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CLINICAL STUDIES OF HYPOTHERMIC PERFUSION WITH HEMODILUTION TECHNIQUE, ESPECIALLY ITS INFLUENCE ON WATER AND ELECTROLYTES CHANGES, AND RENAL FUNCTION

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SUMMARY

Hypothermic low flow cardiopulmonary bypass with hemodilution technique was performed in open-heart surgery in the author's clinic. To evaluate the usefulness of this perfusion, renal hemodynamics during total bypass, and its influence on renal function were studied.

The average effective renal blood flow during total bypass at the perfusion rate of 50 to 60 ml per kg per minute under mild or moderate hypothermia was 7.7 ml per kg per minute. Osmolality, blood urea nitrogen, free plasma hemoglobin, electrolytes and urea excretion and urinary output were studied for evaluating the postoperative renal function.

Osmolality was one of the most convenient indicator of predicting renal insufficiency.

It was concluded that the hypothermic perfusion with hemodilution technique was a commendable method in carrying out complicated intracardiac procedure.

INTRODUCTION

Recently clinical experiences with extracorporeal circulation have made surgical correction of numerous congenital and acquired heart diseases possible. While the blood circulates through a heart-lung machine, it is subjected to an abnormal physicochemical environment. To get full benefit from complicated operative procedures, it is desirable to improve bypass technique in order to prevent many complications due to bypass such as cerebral and pulmonary complications, hemodynamic alteration, renal impairment and metabolic acidosis. Particularly, renal failure, although rarely encountered, is still a lethal complication in this field.

This investigation was undertaken in an attempt to evaluate hypothermic hemodilution perfusion practiced in this clinic, and the applicability of routine laboratory tests for early recognition of functional renal impairment resulting from, most likely, the above bypass method.

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HISTORY OF EXTRACORPOREAL CIRCULATION

Experimental study of extracorporeal circulation using a heart-lung machine was first undertaken by Gibbon[1] in 1937. Clinical application was tried by Dennis *et al.*[2] in 1951, and the first successful open-heart operation using heart-lung bypass was reported by Gibbon in 1954. Subsequently, many clinical experiences with various types of heart-lung machine were reported[3][4].

In this country, an experimental study of extracorporeal circulation was started by Toda *et al.*[5] in 1951. Manabe *et al.*[6] reported the first successful open-heart operation using a heart-lung machine in 1956. In recent years, numerous experimental and clinical experiences have been reported by many investigators.

Since open-heart surgery was widely undertaken, much attention have been said to the problems like the need for massive amount of fresh blood, occult blood incompatibilities such as homologous blood syndrome, and serum hepatitis due to massive blood transfusion.

In order to solve these disadvantages, improvement of an artificial heart-lung machine and hemodilution technique were applied by Zuhdi *et al.*[7][8], and Lillehei *et al.*[9][10]. Zuhdi emphasized the effectiveness of low perfusion rate utilizing moderate hypothermia and priming a small pump oxygenator with 5 per cent dextrose in water. Since then, 5 per cent dextrose in water, low molecular weight dextran, balanced electrolyte solution, artificial plasma, physiologic saline and others have been used as blood substitutes by many investigators[10][11][12][13][14][15].

On the other hand, hypothermia in surgical treatment of the cardiac lesion was first applied by Bigelow *et al.*[16] in 1950, and successful operations with this method were reported by Lewis *et al.*[18], and Swan *et al.*[19] in 1952.

Simple hypothermia has two disadvantages; that is, time limitation for permissible circulatory occlusion and the time required in cooling and rewarming of the patient. Combination of extracorporeal circulation with hypothermia was considered to be a secure method to perform intracardiac operation. Sealy *et al.*[20] was the first in performing open-heart operation using extracorporeal circulation with surface cooling clinically. Brown *et al.*[21] used a heat exchanger in extracorporeal circuit to obtain more effective cooling and rewarming.

Recently, in the field of cardiac surgery, hemodilution perfusion under mild or moderate hypothermia is one of the most practiced method to correct the complicated lesions of the heart.

MATERIALS AND METHODS

Materials

The data for this report were obtained from selected 50 patients who underwent open-heart operation under hypothermia hemodilution perfusion at

TABLE 1

Case No.	Sex Age	Weight (kg)	Diagnosis	Ope. procedure	Perfusion time (min)	Lowest rectal temp. (°C)	Flowrate (ml/kg/m)	Diluent (ml/kg)	Results
1	M 24	47.9	MSI	Mitral valve repl.	149	25.6	42	28.4	L and W
2	F 7	17.1	TF	Total correction	164	25.6	46.7	40.3	L and W
3	F 20	47.8	MSI	Mitral valve repl.	135	24.0	31	30.4	L and W
4	F 5	13.0	VSD	Direct suture	50	28.0	31	47.3	L and W
5	F 42	59.2	MSI	Mitral valve repl.	197	25.0	41	21.9	L and W
6	M 8	17.0	VSD	Direct suture	41	28.7	41	40.4	L and W
7	M 4	14.2	VSD	Direct suture	80	26.3	43	45.9	L and W
8	F 20	39.2	ASI+MS	Aortic valve repl. mitral commissurotomy	236	25.0	39	28.4	Died renal insuff.
9	F 9	19.0	ASD	Direct suture	46	29.1	42	34.9	L and W
10	F 21	39.5	TF	Total correction	145	25.4	38	28.0	L adn W
11	M 9	22.0	VSD	Direct suture	54	27.1	41	34.9	L and W
12	F 6	19.5	ASD	Direct suture	46	28.3	41	36.8	L and W
13	F 17	37.0	TF	Total correction	148	24.5	46	27.3	Died card. insuff.
14	M 8	24.0	ASD	Direct suture	63	27.7	42	37.0	L and W
15	F 24	49.1	MSI	Mitral valve repl.	134	23.2	40	25.6	Died card. insuff.
16	M 15	34.5	PS	Pulmo. valvulotomy	73	27.1	43	34.2	L and W
17	M 24	58.8	ASI	Aortic valve repl.	166	24.6	34	36.1	L and W
18	F 5	13.5	VSD+PH	Patch suture	91	27.9	44	44.6	L and W
19	F 22	42.5	MSI	Mitral valve repl.	100	24.5	47	30.5	L and W
20	M 15	35.8	TF	Total correction	189	24.2	50	31.5	Died bleeding
21	F 5	13.5	VSD+PH	Patch suture	133	26.6	59.5	49.9	L and W
22	F 23	46.6	ASD	Direct suture	60	27.6	42	32.8	L and W
23	F 15	14.7	TF	Total correction	143	23.5	59	36.7	L and W
24	F 10	32.4	TF	Total correction	126	25.1	67.6	35.0	L and W
25	M 8	23.4	TF	Total correction	149	25.0	64	39.9	L and W
26	M 6	16.5	VSD	Direct suture	74	28.5	60.6	42.6	L and W
27	M 5	17.0	TF	Total correction	127	24.4	58	43.1	L and W
28	M 10	31.0	TF	Total correction	165	24.7	64	35.6	L and W
29	M 9	30.1	ASD	Direct suture	24	32.8	66	36.7	L and W
30	M 11	24.6	TF	Total correction	145	25.5	61	38.7	L and W
31	F 6	17.2	VSD	Patch suture	104	28.6	58	43.7	L and W
32	M 30	54.0	AI	Aortic valve repl.	170	25.0	37	34.8	L and W
33	F 5	12.0	VSD	Direct suture	45	28.2	62	51.0	L and W
34	M 9	28.1	VSD	Direct suture	78	30.0	64	35.7	L and W
35	M 27	55.8	MS	Open mitral commissurotomy	96	29.8	53	30.1	L and W
36	F 35	43.0	ASD	Direct suture	44	26.8	46	29.2	L and W
37	F 5	13.5	VSD+PH	Patch suture	48	30.0	56	68.0	L and W
38	F 10	23.0	ASD	Direct suture	35	29.5	52	38.0	L and W
39	F 19	42 3	MSI	Mitral valve repl.	112	24.4	49	36.3	L and W
40	M 10	27.6	VSD	Direct suture	44	28.5	44	36.7	L and W
41	M 19	58.1	AI	Aortic valve repl.	127	26.0	41	31.7	L and W
42	F 10	20.2	VSD+PH	Patch suture	84	28.4	50	45.7	L and W
43	M 7	20.4	TF	Total correction	110	25.0	59	40.3	L and W
44	M 5	17.2	PS	Pulmo. valvulotomy	29	30.0	58	44.9	L and W
45	M 5	17.7	TF	Total correction	93	25.7	56	39.1	L and W
46	M 25	46.0	TF	Total correction	177	24.5	52	38.0	L and W
47	F 26	52.9	TF	Total correction	149	27.7	57	25.1	L and W
48	F 27	47.5	TF	Total correction	148	25.1	52.4	33.0	L and W
49	F 7	20.2	TF	Total correction	110	29.3	59.2	42.7	L and W
50	M 10	33.5	TF	Total correction	114	25.2	59.7	28.8	L and W

TF : Tetralogy of Fallot
MSI: Mitral stenoinsufficiency
ASI: Aortic stenoinsufficiency
PS : Pulmonary stenosis
VSD : Ventricular septal defect
ASD : Atrial septal defect
PH : Pulmonary hypertension
L and W: Living and well

the Nagoya University Hospital from February, 1966 to March, 1967. The age of these patients varied from 4 to 42 years old, and weight from 12 to 60 kg. Twenty-seven patients were female, and twenty three male. Ten patients underwent valve replacement using a Starr-Edwards prosthesis, one patient open mitral commissurotomy, and 39 patients corrective procedure for congenital cardiac lesions (Table 1). Two patients (Nos. 13 and 15) died from cardiac insufficiency 2 days postoperatively, one (No. 8) from renal insufficiency on the 8th postoperative day, and another (No. 20) from intrathoracic hemorrhage on the 2nd postoperative day.

Apparatus

The apparatus in the author's clinic, as reported previously[22)23)24)], was devised on the Zuhdi's principle. It consisted of a rotating disc-oxygenator of Kay-Cross type, two roller pumps of DeBakey type for an arterial cannule and a cardiotomy sucker, and a heat exchanger placed on the arterial side of the circuit. According to patient's body weight, a suitable disc-oxygenator (containing 33, 45, 60, 80 or 100 discs) was selected. The number of discs was about 1.5 to 2.0 time the body weight in kilogram. The heat exchanger was made of a pyrex glass cylinder and a stainless-steel helical coil therein, and served as an arterial reservoir and a bubble trap. While cold or warm water was pumped through this helical coil, heat transfer took place between water and surrounding blood (Fig. 1).

The priming volume of this apparatus and the connecting tube varied from 1,400 ml to 2,500 ml depending on the capacity of the disc-oxygenator used. Other roller pumps of DeBakey type for coronary perfusion and the second sucker were used if necessary.

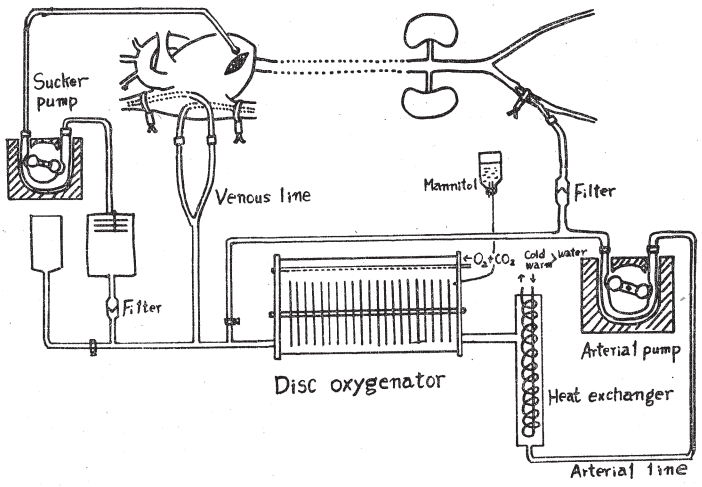

FIG. 1. Extracorporeal circulation system.

Priming solutions

The system was primed with 5 per cent dextrose in water, the volume being roughly equivalent to one third of the patient's daily fluid requirement. Three fourths of the difference between the real priming volume of the used apparatus and the calculated volume were filled with the fresh heparinized blood, and one fourth with blood substitutes. Low molecular weight dextran (0.5 g per kg) and ascorbic acid (500 mg) were used to eliminate red blood cell sludging, 7 per cent sodium bicarbonate to correct base deficit of the body and the priming fluid, heparin sodium (2 mg per kg) as anticoagulant, and K-aspartate* (2.9 to 5.8 mEq) to prevent postoperative hypokalemia. These diluent amounted from 68 to 21.9 ml per kg (average, 36.9) of the body weight. Twenty per cent mannitol solution (5 ml per kg) was dripped into the disc-oxygenator during bypass procedure to protect renal function.

Bypass procedure

After patients were anesthetized with a gas mixture of oxygen, ether and nitrous oxide, surface cooling with a blanket was begun on the operating table. Median sternotomy or right thoracotomy was performed. After pericardiotomy, tapes for occlusion were placed around the aorta, the pulmonary artery, and the both venae cavae. The patient was then heparinized with 2 mg per kg of heparin. The femoral artery cannula and two caval cannulae were inserted, and connected to the heart-lung machine as routine. The venous return was obtained by gravity drainage. Four to six liters of gas, 98 per cent be oxygen and 2 per cent carbon dioxide, was used with the disc rotation varying from 80 to 90 rpm. When the rectal body temperature fell to 28 to 30°C after about 10 minutes of partial cooling bypass, the great vessels were occluded by tieing up, and cardiotomy was carried out. In cases with complicated intracardiac lesions such as tetralogy of Fallot, further cooling was employed so that the rectal temperature reached to 24 to 26°C. Esophageal and rectal temperatures, and pressures of both the venae cavae and the femoral artery were monitered to carry out the adequate bypass procedure in most cases.

Due to hypothermia, the heart was well protected from hypoxia during occlusion of the great vessels, and the operative field became quiet and dry with the arrested heart and almost no bleeding. Every twenty minutes, aortic occlusion was released to perfuse the coronary arteries for two minutes. In cases of aortic valvular lesion, another pump was used for coronary perfusion.

To prevent air embolism, the operative field was filled with 4 liters per minute of carbon dioxide.

Soon after the cardiotomy wound was closed, partial rewarming bypass was started. In majority of the cases, the heart was defibrillated spontaneously by rewarming. If fibrillation persist, DC shock is utilized. When blood level in

* Commercially available potassium preparation.

the oxygenator became less during rewarming, heparinized or ACD blood was added into the circuit. The perfusion was stopped when the rectal temperature returned to 33 to 34°C.

Perfusion rate varied from 20 to 40 ml per kg of body weight per minute during partial bypass, and 30 to 60 during total bypass.

After the termination of bypass, the remaining fluid in the oxygenator was slowly infused into the patient through the inflow line, while monitoring both caval pressures, femoral arterial pressure, and also according to the size or tension of the heart. In case of non-blood priming applied, the remainder in the reservoir was returned to the patient to the bottom by layering 5 per cent dextrose in water. Protamin sulfate (1 to 1.5 times the dose of heparin used) was administered intravenously after decannulation of both caval cannulae.

Blood loss from the operative field was measured and, to compensate for this loss, ACD blood was transfused after bypass.

An indwelling catheter was kept in place for urinary collection.

Laboratory examinations

Serum electrolytes and blood urea nitrogen: Blood samples for measurement of serum electrolytes (Na, K, Cl) and blood urea nitrogen (BUN) were drawn by venipuncture on the preoperative day, just before and one hour after the end of bypass, and the first, second, fourth and 7th postoperative days. Sodium and potassium were determined with a flamephotometer, chloride with chloridometer, and BUN by the Urease-Nessler's method.

Urinary excretion of electrolytes and urea: Twenty four hours urine specimen was collected on the preoperative day. Urine specimen during bypass, the first 3 hours period after bypass, and that of the following period until the midnight of the day of surgery, and on the first, second, third and 7th postoperative days were also collected. The amount of urine was measured on each sample. Electrolytes and urea were determined by the same method for blood samples.

Protein and sugar in the urine: Protein and sugar in urine samples were measured quantitatively.

Hematocrit: Hematocrit measurement was made with the use of microhematocrit centrifuge.

Osmolality of the blood and the urine: Blood samples were drawn by venipuncture on the preoperative day, during partial and total bypass, during postoperative period and on the first postoperative day. Osmolality of the priming fluid was also measured and the urine was collected at the same time for examination of electrolytes content. The serum and urine osmolality was determined by the freezing point depression method using an Advanced Osmometer (Model 64-31)[25].

The specific gravity was measured by a hydrometer onthe aliquot urine

specimens.

Renal blood flow: Effective renal blood flow and renal fraction were calculated by the clearance of para-aminohippurate (PAH)[26] in 9 cases and by the single injection method of radiohippuran (^{131}I; 10–30 μ C)[27][28] in 11 cases during bypass.

Plasma hemoglobin: The plasma hemoglobin content was measured by the cyan-methohemoglobin method on samples obtained at the termination of the perfusion[29].

Circulating blood volume: Circulating blood volume was measured with RISA (^{131}I; 5–10 μ C) on the preoperative day, during the postoperative period and on the first postoperative day.

Extracellular fluid volume: In 14 cases, the extracellular fluid volume was determined by the sodium thiocyanate method on the day prior to the operation, 3 hours after operation and on the 7th postoperative days.

RESULTS

Serum electrolytes: The levels of serum electrolytes (Na, K, Cl) fell approximately 95 per cent in sodium, 79 per cent in potassium, and 90 per cent in

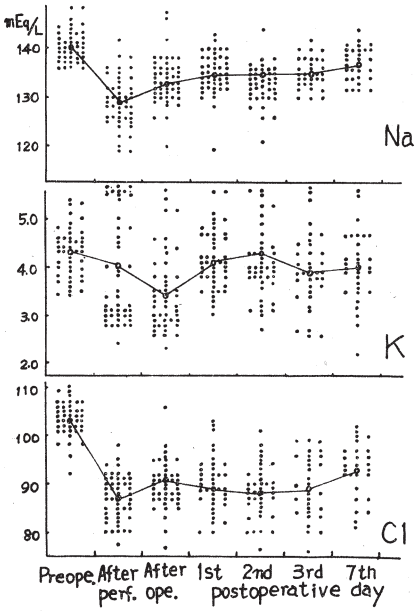

FIG. 2. Serum electrolytes. Serum electrolytes fell after bypass, and returned to normal on the first postoperative day. The concentration of chloride remained low till the 7th postoperative day.

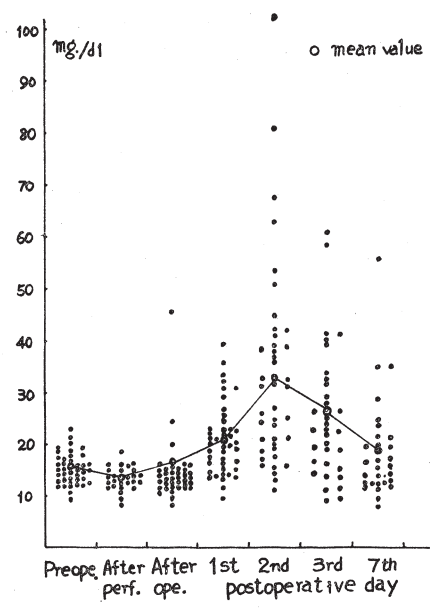

FIG. 3. Blood urea nitrogen. Blood urea nitrogen increased till the second postoperative day, and gradually returned to the normal value.

chloride of the preoperative average values after operation. However, no significant change in symptoms was noted except, in few cases, arrhythmia or restlessness due to hypokalemia. These symptoms disappeared by administration of small doses of K-aspartate or KCl solution into priming fluid or after perfusion. The levels of sodium and potassium returned within normal limits on the first postoperative day. Hypochloremia persisted even on the 7th postoperative day (Fig. 2). In a few cases, hyperkalemia was noticed at the end of the perfusion, and the value of potassium concentration was independent to the blood urea nitrogen after operation.

Blood urea nitrogen (BUN): Change of the BUN value is presented in Fig. 3. The average preoperative value was 15.3 mg per 100ml. It increased on the first (average, 20.9 mg per 100 ml), and second (average, 32.9 mg per 100 ml) postoperative days, and returned to normal by the 7th postoperativeday. The highest value noted was 106.4 mg per 100 ml on the second postoperative day in a case with tetralogy of Fallot. BUN was elevated in cases of prolonged perfusion.

Urinary excretion of electrolytes: The total excretion of electrolytes is shown in Fig. 4. The average daily excretion of sodium was 3.4 mEq per kg

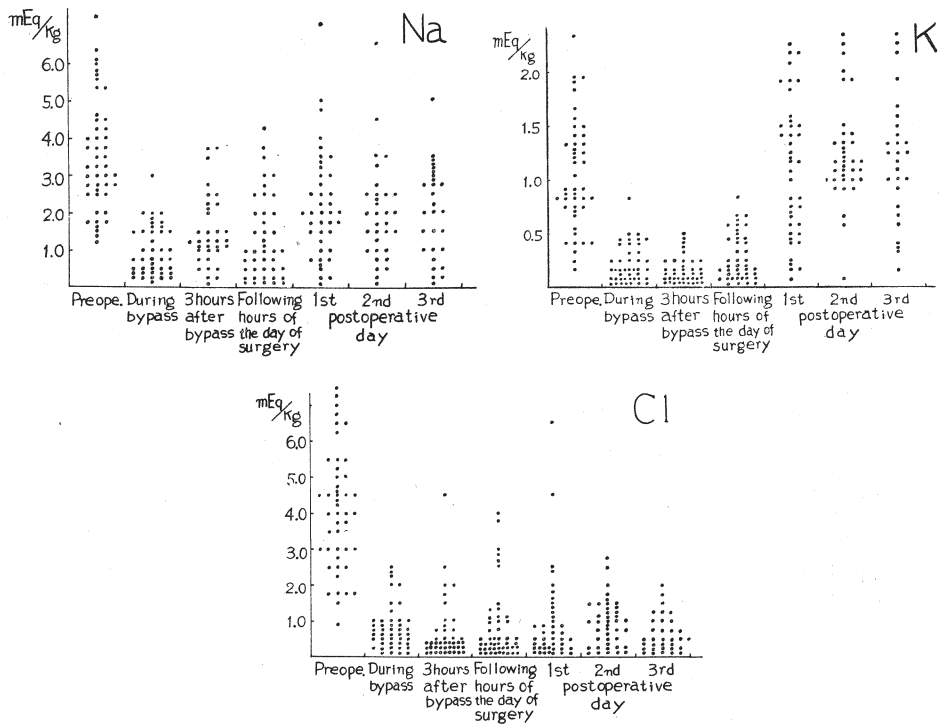

FIG. 4. Urinary excretion of electrolytes. Sodium excretion decreased, and potassium excretion increased after operation. Chloride excretion decreased markedly after operation.

preoperatively. It slightly decreased on the day of surgery (average, 3.16 mEq per kg per day), and moderately on the first and second postoperative days (average, 2.01 and 1.83 mEq per kg per day, respectively). The average excretion of potassium was 1.05 mEq per kg on the preoperative day, 0.84 mEq per kg on the day of surgery, 1.09 and 1.17 mEq per kg on the first and second postoperative days. The excretion of chloride considerably decreased on the postoperative day.

Urinary excretion of urea: The average preoperative excretion of urea in urea was 190 mg per kg per day. It decreased on the day of surgery (average, 97.6 mg per kg) and on the first postoperative day (average, 166.5 mg per kg), and increased on the second postoperative day (average, 275.1 mg per kg). The concentration of urea in the urine decreased on the day of surgery as well, and increased on the first postoperative day. These are shown in Fig. 5.

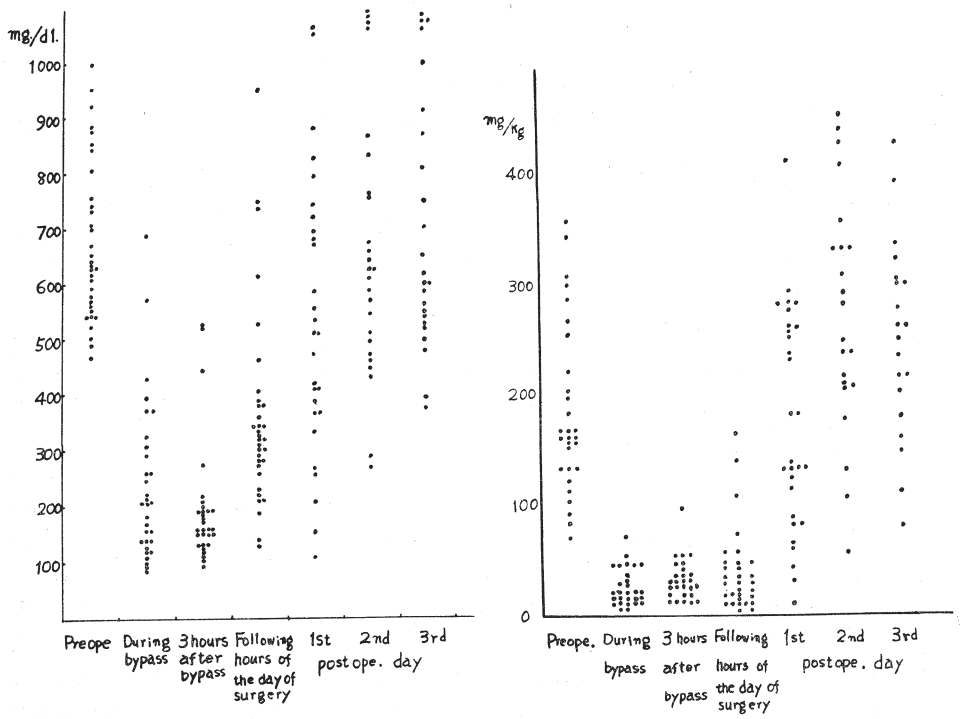

FIG. 5. Urea excretion. Urea excretion decreased postoperatively, and increased gradually.

Hematocrit: A fall of the hematocrit value was seen as the result of hemodilution. The value during total perfusion varied from 81 to 49 per cent (average, 64.9) of the preperfusion value, and returned to the normal or slightly increased value soon after the operation (Fig. 6).

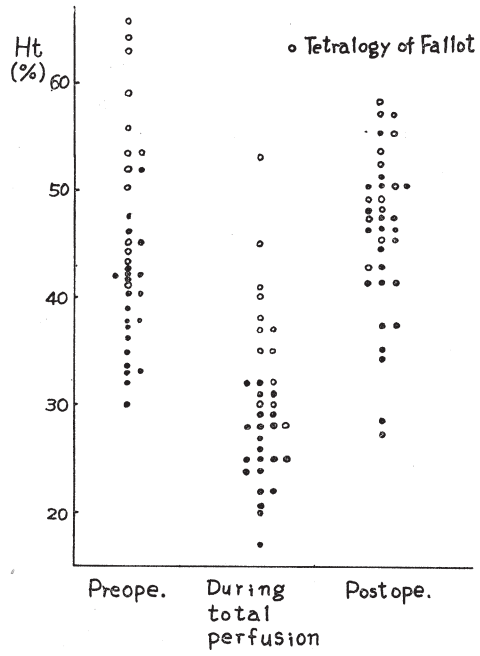

FIG. 6. Hematocrit. The hematocrit value dropped during bypass due to hemodilution and returned to normal limits.

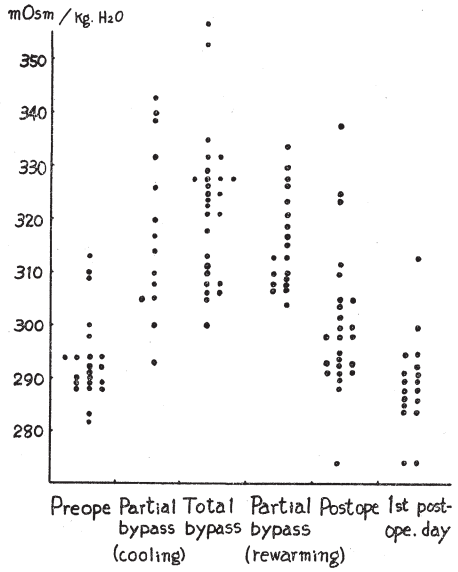

FIG. 7. Osmolality of plasma. High osmolality level was observed during bypass, but returned to normal after bypass.

Plasma osmolality: The average preoperative plasma osmolality was 293 mOsm/kg H_2O. In the early cases from No. 1 to No. 15, the high osmolality of the priming fluid was noted, which was caused by mixing mannitol into the priming fluid prior to the perfusion. In other cases from No. 16 to No. 50, osmolality of the priming fluid decreased (average, 351 mOsm/kg H_2O), as mannitol was administered by drip method into the disc-oxygenator. Osmolality of the plasma during total perfusion varied from 357 to 300 (average, 322) mOsm/kg H_2O, and from 338 to 274 (average, 298) mOsm/kg H_2O postoperatively. On the first postoperative day, it returned to the preoperative value (Fig. 7).

Osmolality of the urine: Urinary osmolality is summarized in Fig. 8. It was over 500 mOsm/kg H_2O on preoperative days, and decreased due to diuresis during perfusion (average, 469) and also 3 hours after perfusion (average, 443). The osmolality of the urine collected in the following hours of the operation until the midnight of the day of surgery increased (average, 530). On the first and second postoperative days, the value fluctuated due to the use of diuretics. The low osmolality with oliguria or anuria was noted in those who did not survive.

Specific gravity of the urine: The specific gravity of the collected urine during perfusion and 3 hours after perfusion was not low in spite of the low

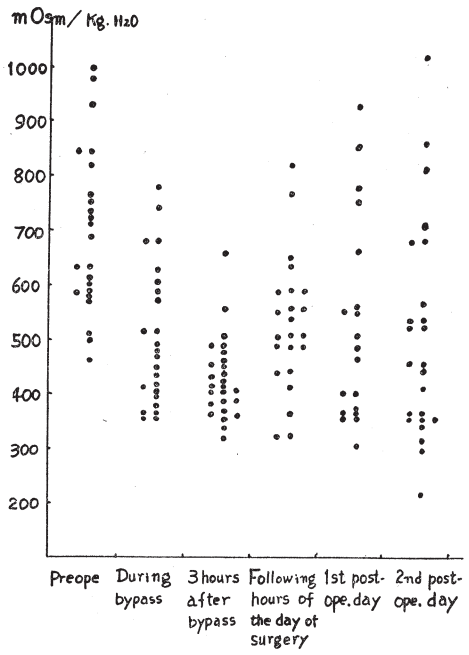

FIG. 8. Osmolality of urine. Osmolality decreased during bypass, and increased after operation.

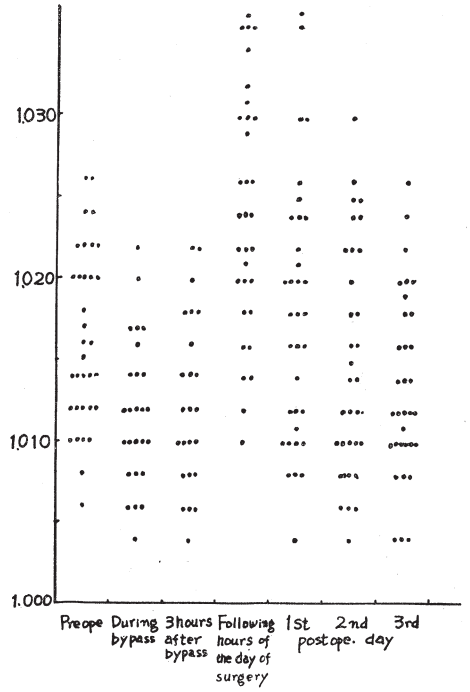

FIG. 9. Specific gravity of urine. Marked decrease was not observed during bypass.

osmolality level. On the postoperative days, the urine specific gravity varied mainly by the use of diuretics. No apparent difference between the survival and the non-survival patients was noted as to the specific gravity of the urine (Fig. 9).

Urinary output: The average urinary output on preoperative days was 1.27 ml per kg per hour. It increased during the perfusion (average, 3.39 ml per kg per hour), as well as 3 hours after perfusion (average, 5.84 ml per kg per hour). The average urinary output of the following hours of the day of surgery, the first, second and the third postoperative days were 1.62 ml, 1.30 ml, 1.65 ml, and 1.62 ml per kg per hour, respectively. In non survival patients, urinary output was reduced markedly. These are shown in Fig. 10.

Renal blood flow: The effective renal blood flow during the total bypass, shown in Table 2, varied from 16.5 to 4.2 (average, 7.7) ml per kg per minute. The average value fell approximately one third of the normal. The renal fraction, percentage of the renal flow on the total flow, varied from 26.3 to 10.8 (average, 15.2) per cent. The effective renal blood flow increased with increase of the perfusion rate.

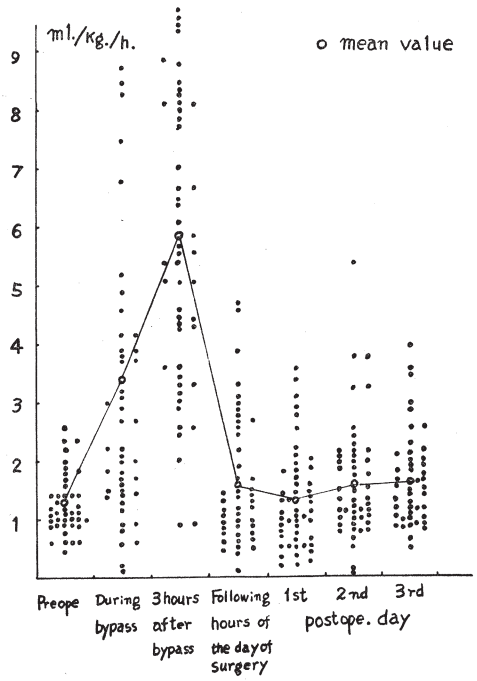

FIG. 10. Urinary output. Urinary output increased during bypass and soon after the bypass.

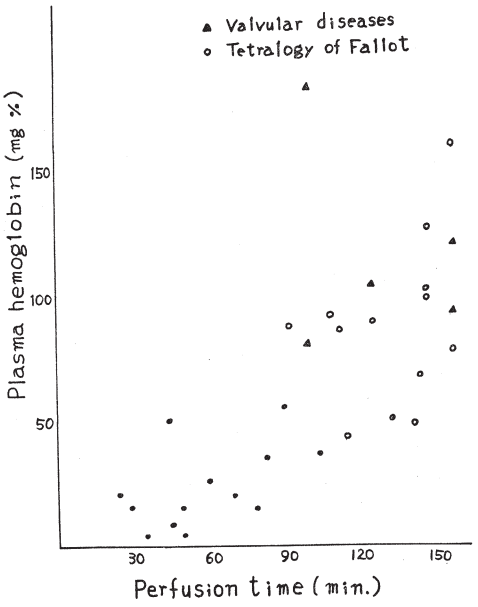

FIG. 11. Plasma hemoglobin. Plasma hemoglobin related to the perfusion time.

TABLE 2. Renal Blood Flow Renal blood flow during total bypass increased together with the perfusion rate.

Case No.	RBF		Flow rate (ml/kg/min)	F. A. Pressure (mmHg)	Renal fraction (%)	Renal vascul. resistence (mmHg/ml/kg/min)
	ml/min	ml/kg/min				
8	162	4.2	39	35	10.8	8.3
12	88	4.6	41	35	11.0	7.6
13	261	7.1	46	60	16.3	8.5
15	286	5.8	40	40	14.3	6.8
17	279	4.7	34	70	13.9	14.8
19	270	6.3	47	70	13.5	11.1
23	580	16.5	60	80	26.3	4.8
28	365	11.7	64	70	18.2	6.0
35	638	11.4	53	120	21.2	10.5
40	225	8.1	44	70	16.9	8.6
41	307	5.2	41	80	12.7	15.4
42	225	11.1	50	—	22.5	—
44	118	6.8	58	—	11.8	—
45	132	7.4	56	50	13.5	6.8
46	307	6.6	52	80	12.7	12.1
47	358	6.8	57	100	11.9	14.7
48	323	6.8	53	80	12.9	11.7
50	293	8.4	60	50	14.6	5.9

Plasma hemoglobin: The plasma hemoglobin concentration at the termination of the perfusion is shown in Fig. 11. The increase of plasma hemoglobin was related to the perfusion time and amount of the bronchial return. A high plasma hemoglobin value was seen in the cases of total correction of tetralogy of Fallot or valve replacement requiring prolonged perfusion. The bronchial return, measured in cases with tetralogy of Fallot, varied from 93 to 654 ml per minute.

Circulating blood volume: The average preoperative values varied from 99 ml per kg of body weight in the cyanotic group, and 76.5 ml per kg in acyanotic group. Circulating blood volume decreased after open-heart operation, especially in cases of the former half in which the blood loss from the operative field was compensated with the exactly equal amount of ACD blood. In cases of the latter half, circulating blood volume slightly increased due to transfusion of blood at the intentional over doses (Table 3).

Extracellular fluid volume (ECF volume): The average ECF volume increased from 19.3 to 23.2 per cent of body weight (kg) after open-heart operation in spite of unhalted diuresis during this period in most patients (Table 4). On

TABLE 3. Circulating Blood Volume Circulating blood volume decreased after bypass in the former half when the blood loss was compensated with an equal amount of blood. In later half, criculating blood volume increased by over doses of blood.

Case No.	Preope			Postope			Change (ml/kg)
	CBV (ml)	ml/kg	CPV (ml)	CBV (ml)	ml/kg	CPV (ml)	
1	5040	105.0	2390	3700	77.2	2072	−82.0
3	3552	74.2	2131	3668	76.6	1981	+ 2.4
4	1078	83.0	636	916	70.5	522	−12.0
5	4815	81.3	2937	3170	53.5	1966	−24.0
6	1510	89.3	877	1340	79.3	673	− 1.0
8	3250	84.0	1983	2717	70.0	1522	− 1.3
9	1758	92.5	1055	1600	84.2	944	− 8.0
10	3424	86.7	1712	4000	101.3	1700	+14.0
13	2716	73.4	1304	2200	59.5	1213	−14.0
15	1861	78.2	1098	1827	76.8	1023	− 1.4
16	3998	81.4	2479	4190	85.3	2472	+ 4.0
17	5415	92.1	3490	4585	78.0	2421	−14.0
19	3898	91.7	2608	3589	84.4	1615	− 7.3
20	4600	128.5	2162	3608	100.8	1840	−27.7
21	1358	100.6	774	1467	108.7	851	+ 8.0
22	3912	83.9	2660	2959	63.5	1873	−18.3
23	3615	102.9	2133	3852	106.7	2080	+ 6.7
24	3257	100.5	1563	2844	87.8	1422	−13.0
25	1921	82.0	1105	2690	114.9	1151	+32.8
26	1505	91.2	1039	1645	99.7	938	+ 7.0
27	2020	118.8	1132	2066	121.5	1013	+ 2.7
29	2390	79.4	1291	3014	100.1	1507	+20.9
30	2442	99.2	1294	2620	106.5	1232	+ 7.2
31	1749	101.6	840	1725	100.2	863	− 1.3
32	3915	72.5	2349	4103	76.0	2174	+ 3.3

TABLE 4. Extracellular Fluid Volume Extracellular fluid volume was elevated after bypass.

Case No.	Preope		Postope		Change Change (%)
	ECF volume (l)	Body weight (%)	ECF volume (l)	Body weight (%)	
5	10.80	18.0	14.40	24.0	+ 6.0
6	3.62	21.2	3.25	19.0	− 2.2
7	2.77	18.5	3.08	22.0	+ 3.5
8	5.90	15.8	8.00	20.0	+ 4.2
10	5.74	15.2	11.80	28.0	+12.8
13	9.87	25.0	10.80	28.0	+ 3.0
15	10.00	20.0	11.71	27.0	+ 7.0
16	6.10	17.4	6.32	18.5	+ 1.1
17	10.90	18.3	12.20	21.0	+ 2.7
19	11.12	28.0	10.93	27.0	− 1.0
20	8.91	24.9	11.10	28.0	+ 3.1
22	8.30	17.0	9.30	20.2	+ 3.2
23	6.50	18.5	8.50	24.0	+ 5.5
24	4.12	13.4	5.80	18.0	+ 4.6

determining the extracellular fluid volume, it was noted that an elevation of extracellular fluid volume was present even on the 7th day after the operation.

Sodium/potassium ratio in the urine: The ratio of sodium to potassium in the collected urine is presented in Fig. 12. It decreased after the operation,

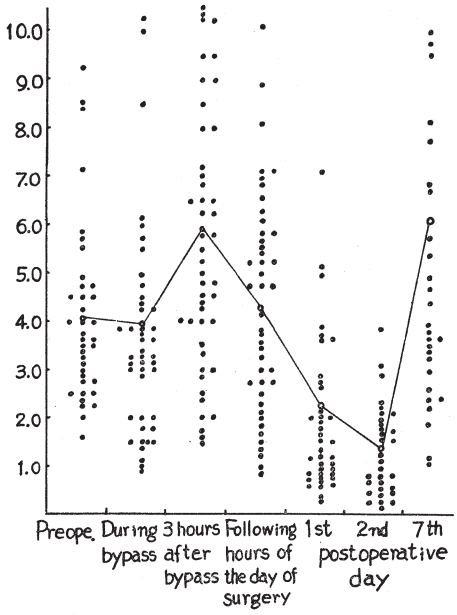

FIG. 12. Sodium/potassium ratio in urine. Sodium/potassium ratio in urine decreased after operation, and returned by the 7th postoperative day.

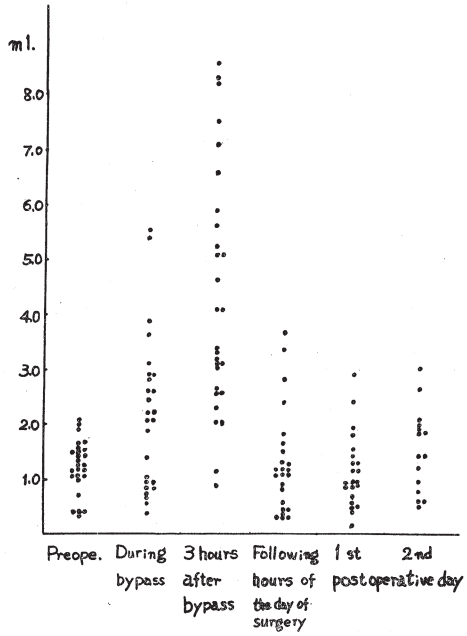

FIG. 13. Renal osmolar clearance (Cosm) Cosm increased during and soon after bypass, and returned to the preoperative value on the first postoperative day.

and returned to the preoperative level by the 7th postoperative day.

Renal osmolar clearance (C_{osm}), renal concentrating operation (T_cH_2O), and urine/plasma osmolality ratio (U: P_{osm}): These are presented as follows.

$$C_{osm} = \frac{U_{osm}}{P_{osm}} V, \qquad T_cH_2O = C_{oms} - V$$

Renal osmolar clearance, renal concentrating operation and urine/plasma osmolality ratio, calculated from osmolality of the urine and blood, are shown in Figs. 13, 14 and 15. The average renal osmolar clearance on the first

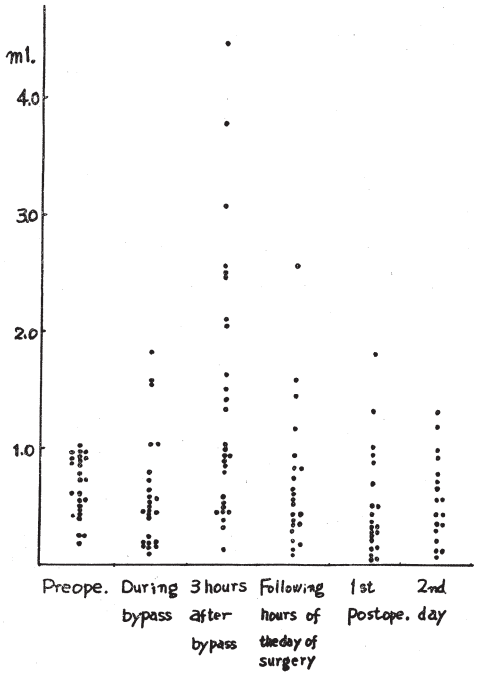

FIG. 14. Renal concentrating ability (T_cH_2O).

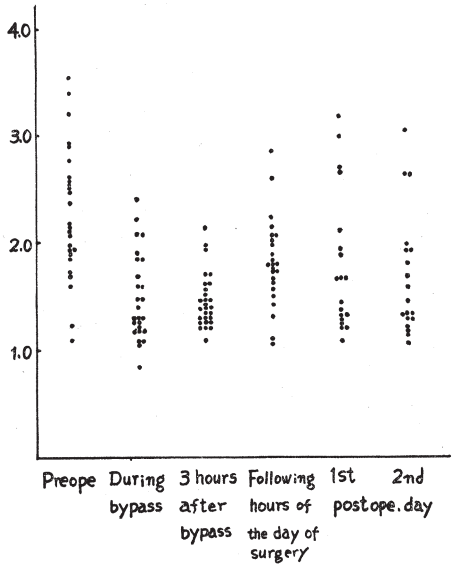

FIG. 15. Urine/plasma osmolality ratio.

postoperative day was 1.38 ml per minute in the survivals, and 0.24 ml per minute in the non-survivors. The average concentrating operation of the kidney was 0.57 ml per minute in the survivings and 0.21 ml per minute in the non-survival patients. The ratio of osmolality of the urine to that of the plasma was 1.90 in the survivings and 1.50 in the non-survival patients, respectively.

Protein and sugar in the urine: Protein and sugar were detected on each sample till the second postoperative day. Average values are presented in Table 5.

TABLE 5. Protein and sugar in urine Protein and sugar in urine were observed till the third postoperative day.

	During bypass	3 hours after bypass	Following hours of ope. day	1 st postope. day	2 nd postope. day	3 rd postope. day
Protein	0.01	0.04	0.04	0.03	0.01	0.01
Sugar	2.12	2.46	1.09	0.23	0.16	0.07

(g/dl)

DISCUSSION

Since the successful application of heart-lung bypass was performed in 1953, numerous clinical and experimental studies have been carried out to eliminate disagreeable complications encountered in prolonged perfusion. The ideal perfusion is that which adequately replaces the function of the heart and lungs, and the hemodynamics, acid-base balance and function of the vital organs gives an important clue in judging the adequacy of the bypass procedure. In clinically applied extracorporeal circulation primed only with heparinized blood, homologous blood syndrome and renal functional impairment were described. Hemodilution technique with plasma expander has improved peripheral circulation, red blood cell sludging, and renal function.

Oxygen consumption decreases with lowering the body temperature. Making use of this phenomenon, hypothermic low flow perfusion was originated by Zuhdi *et al.*[7][8]. However, it has been said that the greater flow rate than the calculated rate is desirable to maintain adequate hemodynamics and proper organic function[33]. The apparatus devised in the author's clinic has a low prime design for low flow perfusion with hypothermia using hemodilution. In prolonged perfusion, the flow rate of 50 to 60 ml per kg per minute (1.3 to 1.81 per M_2 of body surface per minute) was used. Acid-base balance during and after this perfusion was almost satisfactory as described above[22][24]. Function of organ was studied on renal function.

Change in serum electrolytes and their excretion

The hemodilution perfusion lowered serum electrolyte concentration[9][34]. The importance of potassium in maintaining the normal heart action has been known, and severe arrhythmias are seen in patients with low plasma potassium level, especially when digitalis has been administered. The causes of hypokalemia have been thought to be the result of hemodilution, urinary loss and alkalosis. It is said that potassium is related with serum hydrogen ion concentration, and serum potassium is increased in acidosis, and decreased in alkalosis[36]. Lockey *et al.* demonstrated that a fall of plasma potassium concentration occurred even when potassium had been added to the aqueous part of the priming solution

in an attempt to exclude the dilution factor. According to them, patients who had previously had diuretic therapy seemed to be prone to have hypokalemia after bypass, and the major cause of potassium depletion during the postoperative period is excess diuresis. Miyauchi *et al.*[38] and Sumida[15] described that the choice of an adequate solution for priming was most important for success in prolonged perfusion. The postoperative hypokalemia was prevented by adding small doses of K-aspartate or KCl solution as much as 2.9 to 5.8 mEq into the priming fluid, and postoperative arrhythmias due to hypokalemia may be eliminated by administration of potassium. Selmonosky *et al.*[39] reported that the effect of potassium administration was not due to elevation of the serum level but to its action through a triggered mechanism in the metabolic pathways of the conduction system.

Many investigators confirmed that excretion of electrolytes was less during bypass. Excretion of potassium is said to be increased postoperatively, and that of sodium decreased. Sodium/potassium ratio in the urine is smaller on the immediate postoperative day. This is said to be caused by the responce of the abnormal secretion of aldosteron and other hormons. In the author's cases, the total sodium excretion on the day of surgery was as high as on preoperative days, and this was speculated as due to the expansion of extracellular fluid volume, as described by Gann *et al.*[40], and also to osmolar diuresis due to glucose[41]. When renal function was impaired postoperatively, total excretion of electrolytes was much more decreased in this group. A decrease of sodium excretion and an increase of extracellular fluid volume observed after open-heart surgery is worthy of special attention in the postoperative fluid therapy.

Osmolality

Constant osmolality of the serum is regulated by the neurohypophyseal renal system. When the relative volume of water to the solutes is decreased, thirst is felt and antidiuretic hormon secretion is increased due to the reaction of the osmoreceptor in the hypothalamus. On the contrary, when water to the solutes is increased, excess of water is excreted due to decreased antidiuretic hormon. In hemodilution perfusion, osmolality of the priming solution should be considered as well as content of the blood substitutes. By adding low molecular weight dextran, sodium bicarbonate, and K-aspartate into 5 per cent dextrose in water, the osmolality of perfusate was adjusted approximately to 350 mOsm /kg H_2O. At first, electrolyte solution (Solita-T_3)* was used as the basic hemodiluent, and mannitol solution was mixed into the perfusate, causing a high osmolality (580 mOsm/kg H_2O). Attention was pointed to osmolality, not to conduce antidiuretic hormon secretion. As the osmolality of mannitol

* Commercially available electrolyte solution.

is very high, mannitol should be administered as dripping into the extracorporeal circuit.

The estimation of the urinary specific gravity has been a useful means and widely accepted as a parameter of renal concentration and dilution. There is a high degree of correlation between the specific gravity of the urine and urinary osmolality in a normal adult, as Schoen *et al.*[42] described. However, the specific gravity gives no information about the number of molecules in solution. Osmolality represents the total number of molecules in a solution regardless of the molecular weight. Frank *et al.*[43] and Miles *et al.*[44] indicated that a more accurate estimation of the renal mechanisms could be made on the basis of urinary osmolality than by determination of the specific gravity. Grismer *et al.*[45] described that fixation of the osmolality to a low level, ranging 350 to 400 mOsm/kg H_2O, presaged acute renal failure. It has been shown that glucose and protein raise the specific gravity more than they increase osmolality[47].

In author's experience, glucose and protein were observed in each sample for 2 days following extracorporeal circulation. Osmolality varied from 320 to 830 mOsm/kg H_2O after the operation, but the specific gravity showed no notable alteration. Oliguria was observed in few cases on the postoperative day. In these cases, low osmolality was seen, but the specific gravity of the excreted urine was greater than 1,016. Within the range between 1,005 and 1.020, the specific gravity may be misleding as an indication of urinary total solute concentration. With a currently available equipment osmometer, osmolality of the urine, as well as other body fluid, can be easily and accurately determined. To pick up early signs of renal functional impairment, urinary osmolality should be measured to find the impairment of the renal concentrating ability after the operation.

Hemolysis

Hemolysis is unavoidable when the artificial heart and lung system is used. As excessive hemoglobinemia aggravates acute renal failure following extracorporeal circulation, it is worthy of taking special precaution to minimize hemolysis. Usually free plasma hemoglobin is disposed by the reticuloendothelial system, however, the excess of hemoglobin over 135 mg per 100 ml or more is excreted from the kidney[48]. The origin of free plasma hemoglobin during bypass has been thought to be from mechanical factors such as perfusion pumps, oxygenators, and cardiotomy suckers. Five per cent dextrose in water, and the use of ethylen oxide sterilization have been said to accerelate hemolysis. The use of mannitol and hemodilution technique contributed to minimize hemolysis. Porter *et al.*[49] reported some unknown mechanism of mannitol which reduces, besides renal excretion, the build-up rate of plasma hemoglobin.

In Yeh's statistical analysis[50] on 170 clinical cases, hemolysis below 50 mg

per 100 ml resulted in no renal involvement; less than 100 mg per 100 ml, 5 per cent; between 100 to 200 mg per 100 ml, 13 per cent; and when it was over 200 mg per 100 ml, 50 per cent developed renal complication. Taguchi *et al.*[51] reported on the correlation between renal complication and hemolysis, and stated that 125 mg per 100 ml or more of plasma hemoglobin is an important cause of renal damage. The most abominable cause of hemolysis is a cardiotomy sucker. The higher the perfusion rate, the more there is cardiotomy return.

In author's experience, hemolysis of under 50 mg per 100 ml was seen in perfusion within 90 minutes, 100 mg per 100 ml or more, in perfusion over 90 minutes especially in cases of total correction of tetralogy of Fallot or valve replacement, in which bronchial or coronary return blood was abundant. The low flow rate perfusion and anoxic arrest by clamping the aorta minimized coronary or bronchial return, thus minimizing hemolysis. From the above evidences, combination of extracorporeal circulation with hypothermia is considered to be advantageous.

Urinary output

Urinary output is primarily influenced by renal function. Cooley *et al.*[14], Zuhdi *et al.*[8], and Lillehei *et al.*[9] showed an adequate urinary output when 5 per cent dextrose in water was used as a diluent. Mannitol and low molecular weight dextran have an advantagous effect on renal fuction when used in extracorporeal circulation. Camishion *et al.*[52] demonstrated that mannitol had a specific effect in lowering renal vascular resistance. According to Lilien *et al.*[53], the mechanism of mannitol diuresis is an osmotic diuresis due to the lowered renal vascular resistance and the increased renal blood flow especially that of medullary circulation. Experimental pathologic studies have shown that the canine kidneys subjected to extracorporeal circulation with a low urine flow have tubular hydropic changes, together with the separation of the tubular cell from the basement membrane, a loss of the nuclear structure, and accumulations of tubular casts. These pathologic changes of the tubule can be prevented experimentally when high urine flow rates are produced by osmotic diuresis. A high urine flow protects renal tubular integrity during and after bypass[41].

In the author's cases, urinary output was good, and the solution used as a diluent was almost excreted during 3 hours after perfusion. Hemoglobinuria was seen only in a few cases. In the group with the flow rate of 31 to 46 ml per kg per minute (No. 1 to 17), urinary output during bypass was 1.79 ml per kg per hour, and in the other group with the flow rate of 37 to 68 ml per kg per minute (No. 18 to 50), urinary output was 3.58 ml per kg per hour during bypass. A low renal vascular resistance and a high perfusion rate increased renal blood flow and resulted in good urinary output.

Blood urea nitrogen and urea excretion

Blood urea nitrogen (BUN) is influenced by the rates of urea excretion and

production. Measurement of the BUN level is one of the convenient and easily carried out methods to confirm renal insufficiency. The impaired renal function is usually confirmed if oliguria with rising BUN and serum potassium is present. These are often observed as the result of dehydration and the negative nitrogen balance after major operation. Yeh *et al.*[50] classified their clinical cases into following four patterns by their renal function.

Group I, no renal damage; BUN below 30 mg per 100 ml, serum K within normal limit, and urinary output above 600 ml daily for adults.

Group II, borderline damage; BUN 31 to 60 mg per 100 ml, serum K and urinary output being the same as the Group I.

Group III, moderate renal damage (renal tubular acidosis); BUN 60 to 130 mg per 100 ml, urinary output normal, and serum K within normal value or transient elevation.

Group IV, severe renal damage (renal tubular necrosis); BUN 130 to 300 mg per 100 ml, serum K above 6 mEq, and urinary output below below 400 ml daily.

In author's experience, BUN was elevated for 2 days after the operation, and returned to the normal value by the 7th postoperative day. Urinary output and serum K were within normal limits except in a few cases. It is said that the BUN level is lowered and urinary output is increased by the use of mannitol in acute renal failure[54]. Mannitol, however, is not used in the author's cases except a few, since a good amount of urinary output was obtained postoperatively.

The effect of urea on concentrating ability of the kidney has been investigated by many investigators. It has been said that the concentrating ability is lowered by low protein diet, and is recovered by adding urea. In regard to the mechanism of urea transport, Schmidt-Nielsen considered that urea was actively transported in the Henle's loop, but Gottchalk described that urea transport should not be considered to be active[55]. Nagatsu[56] reported that excretion of urea resulted from diffusion, and no correlation was found between the urea content and renal function. However, the urea in the urine has been implicated as a sensitive index of the tubular cell function. The degree of concentration of urea may indicate the extent of the renal damage[47]. Grismer *et al.*[46] demonstrated that the low urine osmolality and the low concentration of urea were evident during the postbypass period in the patients who did not survived espite of adequate urinary output, and that renal function could rapidly be evaluated by osmolality and urea concentration.

In author's experience, there was a lowering in urea concentration and excretion during and after bypass, gradually returning to the preoperative value on the first postoperative day. The existence of a correlation between the urea concentration and the renal function was not clearly proved during the postoperative period.

Extracellular fluid volume

The fnnctional extracellular fluid volume is influenced by many factors. After a major operation, it is said that urinary output is decreased, sodium is retained, and excessive amount of potassium is excreted by antidiuretic hormon and aldosterone. On the patients in this study, these phenomena could be speculated to take place. Elevation of extracellular fluid volume was considered the reflection of sodium retention. Employing the hemodilution technique, Beall *et al.*[58] demonstrated that extracellular fluid volume following open-heart operation increased for seven to ten days after operation, and this was attributed to antidiuretic hormon and aldosterone and also to the mild temporary depression of the myocardial function. Massive administration of fluid after surgery may cause the risks of pulmonary edema, cardiac insufficiency and water intoxication. Sturz *et al.*[59] claimed that the administration of sodium after cardiac surgery was not indicated so that the water retention will be avoided, but Tsuchida[60] reported that sodium of 40 to 50 mEq per M_2 of body surface per day was the optimal dose to maintain sodium balance after open-heart surgery. The increase of extracellular fluid volume causes insidious edema. Therefore, restriction of the intravenous administration of fluid, especially of sodium, should be imposed until the patient recovers from a transient depression of cardiopulmonary function after open-heart surgery.

Circulating blood volume

In order to determine the blood distribution, isotopes (^{51}Cr, ^{32}P and ^{131}I) have been utilized. RISA (^{131}I) is the tracer of choice because it stays in the vascular system. Many investigators proved an intravascular pooling during extracorporeal circulation. Ankeney *et al.*[61] also mentioned the splanchnic pooling. Litwak *et al.*[62] reported the increased body weight and also a retention of blood in the hepatic and mesenteric vascular systems after open-heart surgery. Hayashi *et al.*[63] demonstrated that the splanchnic pooling occured least when low molecular weight dextran was used as a diluent. Hemodilution technique improves peripheral circulation and prevents blood pooling.

Study of circulating blood volume in open-heart surgery using this apparatus has already been reported[22]. In author's experience, a decrease in circulating blood volume was observed as well. The blood of slightly excess in volume should be transfused after surgery to have smoother postoperative course.

Renal blood flow

Renal hemodynamics in extracorporeal circulation using the heart-lung machine devised in the author's clinic was measured. Acute renal failure has been one of the fatal complications resulting from prolonged perfusion. The prevention of this renal failure still remains to be solved in spite of numerous studies. Two categories have been recognized as to the cause of acute renal failure following a major surgery[64].

1) Renal ischemia; hypotension, decreased circulating blood volume and severe dehydration.

2) Nephrotoxic agents; hemoglobin, myoglobin, mismatched blood transfusion, heavy metals, sulfonamid, and other chemical substances. Combinations of these may easily produce acute tubular necrosis. Surgical stress results in renal vasoconstriction for which serotonin may be responsible[65]. In extracorporeal circulation as well as in other major surgery, the diminution of renal blood flow as a sequel to the renal vasoconstriction may result. Ablaza[66] and Long *et al.*[11] reported a sufficiently well maintained renal function by using low molecular weight dextran. Beall *et al.*[67], in regard to the renal hemodynamics, compared the effect of 5 per cent dextrose in water with that of the fresh heparinized blood, and found that 5 per cent dextrose to be more adequate in maintaining renal function. During bypass, as many investigators indicated, mean blood pressure fell in all cases. Onodera[68] noticed certain relationships between the perfusion rate and mean blood pressure.

In the author's cases, the high femoral blood pressure was maintained more easily at the flow rate of 50 to 60 ml per kg per min than at 30 to 40 ml per kg per min.

In circulatory deterioration, the kidney is the organ to be affected by functional inpairment first. It has been observed that the renal function is arrested when the arterial pressure drops below the critical level. However, perfusion at the low flow rate of 7 ml per kg per min with the arterialized blood is sufficient to maintain adequate urinary excretion, supporting an animal's life without an evidence of renal damage[69]. Senning *et al.*[32], Beall *et al.*[70] and Halley *et al.*[71] demonstrated a diminution of renal blood flow during low flow rate perfusion, and Beall stated that total flow perfusion of 35 ml per kg per min was sufficient to prevent the development of ischemic damage with only a transient depression of the renal function. Connolly *et al.*[72] stated that acidosis resulting from poor tissue perfusion diminished renal blood flow despite of the normal or elevated mean arterial pressure, and correction of acidosis with the administration of Tris (hydroxymethyl) aminomethane (THAM) or treatment of the inadequate ventilation prevented renal shutdown. Halley described that the responce to perfusion was found to be different on each organ according to individual vascular resistance; cerebral blood flow was essentially dependent on the systemic blood pressure, but renal blood flow was not correlated with the systemic blood pressure because of the greater role played by the vascular resistance. When primed with the homologous blood, the renal vascular resistance increased probably from a reflection of capillary sludging and aggregation of the erythrocytes. Elimination of homologous blood priming and use of low molecular weight dextran or mannitol contributed in lowering to the renal vascular resistance, and thus increasing renal blood flow. Mannitol has widely been utilized to improve the renal hemodynamics. Tontz

et al.[73] found a linear relationship between the rate of total body perfusion on the one hand and the arterial pressure as well as renal blood flow on the other. Onodera also described that renal blood flow correlated lineally with the perfusion rate.

In the author's cases, decreased renal blood flow (average, 7.7 ml per kg per min) was observed in moderate hypothermia during total bypass. However, urinary output was excellent during and following bypass. No significant renal functional impairment was observed when the cardiac function was restored after a satisfactory intracardiac correction and with no postoperative hypotension.

Renal osmolar clearance and the concentrating ability of the kidney

The combined effect of adrenalin, antidiuretic hormon and aldosterone which are consequent on surgical stress is the commonly seen postoperative oliguria. This physiologic oliguria has several characteristics such as reduced urinary output, increased total urea and potassium content, decreased sodium content, and the higher specific gravity and osmolality. The free water clearance shows a negative figure, thus concentrating operation of the kidney becoming a positive figure.

In the pathologic oliguria of renal insufficiency, urinary volume can be similar to that of the physiologic oliguria. However, total solutes excretion decreases and osmolality falls. The specific gravity will be within the range of 1,010 to 1,020 in spite of low solute excretion, as described above. The most important aspect of the renal function is water and solute excretion. In the postpoerative period, analysis of the urine contributes in evaluating the cardio-renal status. The differentiation between the physiologic and the pathologic oliguria is important in indicating the proper treatment.

It has been said that C_{osm} below 0.3 ml per min is indicative of the renal shock, and T_cH_2O of less than 0.2 ml per min during the period of the maximum antidiuretic activity is considered an evidence of impaired tubular function, and the U/P osmotic ratio is considered abnormally low if it falls below 1.5 during this same period.

After the excess of water is flushed out during the postbypass period, the determination of osmolality of the urine and the serum, as well as the measurement of urinary output, are useful in evaluating the renal function. From calculation of C_{osm} and T_cH_2O, differentiation of oliguria can be easily made.

In the author's cases, only one patient had the pathologic oliguria after operation. The renal shutdown seems to be due more frequently to the postoperative hypotension originating from cardiac insufficiency rather than the bypass procedure itself.

SUMMARY AND CONCLUSION

Hypothermic perfusion with the hemodilution technique was performed in

50 cardiac patients, and following results were obtained.

1) After bypass, the concentrations of the principle serum electrolytes were slightly decreased as a result of hemodilution, but returned to the normal values on the first postoperative day. Postoperative arrhythmias due to hypokalemia were prevented or treated by a small dose of potassium.

2) Decreased urinary excretion of sodium and expansion of extracellular fluid volume were observed after bypass.

3) Measurement of osmolality of the urine was the more convenient and reliable method in evaluating the renal function than the measurement of the urinary specific gravity.

4) The average effective renal blood flow during total bypass was 7.7 ml per kg of body weight per minute and the average renal fraction was 15.2 per cent of the total flow. Renal blood flow increased together with the perfusion rate.

5) Blood urea nitrogen remained within 100 mg per 100 ml.

6) Circulating blood volume decreased after the bypass procedure even with transfusion of the equal amount of blood as lost in surgery.

7) Urinary output was excellent during and after perfusion. It increased with the increase of the perfusion rate.

8) To confirm the renal function, C_{osm} and T_cH_2O, calculated from osmolality and urinary output, were useful.

It was concluded that the hypothermic perfusion with the hemodilution technique to be an advantageous one in performing cardiac surgery. To maintain the adequate hemodynamics and vital signs in a prolonged perfusion, the flow rate of 50 to 60 ml per kg of body weight per minute (1.5 l per M_2 of body surface per minute) may be preferrable even when moderate hypothermia is used.

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