A Comparative Study between Hypothermic and Normothermic Cardiopulmonary Bypass in Open Heart Surgery in Dogs
—Effects on Systemic Hemodynamics—

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ABSTRACT. Open heart surgery was performed on two groups of dogs under extracorporeal circulation with or without hypothermia to investigate hemodynamic changes during extracorporeal circulation. During hypothermic cardiopulmonary bypass (CPB), arterial O_2 tension and postoperative blood pressure were favorably maintained, indicating that hypothermic extracorporeal circulation can be performed for a long period of time. On the other hand, during normothermic CPB, the average surgical duration was significantly shorter, and marked shifts in the concentrations of various enzymes were suppressed. However, due to reductions in arterial O_2 tension, the length of cardiac arrest time was restricted, demonstrating that this method is suitable for performing extracorporeal circulation for CPB of relatively short duration. If circulation circuitry can be improved, such as through the development of a surpassing oxygenator, normothermic CPB would incur less stress on the body, thus making it preferential to hypothermic CPB in most cases.—KEY WORDS: canine, extracorporeal circulation, hypothermia, normothermia.

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Current techniques in open heart surgery in humans involve establishing extracorporeal circulation using an artificial heart-lung machine. In this method, the artificial heart-lung machine performs systemic respiration and circulation so that the heart can be temporarily stopped and abnormal lesions can be repaired by open heart surgery in a blood-free surgical field. During extracorporeal circulation, patients are exposed to non-physiological conditions, such as hemodilution, low blood pressure, and non-pulsating flow of the blood. Therefore, necessary measures must be taken to ensure safe surgery. One of these methods involves hypothermia to suppress systemic metabolism and reduce oxygen consumption. Since Bigelow *et al.* first introduced simple hypothermia in cardiac surgery [3], this technique has been used under a variety of conditions. Simple hypothermia was also applied in the field of veterinary medicine by Breznock *et al.* who closed an intraventricular septal defect in a dog by open heart surgery [4].

Nonetheless, the concurrent usage of hypothermia adds stress to the body, and shifts in hemodynamics and the endocrine system and reductions in various enzymatic reactions cause persistent postoperative complications, such as hypertension, low output syndrome [15, 20], and acid-base balance disturbances [1]. Furthermore, since the cooling and rewarming procedures take time, the surgical duration is extended. This has rekindled, interest in the use of normothermic cardiopulmonary bypass (CPB) [9, 13], leading to comparative studies between hypothermic and normothermic CPB. However, few researchers have investigated the pathophysiology of dogs undergoing such surgery [11]. Moreover, no long-term comparative studies have been conducted and the effects of hypothermic or normothermic CPB in humans have yet to be fully clarified.

The present study investigate the effect of extracorporeal circulation using an artificial heart-lung machine with or without hypothermia on pathophysiology of dogs (in particular, hemodynamics).

MATERIALS AND METHODS

Animals: Fourteen clinically healthy male beagles were examined. All dogs were cared for in accordance with the experimental animal guidelines of Tokyo University of Agriculture and Technology. The animals were randomly divided into two groups. Group H (hypothermic CPB, age 2.2 ± 1.2 years (mean ± standard error), weight 10.0 ± 0.8 kg, n=7), in which their body temperature was reduced to 24–26°C, and Group N (normothermic CPB, age 2.0 ± 0.4 years, weight 10.4 ± 0.3kg, n=7), in which their body temperature was maintained at 36°C. To obtain clinically useful data, open heart surgery was performed assuming that the dogs would live for at least one month after surgery.

Surgical technique and cardiopulmonary bypass system: Dilation and remodeling of the right ventricular outflow tract of all dogs was performed using a patch graft technique as if they had pulmonary stenosis. The artificial heart-lung machine (NAPS-III, Fig. 1) [18, 19, 21] that was used in the present study consists of three two-roller pumps, a membrane oxygenator, a heat exchanger, and a circuit. Before starting extracorporeal circulation, the machine was primed with lactated Ringer solution, 5% glucose, 7% sodium bicarbonate, and 20% mannitol, without using whole blood. The dogs were pretreated with atropine sulfate (0.04 mg/kg) and acepromazine maleate (0.4 mg/kg), and when

Fig. 1. Artificial heart-lung machine for animals (NAPS-III). It has three roller pumps for blood supply and suction, and two water baths for cooling and warming patient by heat exchange.

sufficiently sedated, the dogs were anesthetized with thiamylal sodium (10 mg/kg). Each dog was then intubated with an endotracheal tube, and inhalation anesthesia using a mixture of oxygen and isoflurane, and intravenous anesthesia using 0.1% ketamine micro-mini drip administration technique [7, 14, 22] were started. While performing thoracotomy, 0.2 mg/kg of suxamethonium chloride (a muscle relaxant) was administered intravenously as necessary under the management of controlled respiration [14]. Heparin sodium was administered to prevent blood coagulation: activated coagulation time (ACT) > 400 sec [8]. Thoracotomy was performed by median sternotomy and the pericardium was exposed. Then, preparing a pericardial tent, catheters were inserted through the right auricle to the anterior vena cava and through the right atrium to the posterior vena cava to drain the blood from the heart. The surgical field, NAPS-III and circuit were connected to perform extracorporeal circulation. Following partial extracorporeal circulation for a few minutes, total extracorporeal circulation was achieved, and after stabilizing hemodynamics, cardiac arrest was induced by antegrade injection of cold Young's solution. The myocardium was protected by antegrade injection of cold cardioplegia, and the surface was cooled regionally using ice slush. After completing the necessary procedures, the heart was massaged manually and the heart beat was reinitiated using a defibrillator to switch back to partial extracorporeal circulation. After being weaned off extracorporeal circulation, thoracic drainage tubes were placed, and the chest was closed by the conventional method. After surgery, all dogs received flunixin (1.0 mg/kg every 12 hr) as necessary for analgesia.

Sampling techniques: A total of five blood samples were collected from before to after surgery (period 1: after inducing anesthesia, period 2: five min after switching to total extracorporeal circulation, period 3: five min after switching back to partial extracorporeal circulation, period 4: five min after the completion of extracorporeal circulation, and period 5: one hr after surgery). Blood samples were analyzed using the standard hematological tests (red blood cell count, white blood cell count, hemoglobin concentration (Hb), hematocrit (Ht), and plasma total protein concentration (TP)), biochemical tests (AST, ALT, ALP, BUN, creatinine, blood sugar, creatine kinase (CK), blood electrolytes (Na, K and Cl), and plasma osmotic pressure), and blood gas tests (arterial O_2 tension (PO_2), arterial CO_2 tension (PCO_2), plasma bicarbonate concentration (HCO_3^-), pH and base excess (BE) of the blood that passed through the artificial lung). In addition, mean arterial pressure (MAP), central venous pressure (CVP), cardiac output (CO), and urinary output (UO) were measured at the same time. Furthermore, the amount of the blood supplied by the artificial heart and the amount of oxygen flow to the artificial lung were measured eight times during extracorporeal circulation: 2 and 5 min after starting partial circulation, 5, 15 and 25 min after switching to total circulation, 5 and 20 min after releasing the aortic clamp, and just before weaning off the CPB pumps.

Statistical analyses: Data are expressed as mean ± standard error. Statistical analyses were performed using the Wilcoxon's signed rank test, and statistical significance was established at the $p<0.05$ level.

RESULTS

Surgical duration: Average age and weight did not differ significantly between the two groups. Although the length of cardiac arrest time during surgery did not differ significantly between the two groups (Group H: 32.0 ± 2.5 min, Group N: 28.7 ± 2.1 min), the surgical duration was significantly shorter for Group N (212.1 ± 13.0 min) than for Group H (254.7 ± 13.5 min). Body temperature during extracorporeal circulation differed significantly between the two groups (Group H: 26.57 ± 0.65°C, Group N: 36.00 ± 0.26°C)

Hematological findings: Table 1 shows the results of the general hematological tests. Although no significant differences were seen in red blood cell count, Ht, Hb, or TP at any time between the two groups, white blood cell count was significantly lower in Group H than Group N at periods 2 and 3. In addition, although no significant differences in ALT, ALP, BUN, creatinine, blood sugar or plasma osmotic pressure were seen at any time between the two groups, AST and CK were significantly higher in Group H than Group N at periods 4 and 5. Of the various plasma electrolytes, no significant difference was seen in the

Table 1. Results of the general hematological tests*

VARIABLE	GROUP	PERIOD 1	CPB PERIOD 2	CPB PERIOD 3	CPB PERIOD 4	PERIOD 5
Body Temperature	H	36.0 ± 0.7	26.6 ± 0.7 †	27.9 ± 1.3 †	36.2 ± 0.2	36.7 ± 0.2
(°C)	N	35.5 ± 0.5	36.0 ± 0.3	36.1 ± 0.2	36.2 ± 0.1	36.7 ± 0.4
Red Blood Cell	H	584.7 ± 36.2	348.4 ± 35.0	371.0 ± 38.7	495.2 ± 34.4	545.1 ± 34.7
(× 104/μl)	N	582.9 ± 27.7	380.4 ± 19.6	371.1 ± 19.0	451.9 ± 20.5	501.6 ± 27.6
White Blood Cell	H	55.3 ± 2.9	18.1 ± 1.3 †	18.1 ± 2.9 †	62.7 ± 11.8	91.1 ± 20.4
(× 102/μl)	N	58.9 ± 4.0	38.3 ± 4.0	44.3 ± 4.7	54.0 ± 5.5	76.6 ± 12.2
Hemoglobin	H	12.2 ± 0.3	7.0 ± 0.7	7.4 ± 0.7	9.6 ± 0.6	10.8 ± 0.6
(g/dl)	N	11.3 ± 0.3	7.1 ± 0.3	6.9 ± 0.7	8.9 ± 0.4	9.5 ± 0.4
Hematocrit	H	40.0 ± 0.8	20.5 ± 3.2	22.8 ± 2.3	30.6 ± 2.2	36.6 ± 1.8
(%)	N	37.3 ± 1.2	23.4 ± 0.8	24.4 ± 1.2	29.9 ± 1.4	31.9 ± 1.5
Plasma Total	H	5.5 ± 0.2	2.5 ± 0.3	2.5 ± 0.2	3.7 ± 0.3	4.6 ± 0.4
Protein (g/dl)	N	5.6 ± 0.1	3.0 ± 0.1	3.0 ± 0.1	3.5 ± 0.1	3.8 ± 0.2
AST	H	26.9 ± 4.9	13.6 ± 4.5	28.7 ± 5.1	112.4 ± 16.9 †	168.1 ± 30.6 †
(IU/l)	N	22.6 ± 2.1	14.0 ± 2.9	17.9 ± 3.1	49.3 ± 8.3	90.4 ± 11.5
ALT	H	43.3 ± 14.5	15.1 ± 6.8	15.9 ± 6.2	25.6 ± 4.3	39.7 ± 9.5
(IU/l)	N	46.9 ± 20.4	19.6 ± 9.7	19.7 ± 9.8	32.1 ± 14.7	31.3 ± 10.1
ALP	H	81.1 ± 17.5	35.1 ± 15.0	44.4 ± 19.9	35.9 ± 21.2	22.2 ± 13.3
(IU/l)	N	122.7 ± 22.9	83.6 ± 14.8	82.3 ± 14.9	90.3 ± 22.0	86.4 ± 21.5
BUN	H	10.5 ± 1.1	9.9 ± 1.1	10.6 ± 1.1	11.3 ± 1.1	11.2 ± 1.3
(mg/dl)	N	9.7 ± 0.8	10.3 ± 0.9	10.8 ± 0.9	11.1 ± 0.8	12.1 ± 0.6
Creatinine	H	0.69 ± 0.07	0.59 ± 0.04	0.57 ± 0.04	0.64 ± 0.02	0.70 ± 0.08
(mg/dl)	N	0.74 ± 0.15	0.80 ± 0.17	0.84 ± 0.23	0.81 ± 0.14	0.85 ± 0.15
Glucose	H	246.2 ± 36.7	794.0 ± 70.3	829.8 ± 100.9	465.0 ± 76.2	258.1 ± 54.7
(mg/dl)	N	138.0 ± 19.9	641.1 ± 52.8	655.2 ± 77.7	397.8 ± 53.2	206.2 ± 28.4
CK	H	203.6 ± 45.6	204.4 ± 41.4	461.6 ± 67.4	1598.3 ± 258.7 †	3232.0 ± 346.2 †
(IU/l·37°C)	N	221.7 ± 51.2	245.7 ± 53.7	348.9 ± 57.7	875.3 ± 144.7	1744.3 ± 303.9
Plasma Osmotic	H	295.5 ± 0.3	300.0 ± 8.0	300.0 ± 8.6	310.5 ± 0.3	303.0 ± 1.6
Pressure (mOsm/kg)	N	293.8 ± 2.7	302.6 ± 4.4	305.6 ± 3.3	309.0 ± 5.1	296.8 ± 1.7
Na	H	138.0 ± 2.0	116.7 ± 2.9 †	119.6 ± 1.4	124.9 ± 5.1	296.8 ± 1.7
(mEq/l)	N	138.7 ± 0.7	124.4 ± 0.6	125.1 ± 1.1	131.7 ± 1.2	135.6 ± 0.8
K	H	3.6 ± 0.3	3.0 ± 0.2	2.7 ± 0.1	2.6 ± 0.4	2.8 ± 0.1
(mEq/l)	N	3.8 ± 0.1	2.6 ± 0.1	2.8 ± 0.1	2.5 ± 0.1	3.3 ± 0.2
Cl	H	105.1 ± 1.2	85.4 ± 1.7 †	85,7 ± 2.0	92.3 ± 1.8	96.7 ± 2.8
(mEq/l)	N	106.0 ± 0.2	90.0 ± 0.6	90.6 ± 1.4	95.4 ± 1.6	98.3 ± 1.3

* Data are shown as mean ± standard error.
† : P<0.05.

concentration of potassium. However, the concentrations of sodium and chlorine at period 2 were lower in Group H, and significantly different from those of Group N.

Blood gas findings: Table 2 shows the results of the blood gas tests. The PO_2 at periods 2 and 3 and the PCO_2 at period 4 was significantly higher in Group H than Group N. However, no significant changes in the levels of HCO_3^- and BE were observed. Analysis of the pH of the blood samples showed that acidosis was more pronounced in Group H, and in particular, there was a significant difference at period 4 between the two groups .

Hemodynamics findings: MAP remained almost constant before and during extracorporeal circulation, and shifts in MAP were similar in both groups (Table 3). However, at periods 4 and 5, MAP of Group N was significantly lower than that of Group H. CVP at period 2 was significantly lower in Group H than Group N. No significant differences in the CO and UO were observed between the two groups.

Blood supply and oxygen supply: The amount of blood supplied during extracorporeal circulation was generally higher in Group N, and there was a significant difference between the two groups 15 min after total extracorporeal circulation (Fig. 2). In addition, the amount of oxygen flow to the artificial lung was higher at all times in Group N, and the difference in oxygen supply between the two groups increased with time. The amount of oxygen supply during total extracorporeal circulation and 20 min after releasing the aortic clamp differed significantly between the two groups (Fig. 3).

Prognosis: Except for one dog that died due to poor postoperative care, the postoperative course of all dogs has been favorable, and at present (one year after surgery), none of them require regular drug administration (antibiotics were administered for several days after surgery).

The significant differences in AST and CK at period 5 were not seen at the third post-operative day check up. Furthermore, no other significant differences in biochemical tests, hematological tests or blood electrolytes tests were seen after surgery.

Table 2. Results of the blood gas tests*

VARIABLE	GROUP	PERIOD 1	CPB PERIOD 2	CPB PERIOD 3	CPB PERIOD 4	PERIOD 5
PO_2	H	531.0 ± 19.9	624.1 ± 45.7 †	530.0 ± 69.0 †	372.0 ± 48.9	494.0 ± 34.0
(Torr)	N	497.7 ± 36.6	301.7 ± 59.7	179.2 ± 44.0	300.1 ± 76.4	389.8 ± 58.9
PCO_2	H	45.0 ± 4.4	40.2 ± 5.3	46.9 ± 12.6	38.6 ± 2.7 †	44.2 ± 6.0
(Torr)	N	41.8 ± 4.5	31.1 ± 3.4	33.3 ± 3.8	27.3 ± 2.2	52.9 ± 7.2
HCO_3	H	23.0 ± 0.8	22.8 ± 1.1	21.8 ± 1.0	21.3 ± 1.7	20.8 ± 0.9
(mmol/*l*)	N	22.6 ± 1.1	24.3 ± 1.1	20.5 ± 1.0	19.3 ± 0.9	23.0 ± 2.4
pH	H	7.29 ± 0.03	7.36 ± 0.04	7.33 ± 0.05	7.37 ± 0.02 †	7.29 ± 0.03
	N	7.32 ± 0.04	7.46 ± 0.01	7.40 ± 0.03	7.46 ± 0.02	7.29 ± 0.09
BE	H	−5.7 ± 1.1	−4.4 ± 1.0	−5.1 ± 1.2	−2.9 ± 1.5	−5.3 ± 1.2
	N	−3.3 ± 0.9	−0.4 ± 1.8	−3.0 ± 0.9	−2.4 ± 0.6	−3.7 ± 1.6

* Data are shown as mean ± standard error.
† : P<0.05.

Table 3. Results of the hemodynamic parameter*

		CPB PERIOD 1	CPB PERIOD 2	CPB PERIOD 3	CPB PERIOD 4	CPB PERIOD 5
Mean arterial	H	125.0 ± 4.3	53.0 ± 3.2	63.0 ± 3.1	78.3 ± 5.5 †	89.3 ± 7.3 †
Pressure (mmHg)	N	120.4 ± 4.4	55.6 ± 4.5	66.3 ± 5.8	60.6 ± 6.2	54.0 ± 2.4
Central Venous	H	5.0 ± 0.0	0.3 ± 0.6 †	4.8 ± 1.4	7.8 ± 1.6	6.2 ± 1.6
Pressure (cmH_2O)	N	5.0 ± 0.0	6.8 ± 1.0	8.3 ± 0.7	6.8 ± 0.5	4.8 ± 0.5
Cardiac Output	H	1.9 ± 0.34			2.0 ± 0.32	
(*l*/min)	N	2.0 ± 0.43			1.6 ± 0.1	
Urinary Output	H	27.6 ± 4.6	101.4 ± 19.4	91.2 ± 22.1	243.2 ± 46.1	127.2 ± 53.4
(m*l*/h)	N	23.4 ± 6.1	61.7 ± 15.4	91.6 ± 24.7	122.6 ± 29.1	29.4 ± 3.3

* Data are shown as mean ± standard error.
† : P<0.05.

Table 4. Time of collection of blood samples (CPB: Cardiopulmonary Bypass)

Sample	Time
1	2 min after starting partial circulation
2	5 min after starting partial circulation
3	5 min after switching to total circulation
4	15 min after switching to total circulation
5	25 min after switching to total circulation
6	5 min after releasing the aortic clamp
7	20 min after releasing the aortic clamp
8	weaning off the CPB pump

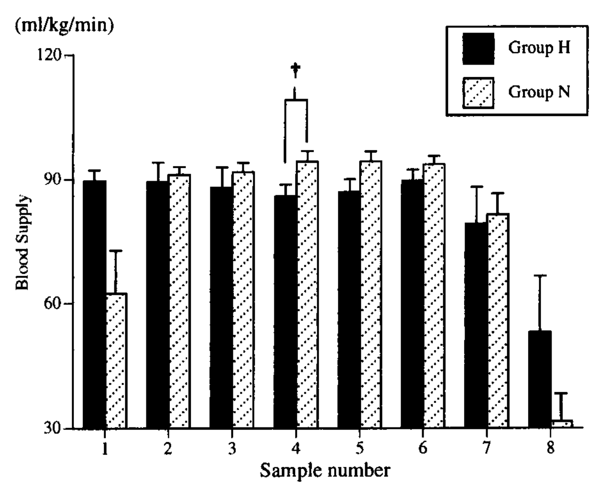

Fig. 2. Amount of the blood supplied by artificial heart. Data are shown as mean ± standard error. Sample number same as in Table 4. † : P<0.05.

DISCUSSION

Although there were no significant differences in the length of cardiac arrest time between the two groups, as expected the average surgical duration of the normothermic group (Group N) was significantly shorter, since the cooling and rewarming procedure is unnecessary for starting CPB and weaning off the extracorporeal circulation circuit [2, 5, 12].

In the present study, hemodilution was performed in the same manner using the same machine in both groups. As a result, red blood cell count, Ht, Hb, TP and plasma osmotic pressure did not differ significantly at any time between the two groups, suggesting that this degree of difference in body temperature during extracorporeal circulation does not affect these parameters.

Many studies have documented reductions in white blood

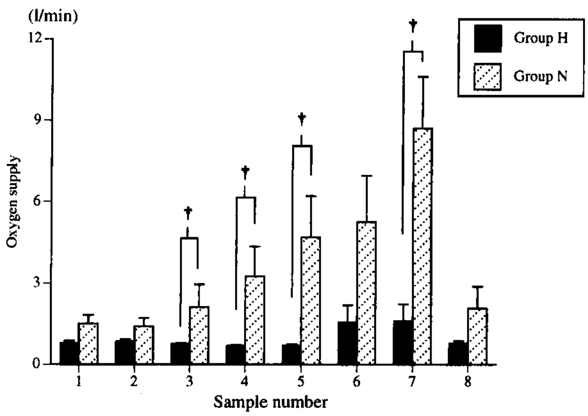

Fig. 3. Oxygen flow to the artificial lung. Data are shown as mean ± standard error. Sample number same as in Table 4. †: $P<0.05$

cell count during extracorporeal circulation, possibly due to such factors as contact with foreign surfaces, insufficient hemodilution, intrapulmonary storage, release of chemical mediators accompanied by the activation of complement [6, 10, 17]. Although the relationship between white blood cell count and body temperature during extracorporeal circulation has not been elucidated, since white blood cell count significantly decreases upon hypothermia, there appear to be a direct connection between the cooling procedure and the reduced white blood cell count. Furthermore, the white blood cell count was higher one hr after the completion of extracorporeal circulation than before surgery in both groups, suggesting mobilization of white blood cells from the leukocyte pool or over production of white blood cells by the bone marrow occurs.

Of the various biochemical parameters tested, there were significant differences in AST and CK between the two groups, and both markedly increased in Group H over time. Since the same surgical techniques were performed using the same set of equipment in both groups, these increase in the secretion of these enzymes suggests that the effect of cooling on the homeostasis of the body is great, and that the concurrent use of hypothermia and extracorporeal circulation enhances nonphysiological conditions. Although we expected the level of CK to decrease in Group H, it actually increased. Nonetheless, when the level of CK was compared among dogs in the same group, the tendency was that the shorter the surgical duration, the lower the level of CK, suggesting that increases in enzyme release could be suppressed to some degree by shortening surgical duration.

During surgery, shifts in the concentration of potassium were corrected as necessary according to conventional techniques and consequently, there were no significant differences in the concentration of potassium between the two groups. However, the concentrations of sodium and chloride were significantly lower during surgery in Group H than in Group N, and were approximately equal between the two groups after surgery. Therefore, because extracorporeal circulation using hypothermia lowered the concentration of sodium and chlorine, the concentrations of these electrolytes should be monitored during bypass surgery and should be replenished as necessary.

The PO_2 of Group H was higher than that of Group N due to increases in the solubility of oxygen attributable to the lower body temperature [16] and reductions in oxygen consumption. The PO_2 of Group H was particularly high from the start to completion of total extracorporeal circulation. In Group N, although the amount of oxygen flow to the artificial lung was several times higher than that of Group H, the PO_2 kept decreasing during total extracorporeal circulation, and when the aortic clamp was released, it was remarkably low. Stabilization of PO_2 during extracorporeal circulation is essential in performing heart surgery, and greatly affects the duration of surgery. As a result, PO_2 should be carefully assessed when performing normothermic CPB over a long period of time. The PCO_2 of Group N was generally lower. We believe this was caused by an increase in the amount of carbon dioxide released from the blood, since the amount of oxygen flow to the artificial lung was higher in this group. These findings suggest that we need to be aware that carbon dioxide is mixed with perfusion gas in the artificial lung during normothermic CPB. In Group N, due to decreases in PCO_2, the pH of the blood increased. The pH of the blood generally increases as body temperature decreases, but this tendency was not seen in Group H. Nonetheless, the results of the present study suggest that intentional PO_2 elevation greatly affects blood gases, which in turn affects the acid-base balance.

During extracorporeal circulation, blood was supplied at a rate of about 80–100 m*l*/min/kg with an MAP of about 55–65 mmHg. Consequently, there were hardly any differences in MAP between the two groups up to the completion of extracorporeal circulation. However, after the dogs were weaned off extracorporeal circulation, MAP of Group N decreased to less than 60 mmHg, suggesting that monitoring MAP after normothermic CPB is essential.

In the present study, in hypothermic CPB, the PO_2 remained high, and therefore, the postoperative MAP remained relatively high. However, because the time to control body temperature was longer, the average surgical duration was longer. Furthermore, the concentrations of enzymes such as AST and CK increased, and the degree of shifts in plasma electrolytes was larger. On the other hand, with normothermic CPB, the average surgical duration was shorter, and the degree of shifts in various parameters was lower, suggesting less stress on the body. However, the capacity of the oxygenation of the blood oxygenator decreased with time, and the length of cardiac arrest time was limited.

Thus, overall the present results show that normothermic CPB is suitable for performing relatively short durational open heart surgery, and that hypothermic CPB is more suited to longer durational open heart surgery. If the circulation circuitry can be improved, normothermic CPB may eventually place less stress on the body than hypothermia, thereby becoming the extracorporeal circulation procedure of chice.

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