15.0) of both sexes were used. The trachea was intubated after a dose of 20 mg/kg of Isozol, sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate was administrated intravenously. The animal was anesthetized with ether. 3.0 mg/kg of heparin was given intravenously. The blood was withdrawn through both cavae into the oxygenator by gravity, and was sent back through the femoral artery by means of an arterial pump via a filter. Two heat exchangers were used; one for cooling at the arterial side of the oxygenator and the other for rewarming at the venous. The animal was cooled by partial bypass with water temperature in the heat exchanger adjusted to 4°C. When a desired body temperature was reached, cooling was discontinued and complete bypass was established. Right ventriculotomy was performed for 30 min under anoxic cardioplegia. The aortic occlusion was released intermittently for myocardial protection.

As soon as ventriculotomy ended, rewarming was started with water temperature of the heat exchanger at 40 to 45°C. In order to shorten the hypothermic period and to obtain more equalized temperature distribution to the whole body, blanket cooling and rewarming were combined.

During the procedure, esophageal and rectal temperature, arterial and venous pressure, EEG, ECG, blood pH, hematocrit, blood gases and plasma free hemoglobine were monitored. In some cases, the brain, myocardium, liver, lung and kidney were biopsied.

Temperature was read by an electrothermister. Arterial and venous pressures were measured by mercury and water manometers, respectively.

pH was measured by Metrohm glass pole pH-meter. Gas analysis was made by Van Slyke-Neil method[22]. PCO_2 and buffer base were read from the Singer-Hasting nomogram[23]. EEG and ECG were recorded with Nihonkoden amplifier recorder. Plasma free hemoglobin was measured by means of cyan-methohemoglobin method[24].

RESULTS

1. Mortality and Morbidity

Fifteen animals out of 26 survived and stood up by themselves. Causes

TABLE 1. Results of the experimental hemodilution hypothermic cardiopulmonary bypass. Fifteen dogs out of 26 survived

	body weight (kg)	cooling (min)	rewarming (min)	flow rate (ml/kg/min)	result
1	19.0	40	32	21	survived
2	16.0	35	90	21	died, bleeding
3	16.0	29	18	26	died, bleeding
4	23.0	33	27	18	survived
5	16.0	11	24	25	survived
6	11.5	14	18	26	survived
7	11.5	11	14	34	died, heart failure
8	11.5	7	17	43	survived
9	16.5	20	19	27	survived
10	19.5	8	32	25	survived
11	10.0	11	19	26	survived
16	17.0	13	27	23	died, pulm. collaps
17	12.0	3	32	25	died, pulm. collaps
18	15.0	11	17	27	survived
19	8.0	7	9	37	died. vent. fibrillation
20	10.0	6	28	40	survived
21	12.5	7	32	30	survived
22	10.0	11	26	35	died, brain embolism
23	19.0	7	31	33	dieb, brain damage
24	12.0	5	11	30	died, filariasis
25	18.0	7	20	28	died, heart failure
26	11.0	7	39	38	survived
27	18.5	7	38	32	survived
28	14.0	6	22	28	died heart failure
29	17.0	6	25	29	survived
30	18.0	15	30	33	survived
mean	15.0	13	27	29	—

of death were heart failure in 3 cases, pulmonary collaps in 2 postoperative hemorrhage in 2 and one case each of cerebral embolism, brain damage, ventricular fibrillation and filariasis.

Cerebral embolism is believed to be due to failure of perfusion technique (Table 1).

2. Flow Rate and Body Temperature

A) Elow rate

Flow rate varied from 18 to 43 ml/kg/min (average 29). First the bypass was performed with a flow rate of about 20 ml/kg/min, but with this rate, it was often difficult to maintain good levels of the EEG and arterial pressure. Therefore the flow rate was finally increased to about 30 ml/kg/min (Table 1).

B) Body temperature

On the average, esophageal temperature decreased from 34.4 to 27,2°C for 13 min, and increased from 25.4 to 32.8°C for 27 min; and, rectal temperature decreased from 35.2 to 25.1°C for 13 min, and increased from 24.6 to 31.0°C for

TABLE 2. Changes in body temperature

	rectal temp. (mean value) (°C)	esophageal temp. (mean value) (°C)
cooling, start	30.0-38.7 (35.2)	30.0-38.2 (34.4)
cooling, end	16.5-29.8 (25·1)	22.0-32.2 (27.2)
rewarming, start	18.0-30.0 (24.6)	22.0-29.2 (25.4)
rewarming, end	24.0-36.6 (31.0)	26.7-35.4 (32.8)
lowest body temp.	15.8-28.0 (23.3)	20.0-28.0 (24.0)

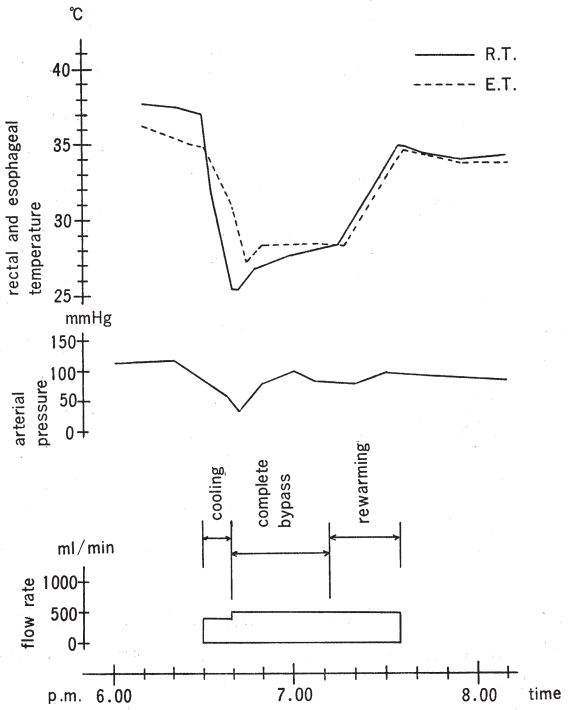

FIG. 7. Case No. 29, 17.0 kg, ♂.

27 min, as seen in Table 2. Therefore, the animal was cooled at an average speed of 0.57°C/min, esophageally, or 0.77°C/min, rectally, and rewarmed at an average speed of 0.27°C/min, esophageally, or 0.24°C/min, rectally (Table 1 and 2, and Fig. 7).

3. Arterial Pressure and Venous Pressure

The mean arteiral pressure of 68 mmHg during cooling dropped to 46 mmHg at initiation of complete bypass. In cases of Nos. 4, 7, 8, 9 and 19, hypotension of about 20 mmHg developed at 5 min of complete bypass, whch recovered. When profound hypotension was manifested, a small dose of vasopressor was administrated without changing the flow rate.

Mean arterial pressure recovered gradually thereafter, wrth pressures of

55, 64 and 69 mmHg at 10, 20 and 30 min of complete bypass time, respectively.

Entering partial bypass for rewarming, the mean arterial pressure increased to 70 mmHg (Fig. 8).

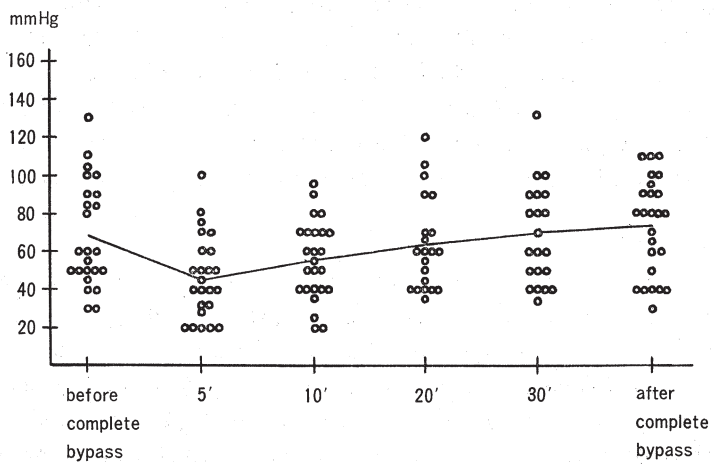

FIG. 8. Femoral arterial pressure.

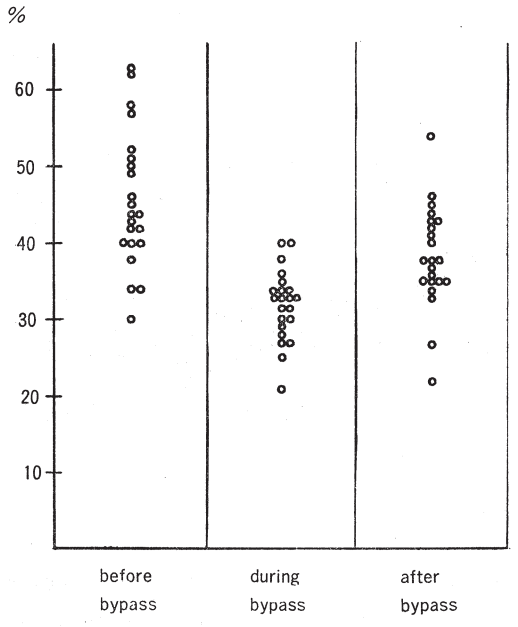

FIG. 9. Hematocrit changes.

During bypass both caval pressures were kept as near 100 mmH_2O as possible. Actually, however, they were scattered widely and showed a tendency to stay below.

4. Hematocrit

Hematocrit, lowered due to hemodilution, showed a tendency to recover at the end of the bypass except for Nos. 2 and 26; before the perfusion being 30 to 68% (average 48), during perfusion 21 to 40% (average 32) and after perfusion 22 to 54% (average 38). (Fig. 9). The lowest hematocrit volue was on an average 70% (range, 50 to 85) of the control, and it recovered after perfusion to an average of 85% (range, 55 to 113) of the control (Fig. 10).

5. Arterial Blood pH

Arterial blood pH value was scattered somewhat already durng the pre-perfusion period because of hypoxia probably due to bleeding from the operating field or hypocapnea due to hyperventilation of anesthesia. During perfusion the pH of arterial blood fell from the control value of 7.28 to 7.68 (average 7.47) to 7.20 to 7.52 (average 7.32). After perfusion the arterial blood pH showed gradual recovery to the cotrol level in some cases, whereas it showed a further decrease in others; the values ranging from 7.00 to 7.51 (average 7.29) (Fig. 11).

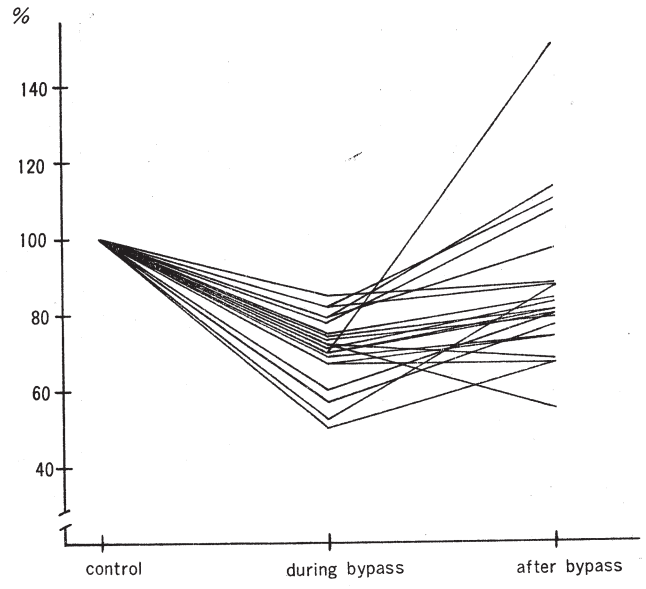

FIG. 10. Rate of hemodilution, (Ht before hemodilution/Ht after hemodilution).

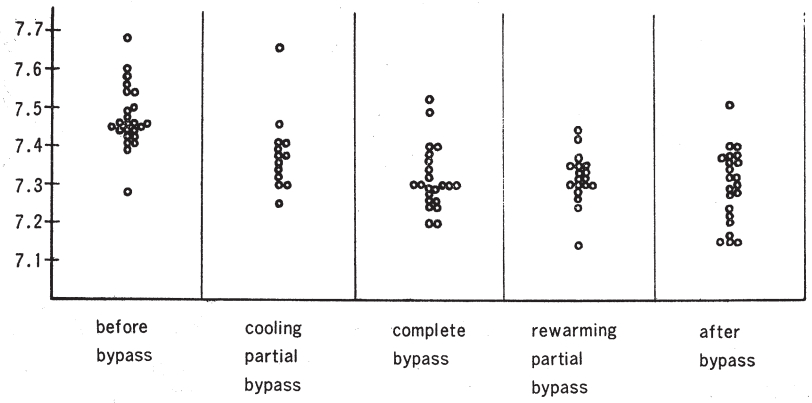

FIG. 11. PH changes in arterial blood.

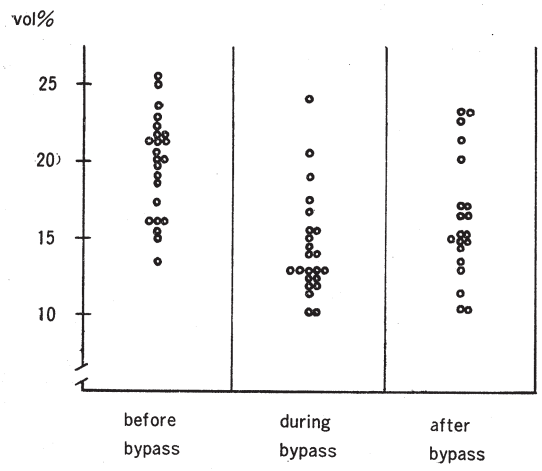

FIG. 12. O_2-content changes in arterial blood.

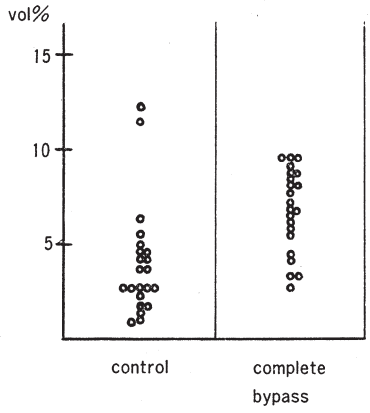

FIG. 13. Oxygen A-V difference.

6. Blood Gases

A) Arterial oxygen content

As seen in Fig. 12, arterial oxygen content decreased from 19.8 in the control to 13.9 vol% during hypothermic perfusion due probably to hemodilution. Similar to changes in the hematocrit, the decreased arterial oxygen content showed a tendency to recover to 15.9 vol% at the end of perfusion.

B) Oxygen A-V difference

Oxygen A-V difference showed a progressive increase, and its values before, during and after perfusion were 5.1, 6.8 and 9.9 vol%, respectively (Fig. 13).

TABLE 3. Blood gas changes during complete bypass

	during complete bypass	(mean value)
flow rate	17.4-43.0 ml/min	(29.0)
O_2 saturation in A.	80.5-100%	(91.7)
O_2 saturation in V.	20.4-79.0%	(45.2)
O_2 consumption	0.9-3.1 ml/kg/min	(2.0)
pCO_2 in A.	12.0-45.0 mmHg	(23.0)
$(Bb^+)b^-$ in A.	25.0-38.0 mEq/l	(33.0)

C) Oxygen saturation

During complete bypass, arterial oxygen saturation averaged 91.7%. The lowest arterial oxygen saturation of 80.5% was observed in dog No. 24, in which the minimal temperature was 27.5°C, both rectal and esophageal. This animal survived. In some cases, oxygen saturation reached 100%. On the otherhand, venous oxygen saturation was between 20.4 and 79.0%; in 9 cases out of 22 being below 40%, and in 8 cases above 50% (Table 3).

D) Total oxygen consumption during complete bypass

Oxygen consumption was calculated according to the following formula,

$$\text{Oxygen consumption} = \frac{1}{100} \text{ (A-V difference } X \text{ flow rate)}$$

Total oxygen consumption at esophageal temperature of 25.3°C, or rectal temperature of 25.0°C, ranged from 0.9 to 3.1 ml/kg/min (average 2.0) (Table 3).

E) Arterial pCO_2 and $(Bb^+)b^-$

A low arterial pCO_2 was already seen before perfusion due probably to hyperventilation of anesthesia. Arterial pCO_2 showed a gradual decrease, and its average values during and after bypass were 23.0 and 19.5 mmHg, respectively.

$(Bb^+)b^-$ showed a tendency similar to pCO_2. In all cases, $(Bb^+)b^-$ began to fall as soon as perfusion started. During complete bypass, it was between 25.0 and 38.0 mEq/l (average 33.0) (Table 3).

7. Electroencephalogram

EEG changes during hypothermic perfusion will be reported in detail elsewhere by Yoshizawa, one of the co-workers. As far as an ideal perfusion was carried out, minimal changes were observed in EEG throughout the procedure. Generally, however, the voltage decreased gradually following the decrease in body temperature, and some slow waves appeared at the initiation of complete bypass. All but 6 showed a low voltage less than 5 μV, and the slow waves were observed in 17 cases. EEG tracings from dog No. 22, a survivor, are

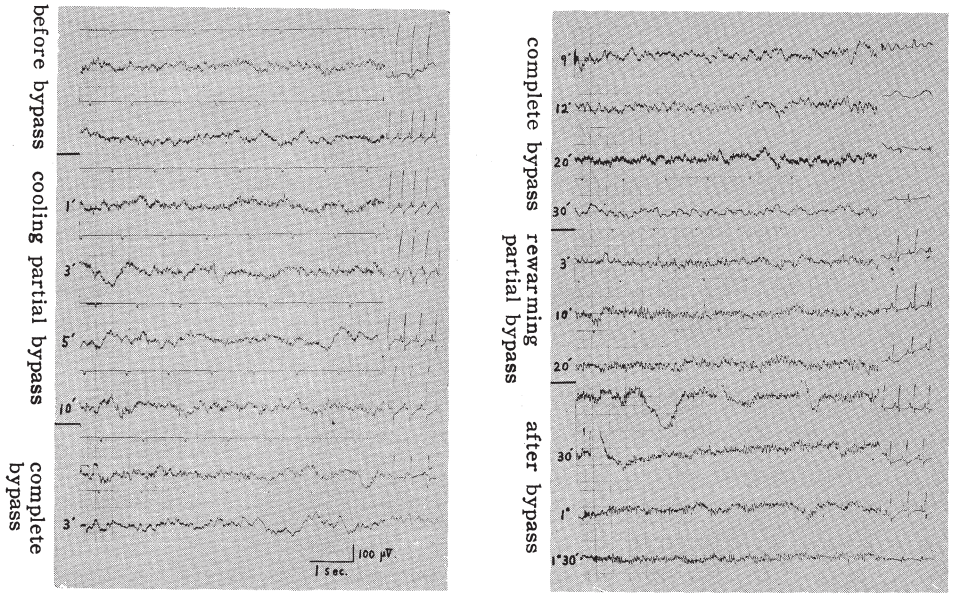

FIG. 14. EEG and ECG changes, case No. 22.

shown in Fig. 14.

EEG never disappeared during complete bypass even at a low flow rate, though the voltage and tbe frequency decreased. Recovery of the frequency and the voltage during rewarming was prompt, and a delayed recovery of EEG resulted in poor prognosis.

8. Electrocardiogram

As body temperature fell, cardiac rate slowed. During complete bypass 5 animals out of 26 kept showing sinus rhythm but marked bradycardia, and 21 animals developed ventricular fibrillation.

AC defibrillator, 110 volts for 0.1 sec, was apllied for defibrillation during rewarming. Fifteen dogs out of 21 responded well to 1 to 3 times of shock, and recovered the normal sinus rhythm. In dog No. 5, spontaneous defibrillation occurred.

Immediately after the heart beats recovered, ST-T changes were noted in many cases. These ECG changes, however, subsided quickly as temperature rose; cardiac rate increasing, QRS interval shortening and ST-T changes disappearing to show the normal pattern at the end of the bypass (Fig. 14).

Dog No. 15 developed ventricular fibrillation 2 hours after bypass and died.

9. Hemolysis

Plasma free hemoglobin never exceeded 100 mg/dl, and ranged from 13.1

to 90.0 mg/dl (average 44.7). Since the average bypass time was 70 min, the mean plasma free hemoglobin was 38.2 mg/dl/hr (Fig. 15).

10. Pathology

Pathological specimens were obtained from 20 cases. Specimens were fixed in 10% formalin, and hematoxilin-eosin staining was adopted.

A) Brain

Important findings were widening of the perivascular spaces, and sporadic nuclear dark staining or homogenization. No massive necrosis or softening was noted (Fig. 16).

B) Lung

Slight degree of hemosiderosis, alveolar atelectasis partially, alveolar wall thickening, and lymphocyte infiltration were the main findings (Fig. 17).

C) Myocardium

Slight degree of myocardial edema was observed. Otherwise no remarkable changes were seen (Fig. 18).

D) Liver

The sinusoids and Kupper cells were swollen and hyperplasied. In parts irregular vacuoles that seem to be fat, were seen intracellularly. No particular changes otherwise were seen (Fig. 19).

E) Kidney

Compared with other organs, the most prominent changes were seen in the kidney. Hyalin droplet degeneration was seen in the upper portion of the tubules, and edematous changes were observed in the lower portion of the tubules. The blood volume in Bowmann's capsule was within normal limits, while hyperplasia of the vessel loop cells was observed (Fig. 20).

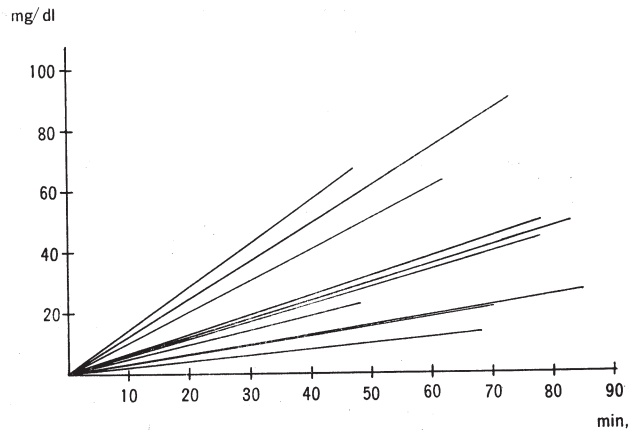

FIG. 15. Plasma free hemoglobin.

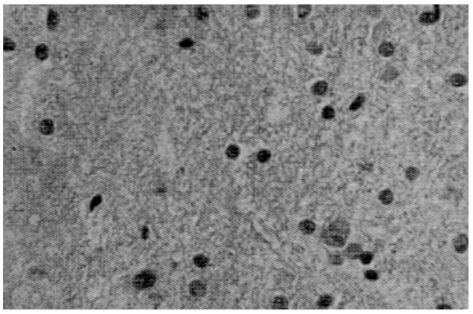

FIG. 16. Brain, hematoxilin-eosin, ×400. Showing sporadical nucleal dark staining or homogenization.

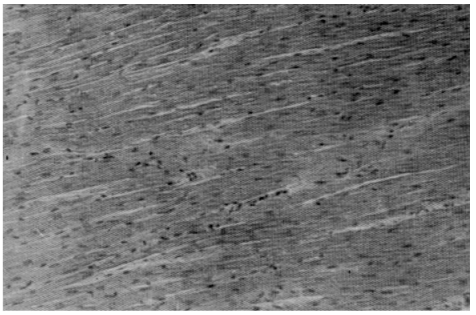

FIG. 18. Myocardium, hematoxilin-eosin, ×100. No remarkable changes.

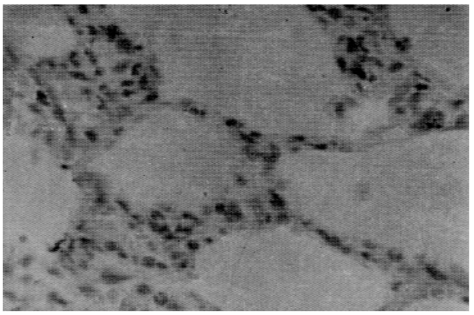

FIG. 17. Lung, hematoxilin-eosin, ×400. Showing alveolar wall thickening and lymphocyte infiltration.

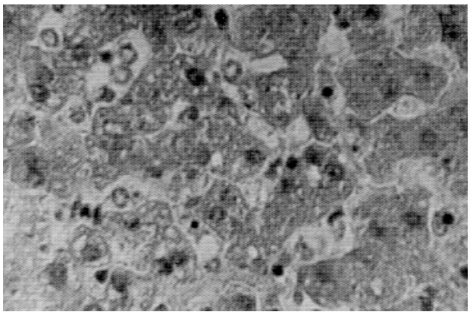

FIG. 19. Liver, hematoxilin-eosin, ×400. The sinusoid and Kupper cells are swollen, and partially irregular vacuoles seen intracellularly.

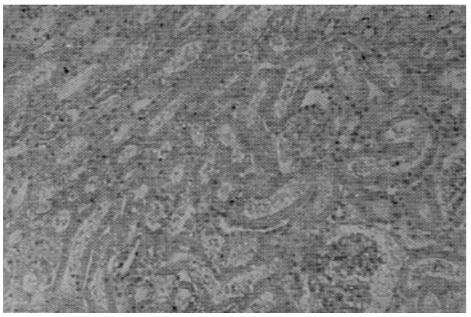

FIG. 20-a. Kidney, hematoxylin-eosin, ×100.

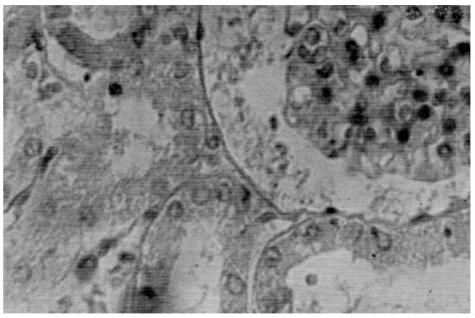

FIG. 20-b. Kidney, hematoxilin-eosin, ×400.

Hyalin droplet degeneration seen in upper portion of the tubules, and edematous changes observed in the lower portion.

TABLE 4. Priming volume of the extracorporeal circulating system, and O_2 carrying efficiency of the disc.

		(mean value)
priming volume	800-1200 ml	(1050)
5% dextrose in water	300- 600 ml	(455)
heparinized bllod	400- 700 ml	(595)
discs (to be used)	1.0-2.5/kg of body weight	(1.5)
O_2 uptake of one disc	0.6-2.8 ml/min/disc	(1.3)

11. Miscellaneous

Priming volume was between 800 and 1200 ml. The amount of 5% dextrose in water and heparinized blood utilized for priming averaged 455 ml and 595 ml, respectively. Number of discs utilized was 1.5 discs/kg of body weight, and oxygen uptake per disc was 1.3 ml/min, on the average (Table 4).

DISCUSSION

Heat Exchanger

The development of an efficient heat exchanger by Brown *et al*[25]. in 1958 contributed to shorten the duration of time for cooling and rewarming of hypothermia. Since then, the clinical application of hypothermic cardiopulmonary bypass has become common with either a Brown-Harrison heat exchanger or other models using a similar idea[26)27)28)29)30)31)32)].

The heat exchanger specially designed for this series of experiments has meny advantages. Firstly, the heat exchanger serves as a heat exchanging apparatus and a reservoir, simultaneously. The heat exchanging capacity is excellent. as shown in Fig. 6. The equalization of the blood level both in the heat exchanger and in the oxygenator makes the level controlling of the extracorporeal system very convenient. Secondly, no bubble trap is needed because of this apparatus being placed at the arterial side of the oxygenator, between the oxygenator and patient. Finally, by changing the combination of pylex cylinders, priming volume can be adjusted according to the body weight.

Though cooling and rewarming in hypothermic cardiopulmonary bypass have been mentioned to be made as quickly as possible[33)34)], too much temperature difference between the blood and the water in the heat exchanger may injure the blood elements[35)] or provoke bubble formation[35)36)37)].

Moreover, quick cooling may induce brain damage from hypoxia[33)39)40)] for which the impaired oxygen transportation from the blood already cooled to the brain tissue still remain relatively warm due to the shift of the oxygen dissociation curve of hemoglobin toward the left, cerebralvascular spasm due to an important temperature difference between the blood and the brain tissue, or blood sludging in the capillaries due to hemoconcentration or increased vis-

cosity under hypothermic state may be responsible.

In rewarming it has been reported that the temperature difference between the blood and the water in the heat exchanger or that between the inflow blood and the outflow should be less than 12°C[41] or 8°C[30], respectively. At first the heat exchanger placed at the venous side of the oxygenator had been used for rewarming only to prevent bubble formation. The danger of bubble formation was soon excluded by elevating the water temperature stepwise, keeping the water-blood temperature difference less than 15°C. Since then both exchangers have been used for cooling and rewarming simultaneously. Considering the excellent efficiency of this apparatus, the use of two exchangers seem to be unnecessary.

Priming volume can be saved, also, by as much as 100 to 400 ml by omitting one heat exchanger. In clinical cases, therefore, one heat exchanger is used only at the arterial side of the oxygenator; the venous blood from the patient draining directly into the oxygenator by gravity, and the oxygenated blood going back to the patient via the heat exchanger and the arterial pump.

Blanket

Unequal temperature distribution in various organs during core cooling has been discussed occasionally[33)42)43)44)45)46)]. Wolfson *et al.*[43] combined blanket cooling with core cooling to reduce the unequal temperature distribution, and clarified the advantage of this combination with their data concerning acid-base balance.

In addition to minimizing the unequal temperature distribution, the combination of blanket and core method is beneficial in shortening the duration of hypothermia. With a blanket, the animal is cooled somewhat by the initiation of core cooling; with blanket, core cooling and rewarming can be accelerated to make their duration shorter; and, with a blanket the animal can be kept warmed even after termination of core rewarming, if necessary.

Flow Rate

There are many reports on adequate flow rates under hypothermia[18)19)21)47)43)49)50)]. Initially, a flow rate of 20 ml/kg/min was utilized according to Zuhdi's method. At this flow rate, however, it was very difficult occasionally to maintain a proper arterial pressure and an adequate EEG pattern even with a vasopressor. In such a case, the flow rate was increased somewhat. On the average, therefore, the flow rate utilized has heen 29 ml/kg/min. Retrospectively, a 30 ml/kg/min seems to be an adequate flow rate to meet the purpose of this experimental state.

No difficulty in venous return due to gravity has been encountered even at such a low flow rate, and the flow rate may be increased to up to 50 ml/kg/

min, if necessary.

The administration of a vasopressor during cardiopulmonary bypass has been controversial. In our cases a minimal dose of vasopressor was used without any untoward reaction.

Hemodilution

Answering a recent trend to reduce the amount of blood for cardiopulmonary bypass because of the shortage in heparinized fresh blood, either the reduction in priming volume or the utilization of hemodilution method may be considered. Besides a saving of blood, the maintenance of microcirculation, the prevention of serum hepatitis and the protection against homologous blood syndrome are the advantages of hemodilution method[14)17)51)25)53)54)].

Concerning the amount of non-blood perfusate, a 30% of circulaing blood volume[17)], a 16 ml/kg[15)] or 20 ml/kg of body weight[51)] have been reported.

Neville *et al.*[20)] have stressed that hemodilution could be obtained safely with 33 to 52 ml/kg of non-blood perfusate. In their cases, the lowest hematocrit reached 18%, and $NaHCO_3$ was utilized to correct metabolic acidosis. Reduction in blood cell count manifested by hemodilution was corrected by returning the blood left in the extracoporeal system back to the body after the termination of cardiopulmonary bypass.

In our cases, the lowest hematocrit averaged 70% of the control. Since a poor prognosis was obtained in experimental cases, when the hematocrit decreased to below 70% of the control, too severe hemodilution should be avoided.

Non-blood Perfusate

Five percent dextrose in water was used as a non-blood perfusate. Since 5% dextrose in water has a lower viscosity and a lower molecular weight, its transfer into the tissue from the blood stream and excretion through the kidney are quicker than those of LMWD or PVP. Consequently, the volume of the circulating blood, actually consisting of blood and 5% dextrose in water, may gradually be decreased as the perfusion progresses. In such a circumstance, a certain amount of non-blood perfusate should be added during the perfusion to make up for the loss of circulating blood volume, though the additional amount of non-blood perfusate is different with each case according to the duration of perfusion. For this reason, LMWD may be mixed with 5% dextrose in water in advance, because the former remains longer in the blood stream than the latter.

Five percent dextrose in water has been reported to cause hemolysis in vitro[55)56)]. Hemolysis, however, did not seem to be increased in vivo; the highest plasma free hemoglobin being 90.0 mg/dl.

Agglutination-like phenomenon is observed in vitro when the blood is poured into 5% dextrose in water. This phenomenon, however, disappears when gentle

shaking is applied to the container of the mixture, and no embolic phenomenon has been encouctered in the bypass, also. Difference in tonicity between 5% dextrose in water and blood, and changes in electrical charge of red cells induced by dextrose may contribute to the phenomenon.

Five percent dextrose in water alone seems to be an excellent nonblood perfusate for hemodilution technique; however, a combination of 5% dextrose in water with electrolites solution and LMWD may be recommended to adjust the tonicity and to prevent the agglutination-like phenomenon.

Oxygenation

In this study oxygen uptake of each disc averaged 1.3 ml/min, whereas total oxygen consumption averaged 2.0 ml/kg/min. On the average, therefore, each disc does not seem to provide enough oxygen to meet the demand of each kg of body weight. However, considering the fact that one disc can maximally take 2.8 ml/min of oxygen in some cases, each disc could provide enough oxygen for each kg of body weight. For safety sake, one disc and a half should be considered to cover the oxygen demand of each kg of body weight clinically, especially in cases of infant baby.

Entering the complete bypass, the venous oxygen content decreases gradually, and oxygen A-V difference increases to an average of 6.6 vol%. DeWall *et al.*[57] reported a 7.1 vol% of mean maximum oxygen A-V difference at a body temperature of around 30°C, also.

In the present study oxygen A-V difference increases further during rewarming. This fact may indicate that some organs have developed hypoxia during complete dypass at a flow rate of 30 ml/kg/min, and the hypoxia manifests itself during rewarming with increasing oxygen A-V difference.

Equalization of temperature distribution and better peripheral circulation in the hypothermic state may lessen the large oxygen A-V difference during rewarming. Flow rate, also, may be increased, if necessary.

Oxygen consumption under hypothermia of 25 to 30°C has been stated to be 23 to 50%[33], 48 to 52%,[53] or 30%[59] of that under normothermia. If so, oxygen consumption of 2.0 ml/kg/min in the present study does not seem to indicate a lack of oxygen supply. Kameya[60] has warned on the flow rate during hypothermic perfusion based on the fact that highest oxygen consumption was encountered at a temperature of 10°C at a flow rate of 25 to 40 ml/kg/min.

Metabolism

Since pH, pCO_2 or buffer base have not yet been standardized definitely under hypothermia and hemodilution, it is very difficult to evaluate the acid-base balance in this study. When bypass start the pH read at 37°C decreased gradually suggesting the presence of acidosis. This acidosis is considered to be due to

the decreased pCO_2 and buffer base together with the increased lactic acid which has anaerobically been produced in hypoxic organs somewhere in the body and remained longer in the blood stream under hypothermically deteriorated liver function[61)62)63)].

Since no correction has been proposed when using $NaHCO_3$ or THAM, the acidosis progressed continuously, with pH lowered. As far as an optimal blood pressure is kept and homogenous cooling maintained, no irreversible metabolic acidosis develops. Since 5% dextrose in water, pH being 3.6 to 6.5, has no buffering action, $NaHCO_3$ or THAM may be added at time of priming to prevent profound metabolic acidosis which may be encountered during perfusion. Kogure, one of the co-workers, will report on the details of acid-base balance during hypothermic perfusion.

A low pCO_2 appearing in the preperfusion period is considered to be due to hyperventilation of anesthesia. Pure oxygen flowing into the oxygenator resulted in a further decrease of pCO_2. By inducing vascular spasm in the brain and preventing the dissociation of oxygen in the tissue, an extremely low pCO_2 should be avoided at all times. The amount of oxygen flowing into the oxygenator should be adjusted or CO_2 mixed[7)65)66)67)].

Electroencephalogram

EEG is one of the best parameters for evaluating blood circulation to the brain or to catch hypoxia in the brain, if the anesthesia level is constant. Contrary to hypothermic circulatory arrest, EEG never disappear during hypothermic perfusion even at a low flow rate.

Sakaguchi[68)] reported that no important EEG changes were recognized in deeply ether anesthetized hypothermic dogs until the body temperature fell to 33°C. In some cases rhythmical patterns were maintained even at temperatures of between 30 and 26°C. According to his conclusion, EEG is mainly affected by the hemodynamical condition rather than by the lowered temperature itself. Yoshizawa, one of the co-wokers, will present EEG findings during hypothermic perfusion in detail in the near future.

Since the anesthesia level was kept rather low during experimental procedures, the frepuency and voltage of EEG decreased gradually in some cases according fall in to body temperature. When a complete bypass was established, EEG developed the slow wave pattern in some cases, or, showed no remarkable changes in others. Since EEG is affected mainly by the hemodinamical condition, the presence of a rhythmical pattern during bypass means an adequate blood supply to the brain; that is, the perfusion should be carried out in such a manner as to maintain a rhythmical EEG pattern, if complete recovery is expected.

Pathology

Histological changes during simple hypothermia have been said to be mini-

mized in proper cases[69)70)71)] even after circulatory arrest of 30 minutes' duration at 28°C. Histological changes during hypothermic perfusion have been reported to be edema mainly[72)], and these changes, also, can be prevented by adequate cooling and rewarming.

Hemodilution has been reported to induce hypoxic changes; the more the volume of non-blood perfusate, the severer the changes, becoming reversible to irreversible[17)]. From this point of view, the application of hemodilution may be self-limited. In the present study, the severest changes were seen in the kidney. These changes may or may not be due to the hypoxia during perfusion; that is, they may be reversible and disappeare as soon as the hemodynamical state is improved after perfusion.

Changes in the brain, also, may be reversible, and, the dark stained and homogenously degenerated nuclei could be explained as postmortem changes or artifacts of the slide preparations. No changes seem to be fatal, and it is very difficult to decide if perfusion is responsible for all changes. Anyway, proper management could reduce the occurrence of histological changes.

Contrary to our method using a small rotating disc oxygenator, many reports have recommended a bubble oxygenator for hemodilution technique because of its smaller priming capacity. Using a small disc oxygenator, however, hemodilution hypothermic perfusion can safely be carried out as described and discussed above.

Moreover, this technique can be extended to clinical use with non-hemic priming modification in cases of body weight exceeding a certain limit, approximately 40 kg.

CLINICAL APPLICATION

The success of experimental hypothermic hemodilntion perfusion stimulated us to apply an almost similar technique in 52 cardiac patients undergoing open heart surgery, as reported in detail by Nakai, one of the co-workers. The ages ranged from 3 years to 27 years, and the body weight from 12.6 kg to 55.3 kg. The classification of diseases and the results of operation are shown in Table 5. Causes of death were varied, and perfusion itself was responsible for one case.

In the initial 25 cases, two heat exchangers were used; one at the arterial side of the oxygenator and the other at the venous. In the recent 27 cases, the heat exchanger at the venous side of the oxygenator was eliminated. Consequently, the priming volume was reduced markedly.

The degree of hemodilution has been increased gradually, and non-hemic priming was carried out in 8 cases. A calculated amount of 7% $NaHCO_3$ solution was added in advance into the oxygenator to compensate for the prospected

TABLE 5. Clinical applications of hemodilution hypothermic perfusion technique using newly designed heart lung apparatus. Classification of diseases and the results of operation.

	number of cases	age	body weight (kg)	died
A.S.D.	24	3-27	15.0-55.3	4
V.S.D.	12	3-14	12.6-42.0	1
P.S.	3	9-16	21.5-43.5	0
Tet. of Fallot	2	12-27	36.2-41.4	0
E.C.C.D.	1	5	15.5	0
E.C.C.D.+P.S.	1	15	38.4	0
P.S.+A.S.D.	3	9-17	24.0-55.0	0
A.S.D.+P.D.A.	1	4	17.0	0
A.S.D.+M.I.	1	9	22.8	0
V.S.D.+P.H.	1	15	34.5	0
P.S.+A.S.D.+V.S.D.	1	15	40.5	1
A.S.D.+A.P.V.D.+P.S.	1	7	19.7	0
T.A.P.V.D.+A.S.D.+P.S.	1	17	43.8	1
total (mean value)	52	(11)	(29.5)	7

basal deficit, and a gas mixture of 2% CO_2 and 98% O_2 was blown into the oxygenator during cooling and the initial period of complete bypass to prevent a low pCO_2.

In all cases, a stabilized bypass was achieved, the heat exchanging efficiency being excellent, and no difficulty in blood level controlling was encountered. Bypass time ranged from 28 min to 141 min and 38 sec (average 82 min and 31 sec); 13 min and 32 sec for cooling, 33 min and 52 sec for complete bypass, and, 35 min and 7 sec for rewarming on the average.

One of the remarkable findings seen in the clinical cases was the large urinary output noted during rewarming and after bypass. In many cases the urinary output was so great already during rewarming that an additional amount of non-blood perfusate was necessary to prevent the development of hypovolemia manifested by lowered blood level in the extracorporeal system and decreased venous pressure. Changes in hematocrit, blood gases, hemodynamical condition, acid-base balance, coagulation mechanism, EEG and ECG were far less in clinical cases than in the rxperimental, and a conclusion was reached that this is one of the best and safest methods to aid open heart surgery.

CONCLUSION

A new type of heart-lung machine consisting of a small rotating disc oxygenator, two helical heat exchangers and two DeBakey type roller pumps were devised. Using this apparatus hypothermic hemodilution perfusion was performed experimentally in 26 dogs and clinically in 52 cardiac patients.

As a non-blood perfusate, 5% dextrose in water was used. Experimental data were analyzed, discussed and summarized, as follows;

(1) The heat exchanger serves as a reservoir, a heat exchanging apparatus and a bubble trap, simultaneously. Esophageal and rectal temperatures were decreased at rates of 0.57°C/min and 0.77°C/min, and, increased at rates of 0.27°C/min and 0.24°C/min, respectively.

(2) One disc and a half, 130 mm in diameter, can supply enough oxygen to meet the demand of each kg of body weight at a flow rate of 30 ml/kg/min under hemodilution of 70%; hematocrit being reduced to 70% of the control level.

(3) Effects of hypothermic hemodilution perfusion on hematocrit, oxygen content, hemodynamical condition, EEG and ECG were diminished during rewarming, and almost disappeared by the closure of bypass.

(4) PH and pCO_2 decrease after entering the complete bypass. Basal deficit should be corrected using $NaHCO_3$ or THAM, and a low pCO_2 shold be prevented using a gas mixture of 2% CO_2 and 98% O_2, especially in clinical cases.

(5) Five percent dextrose in water utilized as a non-blood perfusate does not increase hemolysis at all.

(6) No pathological findings beleved to be fatal were encountered; all changes being reversible.

(7) Clinical use of this technique showed excellent results.

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