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Experimental Studies on Continuous or Intermittent Selective Brain Cooling by Means of Carotico-carotid Shunt in Dogs

—Especially on the Application of Polarographic Measurement for the Prevention of Cerebral Anoxia—

by

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INTRODUCTION

Satisfactory control of hemorrhage during intracranial operations has always been problematical in neurosurgery. Several devices, especially the techniques of hypothermia, have been developed for this pourpose. The means of hypothermia may be classified into two major groups : one is general hypothermia, and the other is so-called selective or differential cooling of the brain. Among these methods, general surface cooling is the most simple and practical technique. It has, however, inherent limitations in terms of safe period of time within 10 to 15 minutes with only mild hypothermia above 28 degrees C. The techniques of the profound general hypothermia combined with extracorporeal circulation have also considerable disadvantages in using a large capacity of extracorporeal circuit and excessively troublesome surgical procedures involving thoracotomy, cardiac cannulations, cardiac standstill and resuscitation, etc [1)2)4)10-13)18)19)21)43)46)62)68-70)72)79)81)88)95)96)101)102)108)109)111)114)115)118)119)120)122)123)124)126)130)134)137)138)158)159)168)].

Therefore, the selective brain cooling by means of arterio-arterial shunt is considered to be applicable for an adequate method of hypothermia[97)98)]. This method was first adopted in cardiac surgery by PARKINS et al.[125)] (1954) and by KIMOTO et al.[93)] (1955) and was thereafter introduced into neurosurgery by LOUGHEED and KAHN[105)106)] (1955) and modified by HAYASHI[71)] (1959). However, the conventional techniques of this method have the following problems for clinical use : (1) the tendency to ventricular fibrillation due to infinite inflow of the cooled blood into the heart during hypothermic cerebral perfusion, (2) the posthypothermic hemorrhagic tendency within the cooled brain, and (3) posthypothermic cerebral damage. These problems not only involve technical factors but also pathophysiological factors of hypothermic ischemia within the brain. They may, however, be eliminated if the well-balanced circumstances are obtained in cerebral microcirculation throughout the entire period of selective brain cooling.

In the present study, therefore, the effect of the systemic hemodilution combined with intermittent or continuous cerebral perfusion on the cerebral microcirculation was investigated by polarographical technique to obtain an ideal technique of selective brain cooling by means of carotico-carotid shunt.

METHODS AND METERIALS

1) POLAROGRAPHICAL MEASUREMENT OF OXXGEN AVAILABILITY

Oxygen availability was measured by means of electropolarography using a CLARK oxygen electrode (YELLOW SPRINGS) and recorded with a SHIMADZU Oxygraph OX-Ⅱ and a YANAGIMOTO Polarograph Recorder AP-20 PR-2. Saturated KCl solution was used for the supporting electrolyte of the electrode. A polyethylene or teflon membrane below 0.01 mm in its thickness and an electrode-cuvette were employed (Fig. 1).

Oxygen waves were obtained with 100 per cent oxygen, air, and physiological saline solution which was saturated with oxygen at 20 degrees C, by either continuous or alternate polarization. The cathode of electrode was kept in action at -0.6 volts in continuous polarization and at -0.6 and $+0.7$ volts at 4 c.p.m. in alternate polarization. Fifty per cent-response was permitted within 15 seconds, and allowable errors were restricted within 2 % as for stability and reproducibility in the course for 360 minutes. Temperature effects on the diffusion current of oxygen were determined in the medium whose oxygen concentration was known or kept constant. Fluid was saturated with oxygen at 40 degrees C and perfused into the cuvette and cooled gradually via cuvette-heat exchanger down to 5 degrees C, or warmed up to 40 degrees C after equilibrated to air at 5 degrees C. The rate of cooling or warming was controlled below 1.0 degree C per minute, and perfusion was regulated at the steady rate of flow ranging from 1.0 to 20.0 ml per minute. The temperature coefficient of diffusion current of oxygen was measured in every electrode. Polarographical zero level of oxygen was given by tank nitrogen usually containing 0.7 % of oxygen. Absolute values of oxygen tension in mmHg were given by calibrating the electrode with oxygen, tank nitrogen and air at the steady temperature. Relative values of oxygen availability were necessarily given by diffusion currents of oxygen in microamperes or per cent variations to a standard original value.

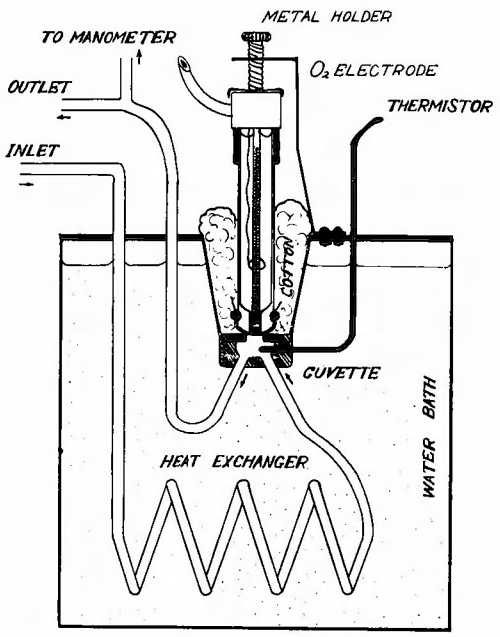

Fig. 1. Schematic diagram of calibration and measurement cuvette for Clark oxygen electrode. The temperature of the cuvette can be controlled at desired degree.

The oxygen electrode set with a thermistor needle probe was placed on the cortical surface through a small burr hole on the skull. The bared brain surface was

sealed with cotton and liquid paraffine to protect it from air contamination and evironmental temperature variations. The thermistor needle probe was inserted 1 to 3 mm into the brain. The determinations were quantitated as 100 % by the values obtained in the normothermic animal breathing pure oxygen controlled constantly at 27 respirations per minute, and as zero % with the animal deoxygenated by nitrogen inhalation. Temperature coefficient was introduced to the values of oxygen availability.

2) EXPERIMENTAL PROCEDURES IN ANIMALS

Forty-nine mongrel dogs, weighing 5.0 to 17.0 kg and unselected as to age and sex, were used. The animals were anaesthetized intravenously with pentobarbital sodium (nembutal), 30 mg per kilogram of body weight, and intubated. Respirations were controlled at 27 respirations per minute with a automatic respirator of HARVARD type. The left femoral artery was cannulated with a polyethylene catheter and arterial blood pressure was recorded continuously. The femoral vein was also exposed to permit the intravenous administration of drugs or infusion or depletion of the fluid. Serial electrocardiograms and electroencephalograms were also taken. Hematocrit was determined by the technique of WINTROBE or with the capillary method. Relative viscosity was measured with a HESS viscometer (Erma) at various temperatures.

3) PROCEDURE OF ARTERIAL ISOLATION OF THE BRAIN

The common carotid, vertebral, subclavian, brachiocephalic and internal mammary arteries were exposed on both sides by median incision in the anterior cervical region without performing thoracotomy. Arterial isolation of the brain was carried out temporarily by ligating these vessels in a variety of their combinations. Cervical cuff method of KABAT and DENNIS[87] was employed in some experiments by inflating 500 mm Hg pressure to produce more complete block of arterial inflow into the brain, avoiding compression on the trachea, vagus nerves, external jugular veins, and the common carotid artery. In some cases, concomitant lowering of the systemic blood pressure was applied to produce the complete block of arterial inflow to the brain. Venous isolation of fhe brain was not carried out.

4) EXTRACORPOREAL CIRCUIT AND PROCEDURE OF SELECTIVE BRAIN COOLING

The brain was selectively perfused and cooled using a extracorporeal circuit by means of carotico-carotid shunt. The common carotid artery was cannulated on one side with polyethylene catheters which were threaded 15 to 20 mm into the vessels both proximally and distally. The circuit was primed with physiological saline, Ringer solution or Rheomacrodex. Prior to the start of perfusion, 2 mg of heparin per kg of body weight were administered intravenously. Vascular isolation of the brain was performed 3 minutes after the onset of cerebral perfusion. The blood was pumped out of the proximal carotid cannula into the distal common carotid artery by way of extracorporeal circuit which consisted of a pump, a heat exchanger, a bubble trap and two blood-filters (Fig. 2). A Sigmamotor sigma-pump or TATEBE roller pump of DEBAKEY type was used. The total capacity of the extracorporeal circuit was about 250 ml. A simple or double helical coil heat exchanger was immersed in ice water and capable of the efficiency above 6,000 calories per minute in blood cooling. Glass, vinyl or alminium tube of 5 mm in its inside diameter

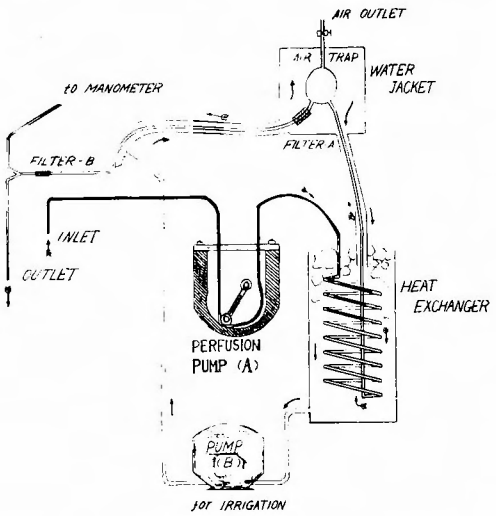

Fig. 2. Schematic diagram of the extracorporeal circuit (Pump-Heat Exchanger Cooling Unit).

was coiled. A glass ball air trap was below 70 ml in its capacity. Glass or polyethylene connectors and vinyl circuit tubes of 5 mm in the inside diameter were put to use. The glass and metal parts of the system were siliconized with DOW CORNING DC-200 Fluid. The circuit system was freed of air trapped during priming and the temperature of the priming fluid was lowered to the required degree by the initial recirculation through the perfusion circuit before carotid cannulation. Perfusion pressure was measured by setting Y-connector near to the distal carotid cannula and recorded continuously with the same method as the blood pressure. Flow rate of perfusion was measured by an air bubble-flowmeter which was set in the circuit. Perfusion was continued until required cerebral hypothermia was induced.

Cerebral ischemia followed cessation of perfusion. Ischemia was relieved by release of the clamped vessels or regulated by successive or intermittent controlled perfusion of the brain.

After experiments, protamine sulfate was given to neutralize the administered heparin on a milligram-to-milligram basis. Throughout these experiments, the brain, esophagus and rectal temperatures were measured with thermistors mounted on 20 gauge needles or enclosed in polyethylene catheters. The thermistor needle probe was inserted 1 to 3 mm into the cerebral tissue through a burr hole on the skull, and the catheter probe was threaded about 20 cm into the esophagus and 15 to 20 cm into the rectum.

5) ACUTE INVESTIGATIONS IN NORMOTHERMIC AND MILD HYPOTHERMIC ANIMALS

1. Cerebral Oxygen Availability in Normothermic Dog :

Anoxic anoxia was produced by inhalation of nitrogen, and ischemic hypoxia of the brain by arterial occlusions to the brain.

2. Cerebral Oxygen Availability in Mild Hypothermic Dog :

Mild hypothermia (in the rectal temperature) 31 to 33 degrees C was generally induced by means of surface cooling. Cerebral arterial occlusions were performed for 30, 60 and 90 minutes, respectively.

6) CONVENTIONAL TECHNIQUE OF SELECTIVE BRAIN COOLING

The brain was cooled down to profound hypothermia between 15 and 23 degrees C with carotico-carotid shunt, and kept for at least 30 minutes (Fig. 3). Selectivity of brain cooling was indicated by temperature gradients between the brain, the esophagus and the rectum.

7) CEREBRAL CIRCULATORY REGULATION IN PROFOUND HYPOTHERMIA WITH HEMODILUTION AND SUSTAINED

HYPOTHERMIC CEREBRAL PERFUSION

1. Preliminary Experiments on Hemodilution

The effects of hemodilution by saline solution on the blood viscosity was measured at 38, 32, 30, 20 and 10 degrees C, and the values measured at the hypothermic conditions were converted into the values at 38 degrees C.

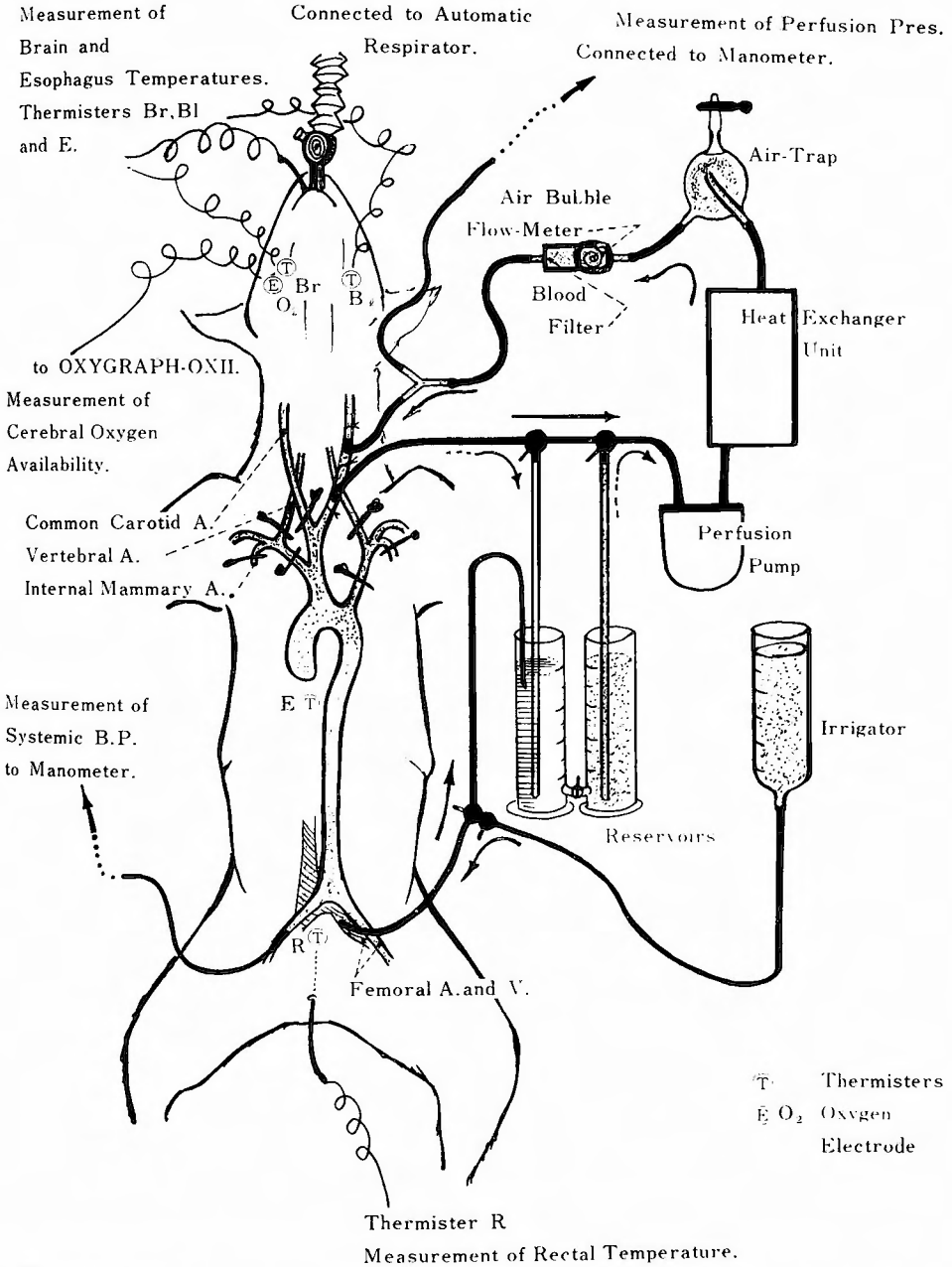

Fig. 3. Schematic representation of the technique of selective brain cooling and surgical interruption of arterial inflow to the brain. The irrigator and reservoirs can be utilized for systemic hemodilution.

2. Preliminary Experiments on Artificial Blood Substitutes

Physiological saline solution, 10 to 40 ml per kg of body weight, was infused into the carotid artery via the extracorporeal circuit and exchanged within 10 minutes for the circulating blood, which was depleted out of the circuit or the femoral vessels.

3. Effective Flow Rate During Hypothermic Cerebral Perfusion

Dogs were cooled intermittently (group-a), or perfused continuously (group-b) by means of selective hypothermic cerebral perfusion with carotico-carotid shunt and carotico-vertebral occlusion.

4. Transplantation of Cooled Isolated Head

The head of a young dog, weighing 5.5 kg, was cooled selectively down to 15 degrees C and amputated at the level between the second and the third thoracic vertebrae including arteria anonyma and vena cava superior and reserved at profound hypothermic temperatures in an ice-box for 200 minutes. The reserved head was transplanted to another adult dog which weighed 10.5 kg. The anonymous artery was anastomosed to the femoral artery and the superior caval vein to the femoral vein respectively. Body temperatures, EEG and ECG were recorded for the period of 12 hours.

8) SELECTIVE COOLING OF THE BRAIN WITH ARTIFICIAL SYSTEMIC HEMODILUTION AND WITH SUSTAINED HYPOTHERMIC CEREBRAL PERFUSION AT EXTREMELY LOW FLOW RATE

Cerebral profound hypothermia was induced selectively at the cooling rate between 0.33 and 1.25 (average : 0.82) degrees C per minute by means of carotico-carotid shunt with cartico-vertebral occlusions. Intentional systemic hemodilution was carried out by priming or infusing into the circuit system with artificial solutions (physiological saline, Ringer solution, Rheomacrodex, 5 % glucose and/or amino acid solutions) during induction of cerebral hypothermia, exchanging the same volume of the circulating blood. Hemodilutions were performed in three serial groups ; a) 15 to 20 ml/kg, b) 25 to 30 ml/kg and c) 35 to 40 ml/kg. After profound hypothermia in the brain was obtained, hypothermic cerebral perfusion was sustained intermittently or continuously at the extremely low flow rate. (Fig. 3).

RESULTS

CONVENTIONAL TECHNIQUE OF SELECTIVE BRAIN COOLING

Selective Brain Cooling & Cerebral Oxygen Availability

1. POLAROGRAPHICAL MEASUREMENT OF OXYGEN AVAILABILITY

1) The typical oxygen waves were obtained with CLARK oxygen electrodes in the physiological saline solutions under different conditions at a steady temperature (Fig. 4). The optimal potentials of polarization of the electrode were found to be around −0.6 volts.

2) The diffusion current of oxygen decreased linearly as the temperature decreased between 40 and 5 degrees C and its zero value of oxygen availability converged constantly between zero and −10 degrees C by extrapolation of the curves (Fig. 5).

2. INVESTIGATIONS IN NORMOTHERMIC AND MILD HYPOTHERMIC ANIMALS

1) Cerebral Oxygen Availabilility in Normothermic Dogs :

(1) Cerebral Oxygen Availability Affected by Inhalation of Gases.

Serial inhalations of pure oxgen, air and nitrous oxide resulted in significant variations in cerebral oxygen availability with the values corresponding to the respective gas. Nitrous oxide gave zero % and air presented approximately 20 % of the standard original value of pure oxygen. These values were followed by transient rebounds and terminated in the original control value when pure oxygen inhalation was imposed upon the animal.

(2) Gerebral Oxygen Availability Affected by Arterial Isolations of the Brain.

Bilateral ligations of common carotid arteries caused only slight decrease in oxygen availability within the brain, the decrease remaining within 5 %, in spite of predominant increase in systemic blood pressure by 25 % on the average. No significant variations in cerebral oxygen availability followed the unilateral occlusion of vertebral artery added to the bilateral occlusion of common carotid arteries. Bilateral carotid and vertebral ligations (bilateral CV occlusion) resulted in significant decrease (13 to 17 %, averaged

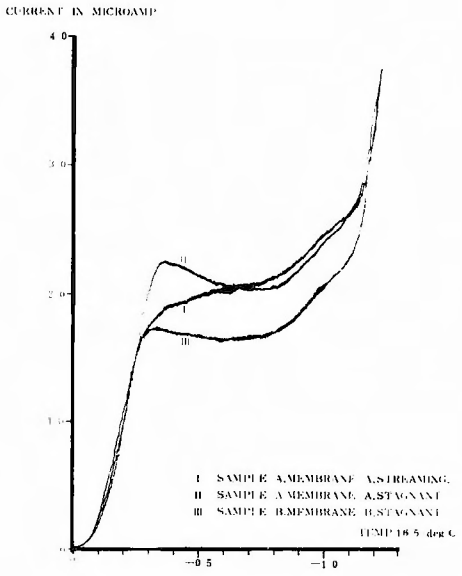

Fig. 4 The Current-Voltage Curves of Oxygen recorded polarographically with the use of Clark Oxygen Electrode in the physiological saline solutions under the various conditions and at the stable temperature of 16.5 degrees C

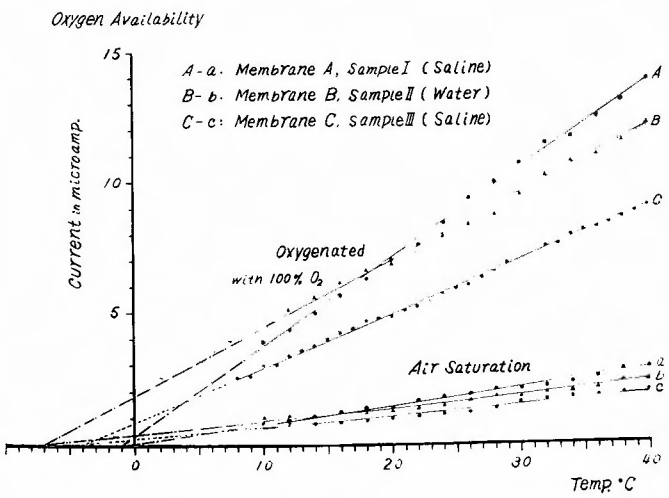

Fig. 5. Temperature effects on the oxygen availability recorded with Clark oxygen electrodes in the physiological saline solution and distilled water. (Temperature Calibration Curves of Oxygen for Clark Oxygen Electrode.)

to 15 %) of cerebral oxygen availability along with significant increase in systemic blood pressure to 135 %. Further predominant decrease in cerebral oxygen availability (33 to 40 %, averaged to 36 %) with significantly marked increase in systemic blood pressure (averaged to 155 %) followed bilateral occlusion of subclavian arteries added to the bilateral carotid and vertebral occlusion (bilateral CVS occlusion). The further decrease in cerebral oxygen availability was frequently observed with sustained predominant hypertension following bilateral occlusion of internal mammary arteries superimposed upon the bilateral CVS occlusion (bilateral CVSM occlusion). Decrease in cerebral oxygen availability averaged 50 %. When systemic blood pressure increased above 50 %, significant compensation in cerebral oxygen availability occurred. The compensation was within 5 % and 10 % when the level of cerebral oxygen availability was maintained about 70 % of the original control value. Sustained significant decrease in cerebral oxygen availability below 70 % to the original standard value over 3 minutes caused a poor recovery in systemic blood pressure and cerebral oxygen availability even after total release of occlusion.

(3) Cerebral Oxygen Availability in Cardiac Standstill.

When cardiac standstill was imposed by pure nitrous oxide, irreversible cerebro-cardiac damages occurred after five to eight minutes' inhalation and cerebral oxygen availability decreased to zero level. When cardiac standstill was induced by acute depletion of the

Table 1 The average variations during the conventional technique of selective brain cooling (22 dogs)

	Brain		Esophagus	Rectum	(Unit)
	(Perf. Side)	(Non-Perf. Side)			
Stage I					
Induced Hypothermia	16.3	19.9	28.9	31.8	(deg. C)
Total Variation	−19.5	−15.5	−6.7	−4.2	(deg. C)
Rate of Cooling (RC_{d15} and RC_{d10})	0.88	0.67	0.29	0.18	(deg. C/min)
Selectivity of Cooling (SI)	100.0	76.1	32.9	20.4	(%)
Stage II					
Sustained Hypothermia	23.0	24.7	30.6	30.8	(deg. C)
Range of Variations					
a. below 23 deg. C	56	50	0	0	
b. below 28 〃	13	15	6	0	
c. not below 28 〃	31	35	94	29	
d. not below 30 〃	—	—	—	71	(% of Cases)
Total Variation	+6.7	+4.8	+1.7	−1.0	(deg. C)
Range of Variations					
A. below 5 deg. C	53	100	100	100	
B. below 10 〃	21	—	—	—	
C. not below 10 〃	26	—	—	—	(% of Cases)
Stage III					
Maximum Variations on Initial Phase of Rewarming	+10.2	+9.4	−2.2	−1.2	(deg. C)

blood out of femoral arteries, immediate decrease in cerebral oxygen availability did not result in zero level, and remained at a lowered value. When cardiac standstill was induced by intravenous administration of nembutal, the pattern of variations in cerebral oxygen availability was equal to that in depletion, remaining somewhat higher.

2) Cerebral Oxygen Availability in Mild Hypothermic Dogs :

(1) Pure Oxygen inhalation

(a) No side effects occurred in cases in which cerebral oxygen availability remained at the level between 50 and 60 % to the original standard value for the period of 30 minutes by arterial occlusion to the brain.

(b) When cerebral oxygen availability was lowered to 40 to 60 % and systemic hypotension continued for 60 minutes by arterial occlusion, dogs died within 24 hours without regaining consciousness.

(2) Air Inhalation

When cerebral oxygen availability was above 70 % to the original standard value during the course of arterial occlusion for 90 minutes, long term survival was obtained without any neurological abnormalities.

These results demonstrate that the comatose condition follows principally the disturbance of cerebral microcirculation which is sustained below the critical values for the certain period of time, and that this condition is indicated by cerebral oxygen availability of polarographic measurements.

3. SELECTIVE BRAIN COOLING

The typical course of hypothermic phenomena in an animal during selective brain cooling is illustrated in Fig. 6. The brain was cooled preferentially down to 14.5 degrees C on the perfused side with only minor degrees of reduction in temperatures in the esophagus and the rectum, which remained at 29.3 and 32.0 degrees C respectively, at the end of hypothermic cerebral perfusion. The highest rate of brain cooling was brought about in the initial 3 minutes and the temperature difference between both hemispheres of the brain was only 3.9 degrees C on average of 22 cases on the cessation of perfusion. Systemic blood pressure showed an acute decrease along with the brain cooling during the period of perfusion. On the cessation of hypothermic cerebral perfusion, an increase in the brain temperature on the perfused side and an immediate significant increase in the esophageal temperature occurred, while a slight decrease in the brain temperature on the contralateral side and a very gradual successive reduction in the rectal temperature were noted. These variations in temperatures indicate that thermal equilibrium occurs separately in the isolated brain and the territories of the systemic circulation during the period of 30 minutes of cerebral ischemia. When the brain was recirculated by releasing cerebral arterial occlusions, an acute increase in the brain temperatures by above 8 degrees C was noted on the initial phase within 10 minutes of cerebral recirculation, while the esophageal and rectal temperatures decreased. The systemic blood pressure remained lowered throughout the period of cerebral hypothermic ischemia, and increased again significantly along with cerebral recirculation and rewarming.

Thus, the course of selective brain cooling is divided into four stages :

Stage I. *The stage of induction of cerebral hypothermia.* This is the period from

the onset of hypothermic perfusion to five minutes after the cessation of perfusion where the lowered brain temperature below 23 degrees C is obtained.

Stage Ⅱ. *The stage of maintenace of cerebral hypothermia with cerebral ischemia.* This is the period from the termination of Stage Ⅰ to the beginning of cerebral recircula-

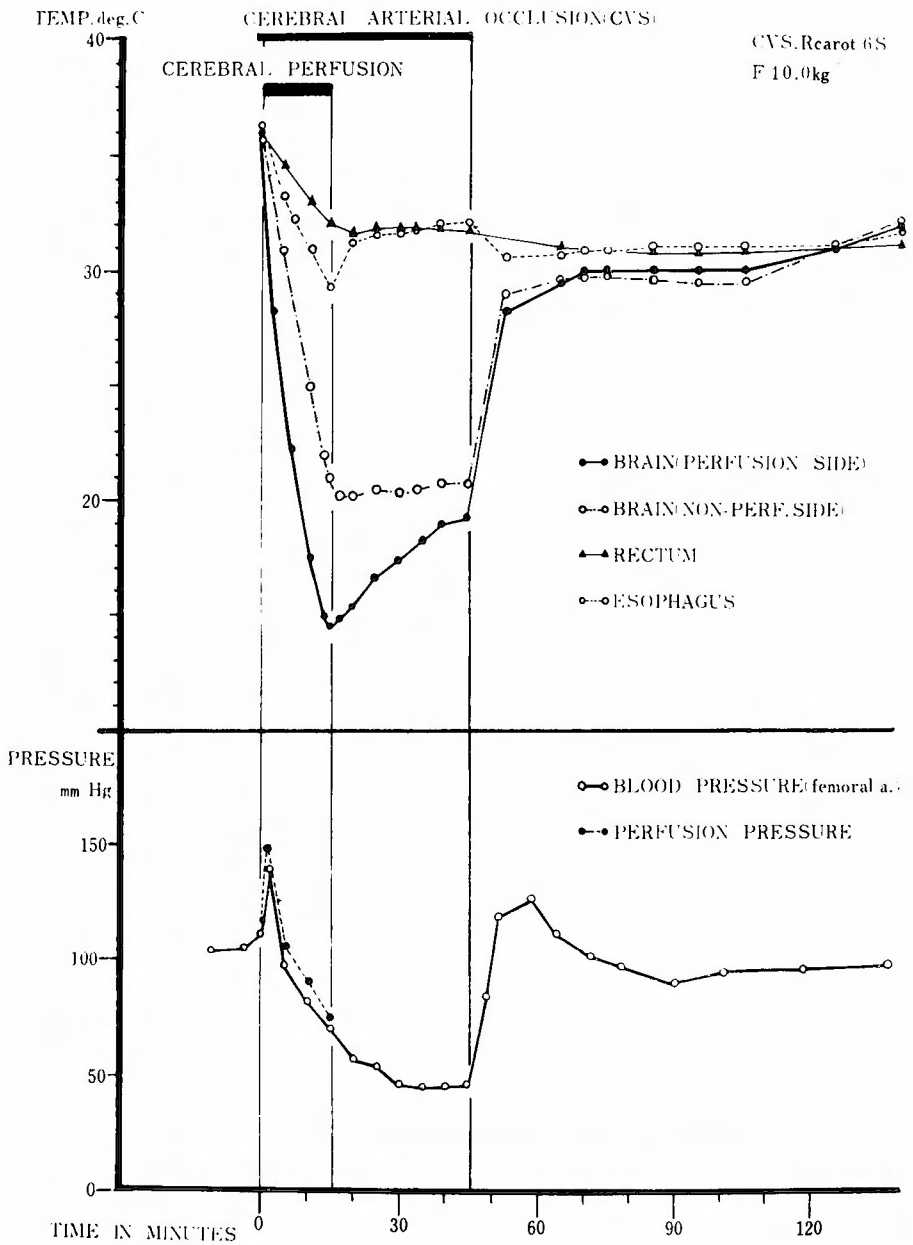

Fig. 6. The process of the variation in temperatures and pressures in the dog (the conventional technique of selective brain cooling.)

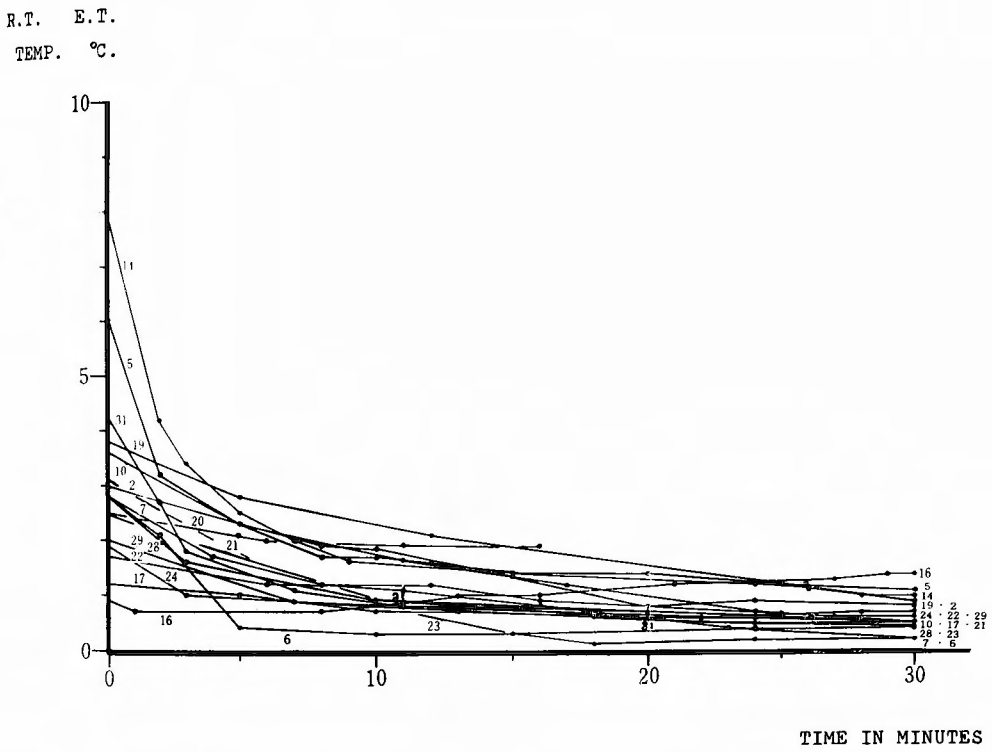

Fig. 7. The variation in temperature difference between esophagus and rectum during 30-minute period of cerebral circulatory arrest and maintenance of profound cerebral hypothermia (the II. stage of the conventional technique of selective brain cooling).

tion by releasing occlusion of arterial inflow to the brain. As a rule, cerebral hypothermia is sustained below 23 degrees C (phase 1), but sometimes above 23 degrees C (phase 2).

Stage III. *The stage of cerebral rewarming.* This stage begins from the institution of cerebral recirculation. In initial 10 minutes, cercebral rewarming occurs acutely (phase 1), followed by terminal and more gradual increase in the brain temperature in the late course of this stage (phase 2).

Stage IV. *The stage of general rewarming.* This is the period of rewarming of the whole body.

At stage I, the time required for cerebral profound hypothermia was 23.3 minutes on the avarage of 22 dogs. The deep-brain temperatures at the end of hypothermic cerebral perfusion averaged 16.3 degrees C on the perfused side and 19.9 degrees C on the contralateral side. The esophagus and the rectum were cooled more mildly to the average temperatures of 28.9 degrees C (esophagus) and 31.8 degrees C (rectum) respectively. Consequently, the average rate of cooling in the brain on the side of perfusion was 0.88 degrees C per minute and in the brain on the contralateral side 0.67 degrees C per minute, while the esophagus was 0.29 and the rectum 0.18 degrees C per minute. Selectivity of the brain cooling and the ratio of rectal or esophageal cooling to cerebral cooling were

given in Table 1, and no definite relationship was found by selectivity and method of arterial occlusion to the brain, although subclavian occlusion and pericervical cuff added to CV occlusion were effective to some extent for selectivity and internal mammary occlusion played some role in protecting warm contamination into the brain from higher levels of blood pressure above 100 mmHg.

At stage Ⅱ, the tendency of increase in the brain temperature was observed, and 53 % of cases showed an increase within 5 degrees C and 26 % of cases exceeded above 10 degrees C. Difference of the temperature between two cerebral hemispheres was 2.7 degrees C to 6.7 degrees C at the end of cerebral perfusion, and below 3.0 degrees C at the end of stage Ⅱ. Cerebral hypothermic temperatures were maintained during the stage Ⅱ if subclavian occlusion were added to CV occlusion and kept the systemic blood pressure at lower level below 100 mm Hg. Difference of the temperature between the esophagus and the rectum decreased in the course of cerebral ischemia and terminated in equilibrium within 1.5 degrees C at the end of stage Ⅱ (Fig. 7).

At stage Ⅲ, an immediate increase in the brain temperature was observed, while the esophageal temperature showed a mild decrease and the rectal temperature a slight decrease. The equilibrium was noted within 30 minutes of the release of cerebral arterial occlusion. The variation in temperatures was dependent upon the levels of the systemic blood pressure. When the blood pressure remained below 50 mm Hg, the release of arterial occlusion was not effective on the increase in the brain temperature, and the systemic blood pressure above the level of 70 mm Hg initiated cerebral rewarming. Decrease in the rectal temperature did not exceed 2.0 degrees C throughout the stages Ⅱ and Ⅲ.

At stage Ⅳ, the rate of rewarming was very gradual in the spontaneous process over 4 to 5 hours, although artificial warming procedures or spontaneous shivering accelerated the rewarming.

Systemic Blood Pressure :

The systemic blood pressure showed a transient rise immediately after ligation of the carotid and vertebral arteries, and decreased progressively below 70 mmHg, as the brain temperature lowered below 20.0 degrees C, and remained around 40 mmHg at the end of perfusion. Heart rate declined to 48 per minute on average. The systemic blood pressure was also affected directly by lower esophageal temperature below 28.0 degrees C (Fig. 17).

The systemic blood pressure and heart rate showed a rapid increase along with cerebral rewarming on the institution of cerebral recirculation. However, in 5 out of 22 cases, so-called paradoxical phenomenon was noted : the blood pressure increased more than preoperative level along with an increase in the brain temperature during the period of cerebral ischemia, while the systemic blood pressure fell following the release of arterial ligations (Fig. 8).

ECG, EEG and Respiration :

Along with the brain temperature below 23 degrees C and esophageal temperature below 28 degrees C, lowering in QRS and prolongation in P-Q time and predominant

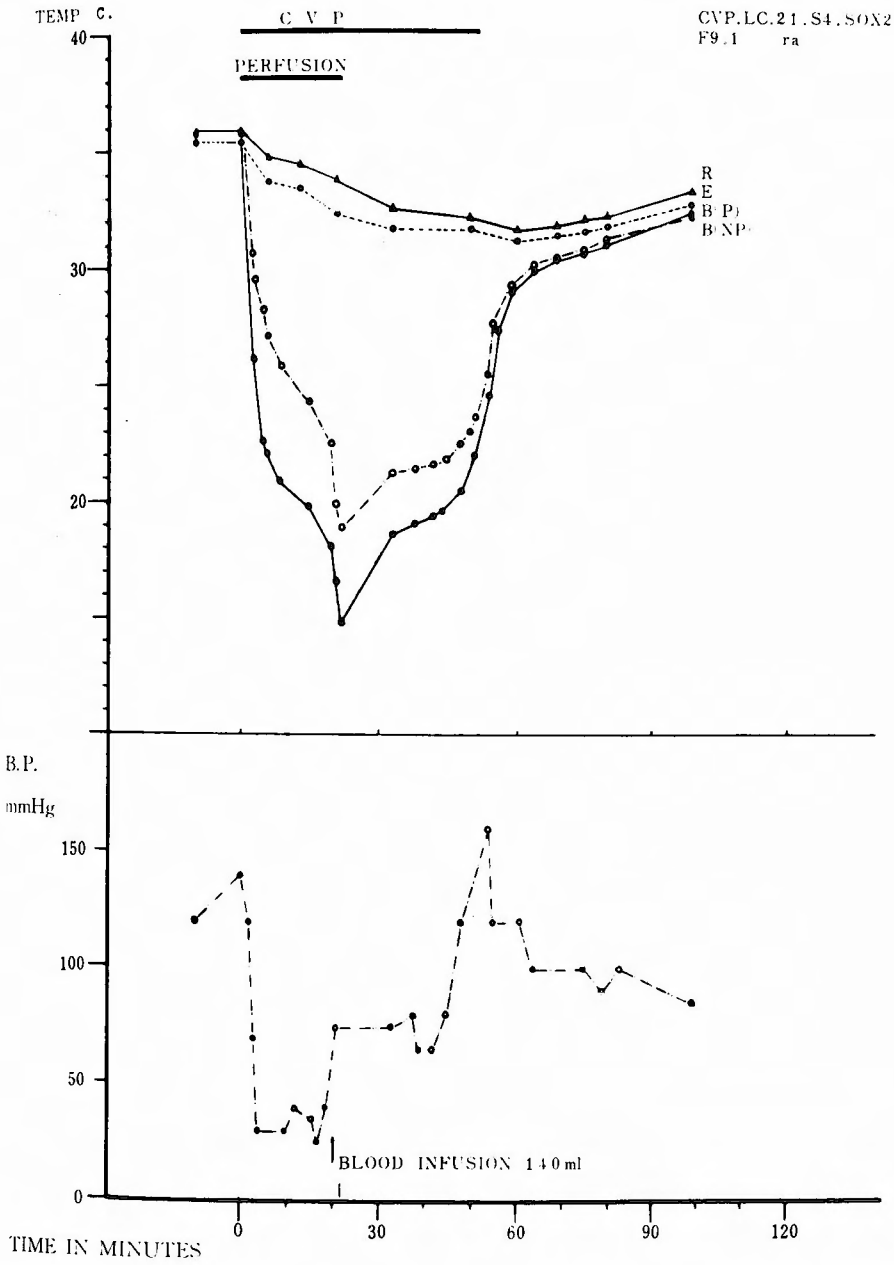

Fig. 8. Ischemic cerebral rewarming and increase in systemic blood pressure in the dog during 30-minute period of cerebral arterial interruption (the II. Stage) of the conventional selective brain cooling. In this case the pericervical cuff technique was added to the bilateral carotico-vertebral occlusions for the inflow interruption to the brain. Increase in blood pressure followed cerebral rewarming and intravenous infusion of the blood.

Table 2 The variation in the cerebral oxygen availability during the period of induction of the selective brain hypothermia in the 13 consecutive dogs. V. CAO_2 represents the variation in the cerebral oxygen availability. Eq. CAO_2 means the equilibrated level of that in the respectively definite period of time. All the values of the cerebral oxygen availability are represented in % values to the control before operation.

Dog No.	Cerebral Oxygen Availability (%)						Type of variat.
	V. CAO_2			Eq. CAO_2	V.- Eq. CAO_2		
	Ph. 1	Ph. 2	Total	Ph. 2	Ph. 3		
14	+15	+103	+118	218	−118	100	gamma-b
10	+ 5	+ 22	+ 27	127	−104	23	gamma-b
29	+11	+ 11	+ 22	122	45	77	gamma-b
16	−41	+ 56	+ 15	115	−110	5	gamma-b
19	+13	0	+ 13	113	0	113	alpha
28	−23	+ 21	− 2	98	+ 2	100	beta
31	−14	+ 3	− 11	89	− 29	60	gamma-a
22	−11	0	− 11	89	− 20	69	gamma-a
24	−35	+ 11	− 24	76	− 26	50	gamma-a
20	+12	− 47	− 35	65	0	65	beta
21	−51	+ 5	− 46	54	− 11	13	gamma-a
23	−13	− 35	− 48	52	+ 2	54	beta
17	−53	− 21	− 74	26	+ 2	28	beta
mean	−14	+ 10	− 1	96	− 35	61	
maxim.	+15	+103	+118	218	+ 2	113	
minim.	−53	− 47	− 78	26	−118	5	
standard deviation	21.8	36.7			43.5		

bradycardia were noted. However, no arrhythmia was observed. Spontaneous respirations disappeared and resumed around the brain temperature of 24 to 25 degrees C. EEG showed flattening and slowing along with lowering of the brain temperature around 24 degrees C and completely flat below 20.0 degrees C.

Polarographical Indication of Cerebral Oxygen Availability in Selective Cerebral Perfusion Hypothermia

Characteristic changes in the cerebral oxygen availability (CAO_2) were a decreasing CAO_2 on the initial and the terminal phases at Stage Ⅰ, the lowered level at Stage Ⅱ, immediate increase with rebounds on the first phase at Stage Ⅲ, and the gradual decrease at Stage Ⅳ.

1) Cerebral Oxygen Availability at Stage I (Table 2).

The mean variation in cerebral oxygne availability was -14 ± 24.8 % on phase 1, the period of perfusion with brain temperatures above 23 degrees C, $+10 \pm 36.7$ % on phase 2, the period of perfusion with brain temperatures below 23 degrees C, and -35 ± 43.5 % on phase 3, the period for 5 minutes immediately following the cessation of perfusion. This fact indicates that the third phase of Stage Ⅰ shows the highest veriation

in CAO_2. There were three types of equilibration within ± 10 % of the variations of CAO_2 : the equilibrium occurred on phase 1 (Alpha type), on phase 2 (Beta type), and on phase 3 (Gamma type). Alpha and beta types occurred in cases in which the brain was cooled at the average rate below 0.7 (0.27 to 0.68) degrees C per minute, while gamma-a type in which the variation in CAO_2 continued in the equal direction, at both the cooling rates below around 0.7 and above 2.50 degrees C, and the gamma-b type in which the reverse precursor was found, at the cooling rate above 1.30 (1.36 to 3.75) degrees C per minute. The gamma-a type showed only minor decrease in CAO_2 on the cessation of the perfusion, no significant decrease on phase 2, and equally sustained the lower levels of CAO_2 similar to the bata type. However, in case of gamma-b type, the predominant increase doubled by the variations on phases 1 and 2 was always offset, and the predominant decrease was seen on phase 3. At any rate, the equilibrium of CAO_2 (Eq. CAO_2) was induced at 61% on the average of 13 cases. These levels of V. CAO_2 and of Eq. CAO_2, especially in cases of gamma types, indicated the condition of hypothermic cerebral perfusion at Stage I.

The relationship between the variation in the cerebral oxygen availability and other factors of perfusion during Stage I is illustrated in Table 3. As a parameter indicating the efficacy of hypothermic cerebral perfusion, especially the condition of microcirculation, the following three kinds of theta, $\theta = \text{Fq. } CAO_2/\text{RC}$ were considered (1) ${}_1\theta_{d10}$ (Eq. CAO_2 phase 1 and RC 10 degrees C), (2) ${}_1\theta_{d15}$ (Eq.CAO_2 phase 2 and RC 15 degrees C), and (3) ${}_2\theta_{d15}$ (Eq. CAO_2 phase 2 and RC 15 degrees C). If plotted on the logarithmic graph (Fig. 9), $\theta = e^n(RC)^{-a}$ is produced. Since "a" was approximately 1 in the consecutive 13 dogs, $\theta = e^n(RC)^{-1}$. Thus, Eq. $CAO_2 = e^n$ is given. (e^n indicates the coef-

Table 3 The relationships between the cerebral oxygen availability and the conditioning factors of the induction of cerebral perfusion hypothermia. (13 dogs)

Dog No.	V. CAO_2 Stage	Eq. CAO_2 (%) Phase 1	2	3	RC (°C/min) ⌟10°C	⌟15°C	$\theta = \frac{\text{Eq. } CAO_2}{RC}$ ${}_1\theta_{d10}$	${}_1\theta_{d15}$	${}_2\theta_{d15}$	Perfusion Time Min.	Ph. 2 %	B. P. (mmHg) Control/minim.	% aver.	S. I. R	E	Induced Brain Temp. (deg. C)
17	β	47	26	28	0.26	0.27	181	170	96	78	37	120/27	23	31	36	20.2
24	γa	65	76	50	0.43	0.35	151	186	217	32	16	110/40	75	24	29	16.7
23	β	87	52	54	0.43	0.47	201	185	111	31	23	100/45	83	11	14	13.0
22	γa	89	89	69	0.48	0.48	185	185	185	32	6	110/30	80	26	35	16.8
20	β	112	65	65	0.67	0.62	167	181	105	46	9	130/50	57	35	45	15.9
19	α	113	113	113	0.52	0.50	217	226	226	41	30	120/15	15	13	35	11.0
28	β	77	98	100	0.77	0.68	100	113	144	25	28	100/20	23	23	33	15.0
21	γa	49	54	43	1.10	0.71	45	69	76	22	9	120/25	51	9	15	11.7
10	γb	105	127	23	1.80	1.36	56	77	93	16	37	125/20	35	34	33	18.7
14	γb	115	218	100	2.00	1.88	58	61	116	20	65	100/10	46	19	53	16.6
16	γb	54	115	5	2.63	2.14	21	28	51	28	74	110/15	31	28	28	13.6
31	γa	86	89	60	1.72	2.50	50	34	36	7	43	140/70	80	13	33	15.3
29	γb	111	122	77	3.57	3.75	31	30	33	30	80	100/35	85	11	17	15.7

ficient of environmental equilibrium of CAO_2 including all kinds of factors, such as the local microcirculation, the local oxygen consumption, the pO_2 in the perfusate, and environmental diffusion coefficient of oxygen within the cerebral tissue under the hypothermia.)

Another parameter indicating the condition of the hypothermic cerebral perfusion was $V.CAO_2$ on phase 3. The relationship between θ and $V.CAO_2$ on phase 3 (V_3CAO_2) was experimentally shown to be $V_3CAO_2 = e^m\theta^{-b}$. As shown in Fig. 10, "b" was approximately 2, and there were two (large and small) groups of e^m. The large value of e^m correlated relatively with the large value of θ, and averaged approximately 80×10^4, while the small value approximately 5×10^4. Thus, V_3CAO_2 was proportional to θ^{-2}. This means that an increase of the value of θ needs a decrease of the value of RC. In the experiment the low RC_{d15} less than 0.7 degrees C per minute resulted in below 30 % of V_3CAO_2 (alpha, beta & gamma-a types). On the other hand, cases, in which the RC_{d15} was higher than 2.0 degrees C per minute, showed the sustained low levels of CAO_2 throughout the following stages Ⅱ, Ⅲ, Ⅳ (Nos. 16, 29 and 31). In one case, in which $_1\theta_{d15}$ was sufficiently high (θ=170) but RC_{d15} was extremely low (less than 0.3), the lowered level of CAO_2 was found throughout all stages (No. 17). These 4 cases resulted in death without regaining the consciousness.

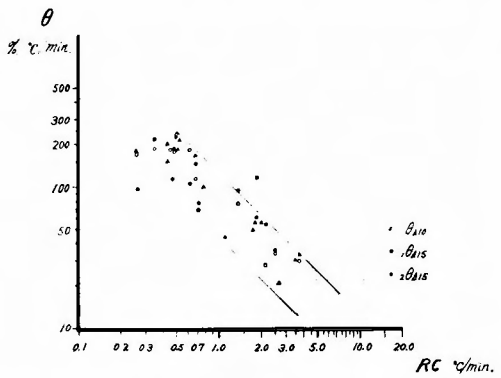

Fig. 9. The experimentally measured correlation between the rate of cerebral cooling (RC) and the ratio of equilibrated values of the cerebral oxygen availability to unit RC (θ=Eq.CAO_2/RC), which is recognized as the coefficient of cerebral microcirculation in the cerebral perfusion hypothermia.

These parameters did not correlate with other factors, such as the systemic blood pressure, SIR or SIE, the mode of occlusions of cerebral inflow, and induced body temperatures. However, it was shown that stage Ⅰ should be kept by the following conditions: (1) the well balanced high levels of Eq. CAO_2, (2) θ is larger than 35, and (3) RC is from 0.3 to 1.2, averaged 0.7.

2) Cerebral Oxygen Availability at Stage Ⅱ

Stage Ⅱ should be monophasic and physiologically silent. However, the cooled brain frequently showed the paradoxical increase in the temperature during the period of cerebral ischemia. The ideal group was well maintained in the profound hypothermia below 23 degrees C, while the paradoxical group showed the considerable spontaneous rewarming above 23 degrees C. In the ideal group, the average Eq. CAO_2 retained a value of 42 to 119 % throughout the period of the second stage (Nos. 14, 19, 21, 24, 22 and 28), while in the paradoxical group (Nos. 23, 29, 16, 31 and 10), there were three patterns of the variations in CAO_2: (a) the considerable increase in CAO_2 along with the increase in the brain temperature (well balanced ischemic rewarming; Nos. 10, 16 and 23), (b) the paradoxical arrest and decrease in CAO_2 unsuited to the cerebral re-

Table 4 The critical values of the cerebral oxygen availability and the process of the conventional technique of the selective brain cooling in the 13 consecutive dogs.

* Cla sifications of the cerebral hypothermia at the II. stage : Hypothermic brain temperatures- A : below 23 C, B : below 28°C and C : not less than 28 C ; Maintenance of hypothermia in temperature variations-a : below 5 C, b : below 10°C and c : not less than 10°C.

Dog No.	Postop.	Induction			Eq. CAO_2 Stage I		Stage II	Stage III	Stage IV	Induced Temp. Brain (Perf.)	Brain (Non-P.)	Esoph.	Rect.	* Cereb. Hypothermia Stage II Br. Temp.	Maint.
		V. CAO_2	RC_{d15}	$_1\theta_{d15}$	Ph. 2	Ph. 3	Aver.	Ph. 1	Aver.	Aver.						
28	Long Term Survival	β	0.68	113	98	100	119	140	159	148	15.0		29.3	31.5	A	a
14		γb	1.88	61	218	100	109	335	229	113	16.6		25.1	32.8	A	a
21		γa	0.71	69	55	43	42	140	109	94	14.7	18.8	32.1	33.6	A	a
23		β	0.47	185	52	54	109	212	158	112	13.0	17.8	31.6	35.1	C	c
19	Neurological Survival	α	0.50	226	113	113	111	100	132	92	14.0	18.1	28.5	32.4	A	a
22		γa	0.48	185	89	69	95	155	137	122	16.8	18.5	28.8	29.9	A	a
24		γa	0.35	186	76	50	63	84	85	100	16.7	20.7	28.0	29.2	A	a
10		γb	1.36	77	127	23	46	113	106	87	18.7		27.4	31.0	B	b
29	Comatose	γb	3.75	30	122	77	78	62	62	<62	15.7		33.3	35.2	C	c
20		β	0.62	181	65	65	68	68	67	<68	15.9	19.9	27.1	29.6	B	b
16		γb	2.14	28	115	5	15	170	125	<64	13.6	16.3	30.2	31.1	B	c
31		γa	2.50	34	89	60	42	48	82	15	15.3	16.5	26.2	30.4	B	b
17		β	0.27	170	26	28	36	39	42	27	20.2	23.4	29.1	30.2	B	a

warming (paradoxical ischemic rewarming ; Nos. 29 and 31), (c) no sustained deep-brain temperatures below 23 degrees C with poor CAO_2 (insufficient hypothermic CAO_2 ; Nos. 17 and 20). (Table 4, and Fig. 11).

Thus, the poor levels of Eq.CAO_2 were caused by the following 3 situations : (1) when the brain was induced to and arrested at the low levels of CAO_2 (No. 17), (2) when the CAO_2 was too poorly induced to recover the good values (No. 16), and (3) when the well induced CAO_2 was affected excessively by the predominant paradoxical ischemic rewarming (No. 31).

The average values of Eq. CAO_2 during stage III were 15 to 119 %. When the value of RC_{d15} was between 0.7 and 0.3 and the values of θ was not less than 100, the average values of Eq. CAO_2 during Stage III always exceed above 60 %. Thus, above-mentioned three situations of CAO_2 were found in cases in which the RC_{d15} was above 2.0 or less than 0.3 and the $_1\theta_{d15}$ being below 35. However, the CAO_2 at Stage III was not correlated with the systemic blood pressure at Stage III. If the blood pressure remined below 70 mmHg, the brain temperature did not exceed above 20 degrees C, and if sustained below 40 mmHg the well balanced Eq. CAO_2 at higher levels above 90 per cent was found (Nos. 19, 22 and 28). When the systemic blood pressure exceed around 70 mmHg and approximated to 100 mmHg, the paradoxical rewarming occurred (Nos. 29 and 31). Around 70 mmHg of the systemic blood pressure, the Eq. CAO_2 was almost always arrested and the cerebral hypothermia was maintained relatively well,

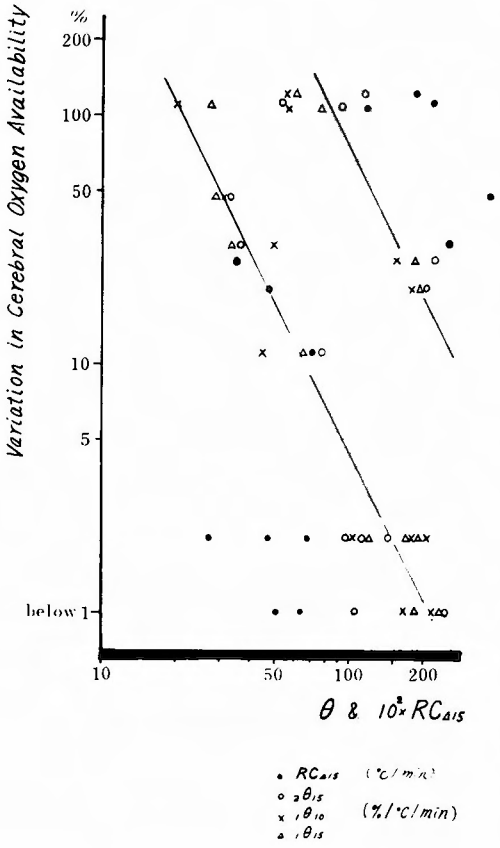

Fig. 10. The correlation of the decrease in cerebral oxygen availability on the cessation of hypothermic cerebral perfusion (gamma-phenomenon) to θ and RC.

without causing the paradoxical rewarming. (Tables 3, 4 and Figs. 11, 12).

3) Cerebral Oxygen Availability at Stages Ⅲ and Ⅳ

In the ideal group, the considerable and immediate increase of the CAO_2 was recorded. However, in some cases, the delayed-action increase (Nos. 19, 28 and 31), the arrested CAO_2 (Nos. 17 and 20), and the considerable decrease in CAO_2 (No. 29) were found. In these cases, the variations in CAO_2 on the initial phase of Stage Ⅲ were considerably dependent upon the variations in the systemic blood pressure on the release of arterial occlusions (Tables 3, 4 and Fig. 12).

The characteristic of the variation in CAO_2 at Stage Ⅳ was the gradual decrease or the arrest of CAO_2 on the relatively long course of general rewarming. The levels of terminal equilibrium in CAO_2 was affected both by the systemic blood pressure and by the brain temperature. If the Eq. CAO_2 was sustained and terminated at the values below 70 % over four hours in the posthypothermic period around 35 degrees C of the brain temperatures, fatal and comatose conditions occurred (Nos. 16, 17, 20, 29 and 31). If the Eq. CAO_2 was terminated in the levels above 80 %, the postoperative conditions were good.

Survival Study and Critical Values of Selective Brain Cooling

All of 4 survival cases were awake within 8 hours of the procedure, and little clinical disturbances of the nervous system, such as a slight tendency to ataxia, were observed over the period of 3 months (Nos. 14, 21, 23 and 28). No abnormalities were found in the brain at necropsy.

Four neurological survival cases were also awake within 8 hours after the procedure, but suddenly died of a large embolus of filariae in the pulmonary artery (2 cases), or the postoperative purulent meningitis or cervical abscess extended into the mediastinum in the course of recovery.

Five fatal cases were comatose without regaining consciousness after the procedure (Tables 2, 3, 4 and Fig. 12). These data indicate that the critical values of perfusion

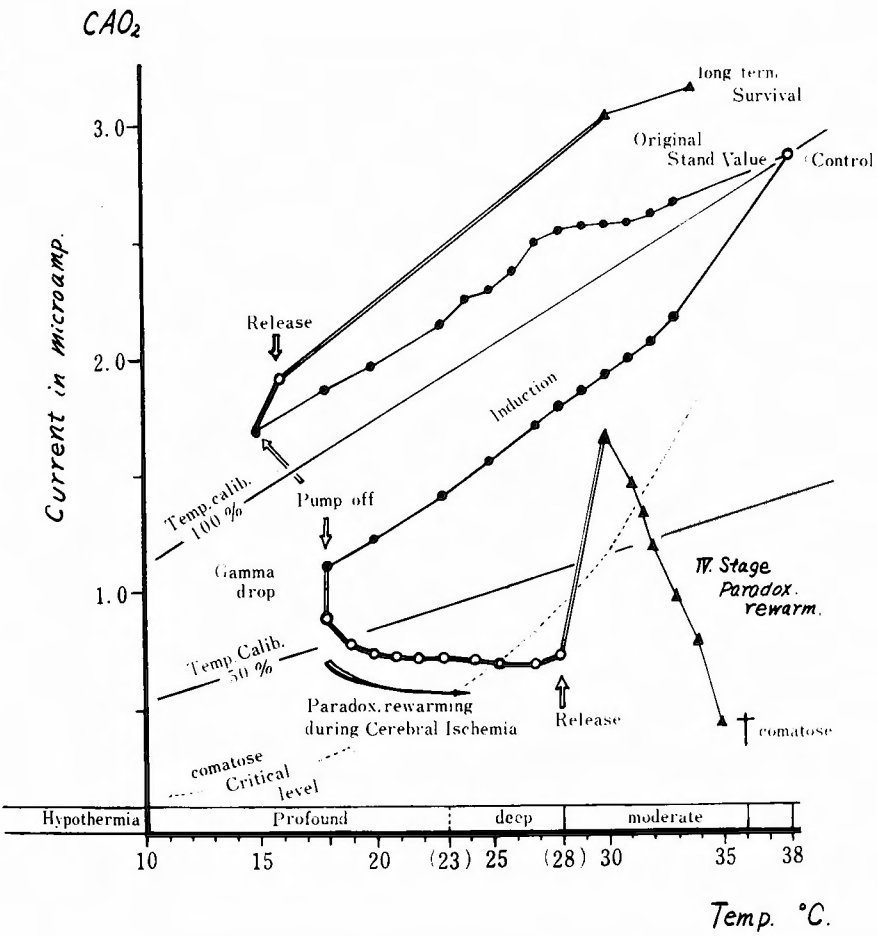

Fig. 11. The schematic representation of the experimentally recorded paradoxical phenomenon in cerebral oxygen availability during each period of the course of selective brain cooling in the dog. The well balanced process of the technique is compared with that in paradoxically poor case.

were the maximum $RC_{d15}=2.0$, the minimum $RC_{d15}=0.3$ degrees C per minute, and ${}_1\theta_{d15}=35$ % per degree C per minute. In other words, the range of the suitable perfusion was RC_{d15} between 0.3 and 2.0, and thereby ${}_1\theta_{d15}$ above 35.

The critical values of Eq. CAO_2 were represented by the following formula ("C" and "K" : the brain temperatures) :

Critical Eq. $CAO_2 = 90\ (70/100)^{\frac{38-C}{5}} = 90\ (70/100)^{\frac{(273+38)-K}{5}}$ (%), and the critical values of Eq. CAO_2 were 90 % at 38 degrees C, 63% at 33 degrees C, 44 % at 28 degrees C, 31 % at 23 degrees C, 22 % at 18 degrees C and 15 % at 13 degrees C of brain temperatures. If the values were below the critical levels, the dogs did not

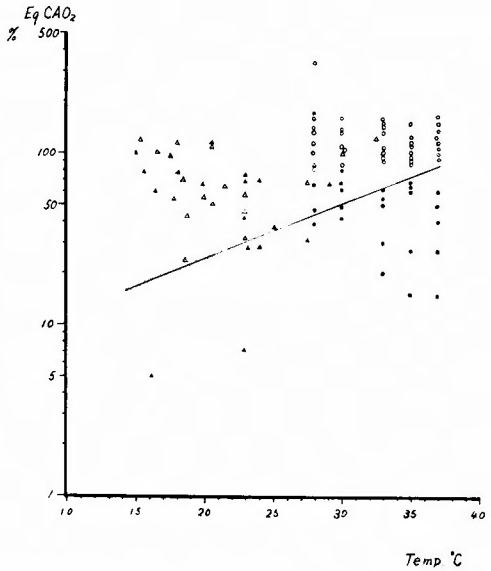

Fig. 12. Distribution of the values of cerebral oxygen availability during cerebral hypothermic procedures. The values of equilibrated cerebral oxygen availability in the postoperatively comatose cases give a almost straight line in the logarithmic graph, which demonstrates the critical levels between survivals (empty marks) and comatose fatal cases (black dots).

Survival △ during inflow occlusion
○ after recirculation

Comatose ▲ during inflow occlusion
● after recirculation

regain consciousness after the procedure, while all of the survivals showed above the critical levels.

The critical value of the systemic blood pressure to initiate the cerebral rewarming was 70 to 90 mmHg which corresponded to about 70 % of the original control value, and Eq. CAO_2 was insufficient when the blood pressure was lowered less than the critical value during Stage Ⅳ.

REGULATION OF CEREBRAL CIRCULATION IN PROFOUND CEREBRAL HYPOTHERMIA BY HEMODILUTION AND SUSTAINED HYPOTHERMIC CEREBRAL PERFUSION

A. Preliminary Experiments

1) Effect of Hemodilution upon Relative Viscosity of the Blood.

Relative viscosity of the blood ($R.RV_{hd}$) was found to be approximately proportional to the proportion of relative hematocrit value in per cent to the control value of the whole blood ($R.Htc_{hd}$) in the hemodilution.

If $R.Htc_{hd}$ was around 60 %, $R.RV_{hd}$ was about 53 % in the series of hemodilution with physiological saline solution. Although these both values showed the linear relationship, rate of decrease in $R.RV_{hd}$ was low in less than 50 % of R. RV. (27 experiments of 9 samples : Figs. 13 a and b).

Fig. 15 illustrates the effect of hemodilution in animals.

2) Effect of Temperature upon Variations in Relative Viscosity of the Blood.

The mean value of relative viscosity of the human venous blood was 3.39 at 32 degrees C and 4.90 at 10 degrees C. Since the viscosity of the distilled water at 10

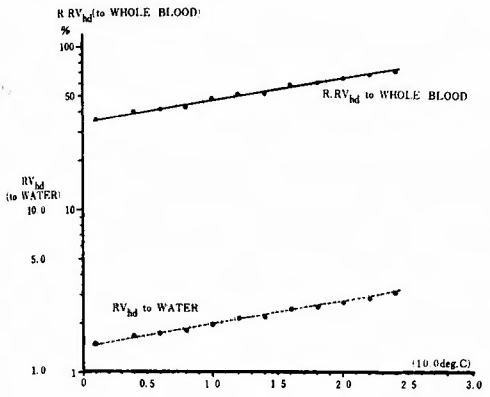

Fig. 13 a.* The relationship between the relative viscosity of the diluted blood and the hemodilution estimated in vitro at 10 C. Hemodilution was standardized by the volume ratio of the whole blood to the added saline solution. The variation in the relative viscosity of the diluted blood was represented in % with the relative value to the control value of the respective whole blood (a upper solid line) or given by the relative value to distilled water (a lower dotted line). (Normal human venous blood).

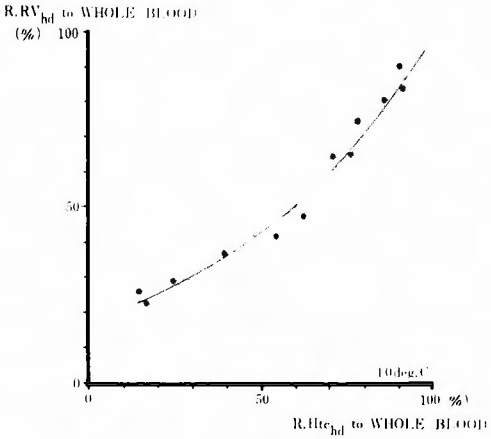

Fig. 13 b.* The relationship between the relative viscosity of the diluted blood and its Hematocrit. The variations in the diluted blood were represented by the relative values to the control values of the respective whole blood. (Normal human venous blood).

$$* \text{ R. } RV_{hd} = e^{(k \cdot C_{wb}/C_s)} \cdot C_{wb}/C_s = \frac{RV_{hd}}{RV_{wb}} \cdot 100 \quad (\%) \qquad R \cdot hd = \frac{C_{wb}}{C_{wb}+C_s} \cdot 100 \quad (\%)$$

$$Htc_{hd} = Htc_{wb} \cdot \frac{R \cdot hd}{100} \qquad R.Htc_{hd} = \frac{Htc_{hd}}{Htc_{wb}} \cdot 100 = R.hd \quad (\%)$$

$C_{wb}/C_s = Htc_{hd}/(Htc_{wb} - Htc_{hd}) = R.Htc_{hd}/(100 - R.Htc_{hd})$

RV : relative viscosity, $-wb$ and $-s$: whole blood and added Solution. R. RV : relative value of RV to the control value of the whole blood (in %). R. hd ; the ratio of hemodilution. Htc and R. Htc : Hematocrit value and its relative value in % to the control value of the whole blood. "k" and "c" : Conditioned constants in each sample of the blood. "C" Capacity of the blood or solution in hemodilution.

degrees C was about 1.91 times as much as that at 38 degrees C, and the ratio of the viscosity of water at 32 degrees C was about 0.77 to 0.68 of that at 38 degrees C, the relative viscosity of the blood at 10 degrees C was calculated to be about 3.17 times as much as that at 38 degrees C. Therefore, it was necessary to reduce the R. RV_{hd} down to about 30 % of the whole blood value at 10 degrees C by lowering the Htc_{hd} down to about 30 % in R.Htc_{hd} (Fig. 14).

B. Effective Flow Rate during Hypothermic Cerebral Perfusion

1) Induction of Cerebral Hypothermia.

Under the initial conditions of RC between 0.3 and 1.0 degrees C per minute and at the levels of systemic blood pressure above 70 mm Hg and of SIR (Index of Selecti-

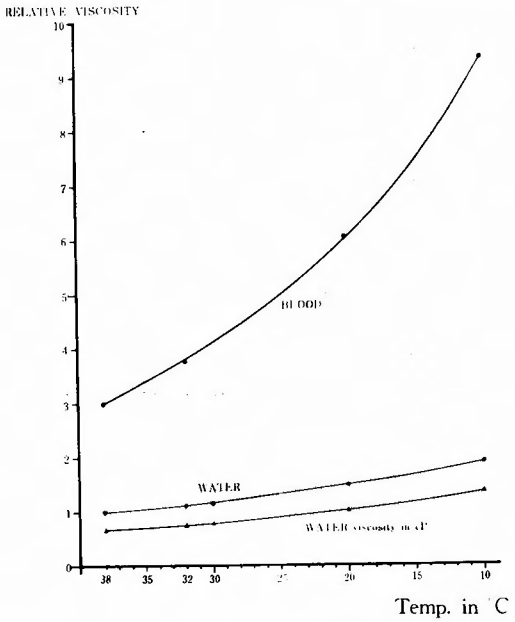

Fig. 14. The variation in the relative vi cosity of the blood due to the temperature variations. The measured values of the relative viscosity are converted into the values compared with that of 38°C water by calculation. (Normal human venous blood).

- Relatiae viscosity to water at 38 deg. C
- ▲ Absolute value of viscosty in cP

Average values of blood samples :
Hb = 14.1g/dl, Htc = 41%,
M.C.D. = 7.6 microns, RBC = 462 × 10⁴/cmm.

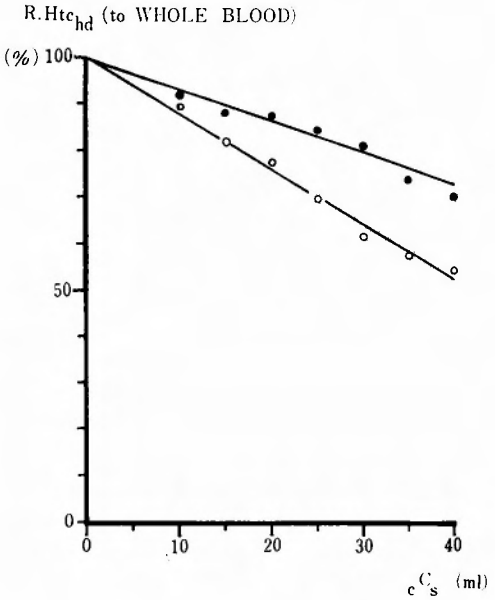

Fig. 15. Hematocrit and hemodilution in the selective brain cooling and hypothermic exchange perfusion in the dog. The variation in hematocrit of the diluted blood is represented by the per cent variation to the control value of the individual whole blood(relative hematocrit to the control whole blood : R.Htc$_{hd}$). Hemodilution is represented by the infused capacity of saline in exchange for blood ($_cC_s$: ml/kg of body weight).

vity as for Rectum) below 40, the value of RC_{d10} or RC_{d15} was approximately 0.3 degrees C per minute when the value of RP (rate of perfusion) was around 3 9 ml per kg per minute, 1.0 degree C per minute when RP was around 5.7 ml/kg/min. and 0.5 when RP around 4.6, showing an exponential relationship between them (Fig. 16).

Thus, the cooling rate of the brain increased in proportion to RP, with the critical value of the systemic blood pressure around 70 mmHg, and the minimal value of RP necessary for obtaining the good condition of induction was about 5 ml/kg/min.

2) Maintenance of Cerebral Hypothermia with Intermittent Hypothermic Cerebral Perfusion.

When the systemic blood pressure decreased and remained between 30 to 50 % to the initial control levels within the range of brain temperatures below 25 degrees C, the well maintained hypothermic cerebral temperatures were obtained by the hypothermic cerebral perfusion at the rates of perfusion below 2.5 ml/kg/min, without decreasing the rectal temperature. If the systemic blood pressure was maintained below the critical level around 70 mm Hg, the extremely low rate of flow less than 1.0 ml/kg/min. of RP was

needed.

3) Maintenance of Cerebral Hypothermia with Continuous Hypothermic Cerebral Perfusion.

The profound hypothermic cerebral temperatures were sufficiently maintained for 50 to 60 minutes by the extremely low rates of hypothermic cerebral perfusion between 1.5 and 2.5 ml/kg/min. The hypothermic cerebral perfusion at these lowered values of RP followed immediately the induction of cerebral hypothermia and sustained continuously throughout the period of maintenance of cerebral hypothermia over 50 minutes. During the period of sustained hypothermic perfusion, the systemic blood pressure was also sustained below the critical level and did not exceed the levels around 50 mm Hg, and the perfusion pressure was controlled adequately low along with the decrease in blood pressure and did not exceed the blood pressure by more than 10 mm Hg. Throughout the whole procedure of continuous cerebral perfusion, there were only minor decreases in the rectal temperature and the esophageal temperature. The rectal temperature was maintained above 31.0 degrees C. The esophagus was also maintained above 29 degrees C, holding the SIE values not above 25.0. The paradoxical phenomenon of ischemic cerebral rewarming occurred at the rate of rewarming not less than 0 8 degrees C per minute on the cessation of this hypothermic cerebral perfusion.

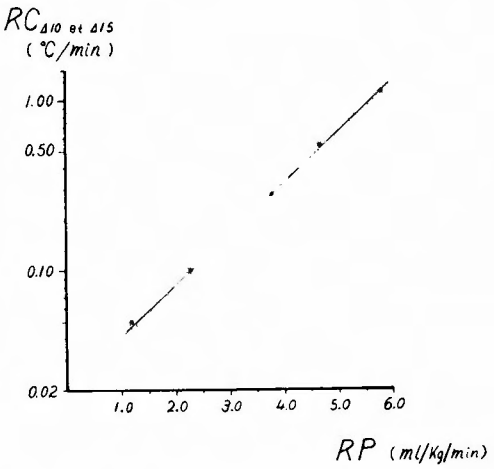

Fig. 16. The relationship between the rate of brain cooling and the rate of cerebral perfusion. The cooling rate is represented by the average rate of brain cooling per minute for 15°C or 10°C decrease in brain temperature (RC_{d15} or RC_{d10}), and the perfusion rate being represented by the average rate of perfusion in ml/kg of body weight/minute in the corresponding period of RC (RP).

The systemic blood pressure recovered to the initial levels and the brain, the esophagus and the rectum were rewarmed smoothly without any cardiac episode during the third and the fourth stages of hypothermia. (Fig. 18).

C. Transplantation of Cooled Isolated Head and Its Cerebral Recirculation

The brain of a young animal was cooled selectively down to 15 degrees C by the RC_{d15} 1.0 degree C per minute. During the period of hypothermic cerebral perfusion, the systemic hemodilution was induced by decreasing the $R.Htc_{bd}$ down to 50 % to the preoperative control value, and the Eq. CAO_2 could be sustained above its critical values with about 98 per cent throughout the period at the deep-brain temperature of 15 degrees C, and the ${}_1\theta_{d15}$ being 98%/degree C/min. The systemic blood pressure was reduced below 50 % to the initial control value. When the brain was cooled down to 15 degrees C, the cardiac arrest was induced by rapid depletion, and thereafter the head was amputated with the neck and vessels to the brain. Isolated head and neck were reserved in an icebox keeping the brain temperature around 15 degrees C. The brain showed then com-

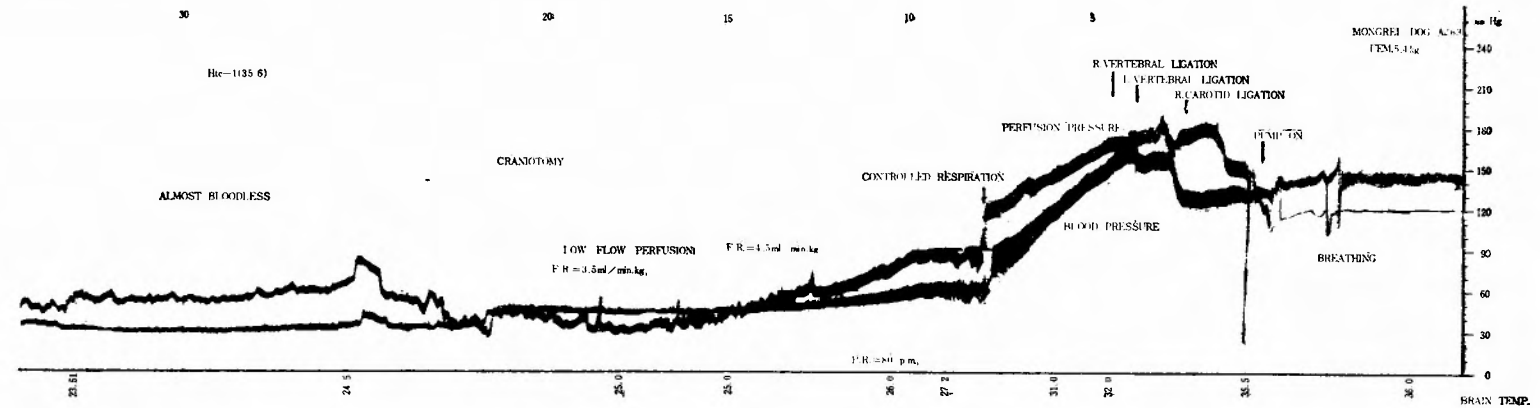

Fig. 17. The recorded variation in the systemic blood pressure and the perfusion pressure during the period of hypothermic cerebral perfusion (Induction Perfusion) in the dog. The parallel correlation in variations is demonstrated between the systemic blood pressure and the perfusion pressure at the constant pumping rate. The correlated rise in pressures is predominant on cervical arterial occlusions to the brain. The tapering decrease in those pressures is significant in the initial period of selective brain cooling. The perfusion pressure and blood pressure below 50 mm Hg are accompanied by the perfusion rate less than 3.5ml/kg/minute and almost avascular surgical procedures.

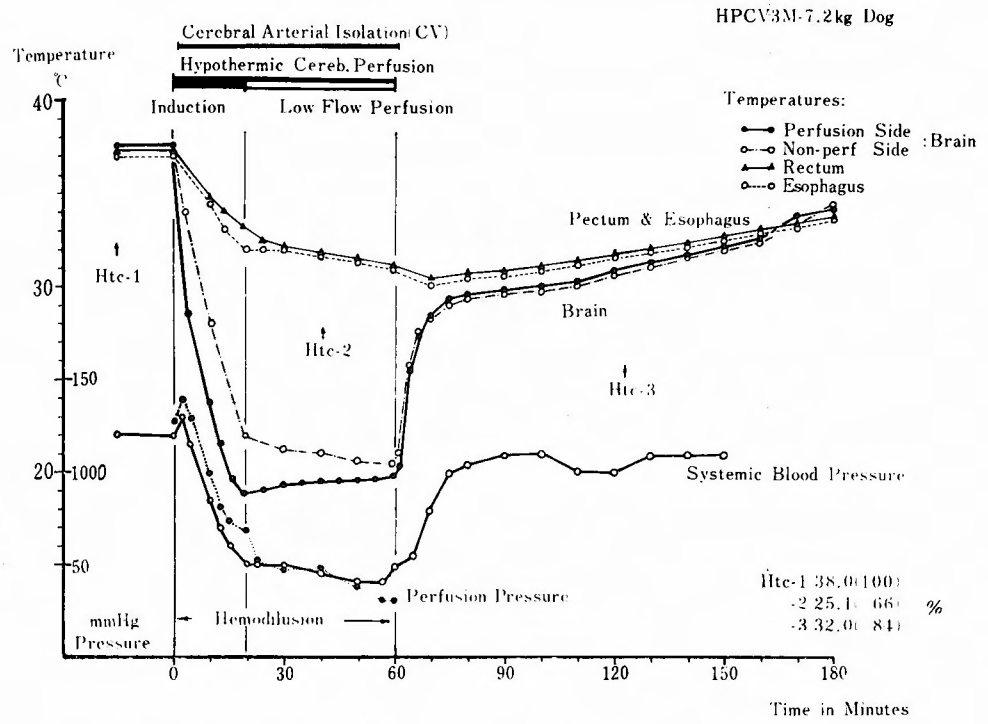

Fig. 18. The typical course of the hypothermic variations in the differential brain cooling combined with the systemic hemodilution and sustained hypothermic cerebral perfusion at low rate of flow.

pletely flattened EEG, and the Eq. CAO_2 was arrested at 88 to 92 %, which was sustained throughout the period of complete cerebral ischemia for 200 minutes. No paradoxical phenomenon was observed.

When the brain was recirculated with the blood of the host dog after the vascular anastomoses, the brain was perfused via unilateral carotid artery, and the Eq.CAO_2 of the transplanted head increased considerably up to the levels above 120 % along with immediate cerebral rewarming. The EEG resumed the waves of cerebral activity following the cerebral rewarming, initiating at the brain temperature around 22 degrees C. When the brain temperature reached about 25 degrees C, respiratory movements were noted in the transplanted head and neck. The pupils, which had completely dilated and shown no response to light before cerebral rewarming above about 29 degrees C, constricted gradually and responded actively to light. Corneal reflex also appeared. Response to pain was observed on the earlobes. Those responses were observed more predominantly on the side of carotid anastomosis than the opposite side.

There was no paradoxical rewarming, and the Eq. CAO_2 was kept above the critical levels throughout the period of cerebral rewarming. However, within 6 to 8 hours of the cerebral recirculation, the Eq. CAO_2 decreased down gradually below the critical values, and terminated in poor values around 50 % above 36 degrees C. This situation followed initially the decrease in the systemic blood pressure of the host dog and caused reductions

Table 5 The course of the variations in the cerebral oxygen availability and the procedures of hemodilution in the differential cooling of the brain combined with the systemic hemodilution and the sustained hypothermic cerebral perfusion at low flow rate. (The 8 consecutive dogs subjected to the improved and combined technique of the differential brain cooling)

Cases																							
			Hemodilution						CAO_2 (%)									Induction			Maintenance		
								Induction Perfusion		Low Flow Rate Perfusion			Rewaraming										
Dog No.	Stage II-Perfusion C : Continuous I : Intermittent	Htc. (%) Before Perfus. 1	Hem. Dilut. 2	After Perfus. 3	Relative Htc. (%) 2	3	(Stage) I Phase 1	2	1	II 2	Av.	III 1	IV 2		$PD_{J15°C}$ (*J10 C) (Mins)	$RC_{J15°C}$ C/Mins	$\theta_{J15°C}$ (%)/(C/Mins)	$BT_{II\text{-}Perf.}$ (C) min.	max.
							Type																
Long Term Survivals	7	C	36.5	25.1	31.0	69	85	x	62	65	59	—	59	148	100	100	12	1.25	52	18.9	23.0		
	9	C	39.6	27.5	40.8	69	103	β	81	55	58	—	58	153	138	111	13	1.15	73	20.0	22.0		
	8	I	31.1	21.8	42.6	73	125	β	58	54	64	81	76	100	90	80	26	0.58	100	18.0	26.5		
	12	I	41.2	28.1	42.1	68	102	x	83	82	86	—	86	85	91	88	*18	*0.56	*116	19.5	21.5		
	11	I	51.5	41.9	18.2	81	91	x	96	—	—	92	92	88	90	85	27	0.56	175	23.5	26.6		
	10	C	44.1	34.6	38.9	78	90	x	78	—	—	94	94	94	85	83	45	0.33	270	22.5	27.8		
N	1	C	46.2	39.6	48.0	86	104	x	71	66	59	60	60	62	65	72	15	1.00	69	19.4	25.9		
S	2	C	38.0	26.0	32.0	68	84	x	102	102	95	—	95	96	128	88	13	1.15	84	18.8	22.2		
	mean					73.8	98.3		79	71	70	82	78	103	98	88	21	0.82	121	20.1	21.4		

av. $J_{max.-min.} = 1.3$

and disturbances in the neurological responses and reflexes in the transplanted head and neck. About four hours later, the host dog was brought down in shock and sacrificed with the transplanted head and neck. One of the causes of the damage in the transplanted brain was considered to be due to the cerebral recirculation with the heterologous blood. At any rate, well balanced cerebral recirculation was maintaineed successfully for about 6 hours in the posthypothermic period within the transplanted brain which had been reserved at 15 degrees C with complete cerebral ischemia for 3 hours and 20 minutes.

DIFFERENTIAL COOLING OF THE BRAIN COMBINED WITH ARTIFICIAL SYSTEMIC HEMODILUTION AND WITH SUSTAINED HYPOTHERMIC CEREBRAL PERFUSION AT EXTREMELY LOW RATE OF FLOW

The cerebral hypothermia was induced at about RC_{d15} 0.82, ranging from 0.33 to 1.25 degrees C per minute with perfusion flow 5.0, ranging between 4.0 and 6.0 ml/kg/min (Table 5, and Figs. 17 & 18). However, the maximum rate of 10 ml/kg/min or more was temporarily needed to initiate the brain cooling in cases in which the systemic blood pressure was sustained higher above 80 mmHg. Under these conditions, the course of hypothermic induction was smooth and successful in 8 consecutive dogs and no case showed the gamma-type of variations in cerebral oxygen availability on the terminal phase of the induction. The average time required for the induction perfusion was 21, ranging from 12 to 45 minutes. The values of θ_{d15} were distributed between 52 and 270, averaged to 121 % per degree C per minute. During the period of hemodilution, the relative hematocrit decreased down to about 73.8 % to the original control value, ranging from 68 to 86 %, with the posthypothermic recovery 98.3, ranging between 84 and 125 %. The lowest value of hematocrit in hemodilution was 24.8 %, whereas of the original control blood being 34.1 %. The maximum hematocrit values of the original control blood and in hemodilution were 51.5 and 41.9 %, respectively. The average values of Eq.CAO_2 on the first and the second phases of induction were 79 (ranging from 58 to 102) and 71 (ranging from 54 to 102) %, respectively.

During the period of maintenance of cerebral hypothermia, the particular cerebral hypothermic perfusion was sustained at the average rate of flow of 2 0, ranging between 1.0 and 3.0 ml/kg/min either continuously or intermittently, under the condition of hemodilution with the average $R.Htc_{hd}$ 73.8 %. The low flow rate of cerebral perfusion was always sustained for at least 10 minutes immediately following the relatively high flow rate of induction perfusion. The gamma phenomenon of CAO_2 was completely absent in each brain. The Eq. CAO_2 declined an average of only 1 % on the third phase of induction. Neither paradoxical phenomenon in CAO_2 nor ischemic cerebral rewarming developed in cooled brain throughout the second stage of hypothermia. The average value of cerebral rewarming was restricted within 4.3 degrees C, ranging from 2 0 to 8.5 degrees C, whereas ranging only between 2.0 and 4.1 degrees C in the cases of profound hypothermia and, on the other hand, restricted within the excess of 2.9 to 4 8 above 23 degrees C in the cases of more mildly profound hypothepmia. The mean of the average Eq.CAO_2 values at the second stage was 78 %, ranging from 58 to 95 % (Table 5). The controlled continuous or intermittent hypothermic perfusion over the period of 50 minutes did not result in decrease either of the rectal or the esophageal temperatures

below 30 degrees C. Moderation of cerebral hypothermia sustained the systemic blood pressure higher.

During the stages of cerebral rewarming after the release of arterial inflow to the brain, the body temperature-variations occurred on the equal course as in the conventional technique to the terminal equilibrium. The Eq. CAO_2 demonstrated the initial immediate recovery to an average of 103, ranging from 85 to 153 % except one case of 62 % in which the recovery was delayed, on the release of cerebral inflow. No severe rebound phenomenon was observed on the second phase of the third stage, the average Eq. CAO_2 being sustained at 98 %. In the equilibrium at the brain temperature of 33 degrees C during the fourth stage (generalized rewarming), the average Eq. CAO_2 was sustained at 88 %, ranging between 72 and 111 %. No paradoxical phenomenon of CAO_2 developed during the period of rewarming in each case of the experiments, except one case of arrested CAO_2 with poor hemodilution at the second and the third stages (Table 5).

All the cases of the 8 consecutive animals survived the procedures, including 2 neurological and 6 long term survivals. Moreover, one female survival became pregnant postoperatively and was delivered of a young. Histological examination showed no pathological findings in each brain.

DISCUSSION

1. Selective Brain Cooling

The theoretical value of the selective brain cooling is based upon the reduction of metabolic activities preferentially within the brain without cooling the systemic organs and tissues unfavourably. However, the practical value of the conventional techniques of selective brain cooling by means of arterio-arterial shunt has still the following problems : 1) the tendency to ventricular fibrillation[143)150)162)] caused by undue cooling of the heart due to infinite return of cooled venous blood from the head and neck (LOUGHEED and KAHN[105)]), 2) the posthypothermic increase in the hemorrhagic tendency within the cooled brain (HAYASHI[71)]), 3) no adequate indicator which can indicate the safe period of time of circulatory arrest[14)28)81)125)135)166)], 4) the posthypothermic cerebral damage, and 5) the intractable arterial leakage into the brain[6)49)81)83)85)147)149)163)], etc.

1) Ventricular fibrillation : No case showed the ventricular fibrillation, when the brain was perfused by the cooled blood below 8 degrees C at the perfusion rate less than 10 ml/kg/min, and when the perfusion was sustained intermittently or continuously below 3 ml/kg/min throughout the entire period of cerebral hypothermia, over 50 minutes.

However, considerable reduction of the systemic blood pressure and heart rate were frequently observed in parallel with lowering of cerebral temperature. These phenomena may be caused not only by cooling of sinoatrial node by cold venous return from the head and neck but also by depressant effect of the cerebral hypothermia, per se, on the cardiovascular system (WHITE & DONALD[164)]). At any rate, these complications, if they occurred, should be eliminated by hypertensors combined with plasma expanders, etc.[165)]

2) Postoperative hemorhagic tendency : Hypothermic cerebral perfusion did not cause the significant alterations in the blood factors of coagulability in our technique, although

a slight deviation was present both in prothrombin time and fibrinogenolysis accompanied with variations in T.E.G. during the period of cerebral hypothermia between the terminal stage of cooling and the initial stage of rewarming (TAKASE[154]). This is probably due to the fact that the capacity of the extracorporeal circuit used in our study was not so large as in the systemic hypothermia, and the perfusion rate was restricted below 10 ml/kg/min[44)160)161)].

3) Indicator : Five out of the 13 consecutive dogs subjected to the conventional technique did not recover from comatose state postoperatively, and all of them revealed the poor values in the cerebral oxygen availability combined with the paradoxical phenomenon in its variation at the individual stage throughout the entire process of selective brain cooling. All cases of the long term survivals and neurological survivals, however, showed the good values in the cerebral oxygen availability. This fact demonstrates that cerebral oxygen availability may be applicable as an indicator for the degree of the cerebral damage[20)36)47)48)82)83)89)112)113)116)136)140)145)167)].

2. Oxygen Tension and Microcirculation

According to KETY[91)92)], the factors influencing the oxygen tension are 1) oxygen tension in the perfusing blood or perfusate, 2) local perfusion rate, 3) rate of oxygen utilization, and 4) certain geometric factors of vascularity, 5) oxygen dissociating ability of the blood including its hemoglobin and plasma, and 6) the rate of extravascular and transvascular diffusion of oxygen.

In this series of experiments, the arterial blood was effectively oxygenated at the moderate hypothermic pulmonary temperatures around 30 degrees C, and then cooled down to the deep-temperatures below 10 degrees C. through the heat exchanger, thereafter perfused the cerebral tissue during hypothermic perfusion.

Under profound hypothermia, rich oxygenation of the blood is significantly necessary because of the leftward shift of oxygen dissociation curve of oxyhemoglobin[12)14)16)22)39)58)119)128)131)151)], although the change with temperature cannot be accounted for solely by the change in oxygen solubility in the water component of the blood. In the physiological state of microcirculation under profound hypothermia, hemoglobin is not effective, and the amount of readily available oxygen which is physically dissolved in the plasma plays the principal role in oxygen consumption in the tissue[128)131)151)]. Consequently, hemodilution is found reasonably effective. However, in the circumstances of tissue hypoxia due to breakdown of equilibrium between microcirculation and metabolic demand of oxygen, the more steep slope of oxyhemoglobin dissociation curve affected by hypothermia combined with rightward shift of its dissociation curve caused by decreasing pH takes a considerable share in homeostatic restoration within the anoxic tissue[22)151)]. Besides, it is reasonably evident that the cold oxygenated blood is more potential to discharge its oxygen to the warmer cerebral tissue due to the rightward return of its dissociation curve and decreasing solubility of the physically dissolved oxygen on its rewarming during perfusion, and vice versa. Therefore, oxygenation of the blood is more effective at the lower temperatures. When pure oxygen is breathed, the total quantity of dissolved O_2 is calculated to approach 2 vol. % of the blood at 38 degrees C. and approximate to 2.45 vol. % at 30 degrees C[22)131)]. Since physiological venous pO_2 is supposed not to be below 35 mmHg,

oxygenation of the blood at 30 degrees C can supply 2.3 vol. % oxygen with respect merely to the dissolved oxygen[156]. Hemodilution is able to increase the readily available amount of the dissolved oxygen in the blood[29-31)37)59-61)63)104]. On the other hand, the CO_2 content is computed to increase as much as 25 % in cooling from 38 degrees C to 20 degrees C without alteration in the pCO_2 and pH[131]. Since the physiological effect of CO_2 depends on pCO_2 and pH, hypothermic increase in blood CO_2 content without alterations in pCO_2 and pH is of importance in the cerebral hypothermia and its evaluation from blood gas variations. PATTERSON[127] reported that increase in pCO_2 as much as 4.5 mm Hg gave an influence on the normothermic cerebral vessels, and NIAZI and LEWIS[120] accordingly utilized carbogen to obtain good microcirculation during hypothermia.

The significant decrease in oxygen consumption is brought about along with the reduction in body temperature with the almost linear relationship between the lowering in body temperature and the reduction in oxygen consumption[12)16)131)132)133].

However, even in the deep hypothermia less than 10 degrees C, the considerable oxygen consumption is still measured within the brain and it may cause irreversible cerebral damage during total circulatory arrest, if excessively prolonged[7)8)119]. An oxygen consumption is said to become approximately 10 % at 10 degrees C, and about 5 % at 5 degrees C to the normothermic control values (GOLLAN[58-60]), an average of 3 to 4 % around 10 degrees C (BJÖRK[14-16]) and approximates 15 to 17 % around 10 degreees C (NEVILLLE et al.[119] and BERNHARD et al.[7)8]).

The decrease of cerebral blood flow is also observed in parallel with the decrease of cerebral oxygen consumption at a rate of 6.7 % per degree C with the almost constant arteriovenous oxygen differences.

Therefore, hypothermia probably produces no hypoxia of brain tissue so long as adequate oxygenation and circulation are maintained.

In the present investigation in dogs with respect to the profound hypothermia below 23 degrees C induced by the conventional technique of selective brain cooling, the critical values were demonstrated by the polarographical cerebral oxygen availability. These critical values are given by an exponential function to the brain temperature. They parallel to the data by GOLLAN and others[58-61)80)146], the rate of reduction in the critical oxygen availability being determined approximately as 6 % per every exponential degree C, or given by crit. Eq. $CAO_2 = (90\ \%$ of control Eq. $CAO_2) \cdot (70/100)^{\frac{38-t}{5}}$. The paradoxisal phenomenon accompanied by decreased cerebral oxygen availability, which being not infrequently observed in the period of rewarming or during hypothermic cerebral ischemia is demonstrated to play an important role in postoperative comatose fate of the animal. This fact is found to be supported by ADOLPH's in vitro studies of tissue homogenates and oxidizing enzyme system (cytochrom oxidase)[9)10)101] and also compatible with the results of OPITZ[50)156].

3. Polarographical cerebral oxygen availability and its value.

The polarographical cerebral oxygen availabilty is the integral of the tissue oxygen metabolism, the microcirculation and the perfusate oxygenation, with respect to the indivi-

dual steady temperature[27)34)35)]. Since the technique concerns the blood cooling followed by cerebral hypothermia, the variations in the cerebral oxygen avilability and the alterations in the cerebral temperature, ought to parallel according to the respective coefficient for the cerebral tissue. Accordingly, the principal agent to cause the variation in the cerebral oxygen availability measured by the use of CLARK[25)] oxygen electrode on approximately 4.2 mm^3 or less of the cerebral cortex involving pia mater is found in the state of microcirculation.

The diffusion coefficient of oxygen for the cerebral grey matter was determined by THEWS[156)] as 1.1×10^{-5} $cm^2/sec.$ at 20 degree C (rat) and calculated to 37 degrees C as 1.6. KROGH's oxygen conductivity "K" is given, by oxygen diffusion coefficient "D" and oxygen solubility coefficient "a" as $D=\frac{K}{60a}$. According to the diffusion theory, the extracapillary diffusion is another determining factor in the condition of oxygen supply to the cerebral tissue. In the cerebral grey matter in rat, mouse and frog, investigated by THEWS, the value of "D" approximates to 65 % and 69 % to that in water at 20 and 37 degrees C, whereas oxygen solubility "a" is about 94 % and 128 %, respectively[156)]. In the steady-state-diffusion, the diffusion layer is determined by $D^{1/2}$, or more dependent upon $K^{1/2}$ within the brain[117)148)152)]. In the state of unstable equilibrium as in the cerebral perfusion hypothermia, these diffusion factors are found, more or less, complicated to concern the oxygen transport within the cerebral tissue following the alterations in the microcirculation[45)136)].

The cerebral oxygen availability in the territory of the middle cerebral artery is supposed to represent the entire brain. Accordingly, the continuous determination of the cerebral oxygen availability on this area indicates the microcirculation in the brain. When the discrepancy of the ability of oxygen uptake takes place during cerebral occlusion, the paradoxical ischemic rewarming occurs. The critical ualue of θ during the induction of cerebral hypothermia was determined as 35 (% Eq.CAO_2 per degree C cerebral temperature fall per minute) with respect to the average rate of the brain cooling down as much as 15 degrees C. The three comatose cases belong to the poor values of θ below 34, whereas above 60 in every case of survivals.

The blood is distributed in accord with the regional metabolic needs of the tissues and the effective removal of cellular byproducts. The chief factors to determine the effectiveness of microcirculation consist of : 1) intrinsic vasomotor adaptations, 2) pressure-flow and pressure-diameter relations within the terminal vascular bed, and 3) the number of the active capillaries, which is selectively affected depending upon the volume flow by the arterial pressure, the venular resistance, the behaviors of the precapillary sphincters, and local changes in smooth muscle tone. The capillary flow is, accordingly, determined by : 1) inflow into arteriolar vessels, 2) capacity of the capillary bed, and 3) outflow via venules. According to ZWEIFACH[169)], the inflow into the capillary via the arterioles is influenced by blood pressure, peripheral vascular resistance (arteriolar tone), and blood volume, and the capacity of the capillary bed is determined by pericapillary behavior, vasomotion, and mean pressure in capillaries, while the outflow via venules being determined by humoral and neurogenic vascular tone, pressure-diameter interaction, shunts and

local or central reflexes. Thus, the local regulation of blood flow is generally considered accomplished by the feed-back phenomena through functional behavior of the microcirculation.

In the present experiments, a predominant increase in the perfusion pressure is a initial routine in conjunction with a significant increase in the systemic blood pressure on cervical arterial ligations, indicating a considerable increase in the cerebral vascular resistance. However, this occurs very transiently and followed by a predominant reduction in the perfusion pressure and the systemic blood pressure as the brain is cooled. Changes in the small vessels may be the cause of most of the unfavourable effects of hypothermia. Increase in peripheral vascular resistance, the constriction of small vassels, and the increase in blood viscosity, follow the reduction in the body temperature during hypothermia[10-13)75)107)]. The constriction of the small vessels, is an important cause of the increase in the vascular resistance in association with the disturbance in cardiovascular function and hemodynamics[6)21)49)64)75)76)78)149)167)]. Another important factor of the increase in vascular resistance is the increase in blood viscosity during hypothermia[17)29)37)63)90)101)110)]. The blood viscosity increases merely physicochemically in parallel with the lowering of its temperature in vitro. The increase of hematocrit due to hemoconcentration during hypothermia is potential to produce the predominant increase in the blood viscosity. These alterations in the small vessels and blood causing the increase in vascular resistance, however, are evidently potential enough to produce the considerable disturbances in the microcirculation during hypothermia. The intravascular aggregation of the blood or blood sludging also accompanies with these alterations[3)16)17)33)40)52-57)61)74)77)90)94)103)121)157)]. BJÖRK[14-16)] reported that the primary cause of brain damage of hypothermia may be attributable to the intavascular aggregation and capillary thrombosis. BOND and his co-workers[17)] also recognized this fact. KEEN and GERBODE[90)] reported that the IVA initiated around 32 degrees C by lowering the arterial pressure 35 mm Hg, although, according to BOND and his co-workers[17)], it initiated at 28 degrees C and increased in parallel with the reduction in temperature to the pronounced state during profound hypothermia. KEEN and GERBODE[90)] reported that the principal agents causing intravascular aggregation of the blood during hypothermia were thought to be prolonged perfusion, which causes denaturation of the plasma proteins and its coating on the erythrocytes surfaces. ÅSEN et al[3)]. and GELIN and LÖFSTRÖM[52)] reported a good correlation between the degree of IVA and the decrease in suspension stability of the blood. Suspension stability of the blood is reduced by alterations in plasma proteins involving the increase of alpha and beta globulin, alpha and beta lipoproteins, and protein bound carbohydrates, fibrinogen and the reduction in albumin and intravascular albumin pool without considerable change in gamma globulin catabolic enzymes[40)41)52)103)]. Thus, the use of low molecular weight dextran was introduced to the treatment of IVA by THORSÉN and HINT[157)] and GELIN[52-57)].

Hemodilution combined with the use of low molecular weight dextran has been reported successfully performed in the extracorporeal circulation hypothermia (COOLEY et al.[29-31)] and DEWALL et al.[37)]). Approximately 16 to 20 ml/kg of 5 % low molecular weight dextran in distilled water are usually used. No homologous blood syndrome[51)] occurred.

In the early experiments of the present study, only 4 dogs of long term survival were obtained, and 5 comatose fatal cases demonstrated poor cerebral oxygen availability and its paradoxical phenomenon. On the contrary, all cases subjected to hemodilution technique combined with sustained cerebral perfusion at extremely low flow rate demonstrated no paradoxical phenomenon in cerebral oxygen availability with poor values below the critical nor the post-operative comatose death. In the later experiments the total cerebral circulatory arrest was obviated and the brain was perfused intermittently or continuously at the low flow rate of 1 to 3 ml/kg/min and the systemic hemodilution was performed to the percent decrease in hematocrit of 68 to 86 % (average : 73 8 %) to the control values. In these the cerebral hypothermia was successfully moderated up to the temperatures between 23 and 28 degrees C utilizing this combined technique. Therefore, the hemodilution combined with the sustained cerebral perfusion could prevent disturbance in the cerebral microcirculation and obviate the posthypothermic cerebral damage.

Throughout the entire process of the procedure and the postoperative course of the technique, it should be regulated adequately in the systemic blood pressure and the perfusion pressure[5)24)26)32)38)42)73)86)99)136)139)141)142)144)153)155)].

Although GOLLAN[58-61)] and others[14-16)95)96)] reported the successful cases of extremely profound hypothermia below 10 degrees C, the hypothermia is always depressant in its effect on the living organs and tissues of non-hibernators[129)] and there have been many reports of the cerebral damage attributable to the severe hypothermia per se. BJÖRK[14-16)] reported the cases of children patients suffered from the posthypothermic cerebral damage which could be attributed to the deep hypothermia per se. The diffuse change involving the cerebral cortex especially in the territory of the middle cerebral artery, the hippocampus, the thalamus, the globus pallidus, and the PURKINJE cells were observed. LEASAGE[100)], reported the spinal cord lesion accompanied with the cerebral damages. Many others also reported the changes in PURKINJE cells. The early breakdown of the blood-brain barrier was added to these reports.[20)] Accordingly, as concerned with the hypothermia by means of extracorporeal thermoregulation, the severe and/or excess cooling of the brain should be obviated[78)84)].

4. Improved technique of selective brain cooling

It should be remembered in neurosurgery that the hypothermia is not only a well designed effective technique to carry out the bloodless or avascular craniotomy but also an arbitrary adjunct if not controlled adequately. Both hazardous techniques and undesirable surplus of influences of the hypothermia per se upon both the cerebral tissue and the systemic organs, to any extent, should be eliminated out of the techniques. Besides, it is an ideal pattern of the techniques that it permits the limitless and safe avascular or bloodless craniotomy clinically.

For these reasons, in the later experiments of the present study, the conventional technique of the selective brain cooling by means of carotico-carotid shunt was attempted to improve based upon following ideas ; 1) the cerebral microcirculation is indicated by the use of polarographical technique throughout the entire process of the hypothermia, 2) the total cerebral inflow occlusion is to be obviated, and the cerebral perfusion is to be sustained and regulated neither to cause cerebral anoxia nor to disturb the avascular

craniotomy, 3) the systemic hemodilution is to be performed in order to prevent the disturbances of both systemic and cerebral microcirculation, 4) the circuit is to be primed with the artificial blood substitutes involving the IVA inhibitor[65-67)104)] (low molecular weight dextran), 5) the cerebral vascular bed is to be washed out prior to the blood perfusion, 6) the moderation of the profundity of hypothermia is to be considered, 7) the systemic blood pressure and the perfusion pressure are to be regulated adequately

Table 6 The process of the combined technique in man.

A Clinical Case of the Avascular Craniotomy utilizing the Differential Brain Cooling Combined with Systemic Hemodilution and Sustained Hypothermic Cerebral Perfusion at Controlled Low Flow Rate

Patient : a 27-year-old man. Y. Y. Operated on, on June 21, 1962.

Neurosurgical Diagnosis : Glioblastoma Multiforme (a huge one in 1. frontal lobe).

I) *Stages, Procedures and Periods of Time*

Stages		Procedures	Arterial Inflow to the Brain	Period of Time (min.)	(Total)
I. Induction	(a)	Preliminary Cerebral Perfusion	free	14	
	(b)	Induction Cooling	occluded	27	41
II. Maintenance	(a)	Total Circulatory Arrest to the Brain	occluded	50	
	(b)	Sustained and Controlled Cerebral Perfusion	occluded	197	247
III. and IV. Rewarming		Release of Cerebral Inflow Occlusion and Cerebral Rewarming above 32 degrees C	recirculated	187	

II) *Main Events during Cerebral Hypothermia*

Total Period of Time of Cerebral Arterial Inflow Occlusion			274 minutes
Maintenance of Cerebral Deep Hypothermia			over 390 minutes
Range of Cerebral Hypothermia			
The Lowest Brain Temperature Induced			
		On Perfused Side	16.6 deg C
		On Non-Perfused Side	20.7 deg C
The Highest Brain Temperature during Hypothermia			
		On Perfused Side	25.5 deg C
		On Non-Perfused Side	27.2 deg C
Conditions of Induction			
(Rate of Cooling)	RC_{d15}	On Perfused Side	0.56 deg C/min.
	RC_{d10}	〃	1.00 deg C/min.
		On Non-Perfused Side	0.44 deg C/min.
θ = Eq. CAO_2/RC	θ_{d15}	On Perfused Side	216 %/deg C/min.
	θ_{d10}	On Non-Perfused Side	252 %/deg C/min.
Cerebral Oxygen Availability (Eq. CAO_2) (% to the preoperative control)			
		During Induction	105 to 125 (average : 115)
		During Maintenance	93 to 123 (average : 106)
		During Rewarming	70 to 114 (average : 87)

not to cause the disturbances of systemic microcirculation, the arterial leakage into the brain, the excess cooling of the heart by the cold venous return with sequel of ventricular fibrillation, nor posthypothermic cerebral damage due to high pressure perfusion.

The characteristics of the improved technique are :

1) The capacity of the extracorporeal circuit is less than 250 ml. The oxygenator is eliminated, the circuit consists of only the pump-heat exchanger unit, and connected with carotico-carotid shunt.

2) The perfusion pressure is regulated in parallel or 10 to 20 mm Hg higher than the systemic blood pressure during induction, and approximately equal to or less than that during low flow perfusion.

3) The cooling rate of the brain is limited within the range of the values between 0.3 and 1.25 degrees C/min. in 15 degrees C cerebral cooling.

4) The hemodilution is so performed as indicated by hematocrit values of around 70 % in percent alteration to the control values. Hemodilution can be done via the circuit or intravenous infusion of 5 % glucose solution, Ringer's solution, and low molecular weight dextran.

5) The circuit is primed with only these solutions, without using the blood. On the initiation of pumping, the solutions wash out the cerebral vascular bed.

6) The cerebral oxygen availability indicates the circumstances of cerebral microcirculation, which are to be regulated above the critical values. The perfusion is sustained throughout the period of hypothermia at the adequate perfusion rates between 1 to 3 ml/kg/min either intermittently or continuously. Intermittent wash-out perfusion is permitted effectively.

7) The systemic blood pressure is to be maintained at 50 to 70 mm Hg during hypothermia, and at above 70 mm Hg during rewarming, and to normal postoperatively.

8) The cirtical values of the cerebral oxygen availability are :

$$\text{crit. Eq. } CAO_2 = 90\ (70/100)^{\frac{38-t}{5}}\ (\%)$$

$$\text{crit. } {}_1\vartheta_{d15} = 35 \quad \cdots\cdots\cdots\cdots\cdots\cdots (\theta = \text{Eq. } CAO_2/RC)$$

$$(\text{max. crit. } RC_{d15} = 2.00,\quad \text{min. crit. } RC = 0.30)$$

9) The profundity of the hypothermia is reduced in its degree. It is to be performed between 23 and 28 degrees C. The profound hypothermia is also applicable between 15 and 23 degrees C.

CLINICAL APPLICATION

In two cases of glioblastoma multiforme, the technique of the differential brain cooling was performed. One case was lost due to the technical failure. However, another case was successful. The patient was a 27-year-old man. Neurological examinations revealed a large brain tumor in the left frontal lobe. On June 21, 1962, the patient's brain was cooled utilizing the combined technique of differential cerebral hypothermia through the left carotico-carotid shunt with systemic hemodilution and sustained intermittent cerebral perfusion (Table 6 and Fig. 18). Bilateral carotid and vertebral arteries were ligated temporarily for the procedure, and the cerebral circulation was brought into the regulation

over the period of 4 hours and 34 minutes (274 minutes) under the conditions of profound cerebral hypothermia. Moderation of cerebral hypothermia was attempted for 26 minutes immediately before the cerebral recirculation on release of cerebral arterial ligations. The hypothermic cerebral temperatures ranged 16.6 to 25.5 degrees C on the side of perfusion, and 20.7 to 27.2 degrees C on the contralateral side of perfusion. The total induction time was 41 minutes, which involved 27 minutes of brain cooling after the ligations of carotid and vertebral arteries. The total cerebral inflow occlusion was performed intermittently for 50 minutes in total. The average cooling rate for 10 degrees C brain cooling was 1.00 ($RC_{d10}=1.00$ degrees C/min.) on the perfusion side, and 0.44 ($RC_{d10}=$ 0.44 degrees C/min) on the contralateral side of perfusion, during induction of the cerebral hypothermia. The value of equilibrated cerebral oxygen availability per unit value of average rate of brain cooling was 216 %/degree C per min for 15 degrees C brain cooling ($\vartheta_{d15}=216$) on the perfusion side, and 252 %/deg. C per min for 10 degrees C brain cooling on the contralateral side of perfusion ($\vartheta_{d10}=252$), respectively. The values of the cerebral oxygen availability were 105 to 125 % (average : 115 %) during induction, 93 to 123 % (average : 106 %) during sustained hypothermic period, and 70 to 114 % (average : 87 %) during rewarming. Each of them was sustained above the critical values. The Eq. CAO_2 was lower during rewarming than others. It may be attributable to the systemic blood pressure.

The data indicated there was no sign of the disturbance of cerebral microcirculation, nor of the cerebral anoxia. The course of hypothermia was smooth and well balanced.

The neurosurgical procedures were carried out fairly in avascular circumstances. No ventricular episode was observed.

The patient was better conscious postoperatively. No clinical deterioration of neurological findings was observed postoperatively over several weeks until the patient died.

SUMMARY AND CONCLUSION

The use of selective brain cooling in neurosurgery must be re-evaluated.

1. Studies have been carried out to determine the cerebral microcirculation and ischemic anoxia during cerebral hypothermia by the use of polarographical technique.

2. Selective hypothermia of the brain has been induced in dogs utilizing the conventional technique with carotico-carotid shunt. By this method the brain can be cooled to the profound hypothermic temperatures below 23 degrees C without the sequel of ventricular fibrillation by regulating the hypothermic cerebral perfusion. No predominant hemorrhagic lesion is resulted.

3. Paradoxical phenomenon has been demonstrated in the cerebral oxygen availability and the disturbance of cerebral microcirculation has been indicated during procedures, followed by posthypothermic cerebral damage. The event has been observed at every stage of the cerebral hypothermia, especially during 30 minutes circulatory arrest to the brain (paradoxical ischemic rewarming) and during cerebral rewarming after recirculation to the brain (paradoxical poor rewarming). The efficacy of hypothermic cerebral perfusion has been demonstrated (gamma phenomenon on the cessation of perfusion).

4. The combined technique of selective brain cooling with hemodilution and sustained

low flow perfusion has been potential to obviate the disturbance of cerebral microcirculation, and to reduce the profundity of the hypothermia. Moderation of the hypothermia has been accomplished to 23 to 28 degrees C by the combined method.

5. The primary agent to cause the posthypothermic brain damage has been attributed to the persistent disturbance of cerebral microcirculation. Initiation of the disturbed microcirculation is thought attributable to the increase in blood viscosity. Intravascular aggregation is found potential to cause persistency of the disturbance of cerebral microcirculation. Low molecular weight dextran has been introduced into the method.

6. A successful case of the combined method has been obtained in clinical application over ther the period of 4 hours and 34 minutes of cerebral circulatory contol and avascular craniotomy.

7. The use of artificial blood substitutes for prime of circuit and hemodilution can eliminate not only troublesome need of fresh blood but also hematological complications such as homologous blood syndrome (Gadbodys et al.[51]) and hepatitis.

8. The combined method permit the almost limitless bloodless craniotomy to be performed under the controlled cerebral blood flow without causing either the disturbance of the cerebral microcirculation followed by the cerebral anoxia or the sequel of the cardiac episode and the systemic implications.

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REFERENCES

1) Adams, J. E., and Wylie, E. J. : Value of hypothermia and arterial occlusion in the treatment of intracranial aneurysms. Surg. Gynec. Obstet., **108** : 631, 1959.
2) Anderson, S. and McKissock, W. : Controlled hypotension with Arfonad in neurosurgery : With special reference to vascular lesions. Lancet, **2** : 754, 1953.
3) Åsén, P., Böttiger, L. E., Engstedt, L., Liljedahl, S. O., Zetterström, B., and Birke, G. : Studies on trauma. I. Intravascular aggregation of erythrocytes and changes in serum proteins and protein-bound carbohydrate. Acta Chir. Scand., **130** : 399, 1965.
4) Bakay, L. and Benediken, H. H. : Central nervous system vulnerability in hypoxaemic state. Isotope uptake studies. Selective Vulnerability of the Brain in Hypoxaemia ; A symposium organized by the Council for International Organizations of Medical Sciences, p 79, Philadelphia : F.A. Davis Co., 1963.
5) Bellman, S., Lambert, P. B. and Fine, J. : Microscopic observations of the mesenteric circulation in rabbits subjected to reversible and irreversible haemorrhagic shock. Shock : Pathogenesis and therapy ; An International Symposium 1961, p. 96, Berlin Göttingen Heidelberg : Springer-Verlag, 1962.
6) Bendandi, G. and Galletti, G. : Temperature distribution in the brain during profound selective cooling and anoxia of central nervous system. J. Cardiovas. Surg., **4** : 65, 1963.
7) Bernhard, W. F., Schwarz, H. F., Leand, P. M. and Carr, J. G. : Studies in balanced hypothermic perfusion. Surgery, **50** : 911, 1961.
8) Bernhard, W. F., Schwarz, H. F. and Mallick, N. P. : Intermittent cold coronary perfusion as an adjunct to open heart surgery. Surg. Gynec. Obstet., **111** : 741, 1960.
9) Bergentz, S.-E. and Danon, D. : Alterations in red blood cells of traumatized rabbits. I. Decreased filterability. Acta Chir. Scand., **130** : 165, 1965.
10) Bigelow, W. G., Callaghan, J. C. and Hopps, J. A. : General hypothermia for experimental intracardiac surgery. Ann. Surg., **132** : 531, 1950.
11) Bigelow, W. G., Lindsay, W. K., Greenwood, W. F. : Hypothermia : its possible role in cardiac surgery.

Ann. Surg., **132** : 849, 1950.
12) Bigelow, W. G., Lindsay, W. K., Harrison, R.C. Gordon, R. A. and Greenwood, W. F. : Oxygen transport and utilization in dogs at low body temperatures. Amer. J. Physiol., **160** : 125, 1950.
13) Bigelow, W. G., Heimbecker, R. O. and Harrison, R. C. : Intravascular agglutination (sludged blood), vascular stasis and sedimentation rate of blood in trauma. Arch. Surg., **59** : 667, 1949.
14) Björk, V. O. : An effective blood heat exchanger for deep hypothermia in association with extracorporeal circulation but excluding the oxygenator. J. Thoracic Cardiovas. Surg., **40** : 237, 1960.
15) Björk, V. O. and Hultquist, G. : Brain damage in children after deep hypothermia for open-heart surgery. Thorax, **15** : 284, 1960.
16) Björk, V. O. and Holmdahl, M. H. : The oxygen consumption in man under deep hypothermia and the safe period of circulatory arrest. J. Thorac. Cardiovas. Surg., **42** : 392, 1961.
17) Bond, T. P., Derrick, J. R. and Guest, M. M. : Microcirculation during hypothermia. (High speed cinematograph studies). Arch. Surg., **89** : 887, 1964.
18) Botterell, E. H., Lougheed, W. M., Scot, J. W. and Vandewarter, S. L. : Hypothermia, and interruption of carotid, or carotid and vertebral circulation, in the surgical management of intracranial aneurysms. J. Neurosurg., **13** : 1, 1956.
19) Botterell, E. H., Lougheed, W. M., Morley, T. P. and Vandewarter, S. L. : Hypothermia in the surgical treatment of ruptured intracranial aneurysms. J. Neurosurg., **15** : 4, 1958.
20) Broman, T. : Comments about the blood-brain barrier in hypoxia and hypocapnia. Selective Vulnerability of the Brain in Hypoxaemia ; A symposium organized by the Council for International Organizations of Medical Sciences, p. 79, Philadelphia : F. A. Davis Co., 1963.
21) Buster, C. D., Pevehouse, B. C. and McKorkle, H. J. : Cardiovascular changes associated with selective brain cooling in the dog. Surg. Forum, **9** : 212, 1958.
22) Callaghan, P. B., Lister, J., Paton, B. C. and Swan, H. : Effect of varying carbon dioxide tensions on the oxyhemoglobin dissociation curves under hypothermic conditions. Ann. Surg., **154** : 903, 1961.
23) Cassie, G. F., Couch, N. P., Dammin, G. J. and Murray, J. E. : Normothermic perfusion and replantation of the excised dog kidney. Surg. Gynec. Obstet., **109** : 721, 1959.
24) Christofferson, E., Hallberg, L., Lindell, S.-E., Sölvell, L. and Westling, H. : Some circulatory reactions during provoked dumping. Acta Chir. Scand., **130** : 224, 1965.
25) Clark, L. C., Jr., Larrabee, M. G., Pandazi, A. A., Shephard, R. H. and Sonnenschein, R. R. : Discussion in the symposium on tissue oxygen tension. Chicago, April 17, 1959. Fed. Proc., **16** : 699, 1957.
26) Cockett, A. T. K. : The kidney and regional hypothermia. Surgery, **50** : 905, 1961.
27) Connelly, C. M. : Method for measuring tissue oxygen tension ; theory and evaluation : the oxygen electrode. Fed. Proc., **16** : 681, 1957.
28) Connolly, J. E., Boyd, R. J. and Calvin, J. W. : The protective effect of hypothermia in cerebral ischemia : Experimental and clinical application by selective brain cooling in the human. Surgery, **52** : 15, 1962.
29) Cooley, D.A., Beall, A. C., Jr. and Grondin, P. : Open-heart operations with disposable oxygenators, 5 percent dextrose prime, and normothermia. Surgery, **52** : 713, 1962.
30) Cooley, D. A. : Extracorporeal circulation in cardiac surgery. Surg. Gynec. Obstet., **106** : 615, 1958.
31) Cooley, D. A., DeBakey, M. E. and Morris, G. C. : Controlled extracorporeal circulation in surgical treatment of aortic aneurysm. Ann. Surg., **146** : 473, 1957.
32) Couch, N. P., Cassie, G. F. and Murray, J. E. : Survival of excised dog kidney perfused in a pump-oxygenator system-I. circulatory changes in hypothermic preparation. Surgery, **44** : 666, 1958.
33) Crowell, J. W. and Smith, E. E. : Effect of fibrinolytic activation on survival and cerebral damage following periods of circulatory arrest. Amer. J. Physiol., **186** : 283, 1956.
34) Davies, P. W., and Brink, F., Jr. : Direct measurement of brain oxygen concentrations with a platinum electrode. Fed. Proc., **1** : 19, 1942.
35) Davies, P. W. and Bronk, D. W. : Oxygen tension in mammalian brain. Fed. Proc., **16** : 689, 1957.
36) Dawes, G. S. : Comments about brain circulation, oxygen supply and anoxic survival. Selective Vulnerability of the Brain in Hypoxaemia ; A symposium organized by the Council for International Organizations of Medical Sciences, p. 37, Philadelphia : F. A. Davis Co., 1963.
37) DeWall, R. A., Lillehei, R. C. and Sellers, R. D. : Hemodilution perfusions for open-heart surgery : Use of five per cent dextrose in water for the priming volume. New Eng. J. Med., **266** : 1078, 1962.
38) De Weese, J. A., Jones, T. I., McCoord, A. and Mahoney, E. B. : The beneficial effects of coronary

perfusion on the hypothermic myocardium during caval occlusion. Surgery, **46** : 733, 1959.
39) Dill, D. B. and Forbes, W. H. : Respiratory and metabolic effects of hypothermia. Amer. J. Physiol., **132** : 685, 1941.
40) Ditzel, J. : The nature of the intravascular erythrocyte aggregation in diseases with particular reference to diabetes mellitus. Acta Med. Scand., **152** : 371, 1955.
41) Ditzel, J. : Relationship of blood protein composition to intravascular erythrocyte aggregation (sludged blood). Acta Med. Scand. Suppl., 345, 1959.
42) Doberneck, R. C., Schwarz, F. D. and Barry, K. G. : A comparison of the prophylactic value of 20 per cent mannitol, 4 per cent urea, and five per cent dextrose on the effects of renal ischemia. J. Urol., **89** : 300, 1963.
43) Drew, C. E. and Anderson, I. M. : Profound hypothermia in cardiac surgery : Report of three cases. Lancet, **1** : 748, 1959.
44) Dybkjaer, E., Berg, E. and Kissmeyer-Nielsen, F. : Coagulation studies in extracorporeal circulation. Acta Chir. Scand., **128** : 350, 1964.
45) Eckert, E. R. G. and Drake, R. M., Jr. : Heat and mass transfer. Sec. Edit. pp 25-120, pp 419-492, New York · McGraw-Hill Book Co., 1959.
46) Edwards, W. S., Tuluy, S., Reber, W. E., Siegel, A. and Ring, R. J. : Coronary blood flow and myocardial metabolism in hypothermia. Ann. Surg., **139** : 275, 1954.
47) Epstein, J. A., Lennox, M. A. and Noto, O. : Electroencephalographic study of experimental cerebrovascular occlusion. E. E. G. Journal, **1** : 491, 1949.
48) Ernsting, J. and Benson, A. J. : Some effects of brief profound anoxia upon the central nervous system. Selective Vulnerability of the Brain in Hypoxaemia ; A symposium organized by the Council for International Organizations of Medical Sciences, p 41, Philadelphia : F.A. Davis Co., 1963.
49) Fisher, B., Fedor, E. J., and Smith, J. W. : Temperature gradients associated with extracorporeal perfusion and profound hypothermia. Surgery, **50** : 758, 1961.
50) Franks, W. R. : Measurement of post-mortem lactic acid concentrations in assessing an ante-mortem hypoxia. Selective Vulnerability of the Brain in Hypoxaemia ; A symposium organized by the Council for International Organizations of Medical Sciences, p 47, Philadelphia : F. A. Davis Co., 1963.
51) Gadboys, H. L., Slonin, R., and Litwak, R. S. : Homologous blood syndrome : I. Preliminary observations on its relationship to clinical cardiopulmonary bypass. Ann. Surg., **156** . 793, 1962.
52) Gelin, L.-E. and Löfström, B. : Study of peripheral circulation during deep hypotherma. Observations on decreased suspension stability of blood and its prevention. Acta Chir. Scand., **108** : 402, 1955.
53) Gelin, L.-E. : Studies in anaemia of injury. Acta Chir. Scand. Suppl., 210, 1956.
54) Idem : Disturbance of the flow properties of blood and its counteraction in surgery. Acta Chir. Scand., **122** : 287, 1961.
55) Gelin, L.-E. and Ingelman, B. : Rheomacrodex-a new dextran solution for rheological treatment of impaired capillary flow. Acta Chir. Scand., **122** : 294, 1961.
56) Gelin, L.-E. and Thorén, O. K. A. Influence of low viscous dextran on peripheral circulation in man. A plethysmographic study. Acta Chir. Scand., **122** : 303, 1961.
57) Gelin, L.-E., Sölvell, L. and Zederfedlt, B. : The plasma volume expanding effect of low viscous dextran and macrodex. Acta Chir. Scand., **122** : 309, 1961.
58) Gollan, F., Blos, P. and Schuman, H. : Studies on hypothermia by means of a pump-oxygenator. Amer. J. Physiol., **171** : 331, 1952.
59) Gollan, F., Grace, J. T., Schell, M. W., Tysinger, D. S. and Feaster, L. B. : Left heart surgery in dogs during respiratory and cardiac arrest at body temperatures below 10 degrees C. Surgery, **38** : 363, 1955.
60) Gollan, F., Hamilton, E. C. and Meneely, G. R. : Consecutive survival of open-chest, hypothermic dogs after prolonged bypass of heart and lungs by means of a pump-oxygenator. Surgery, **35** : 88, 1954.
61) Gollan, F., Tysinger, D. S., Jr., Grace, J. T., Kory, R. C. and Meneely, G. R. : Hypothermia of 1.5 degrees C in dogs followed by survival. Amer. J. Physiol., **181** : 297, 1955.
62) Gott, U. and Röttgen, P. : Experiences with selective brain hypothermia with extracorporeal circulation. Excerpta Medica, International Congress Series. No. **60** : 42, 1963.
63) Greer, A. E., Carey, J. M. and Zuhdi, N. : Hemodilution principle of hypothermic perfusion. A concept obviating blood priming. J. Thorac. Cardiovas. Surg., **43** : 640, 1962.
64) Gregg, D. E. : Hemodynamic factors in shock. Shock ; pathogenesis and therapy : An International

Symposium 1961, p 50, Berlin Göttingen Heiderberg : Springer-Verlag, 1962.
65) Groth, C.-G. and Thorsén, G. : Effect of Rheomacrodex and Macrodex on factors governing the flow properties of human blood. Acta Chir. Scand., **130** : 507, 1965.
66) Groth, C.-G. : The effect of infused albumin and Rheomacrodex on factors governing the flow properties of the human blood. Acta Chir. Scand., **131** : 290, 1966.
67) Groth, C.-G. and Löfström, B. : The effect of infused high and low molecular weight dextran on the tissue oxygen tension. Acta Chir. Scand., **131** : 275, 1966.
68) Handa, H. : Discussion in the symposium on extremely profound hypothermia. (The 23rd. annual meeting of the Japan Neurosurgical Society). Morioka, September 23, 1961. Neurologia medico-chirurgica (Tokyo), **6** : 200, 1964.
69) Handa, H. and Ohta, T. : Surgical treatment of cerebral vascular diseases, especially with the use of deep hypothermia. Surg. Therapy (Tokyo), **6** : 72, 1962.
70) Handa, H., Aoyagi, M., Takase, T. and Teraura, T. : Avascular craniotomy with the use of selective brain cooling combined with hemodilution. (IIIrd. Report). The 95 th meeting of the Kinki Surgical Society. Kyoto, June, 6, 1964.
71) Hayashi, F. . Experimental studies of brain cooling in the field of neurosurgery. (Brain tissue changes at ultra-hypothermia and experimental studies of brain operation by means of selective brain cooling). J. J. S. S. (Tokyo), **60** : 962, 1959.
72) Hayashi, H., Hattori, J., Ishihara, A., Yamaguchi, S., Iwamoto, J., Yamanaka, J. and Hashimoto, A. : Studies on extracorporeal circulation (Application of plasma expander. Ist. report). Arch. Jap. Chir., **31** : 862, 1962.
73) Hardaway, R. M., Chun, B. and Rutherford, R. B. : Coagulation in shock in various species including man. Acta Chir. Scand., **130** : 157, 1965.
74) Harders, H. : Über einige klinische Aspekte der intravasalen Erythrocytenballung. Schweiz Med. Wschr., **87** : 11, 1957.
75) Hegnauer, A. H., Shriber, W. J. and Haterius, H. O. : Cardiovascular response of dog to immersion hypothermia. Amer. J. Physiol., **161** : 455, 1950.
76) Hegnauer, A. H. and Angelakos, E. T. : Excitable properties of the hypothermic heart. Ann. N. York Acad. Sc., **80** : 336, 1959.
77) Helmsworth, J. A., Stiles, W. J. and Elstun, W. : Changes in blood cellular elements in dogs during hypothermia. Surgery, **38** : 843, 1955.
78) Hoffman, B. F. : Hypothermia and vulnerability. Ann. N. York Acad. Sc., **80** : 348, 1959.
79) Hoffman, G. R., Rolly, G., Lateur, J., Brandt, H., Evrard, C. and Thirry, S. : Experience of mild hypothermia in the surgery of intracranial aneurysms and angiomas. Excerpta Medica, International Congress Series. No. **60** : 43, 1963.
80) Horvath, S. M., Hutt, B. K., Spurr, G. B. and Stevens, G. E. : Some metabolic responses of dogs having low body temperature. Science, **118** : 100, 1953.
81) 半田 肇，太田富夫，青柳 実，高瀬卓郎：選択的脳冷却法．医学のあゆみ，**52** : 291, 1965.
82) Ingvar, D. H. : Studies of the regional metabolism and circulation of the cerebral cortex. A discussion in the symposium on circulation, blood flow, oxygen diffusion and metabolism ; Part 2. Selective Vulnerability of the Brain in Hypoxaemia, p 55, Philadelphia : F. A. Davis Co., 1963.
83) Ishikawa, S. : Polarographic studies on cerebral collateral circulation, with special reference to their clinical applications. Arch. Jap. Chir., **30** : 303, 1961.
84) Jacob, H. : CNS tissue and cellular pathology in hypoxaemic states. A discussion in the symposium on patterns of CNS Vulnerability. Selective Vulnerability of the Brain in Hypoxaemia, p 153, Philadelphia : F. A. Davis Co., 1963.
85) Jewell, P. A. : The anastomoses between internal and external carotid circulations in the dog. J. Anat., **86** : 83, 1952.
86) Jones, W. R. and Politano, V. A. : The effects of renal artery occlusion on renal function under normothermia and regional hypothermia. J. Urol., **89** : 535, 1963.
87) Kabat, H. and Dennis, C. : Decerebration in the dog by complete temporary anaemia of the brain. Proc. Soc. Exper. Biol. Med., **38** : 864, 1938.
88) Kabat, H., Dennis, C. and Baker, A. B. : Recovery of function following arrest of the brain circulation. Amer. J. Physiol., **132** : 737, 1941.

89) Kaplan, S., Matthews, E. C., Schwab, L. and Clark, L. C. : Oxygen availability to the brain during inflow occlusion of the heart in normothermia and hypothermia. J. Thorac. Surg., **32** : 576, 1956.
90) Keen, G. and Gerbode, F. : Observations on the microcirculation during profound hypothermia. J. Thorac. Cardiovas. Surg., **45** : 252, 1963.
91) Kety, S. S. : Determinations of tissue oxygen tension. Fed. Proc., **16** : 666, 1957.
92) Kety, S. S. : Regional circulation of the brain under physiological conditions - possible relationship to selective vulnerability. A discussion in the symposium on circulation, blood flow, oxygen diffusion and metabolism ; Part 1. Selective Vulnerability of the Brain in Hypoxaemia, p 21, Philadelphia : F. A. Davis Co., 1963.
93) Kimoto, S., Sugie, S. and Asano, K. : Open heart surgery under direct vision with the aid of brain-cooling by irrigation. Surgery, **39** : 592, 1956.
94) Knisley, M. H., Bloch, E. H., Eliot, T. S. and Warner, L. : Sludged blood. Science, **106** : 431, 1947.
95) Kudo, T. : Differential cerebral deep hypothermia by isolated cerebral vascular irrigation, preliminary report. Keio J. Med. (Tokyo), **11** : 83, 1962.
96) Kudo, T. : Extremely profound hypothermia without blood by means of exchange perfusion of the blood substitute (Preliminary report). Keio J. Med. (Tokyo), **12** : 1, 1963.
97) Kristiansen, K., Krog, J. and Lund, I. : Experiences with selective cooling of the brain. Acta Chir. Scand. Suppl., **253** : 151, 1960.
98) Kristiansen, K. : Selective brain cooling. Excerpta Medica, International Congress Series. No. **60** : 29, 1963.
99) Kramer, K. : Renal failure in shock. A discussion in the symposium on shock, Stockholm, June 27–30, 1961. Shock, pathogenesis and therapy, an international symposium, p 134, Berlin Göttingen Heidelberg : Springer-Verlag, 1962.
100) Lesage, M. A., Sealy, W. C., Young, W. G., Jr. and Lee, J. M. : Experimental studies on profound hypothermia induced and reverted with a pump oxygenator. Ann. Surg., **156** : 831, 1962.
101) Lewis, F. J. : Collective review. Hypothermia. Internat. Abstr. Surg., **13** : 307, 1961.
102) Lewis, F. J., Shumway, N. E., Niazi, S. A. and Benjamin, R. B. : Aortic valvulotomy under direct vision during hypothermia. J. Thorac. Surg., **32** : 481, 1956.
103) Löfström, B. : Induced hypothermia and intravascular aggregation. Acta Anaesth. Scand. Suppl. : 3, 1959.
104) Long, D. M., Sanchez, L., Varco, R. L. and Lillehei, C. W. : The use of low molecular weight dextran and serum albumin as plasma expanders in extracorporeal circulation. Surgery, **50** : 12, 1961.
105) Lougheed, W. M. and Kahn, D. S. : Circumvention of anoxia during arrest of cerebral circulation for intracranial surgery. J. Neurosurg., **12** : 226, 1955.
106) Lougheed, W. M., Sweet, W. H., White, J. C. and Brewster, W. R. : The use of hypothermia in surgical treatment of cerebral vascular lesions. A preliminary report. J. Neurosurg., **12** : 240, 1955.
107) Lynch, H. F. and Adolph, E. F. : Blood flow in small blood vessels during deep hypothermia. J. Appl. Physiol., **11** : 192, 1957.
108) MacCarty, C. S., Michenfelder, J. D. and Uihlein, A. : Treatment of intracranial vascular disorders with the aid of profound hypothermia and total circulatory arrest. J. Neurosurg., **21** : 372, 1964.
109) Marshall, B. M. : Anaesthesia for intracranial aneurysm surgery. Clin. Neurosurg., **9** : 142, 1961.
110) McDonald, D. A. : Blood flow in arteries. pp 11–306, Edward Arnold (Publishers) Ltd., London, 1960.
111) McKissock, W., Paine, K. W. E. and Walsh, L. S. : The values of hypothermia in the surgical treatment of ruptured intracranial aneurysms. J. Neurosurg., **17** : 700, 1960.
112) Meyer, J. S., Fang, H. C. and Denny-Brown, D. : Polarographic study of cerebral collateral circulation. A. M. A. Arch. Neurol. Psychiat., **72** : 296, 1954.
113) Meyer, J. S., Gotoh, F., Tazaki, Y., Hamaguchi, K., Ishikawa, S., Nouailhat, F. and Symon, L. : Regional cerebral blood flow and metabolism in vivo. Arch. Neurol., **7** : 560, 1962.
114) Michenfelder, J. D. and Uihlein, A. : Profound hypothermia and total circulatory arrest in neurosurgery : Method, results and physiological effects. Excerpta Medica, International Congress Series. No. **60** : 30, 1963.
115) Miller, D. R., Hallaba, M. A. S. and Steegman, A. T. : Effect of profound hypothermia with circulatory arrest in dogs. Special reference to changes in cerebrovascular permeability. Ann. Surg., **161** : 272, 1965.
116) Montgomery, H. : Oxygen tension of tissues in vivo. G. E. Brown memorial lecture. Circulation, **15** : 646, 1957.
117) Moor, W. J. : Physical chemistry. The Prentice-Hall, Inc., New York, 1955. (Second Edition)
118) Negrin, J., Jr. : Extravascular perfusion for selective regional hypothermia of the central nervous system

(Brain or Spinal Cord). Excerpta Medica, International Congress Series. No. **60** : 50, 1963.
119) Neville, W. E., Kameya, S., Oz, M., Bloor, B. and Clowes, G. A. : Profound hypothermia and complete circulation interruption. Arch. Surg., **82** : 128/108, 1961,
120) Niazi, S. A. and Lewis, F. J. : Profound hypothermia in the dog. Surg. Gynec. Obstet., **102** : 98, 1956.
121) Odell, L. D., Aragon, G. T. and Pottinger, R. E. : Relationship between erythrocyte sedimentation rate, sludged blood and plasma proteins during pregnancy. Amer. J. Obstet. Gynec., **54** : 596, 1947.
122) Ohta, T., Sagarminaga, J. and Baldwin, M. B. : Profound hypotension with differential cooling of the brain in dogs. J. Neurosurg., **24** : 993, 1966.
123) Ommaya, A. K. and Baldwin, M. : Direct extravascular brain cooling in the normothermic animal. Neurology (Mineap.), **12** : 882, 1962.
124) Ommaya, A. K. and Baldwin, M. : Extravascular local cooling of the brain in man. J. Neurosurg., **20** : 8, 1963.
125) Parkins, W. M., Jensen, J. M. and Vars, H. M. : Brain cooling in the prevention of brain damage during periods of circulatory occlusion in dogs. Ann. Surg., **140** : 284, 1954.
126) Patterson, R. H. and Ray, B. S. : Profound hypothermia for intracranial surgery : Laboratory and clinical experiences with extracorporeal circulation by peripheral cannulation. Ann. Surg., **156** : 377, 1962.
127) Patterson, J. L., Jr., Heyman, A., Battey, L. L. and Ferguson, R. W. : Threshold of response of the cerebral vessels of man to increase in blood carbon dioxide. J. Clinic. Invest., **34** : 1857, 1955.
128) Penrod, K. E. : Cardiac oxygenation during severe hypothermia in dog. Amer. J. Physiol., **164** : 79, 1951.
129) Popovic, V. : Lethargic hypothermia in hibernators and non-hibernators. Ann. N. York Acad. Sci., **80** : 320, 1959.
130) Porter, R. W. and Hayes, G. J. : An experimental evaluation of hypothermia, hypotension and cephalic arterial occlusion as adjuncts to neurological surgery. Excerpta Medica, International Congress Series. No **12** : 21, 1957.
131) Rosenhain, F. R., Penrod, K. E. and Flynn, J. : Blood gas studies in the hypothermic dog. Amer. J. Physiol., **166** : 55, 1951.
132) Rosomoff, H. L. and Holaday, D. A. : Cerebral blood flow and cerebral oxygen consumption during hypothermia. Amer. J. Physiol., **179** : 85, 1954.
133) Rosomoff, H. L and Gilbert, R. : Brain volume and cerebrospinal fluid pressure during hypothermia. Amer. J. Physiol., **183** : 19, 1955.
134) Ross, D. N. : Some experimental observations on selective hypothermia. Guy Hosp. Rep., **108** : 252, 1959.
135) Rush, B. F., Jr., Wilder, R. J., Fishbein, R. and Ravitch, M. M. : Effects of total circulatory standstill in profound hypothermia. Surgery, **50** : 40, 1961.
136) Schneider, M. : Critical blood pressure in the cerebral circulation. A discussion in the symposium on circulation, blood flow, oxygen diffusion and metabolism ; Part 1. Selective Vulnerability of the Brain in Hypoxaemia, p 7, Philadelphia : F. A. Davis Co., 1963.
137) Sealy, W. C., Brown, I. W., Jr., Young, W. G., Smith, W. W. and Leasage, A. M. : Hypothermia and extracorporeal circulation for open heart surgery : Its simplification with a heat exchanger for rapid cooling and rewarming. Ann. Surg., **150** : 627, 1959.
138) Sedzimir, C. B. and Dundee, J. W. : Hypothermia in the treatment of cerebral tumors. J. Neurosurg., **15** : 199, 1958.
139) Senning, A. : Shock and extracorporeal circulation. A discussion in the symposium on shock. Shock, pathogenesis and therapy, an international symposium, p 301, Berlin Göttingen Heidelberg : Springer-Verlag, 1962.
140) Severinghaus, J. W. and Bradley, A. F. : Electrodes for blood pO_2 and pCO_2 determination. J. Appl. Physiol., **13** : 515, 1958.
141) Shumacker, H. B., Jr., Bounous, G. and Onnis, M : Renal blood flow in moderate hypothermia. Arch. Surg., **80** : 593, 1960.
142) Shumway, N. E., Gliedman, M. L. and Lewis, F. J. : Coronary perfusion for longer periods of cardiac occlusion under hypothermia. J. Thorac. Surg., **30** : 598, 1955.
143) Shumway, N. E., Johnson, J. A. and Smith, R. J. : The study of ventricular fibrillation by threshold determinations. J. Thorac. Surg., **34** : 643, 1957.
144) Shumway, N. E. and Lewis, F. J. : Hypothermia and temporary occlusion of the hepatic circulation. Physiology of induced hypolthermia. Washington, D. C. : Nat. Acad. Sc. -Nat. Res. Council Publ. **451** :

1956, p 221.
145) Slack, W. K. and Walter, W. W. : Cerebral circulation studies during hypotensive anaesthesia using radioactive Xenon. Lancet, May **18** : 1082, 1963.
146) Spurr, G. B., Hutt, B. K. and Horvath, S. M. : Responses of dogs to hypothermia. Amer. J. Physiol., **179** : 139, 1954.
147) Spurr, G. B., Horvath, S. M., Hamilton, L. H. and Hutt, B. K. : Temperature gradients in the hypothermic dog. Amer. J. Physiol., **186** : 47, 1956.
148) Stackelberg, M. V. : Polarographische Arbeitsmethoden. Walter de Gruther u. Co., Berlin, 1950.
149) Stone, H. H., Donnelly, C. and Frobese, A. S. : The effect of lowered body temperature on the cerebral hemodynamics and metabolism of man. Surg. Gynec. Obstet., **103** : 313, 1956.
150) Suvorov, V. V. : Cardiovascular changes in induced craniocerebral hypothermia. Fed. Proc., (Translat Suppl.), **22** : T44-T47, 1963.
151) 笹本 浩，尾崎恭輔，高木 康：血液ガスに及ぼす温度の影響について —とくに低体温法に関連して— 日本医事新報，**1964** : 23, 1961.
152) 品川睦明：ポーラログラフ分析法．共立全書 43，共立出版，東京，1957.
153) Takács, L. : The effect of hypovolaemic (stagnant) and arterial hypoxia on the distribution of cardiac output in dogs and rats. A discussion in the symposium on shock, Stockholm, June 27-30, 1961. Shock, pathogenesis and therapy, an international symposium, p 195, Berlin Göttingen Heidelberg, Springer-Verlag, 1962.
154) Takase, T. : Experimental studies on selective brain cooling in dogs : -Espcially on bleeding tendencies and improvement of microcirculation-. Arch. Jap. Chir., **35** : 468, 1966.
155) Terblanche, J., Isaacson, L. C., Eales, L. and Barnard, C. N. : Renal function during and immediate after profound hypothermia. Surgery, **50** : 869, 1961.
156) Thews, G. : Implications to physiology and pathology of oxygen diffusion at the capillary level. A discussion in the symposium on circulation, blood flow, oxygen diffusion and metabolism ; Part 1. Selective Vulnerability of the Brain in Hypoxaemia, p 27, Philadelphia : F. A.Davis Co., 1963.
157) Thorsén, G. and Hint, H. : Aggregation, sedimentation and intravascular sludging of erythrocytes. Acta Chir. Scand. Suppl., 154, 1950.
158) Tokuoka, S., Aoki, H., Higashi, K. and Tatebayashi, K. : Cooling irrigation of the cerebral ventricular system. Excerpta Medic, International Congress Series. No. **36** : 148, 1961.
159) Uihlein, A., Theye, R. A., Dawson, B., Terry, H. R., Jr., McGoon, D. C., Daw, E. F. and Kirklin, J. W. : The use of profound hypothermia, extracorporeal circulation and total circulatory arrest for an intracranial aneurysm. Proc. Mayo Clin., **35** : 567, 1960.
160) Villalobos, T. J., Adelson, E., Riley, P. A., Jr., and Crosby, W. H. : A cause of the thrombocytopenia and leukopenia that occur in dogs during deep hypothermia. J. Clin. Invest., **37** : 1, 1958.
161) Von Kaulla, K. N. and Swan, H. : Clotting deviations in man associated with open-heart surgery during hypothermia. J. Thorac. Surg., **36** : 857, 1958.
162) West, T. C., Frederickson, F. S. and Amory, D. W. : Single fiber recordng of the ventricular response to induced hypothermia in the anaesthetized dog. Correlation with multicellular parameters. Circulation Res., **7** : 880, 1959.
163) Whisnant, J. P., Millikan, C. H., Wakim, K. G., and Sayere, G. P. : Collateral circulation to the brain of the dog following bilateral ligation of the carotid and vertebral arteries. Amer. J. Physiol., **186** : 275, 1956.
164) White, R. J. and Donald, D. E. : Selective hypothermia perfusion and circulatory arrest. Arch. Surg., **84** : 40, 1962.
165) Woodhall, B., Sealy, W. C., Hall, K. D. and Floyd, W. L. : Craniotomy under conditions of Quinidine-protected cardioplegia and profound hypothermia. Ann. Surg., **152** : 37, 1960.
166) Woodhall, B., Reynolds, D. H., Mahaley, S., Jr., and Sanders, A. P. : The physiologic and pathologic effects of localized cerebral hypothermia. Ann. Surg., **147** : 673, 1958.
167) Zingg, W. and Kantor, S. : Observations on the temperatures in the brain during extracorporeal differential hypothermia. Surg. Forum, **11** : 192, 1960.
168) Zuhdi, N., Kimmel, G., Montroy, J., Carry, J. and Greer, A. : A system for hypothermic perfusion. J. Thorac. Cardiovas. Surg., **39** : 629, 1960.
169) Zweifach, B. W. : Functional behavior of the microcirculation. The Charles C Thomas Publisher, Springfield, Illinois, 1961.

和文抄録

持続的ないし間歇的脳選択灌流冷却法による Bloodless Craniotomy に関する実験的研究

殊にポーラログラフ法による脳微細循環の検討，およびその改善について—

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低体温法をもちいた無血開頭術 Bloodless or Avascular Craniotomy は，脳手術において常に問題となる“出血の任意な Control”という課題に対する理想的解答の一つであろう．しかしながら，脳神経外科の見地にたつならば，方法があくまでも脳外科本来の手術に対する補助的手段である以上，(1) 先ず方法そのものが安全であり重大な危険をともなう副作用があつてはならない．(2) 脳手術そのものが既に個体に対して大きな侵襲となるのであるから，これに加えられる二次的侵襲として可及的小さい侵襲に止まるものでなければならならない．(3) 方法が簡易で，(4) 時間的制約なく施行できれば理想的である．これらの点に関して，従来から一般に試みられている表面冷却法や，体外循環装置を導入した血液冷却法等の諸々の低体温法の中，Parkins，木本，Loughed 及び Kahn，林等のもちいた A-A shunt による選択的脳冷却法が最も合理的な方法と考えられる．

この方法の原理的特徴としては，(1) 選択的に脳のみを超低体温域に迄冷却することが可能である．(2) 体外循環回路の容積が非常に少なく（本実験では 250 ml 以下），又，Oxygenator を必要としない閉鎖回路である．(3) 操作が簡単である．(4) 開胸や心停止等の重大な手術侵襲を行なわない．(5) 回路の Prime に大量の新鮮血を必要としない，あるいは全量代用血液でもよい．(6) 回路をすべて disposable なものにできる，等の長所がある．

しかし，従来の A-A shunt による選択的脳冷却法については (1) 冷却された血液の右心への還流に伴なう心室細動の危険，(2) 脳冷却及び Heparinization に伴なう後出血の問題，(3) 術後の非可逆性脳損傷の危険などの問題がある．(1)については冷却方法の技術的な問題であり，木本等の多数の心臓外科臨床成功例の報告，Kristiansen 等による脳外科臨床成功例や Connolly 等 White 等の実験的報告，等々を総合すると技術的に解決可能である．(2)については，諸家の報告及び教室の高瀬の報告によれば，1～2 mg/kg の Heparinization，回路の Siliconization 等により臨床的にあまり問題にしなくてもよい．従つて，(3)の問題が解決されれば，本法の臨床的応用は危険なく可能となる訳である．

(3)については，単に本法のみに限らず，低体温下血流低止に関して，普遍的な問題が含まれてをり，同時に，低体温法を用いた無血開頭術本来の理想である“安全で，時間的制約なく施行できる”という課題を一挙に解決できる鍵ともなる問題である．

低体温下血流低止に後続する非可逆性脳損傷の Pathogenesis に関しては，(1) 冷却の直接侵襲による脳組織損傷，(2) 低体温下残存脳組織代謝に関連する脳 anoxia による，(3) 低体温下における血液及び血管床変化に原因する Cerebral Hemodynamics の永続性障害による脳組織損傷等である．(1)に関しては報告により多少の差異はあるが，脳温13℃以下で発現の可能性があるという．(2)については，脳温10℃前後で38 Cの10%内外の脳酸素消費量の残存をみるので，50分以上の脳血流完全停止で脳損傷の危険性がある．(3)に関しては系統血圧の低下及び血液冷却により発現する“Intravascular Aggregation of red blood cells”及び“White emboli”等により脳微細循環障害がまず発生し，更に血流完全停止によつてそれが永続性障害となるとの報告がある．

一方，従来，低体温下脳血流停止に関して脳冷却と脳代謝低下の検討はなされており，これに基いて一応の脳血流停止時間の安全域のめやすはついているが，安全性を確実に指示する指標の適当なものがなかつた．

そこで著者はポーラログラフ法による脳酸素分圧測定法を低体温法に導入した．この方法は従来常温でしか用いられず低体温法のような温度変化を伴う場合については不確実であるとされていたが，著者はこれをDiffusion Layer が constant な Enclosed Type の電極をもちいて，電極拡散層の温度係数を各測定毎に正確に検討することにより低体温法にも応用し得る事をたしかめた．

従来の選択的脳灌流冷却法について，このポーラログラフ法により犬をもちいて検討した結果，重要な現象を発見した．つまり，脳冷却と脳微細循環とが往々にして相ともなわぬことがあり（Paradoxical phenomenon），その中，脳微細循環の悪化は必ず術後 Comatose のまま死亡する転帰に直接相関々係をみとめた．この現象は，低体温法のどの時期についても発生したが，特に重要なのは，脳血流停止期及び，それに後続する復温期におけるものである．（Paradoxical Rewarming）．Coma についての critical level は術前常温下の対照値に対して，$90\left(\frac{70}{100}\right)^{\frac{38-t}{5}}$であった（t：そのときの脳温）．

従来の本法による脳冷却法の術後著明な脳障害を来たす最大の原因は“術中及び術後における脳微細循環の破綻”であると認められた．更に，術後の脳微細微環の悪化には二つの型があり，その一つは (1) 低体温法施行中に既に発現しているもの，他の一つは (2) 術中は異常がなくて，術後始めて発現するものである．この中，(1) は ⓐ Poor Induction によつても，又 ⓑ 血流停止期における Paradoxical Rewarming（Ischemic）によつても発生し，(2) は主として術後の系統血圧低下（Postoperative shock）によつて発生した．（とくに硫酸プロタミン注入による系統血圧の低下で発生した脳微細循環障害は，末梢循環について Heparinization の必要性を支持すると考えられ，Heparinization に関連して興味ある結果を示す）．

そこで，著者は，脳冷却に伴う脳微細循環の破綻の予防，及びその改善を目的として，動物実験により次のような方法を検討した．(1) 過度な脳冷却をさけ，目的脳温を15℃以上の超低体温域とする（15～23℃．脳波消失脳温域），又更に，可及的軽減する（23～28℃呼吸消失脳温域）．(2) 系統的血液稀釈法（Htc. 減少率で対術前値60～90%）及び導入灌流に先立つて，Cerebral Vascular Bed の Wash-out Perfusion を行なう．(3) 持続的ないし間歇的脳灌流法（低体温下に於ても血流完全停止を行なわず，avascular craniotomy に支障を来たさぬ程度で，脳冷却灌流を維持する．これには 1～3 ml/kg/min. の極低流量，灌流血温10℃以下，をもちいた）．

この結果，系統的血液稀釈法によつて，低温下の血液 Viscosity 上昇は有効に防止され，極低流量脳冷却灌流によつて Paradoxical Rewarming が防止された．両者の Combined method は脳の Paradoxical Phenomenon を防止し，脳微細循環は術中及び術後に亘つてよく保全された．又，脳温23～28℃の脳冷却 moderation にも成功した．

従来の方法では，13例中5例に Comatose Cerebral Damage（38.5%）をみとめ，長期生存例はわずか4例（30.8%）に止つたものが，著者の方法では，8例中 Comatose fatal 例は，1例もなく，長期生存例は6例（75%），と飛躍的に改善された．

系統血液の人工液による稀釈にさいして，Rheomacrodex（low molecular weight Dextran）を併用して，所謂，血液の Suspension Stability をたかめ，Intravascular Aggregation を防止することは合理的である．

以上の方法をもちいて，2例の無血開頭術に臨床的に応用した．その中1例は残念ながら，Technical Failure によつて失なつたが，他の1例では，6時間30分に亘つて脳超低体温を維持し（脳温 16.6℃～27.2℃），1時間34分に亘る Bloodless craniotomy に成功した．この例では，この間，脳血流は完全に control する事ができ脳血流完全停止期間は間歇的に合計50分間に止めた．又，脳微細循環は術中術後を通じて良好に保全され，（Cerebral oxygen availability：70～125），Ventricular Fibrillation の危険もみず，又，著明な出血傾向も来たさなかつた．術後，低体温又は Bloodless Craniotomy に起因する著明な脳障害もなかつた．

以上を総括し著者の方法の概略をのべる：

1. avascular craniotomy を目的とする低体温法に，Carotico-Carotid Shunt による選択的脳冷却法を用いうる．

2. 低体温は，脳温15～23℃及び23～28℃，系統体温（直腸温）32℃とする．食道温は28℃以下に下げない．

3. 体外循環回路は250ml以下の容量に止め Oxygenator を必要としない．

4. 系統血液稀釈法（Htc. 対術前値60～90%）及び Cerebral Vascular Bed の Wash-out Prefusion を行なう．

5. 低体温導入後，1～3 ml/kg/min. の極低流量で維持冷却脳灌流を行なう（持続的ないし間歇的）．

6. ポーラログラフ法をもちいて，Cerebral Microcirculation 及び anoxia の指標とする．

7. 灌流圧は系統血圧＋20mmHg 以下に維持する．Cerebral Oxygen Availability を Critical Level 以上に保持するよう灌流を調節する．導入は脳冷却速度 0.3～2.0℃/min. 内で施行する．系統血圧は，冷却中30～70mmHg，復温期以後80mmHg 以上に維持する．

稿を終るに臨み，本研究の終始に互りあたゝかい御激励と御懇篤なる御指導御校閲を賜わった恩師半田肇教授に深甚なる謝意を表わします．さらに本研究にあたって御教示御協力をいたゞいた太田富雄博士，竹田俊男博士，寺浦哲昭博士，及び協同研究者高瀬卓郎博士に深謝いたします．

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