— Assignment Research —

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Cerebral Circulation in Surgery

BY

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Numerous cases of the heart diseases have been treated surgically in our department. In this report the studies on the cerebral circulation and metabolism observed in those with heart diseases are presented. Also the changes occurring in surgical conditions such as hemorrhage, anoxia and induced hypotension are discussed. In reference to the open heart surgery that had been given special emphasis in our department, general hypothermia and selective brain cooling by irrigation are reported together with the state of circulatory arrest under those procedure. Selective brain cooling by irrigation¹⁾ was originated by our department.

METHODS AND SUBJECTS

To measure the cerebral blood flow both nitrous oxide method^{2,3)} and dye dilution method^{4,5)} are employed, the latter is convenient to follow up the periodical changes. From an anatomical consideration, the methods which are employed for the human beings are not adequate for the experimental dogs⁶⁾. A small hole is bored in the parietal region of the dog's skull to expose superior sagittal sinus, in which a needle is inserted by puncture and the thin polyethylene tube is conducted from the site of puncture to confluens sinus to obtain blood samples. Thus the contamination of the cerebral venous blood was avoided as much as possible.

Apparatus for aspiration of blood (Fig. 1) is so devised as to minimize unbalanced velocity of aspiration which may occur during the process by Scheinberg's method³⁾. By means of this apparatus the aspiration was carried out with constant velocity of 15–20 ml in 10 min. (Fig. 2 a).

When the dye dilution method⁵⁾ is employed a tube is inserted to confluens sinus by the same technic and the internal carotid artery on one side is exposed to introduce 0.5 ml of 0.05 per cent

Fig. 1 Aspiration of cerebral venous blood from confluens sinus.

Fig. 2 "a" shows the apparatus of N₂O method and "b" shows the apparatus of dye dilution method.

Evans blue is rapidly injected. Simultaneously with the injection of the dye, both arterial and venous blood samples are taken at the rate of 2 ml/20 sec. The apparatus is so conditioned as to enable the blood aspiration of 2–5 ml in 20 sec. (Fig. 2 b). In some experiments a bubble flowmeter⁷⁾ is connected to internal carotid artery to read the blood flow.

In clinical cases a catheter is introduced at the cubital vein to internal jugular vein to gain blood

samples. In dye dilution method the average concentration of dyes in both internal jugular veins is used⁵⁾. On the patient with cardiac disease, cerebral circulation is observed at the same time with the cardiac catheterization.

The average values of cerebral circulation measured on clinical cases and experimental animals (dogs) by the methods above mentioned are presented in table 1. The results are nearly in accordance with those former by reported by other workers²⁾³⁾⁸⁾⁹⁾. The readings of the cerebral blood flow and oxygen consumption obtained by dye dilution method give in its entirety (Table 2).

THE CEREBRAL CIRCULATION OF THE CASES WITH HEART DISEASE.

The cerebral circulation of 35 patients with

various type heart diseases, mainly with congenital heart disease were examined. Of these 35 cases detailed readings were obtained on 22 cases which demonstrated a general tendency as presented in table 3.

In patent ductus arteriosus the increase of the cerebral blood flow (CBF), and the decrease of cerebral oxygen consumption ($CMRO_2$), cerebral vascular resistance (CVR) and of mean arterial blood pressure (MABP) are recognized (Table 4).

It is observed in nine cases with atrial septal defect that the values of cerebral circulation is almost within normal range, although with some of the features of the changes shown in table 5.

In mitral stenosis marked diminution of CBF and appreciable increase of CVR are the character-

TABLE I NORMAL VALUES OF CIRCULATION BY N_2O METHOD (OURS AND OTHER WORKERS)

		Kety and Schmidt	Scheinberg and Stead	Bernsmeier and Siemons	Aizawa	Kimoto	
					Internal Clinic of Keio University	Our Surgical Clinic of Tokyo University	Dogs with Venus Injection of 30mg/kg Pentotal to animals
		14 Cases 34 Times	20 Cases 32 Times	30 Cases 30 Times	10 Cases 10 Times	7 Cases 7 Times	5 Cases 5 Times
CBF Cerebral Blood Flow	$\frac{cc}{100g \text{ brain } m}$	54	64.7	58.3	66.1	57.8	53.4
(A-V) O_2 Cerebral Arterial-Venous Oxygen Difference	Vol %	6.3	6.02	6.4	5.17	6.04	4.56
$CMRO_2$ Cerebral O_2 Consumption	$\frac{cc}{100g \text{ brain } m}$	3.3	3.79	3.7	3.41	3.5	2.5
CVR Cerebral Vascular Resistance	$\frac{mmHg}{cc \text{ blood } 100g \text{ brain } m}$	1.6	1.31	1.5	1.30	1.5	2.0
MABP Mean Arterial Blood Pressure	mmHg		84	95	84.7	87	104

TABLE II CEREBRAL CIRCULATION BY DYE DILUTION METHOD ON CLINICAL CASES (RESULTS UNDER INTRATRACHEAL ETHER ANESTHESIA)

SUBJECTS	CBF (Total) cc/M	(A-V) O_2 vol %	$CMRO_2$ cc/M	CVR mmHg/cc/M	MABP mmHg
S. D.	650	7.06	45.9	0.17	103
N. M.	496	5.86	29.1	0.20	93
T. D.	553	4.83	26.2	0.12	67
S. T.	658	6.88	45.3	0.15	90
H. N.	524	5.04	26.3	0.13	70
Mean	576	5.92	35.6	0.15	85

TABLE III CEREBRAL CIRCULATION OF THE CASES WITH HEART DISEASES.

	No. of Cases	CBF	(A-V) O_2	$CMRO_2$	CVR	MABP
Patent Ductus Arteriosus	3	↑↑	↓	↓	↓	↓
Atrial Septal Defect	9	↓	±	↓	↑	±
Mitral Stenosis	3	↓↓	↑	↓	↑↑	↓
Tetralogy of Fallot	7	↓	±	↓	↑↑	↑

↑↑↓ Severe Degree
↑↑ Moderate Degree
↑↓ Slight Degree

TABLE IV CEREBRAL CIRCULATION OF PATENT DUCTUS ARTERIOSUS

Subject	MABP mmHg	SBF l/m	CI l/m/m ²	CBF cc/100g br./m	(A-V)O ₂ vol %	CMRO ₂ cc/100g br./m	CVR mmHg/cc blood/100g br./m
Y.T. 21 j	70	5.2	3.8	72.5	4.47	3.2	1.0
S.S. 7 j	60	4.0	5.5	68.4	4.83	3.3	0.9
A.B. 29 j	100	9.3	6.2	59.5	5.12	3.1	1.7
Mean	77	6.2	5.2	66.8	4.81	3.2	1.2

Note :

S.B.F.- Somatic blood flow

C.I.- Cardiac index

TABLE V CASES WITH ATRIAL SEPTAL DEFECT

SUBJECT	MABP mmHg	SBF e/m	CI e/m/m ²	CBF cc/100g br./m	(A-V)O ₂ vol %	CMRO ₂ cc/100g br./m	CVR mmHg/cc blood/100g br./m
H.G. 11j	100	3.0	2.8	56.0	4.88	2.7	1.8
I.I. 30j	90	4.8	3.5	57.4	5.26	3.0	1.6
Y.N. 10j	85	3.7	3.9	52.4	6.58	3.5	1.7
W.N. 20j	85	4.1	3.8	48.6	6.00	2.9	1.8
K.M. 29j	95	5.0	3.5	58.5	5.51	3.2	1.6
I.N. 13j	84	4.9	4.3	66.0	4.87	3.2	1.3
A.H. 24j	60	4.1	3.0	48.6	6.77	2.9	1.2
T.S. 25j	73	3.6	2.4	46.3	6.47	3.0	1.6
G.J. j	90	3.0	3.0	48.1	6.14	3.0	1.9
MEAN	85	4.0	3.4	53.6	5.83	3.0	1.6

Note :

SBF - Somatic blood flow

CI - Cardiac Index

TABLE VI CEREBRAL CIRCULATION OF MITRAL STENOSIS

Subject	MABP mmHg	SBF l/m	CI l/m/m ²	CBF cc/100g br./m	(A-V)O ₂ vol %	CMRO ₂ cc/100g br./m	CVR mmHg/cc blood/100g br./m
T.S. 27 j	95	4.2	2.8	48.4	5.81	2.8	2.0
G.B. 27 j	63	3.6	2.5	44.3	6.97	3.1	1.4
T.T. 22 j	98	3.0	2.3	38.8	7.82	3.0	2.5
Mean	71	3.6	2.5	43.8	6.87	3.0	2.0

Note :

S.B.F.- Somatic blood flow

C.I. - Cardiac index

ristics. Though cerebral arterial-venous oxygen difference is elevated, $CMRO_2$ is reduced to diminishing CBF. (Table 6).

In tetralogy of Fallot the CVR is increased, which might probably be ascribed to the remarkable rise of the viscosity of the blood. The CBF is moderately reduced, $CMRO_2$ often seems unable to reach normal level. (Table 7).

Comparative readings of these values of cerebral circulation are done before and after operation the case shown in figure 3 whose ductus arteriosus had been closed operatively, as examined one year after the operation, all of the values obtained by the test had in general returned to the normal standard

	MABP mmHg	SBF l/m	CI l/m/m ²	CBF cc 100 gbr. m	(A-V)O ₂ vol%	CMRO ₂ cc 100 cc blood gbr. 100 m	CVR mmHg 100 gbr. m
Before	70	5.2	3.8	72.5	4.47	3.2	1.0
After	95	4.5	3.2	57.9	5.45	3.2	1.6

Fig. 3 Comparison between the cerebral circulations, before and after the operation of patent ductus arteriosus

values.

Seven cases of atrial septal defect were operated under direct vision suturing the defect successfully restoring the patient to health. In these cases cerebral circulation studies were carried out. The test all showed an approach toward the normal values. (Table 8)

In the treatment of Fallot's tetralogy, shunt operation, infundibular resection with pulmonary valvuloplasty under direct vision and a new radical operation, infundibular resection with pulmonary valvuloplasty and high ventriculoseptoplasty have been carried out and the resulting changes in the cerebral circulation studied. (Table 9).

CEREBRAL CIRCULATION UNDER VARIOUS SURGICAL CONDITIONS

(hemorrhage, anoxia and induced hypotension)

The cerebral circulation in the surgical conditions most frequently encountered in practical surgical clinics such as hemorrhagic shock, anoxia and induced hypotension have been investigated.

a) Acute hemorrhage

As an example acute hemorrhage a case of a patient who underwent bleeding of 500 ml or about 14 per cent of circulatory blood volume was studied by dye dilution method. Diminution of CVR associated with low blood pressure and reduced CBF of slight degree is recognized, while $CMRO_2$ remains almost unchanged, because the arterial-venous oxygen difference rises. The tendency of these features is still maintained when blood transfusion is administered in sufficient amount to compensate for the blood lost. The CBF and $CMRO_2$ remain elevated (Fig. 4). When dogs are bleed more than

TABLE VII CASES WITH TETRALOGY OF FALLOT

SUBJECT	Grade of Symptom	A _O Sat. %	MABP mmHg	SBF e/m	CI e/m/m ²	CBF cc/100g br./m	(A-V)O ₂ vol %	CMRO ₂ cc/100g br./m	CVR mmHg/cc blood/100g br./m
T.N. 22j	+	85.6	95	3.7	2.7	52.3	6.64	3.5	1.8
I.I. 6j	+++	61.3	120	3.3	4.6	53.8	3.86	2.1	2.2
O.Y. 16j	++	71.3	106	7.4	5.5	42.1	5.20	2.2	2.5
Y.D. 6j	++	89.5	90	2.9	4.0	39.6	5.77	2.3	2.3
T.T. 20j	+	82.6	95	5.0	3.7	54.6	5.90	3.2	1.7
K.T. 19j	+	81.7	125	3.5	2.2	46.6	6.95	3.2	2.7
T.T. 6j	+	86.8	90	3.8	4.2	54.0	6.48	3.5	1.8
MEAN		79.8	104	4.2	3.8	49.0	5.83	2.9	2.1

Note :

A_O Sat. - O₂ Saturation in Arterial blood
SBF. - Somatic blood flow
CI. - Cardiac Index

TABLE VIII ATRIAL SEPTAL DEFECT OPERATED WITH CLOSING SUTURES
(COMPARISON BETWEEN THE PREOPERATIVE AND POSTOPERATIVE CONDITIONS)

SUBJECT		MABP mmHg	SBF l/m	CI l/m/m ²	CBF cc/100g br./m	(A-V)O ₂ vol %	CMRO ₂ cc/100g br./m	CVR mmHg/cc blood/100g br./m
H. G. 11j	B	100	3.0	2.8	56.0	4.88	2.7	1.8
	A	95	3.9	3.6	59.2	4.81	2.9	1.6
I. I. 30j	B	90	4.8	3.5	57.4	5.26	3.0	1.6
	A	80	4.1	3.0	56.8	6.76	3.8	1.4
W. I. 20j	B	85	4.1	3.8	48.6	6.00	2.9	1.8
	A	90	6.5	4.5	57.4	5.69	3.3	1.6
K. M. 29j	B	95	5.0	3.5	58.5	5.51	3.2	1.6
	A	95	5.0	3.8	58.9	5.53	3.3	1.6
I. N. 13j	B	84	4.9	4.3	66.0	4.87	3.2	1.3
	A	77	4.4	3.8	54.5	5.95	3.2	1.4
A. H. 24j	B	60	4.1	3.0	48.6	6.77	2.9	1.2
	A	104	5.1	3.8	56.4	6.03	3.4	1.8
T. S. 25j	B	73	3.6	2.4	46.3	6.47	3.0	1.6
	A	85	5.4	4.2	53.0	6.35	3.4	1.6
mean	B	84	4.2	3.3	54.5	5.68	3.0	1.6
	A	89	4.9	3.8	56.6	5.87	3.4	1.6

Note:

B.- Before the Operation
A.- After the OperationSBF.-Somatic blood flow
CI.-Cardiac Index

30 per cent of circulating blood volume both cardiac output (CO) and CBF decrease, but the decrease of latter is of slight degree and CMRO₂ is maintained at the level a little higher than that before bleeding, because of the marked increase of the cerebral arterial-venous oxygen difference. (Table 10, Fig. 5).

b) Anoxia

Of the clinical cases of anoxia 7.4 per cent oxygen inhalation is processed to the patients and their cerebral blood flow is read by the dye dilution method. Increase of CBF occurs 2 min. after the onset of inhalation, and continues until 8 min. later. The cerebral arterial-venous oxygen difference increases for 2 to 5 min. and then declines. Sharp decrease of CMRO₂, thus does not result (Fig. 6).

When 10 per cent oxygen was inhaled by dogs,

Fig. 4 Clinical case of acute hemorrhage
(dye dilution method) Fig. 5 Cerebral circulation in the case of hemorrhage
over 30% of the circulatory blood volume (N₂O
method using dogs).

Fig. 6 Clinical cases of 7.4% oxygen inhalation.

TABLE X COMPARISONS OF PRE-AND POST-OPERATIVE RESULTS IN TETRALOGY OF FALLOT

SUBJECTS	METHOD OF OPERATION		A _{O₂} Sat.	MABP mmHg	SBF e/m	CI e/m/m ²	CBF cc/100g br./m	(A-V)O ₂ vol %	CMRO ₂ cc/100g br./m	CVR mmHg/cc blood/100g br./m
T.N.	Shunt Operation	B	85.6	95	3.7	2.7	52.3	6.64	3.5	1.6
		A	86.1	80	4.1	3.0	56.9	6.15	3.5	1.4
O.Y.	Infundibular resection and Valvuloplasty under the Direct Vision	B	71.3	106	7.4	5.5	42.1	5.20	2.2	2.5
		A	89.5	90	4.5	3.3	49.2	6.88	3.4	1.8
T.T.	Infundibular resection and Valvuloplasty + high Ventriculo-Sept-Plasty under the Direct Vision	B	82.6	95	5.0	3.7	54.6	4.90	2.7	1.7
		A	91.3	95	3.7	2.7	51.7	6.73	3.1	1.6

Note :

B. - Before Operation
A. - After OperationA_{O₂} Sat. - Arterial O₂ SaturationTABLE X ALTERATION OF CEREBRAL CIRCULATION AT ACUTE HAEMORRHAGE (N₂O METHOD BY USING DOGS)

Animal No		CB ml	VH ml	YH CB %	MABP mmHg	%	CO l/m	%	CBF cc/100g br./m	%	(A-V)O ₂ vol %	CMRO ₂ cc/100g br./m	%	CVR mmHg/cc blood/100g br./m
201 12.5kg	B	833	320	38.4	120	100	2.14	100.0	53.7	100.0	4.55	2.43	100.0	2.23
	A				40	33	0.84	39.3	30.3	56.4	8.55	2.59	106.7	1.32
202 15.0kg	B	1027	350	34.1	140	100	2.83	100.0	62.6	100.0	4.55	2.85	100.0	2.26
	A				60	43	1.16	41.0	37.6	60.1	8.59	3.23	113.4	1.59
203 13.0kg	B	874	300	34.3	110	100	1.95	100.0	49.1	100.0	5.34	2.13	100.0	2.24
	A				40	36	0.73	37.4	26.4	53.8	8.56	2.26	105.9	1.51
204 14.0kg	B	944	350	37.1	130	100	2.60	100.0	55.0	100.0	5.09	2.80	100.0	2.36
	A				50	38	0.94	36.2	29.2	53.1	9.42	2.75	98.2	1.71
205 11.0kg	B	758	300	39.6	120	100	1.51	100.0	55.6	100.0	5.91	3.17	100.0	2.24
	A				30	25	0.54	35.8	36.4	67.9	7.91	2.88	90.8	0.35
Mean		887	324	36.7	124	100	2.21	100.0	54.8	100.0	5.08	2.68	100.0	2.27
					44	35	0.84	37.9	32.0	58.3	8.61	2.75	103.0	1.40

Note :

C.B. - Circulating Blood Volume
V.H. - Volume of HaemorrhageB. - Before the Process
A. - After the Process

the diminution of the cerebral arterial-venous oxygen difference due to the reduced saturation of oxygen in arteries is compensated by increase of CBF. Declining CMRO₂ is of slight degree and the test of carbohydrate metabolism¹⁰⁾¹¹⁾¹²⁾ also indicate that the cerebral anoxia is not of severe grade (Table 11 and 12). L/P ratio is presented in Fig. 7.

c) Induced hypotension

Induced hypotension by C₆ shows CVR, MABP

Fig. 7 Inhalation of 10% oxygen (using dogs).

and CBF all declining. However, due to a marked rise of the cerebral arterial-venous oxygen difference the average $CMRO_2$ is generally increased concomitantly more than before the administration of C_6 (Table 13, Fig. 8). These results are similar to these reported by Morris et al¹⁴. Very little

change in carbohydrate metabolism is noted in these cases (Table 14).

When the dye dilution method is applied on clinical cases reading the results at 3 min., 9 min. and 20 min. after C_6 injection, CBF and $CMRO_2$ decreases temporarily. These manifestations, after

TABLE XII CEREBRAL CIRCULATION OF DOGS AT 10% OXYGEN INHALATION

Animal No		AO ₂ Sat. %	MABP mmHg	CO		CBF		(A-V)O ₂ vol %	CMRO ₂		CVR mmHg/cc blood/100g br./m
				l/m	%	cc/100g br./m	%		cc/100g br./m	%	
101	B	95.5	100	1.40	100.0	54.4	100.0	5.33	2.90	100.0	1.84
	A	92.3	92	1.70	121.4	62.3	114.5	4.37	2.72	93.8	1.48
102	B	94.6	110	1.62	100.0	60.3	100.0	5.26	3.17	100.0	1.82
	A	90.6	120	1.93	119.1	68.8	114.1	4.27	2.94	92.7	1.74
103	B	92.7	120	2.01	100.0	55.1	100.0	5.05	2.78	100.0	2.18
	A	86.5	100	2.36	117.4	60.3	110.3	4.03	2.45	88.2	1.64
104	B	96.1	120	1.73	100.0	59.8	100.0	5.79	3.46	100.0	2.01
	A	88.2	120	1.92	111.0	65.2	109.0	4.51	2.94	85.0	1.84
105	B	93.8	130	1.21	100.0	56.7	100.0	5.29	3.00	100.0	2.29
	A	76.2	140	1.24	102.5	59.2	104.4	4.26	2.52	84.1	2.36
Mean	B	94.5	116	1.59	100.0	57.3	100.0	5.34	3.06	100.0	2.03
	A	86.8	112	1.83	114.3	63.3	110.4	4.29	2.71	88.8	1.81

Note :

B. - Before the Process
A. - After the Process

TABLE XIII CEREBRAL METABOLISM OF DOGS AT 10% OXYGEN INHALATION

Animal No		AO ₂ Sat. vol %	CBF		CMRO ₂		(A-V)gl. mg %	CMRgl. mggl./100g br./m		(A-V)gl. (A-V)O ₂	(A-V)La mg %	(A-V)Py mg %	L/P
			cc/100g br./m	%	cc/100g br./m	%		mggl./100g br./m	%				
101	B	95.5	54.4	100.0	2.90	100.0	5.0	2.72	100.0	0.94	-0.5	+0.01	6.47
	A	92.3	62.3	114.5	2.72	93.8	2.0	1.25	46.0	0.46	-2.5	+0.03	7.73
102	B	94.6	60.3	100.0	3.17	100.0	6.0	3.62	100.0	1.14	+0.6	+0.06	6.47
	A	90.6	68.8	114.1	2.94	92.7	3.0	2.06	56.9	0.70	+1.4	-0.15	7.92
Mean	B	95.1	57.4	100.0	3.04	100.0	5.5	3.17	100.0	1.04	+0.1	+0.04	6.47
	A	91.5	65.6	114.3	2.83	93.3	2.5	2.66	51.5	0.58	-0.6	-0.06	7.83

Note :

B. - Before the Process
A. - After the Process
AO₂ Sat. - Arterial O₂ Saturation

TABLE XIV CEREBRAL CIRCULATION DURING HYPOTENSION DUE TO C₆ INTRAVENOUS INJECTION (CLINICAL CASES)

Subjects	C ₆ mg		MABP mmHg	CO		CBF		(A-V)O ₂ vol %	CMRO ₂		CVR mmHg/cc blood/100g br./m
				l/m	%	cc/100g br./m	%		cc/100g br./m	%	
M. R. 41j	50 mg iv	B	113	4.3	100.0	52.3	100.0	3.92	2.05	100.0	2.16
		A	88	3.9	89.7	47.8	91.3	4.10	1.96	95.6	1.84
M. T. 21j	110 mg iv	B	97	3.4	100.0	67.9	100.0	6.00	4.07	100.0	1.43
		A	85	3.2	94.1	64.6	95.2	6.70	4.33	106.4	1.32
S. T. 56j	25 mg iv	B	150	6.8	100.0	57.2	100.0	4.23	2.46	100.0	2.63
		A	117	5.5	80.9	47.2	82.5	6.17	2.96	119.3	2.47
Mean	62 mg iv	B	120	4.8	100.0	59.1	100.0	4.71	2.86	100.0	2.07
		A	97	4.2	88.2	53.2	89.7	5.66	3.08	117.1	1.88

iv - Intravenously
B - Before the injection
A - After the injection

TABLE XV CEREBRAL METABOLISM DURING HYPOTENSION DUE TO C₆ INTRA-VEINUS INJECTION (CLINICAL CASES)

Subject	C ₆ mg		CBF		CMR _{O₂}		(A-V) _{gl.} mg %	CMR _{gl.}		(A-V) _{gl.} (A-V) _{O₂}	(A-V) _{la.} mg %	(A-V) _{py.} mg %
			$\frac{cc}{100gbr.}$ m	%	$\frac{cc}{100gbr.}$ m	%		$\frac{mggl.}{100gbr.}$ m	%			
M.R.	50	B	52.3	100.0	2.05	100.0	9.4	6.48	100.0	2.4	-0.9	-0.16
47j	i.v.mg	A	47.8	91.3	1.96	95.6	8.6	5.90	91.0	2.1	-1.5	-0.21
M.T.	110	B	67.9	100.0	4.07	100.0	10.9	7.40	100.0	1.8	-0.7	-0.13
21j	i.v.mg	A	64.6	95.2	4.33	106.4	9.6	6.59	89.1	1.4	-1.2	-0.17
Mean	62	B	60.6	100.0	3.06	100.0	10.2	6.94	100.0	2.1	-0.8	-0.15
	i.v.mg	A	56.2	93.3	3.15	101.0	9.1	6.25	90.1	1.8	-1.4	-0.19

Note :

B. - Before the injection
A. - After the injection

a short time may be restored to the previous level (Fig. 9).

It is noted that under unfavorable circumstances human individuals strive to keep CMR_{O₂} as close as possible to a physiological state first by means of increasing the arterial-venous oxygen difference, secondly by increased cardiac output and thirdly by increased CBF which resulted from the reducing CVR.

CEREBRAL CIRCULATION AND CIRCULATORY ARREST UNDER HYPOTHERMIA, ESPECIALLY UNDER THE SELECTIVE BRAIN COLLING BY IRRIGATION.

Fig. 8 Hypotension due to C₆ by N₂O method (clinical cases)

Studies on the cerebral circulation under the selective brain cooling by irrigation and general hypothermia are detailed from the standpoint of intracardiac surgery. The observations on the cerebral circulation under general hypothermia have been reported by us¹⁵⁾ and other¹⁶⁾¹⁷⁾ workers.

In open heart surgery, it is without question that the circulatory occlusion is necessary. Although human beings react differently to various unfavorable conditions, it is the opinion of various workers¹⁸⁾¹⁹⁾²⁰⁾²¹⁾²²⁾ that patient are unable to survive

Fig. 9 Clinical cases of induced hypotension (dye dilution method)

circulatory occlusion more than five minutes without suffering cerebral damages under such critical situation as the circulatory arrest. The cause of death in these cases is the stopping of the cerebral circulation. In order to prolong the duration of circulatory occlusion, general hypothermia has drawn our attention²²⁾²³⁾. Our department is conducting extended studies in this field and further has originated the selective brain cooling by irrigation¹⁾ in which only the brain is energetically cooled (Fig. 10). This procedure serves as an effective

Fig. 10

measure for the open heart surgery. Recently the coronary perfusion by oxygenated blood has been combined with this method in order to increase the safety of the procedure (Fig. 11). The cases of the atrial and ventricular septal defect are all especially successful with no fatalities. Among our cases was a ruptured aortic sinus aneurysm which was successfully treated surgically. This may be the first such case ever admitted in the medical literature (Table 15). With those who have myocardial lesion or cyanosis, however, the selective brain cooling is not always effective, presenting still problematic conditions even though the coronaries

Fig. 11

TABLE XV CLINICAL CASES TREATED UNDER DIRECT VISION BY MEAN OF THE SELECTIVE BRAIN-COOLING IN OUR DEPARTMENT (INVOLVED THESE CASES COMBINED WITH CORONARY PERFUSION BY OXYGENATED BLOOD)

Diagnosis	Cured	Improved	Died	Total
Atrial septal defect	8	1	0	9
ventricular septal defect	1	0	0	1
Rupture of Aortic sinus aneurysm	1	0	0	1
Pure pulmonary Stenosis	0	0	1	1
Tetralogy of Fallot	0	2	6	8
Mitral failure	0	0	2	2
Miscellaneous	0	0	2	2
Total	10	3	11	24

are perfused by oxygenated blood²⁴⁾.

Five clinical cases under general hypothermia were studied for the values of cerebral circulation and carbohydrate metabolism, the results of which are in table 16 and 17. At rectal temperature 31.5 degrees C. $CMRo_2$ decrease to 50 per cent is seen in the average case and a similar decrease is noted in glucose consumption ($CMRg1$). The results correspond to the empirical results using dogs (Table 18). When the selective brain cooling is experimentally employed, the temperature of the brain falls to 17–18 degrees C., cerebral temperature and 30 degrees C. rectal temperature. $CMRo_2$ comes down to 30 per cent. (Table 19 and 20). The experimental conditions are nearly similar to that observed in clinical cases, but the rate of decrease is more marked, $CMRo_2$ being about 20 per cent (Table 21).

When periodical changes are followed by the dye dilution method it is observed that the cerebral arterial-venous oxygen difference is gradually getting smaller. With the diminution of CBF the $CMRo_2$ declines in a straight line (Fig. 12). Summerizing these experimental results, it can be said that in general hypothermia $CMRo_2$ and $CMRg1$ show 50 per cent decrease at around 30 degrees C. rectal temperature, whereas in selective brain cooling the decrease is about 20 per cent at the same rectal

TABLE XVI CEREBRAL CIRCULATION UNDER GENERAL HYPOTHERMIA (CLINICAL CASES)

Subject		RT °C	MABP mmHg	CO		CBF		(A-V) _{O2} vol %	CMR _{O2}		CVR mmHg cc blood 100gbr. m
				.l/m	%	$\frac{\text{cc}}{100\text{gbr.}} \frac{\text{m}}{\text{m}}$	%		$\frac{\text{cc}}{100\text{gbr.}} \frac{\text{m}}{\text{m}}$	%	
Y.G.	B	37.5	106	2.56	100.0	49.9	100.0	4.33	2.11	100.0	2.12
64j	A	31.4	63	0.84	32.8	30.4	60.9	3.64	1.11	52.6	2.08
O.T.	B	37.4	179	4.95	100.0	55.4	100.0	3.85	2.13	100.0	3.24
54j	A	32.0	52	1.88	38.0	37.1	70.0	3.50	1.30	61.0	1.40
K.O.	B	37.0	110	5.69	100.0	71.9	100.0	4.59	3.30	100.0	1.53
40j	A	31.8	90	2.18	38.3	44.6	63.0	2.48	1.11	33.6	2.02
I.D.	B	37.7	118	6.02	100.0	87.6	100.0	4.04	3.54	100.0	1.35
50j	A	30.1	77	2.15	35.7	52.9	60.1	3.24	1.71	48.3	1.46
H.G.	B	37.1	128	6.18	100.0	73.6	100.0	3.87	2.85	100.0	1.74
22j	A	32.2	80	3.38	54.7	49.0	66.6	3.33	1.63	57.2	1.63
Mean	B	37.3	128	5.08	100.0	67.7	100.0	4.14	2.79	100.0	2.00
	A	31.5	72	2.09	39.9	42.8	64.1	3.24	1.37	50.5	1.72

Note: B — Before the Process

RT — Rectal Temperature

A — After the Process

CO — Cardiac Output

TABLE XVII CEREBRAL METABOLISM UNDER GENERAL HYPOTHERMIA (CLINICAL CASES)

Subject		RT °C	CBF		CMR _{O2}		(A-V) _{gl} mg %	CMR _{gl.}		(A-V) _{gl} (A-V) _{O2}	(A-V) _{La.} mg %	(A-V) _{Py.} mg %
			$\frac{\text{cc}}{100\text{gbr.}} \frac{\text{m}}{\text{m}}$	%	$\frac{\text{cc}}{100\text{gbr.}} \frac{\text{m}}{\text{m}}$	%		$\frac{\text{mggl.}}{100\text{gbr.}} \frac{\text{m}}{\text{m}}$	%			
Y.G.	B	37.5	49.9	100.0	2.11	100.0	10.0	5.00	100.0	2.3	-1.0	-0.26
64j	A	31.4	30.4	60.9	1.11	52.6	8.0	2.40	48.0	2.2	0.1	-0.08
O.T.	B	37.4	55.4	100.0	2.13	100.0	9.0	4.90	100.0	2.3	-0.5	-0.20
54j	A	32.0	37.1	70.0	1.30	61.0	5.0	2.60	53.1	1.4	-1.0	0
K.O.	B	37.0	71.9	100.0	3.30	100.0	9.0	6.50	100.0	1.9	-0.4	-0.03
40j	A	31.8	44.6	63.0	1.11	33.6	5.0	2.20	33.8	2.0	0	0
H.G.	B	37.1	73.6	100.0	2.85	100.0	7.0	5.20	100.0	1.6	-0.5	0
22j	A	32.2	49.0	66.6	1.63	57.2	6.0	2.90	55.8	1.8	0.5	0.14
MEAN	B	37.3	50.2	100.0	2.60	100.0	8.8	5.40	100.0	2.0	-0.6	-0.14
	A	31.9	40.3	65.1	1.29	51.1	6.0	2.53	47.7	1.9	-0.1	0.02

Note :

B. - Before the process

A. - After the process

TABLE XVIII CEREBRAL CIRCULATION AND METABOLISM OF DOGS UNDER GENERAL HYPOTHERMIA (N₂O METHOD)

Animal		RT	MABP	CO		CBF		(A-V)O ₂		CMR _{O₂}		CVR		(A-V)gl.		CMRgl.		A-Vgl.		(A-V) Ia	(A-V) Py.
N o		°C	mmHg	l/m	%	$\frac{cc}{100g\ br.}$ m	%	vol %	$\frac{cc}{100g\ br.}$ m	%	$\frac{mmHg}{cc\ blood}$ $\frac{100g\ br.}{m}$	mg %	$\frac{mg}{100g\ br.}$ m	%	A-V O ₂	mg %	mg %				
401	B	36.7	80.0	1.60	100.0	53.6	100.0	8.99	4.82	100.0	1.49	10.0	5.36	100.0	1.11	-1.0	-0.16				
	A	29.4	50.0	0.77	48.1	25.7	47.9	6.76	1.72	35.7	1.95	7.0	1.80	33.6	1.04	-1.0	-0.04				
402	B	36.0	90.0	3.00	100.0	56.2	100.0	5.63	3.16	100.0	1.60	9.0	5.06	100.0	1.59	-2.0	-0.10				
	A	26.0	30.0	0.90	30.0	28.6	50.9	5.50	1.57	49.7	1.05	6.0	1.72	34.0	1.09	-1.0	-0.14				
403	B	37.5	142.0	2.41	100.0	59.1	100.0	4.93	2.91	100.0	2.40	10.0	5.91	100.0	2.03	-1.0	-0.04				
	A	28.0	72.0	0.77	32.0	37.9	64.1	4.60	1.74	59.8	1.90	8.0	3.03	51.3	1.74	0	-0.04				
Mean	B	36.7	104.0	2.34	100.0	56.3	100.0	6.51	3.63	100.0	1.83	9.7	5.44	100.0	1.58	-1.3	-0.10				
	A	27.8	50.7	0.81	36.7	30.7	54.3	5.62	1.68	48.4	1.63	7.0	2.18	39.6	1.29	-0.7	-0.07				

Note :
B. - Before the Process
A. - After the Process

TABLE XIX CEREBRAL CIRCULATION UNDER THE SELECTIVE BRAIN COOLING BY IRRIGATION (N₂O METHOD BY USING DOGS)

Animal No.		CT °C	RT °C	MABP mmHg	CO		CBF		(A-V)O ₂		CMRO ₂		CVR	
					l/m	%	cc/100g br./m	%	vol %	%	cc/100g br./m	%	mmHg/cc blood/m	%
302	B	37.8	37.5	85.0	3.14	100.0	58.4	100.0	6.06	100.0	3.54	100.0	1.45	100.0
	C	19.3	32.2	13.0	1.35	43.0	23.6	40.7	4.48	74.0	1.07	30.2	0.55	30.2
	W	33.9	36.4	110.0	1.40	44.6	54.2	92.7	6.43	92.7	3.48	98.3	2.03	98.3
303	B	39.6	39.8	115.0	4.72	100.0	48.2	100.0	3.47	100.0	1.67	100.0	2.39	100.0
	C	20.3	33.1	18.0	1.68	45.6	20.9	43.5	1.92	43.5	0.40	24.0	0.86	24.0
	W	33.5	36.1	108.0	2.77	58.7	43.1	89.4	3.71	89.4	1.60	95.8	2.52	95.8
304	B	39.0	38.9	115.0	3.05	100.0	60.1	100.0	4.36	100.0	2.62	100.0	1.91	100.0
	C	15.5	28.2	25.0	1.33	43.6	28.4	47.3	3.01	47.3	0.86	32.8	0.88	32.8
	W	35.2	37.8	90.0	1.47	48.3	56.0	93.2	4.48	93.2	2.51	95.8	1.61	95.8
305	B	38.0	38.0	103.0	1.81	100.0	45.8	100.0	5.21	100.0	2.39	100.0	2.25	100.0
	C	17.5	30.6	12.0	0.88	48.6	22.9	50.0	3.68	50.0	0.84	35.2	0.52	35.2
	W	34.0	37.0	87.0	1.10	60.8	42.0	91.6	5.31	91.6	2.23	93.3	2.07	93.3
306	B	39.0	39.3	100.0	1.76	100.0	55.4	100.0	3.71	100.0	2.05	100.0	1.81	100.0
	C	16.5	34.8	15.0	0.80	45.5	25.0	45.1	1.58	45.1	0.39	19.0	0.60	19.0
	W	34.8	35.9	93.0	1.24	70.5	49.7	89.8	3.63	89.8	1.80	87.8	1.87	87.8
Mean	B	38.7	38.7	103.6	3.43	100.0	53.4	100.0	4.56	100.0	2.45	100.0	1.96	100.0
	C	17.8	31.8	16.6	1.21	45.3	24.2	45.3	2.93	45.3	0.71	28.2	0.68	28.2
	W	34.3	36.6	97.6	1.60	56.6	49.0	91.3	4.71	91.3	2.32	94.2	2.02	94.2

Note :
B - Before
C - Cooling
W - Warming
C.T. - Cerebral Temperature
R.T. - Rectal Temperature
C.O. - Cardiac Output

TABLE XX METABOLISM OF DOGS UNDER SELECTIVE BRAIN COOLING BY IRRIGATION

Animal No.		CT °C	RT °C	CBF		CMRO ₂		(A-V)gl.		CMRgl.		(A-V)gl.		(A-V) Ia		(A-V) Py.	
				cc/100g br./m	%	cc/100g br./m	%	mg %	%	mg/100g br./m	%	mg %	%	mg %	%	mg %	%
303	Before	39.6	39.8	48.2	100.0	1.67	100.0	16.0	7.7	7.7	100.0	4.6	-6.2	-6.2	-6.2	+0.93	+0.93
	Cooling	20.3	33.1	20.9	43.5	0.40	24.0	6.0	1.3	1.3	16.9	3.1	+3.0	+3.0	+3.0	+0.15	+0.15
	re-Warming	33.5	36.1	43.1	89.4	1.60	95.6	18.0	7.8	7.8	101.3	4.9	+2.6	+2.6	+2.6	+0.20	+0.20
304	Before	39.0	38.9	60.1	100.0	2.62	100.0	13.0	7.9	7.9	100.0	3.0	+2.5	+2.5	+2.5	+0.63	+0.63
	Cooling	15.5	28.2	28.4	47.3	0.86	32.8	7.0	2.0	2.0	25.3	2.3	-0.5	-0.5	-0.5	-0.87	-0.87
	re-Warming	35.2	37.8	56.0	93.2	2.51	95.8	12.0	6.7	6.7	84.8	2.7	+1.6	+1.6	+1.6	+0.01	+0.01
305	Before	38.0	38.0	45.8	100.0	2.39	100.0	18.0	8.2	8.2	100.0	3.5	-2.8	-2.8	-2.8	-2.12	-2.12
	Cooling	17.5	30.6	22.9	50.0	0.84	35.2	7.0	1.6	1.6	19.5	1.9	+9.1	+9.1	+9.1	-14.75	-14.75
	re-Warming	34.0	37.0	42.0	91.6	2.24	93.3	14.0	5.9	5.9	72.0	2.6	-13.5	-13.5	-13.5	-6.20	-6.20
Mean	Before	38.9	38.9	51.4	100.0	2.23	100.0	15.7	7.9	7.9	100.0	3.4	-2.2	-2.2	-2.2	-0.19	-0.19
	Cooling	17.8	30.6	24.1	46.9	0.70	30.7	6.7	1.6	1.6	20.6	2.4	+3.9	+3.9	+3.9	-6.16	-6.16
	re-Warming	34.2	37.0	47.0	91.4	2.12	95.0	14.7	6.8	6.8	86.0	3.4	-3.1	-3.1	-3.1	-2.00	-2.00

Note :
CT - Cerebral temperature
RT - Rectal temperature

TABLE XX CEREBRAL CIRCULATION OF THE SELECTIVE BRAIN COOLING BY N₂O METHOD (CLINICAL CASES)

Subject	Diagnosis		VJT	RT	MABP	CBF		(A-V)O ₂	CMR _{O₂}		CVR
			°C	°C	mmHg	cc/100g br./m	%	vol %	cc/100g br./m	%	
H.G.	A.S.D.	B	36.3	36.4	113	51.0	100.0	4.18	2.13	100.0	2.22
		c	19.9	33.5	80	41.3	81.1	1.36	0.56	26.3	1.94
		w		36.2	110	45.1	88.4	4.98	2.24	105.2	2.44
T.H.	M.S.	B	37.4	37.5	93	47.3	100.0	6.05	2.86	100.0	1.97
		c	21.0	35.5	83	40.2	84.9	1.64	0.66	23.2	2.07
		w		35.3	43	34.3	72.7	4.71	1.62	56.6	1.26
W.N.	A.S.D.	B	37.4	37.4	90	44.3	100.0	6.50	2.88	100.0	2.03
		c	18.9	35.2	66	37.7	85.0	1.28	0.48	16.7	1.75
		w		36.4	80	38.8	87.6	3.80	1.47	77.4	2.06
Mean		B	37.0	37.1	99	47.5	100.0	5.58	2.62	100.0	2.07
		c	19.9		76	39.7	83.7	1.36	0.57	22.1	1.92
		w		36.0	78	39.4	82.9	4.40	1.78	79.7	1.92

Note :

A.S.D. - Auricular Septal Defect.

M.S. - Mitral Stenosis.

V.J.T. - Temperature of int. jugular vein.

R.T. - Rectal Temperature.

B. - Before
C. - Cooling
W. - Warming

Fig. 12 Clinical case tested by the dye dilution method under selective brain cooling.

temperature (30 degrees) with simultaneous cerebral temperature 17 degrees C (Fig. 13). The relationship between the cardiac output (CO), CBF and CMR_{O₂} is presented in Fig. 14. During general hypothermia, CBF decreases less as compared with the diminution of the cardiac output, on the other hand on selective brain cooling the decrease of both CBF and CO is nearly the same and a marked decrease of the CMR_{O₂} also results.

Fig. 13 Comparison between general hypothermia and selective brain cooling.

Fig. 14 Comparison between general hypothermia and selective brain cooling.

From the observation on the relationship between the cerebral temperature and $CMRO_2$, including both clinical and empirical experiences (using dogs), it is recognized that the fall of temperature to 30 degrees C is associated with the diminution of $CMRO_2$ to 50 per cent in the average case and a fall of temperature to 20 degrees C is associated with the diminution to 30 per cent (Fig. 15). QO_2

Fig. 15 Relationship between the cerebral temperature and O_2 consumption of the brain (Clinical cases and experimental dogs by N_2O method, dye dilution method and bubble flow-meter).

values of the brain obtained by Warburg's direct method²⁵⁾ are in accord with these results (Fig. 16).

Fig. 16 Relationship between the rate of QO_2 -decrease of various organs and the decrease of temperature measured by direct method of Warburg.

When the blood circulation of the brain is occluded, the cerebral tissues try to survive the circulatory arrest by mobilizing the oxygen in stagnated blood and the reserve oxygen in the brain tissue itself. From this viewpoint as the cerebral temperature comes down, the subsequent diminution of $CMRO_2$ follows enabling the prolongation of duration of possible circulatory occlusion. So far as aerobic metabolism is concerned, the inverse number of $CMRO_2$ is set up as the possible duration

of circulatory occlusion of the brain, and its relation with the cerebral temperature is in Fig. 17.

Fig. 17 Relationship between cerebral temperature and possible and safe duration of circulatory occlusion in reference to the cerebral O_2 consumption.

At cerebral temperature of 25 degrees C the duration of possible circulatory occlusion is twice that at physiological temperature, when cooled to 20 degrees C it is three times prolonged; in other words, if 5 min. is the safety duration of the occlusion at normal temperature 10 min. is tolerable at 25 degrees C and 15 min. is so at 20 degrees C. Practically speaking there are often cases which can withstand longer periods of circulatory occlusion²⁶⁾, but the mentioned "possible duration" may be regarded reasonably as the safety limit.

When the cerebral tissues are taken before and

TABLE XVIII CARBOHYDRATE AND PHOSPHOR METABOLISM OF THE BRAIN UNDER CIRCULATORY OCCLUSION (DOGS)

	Selective brain Cooling by irra- diation			general hypothermia			physiological temperature	
mg %	B	C	A	B	C	A	B	A
Inorganic P	25.7	21.6	32.7	24.3	19.0	32.6	25.1	39.4
Creatin P	10.6	6.8	3.5	10.6	5.7	3.0	7.1	5.6
ATP	9.0	7.3	3.2	10.2	5.0	1.6	7.1	1.0
Total acid soluble P	83.0	78.0	73.0	68.2	65.0	63.0	95.5	83.0
lactic acid	27.0	23.0	92.0	31.4	23.4	138.0	31.2	125.0
Pyruvic acid	4.1	4.0	3.1	5.6	4.2	4.0	7.9	5.1
L/P	6.6	5.7	29.6	5.6	5.6	34.5	3.9	24.5
Free Glucose	114	91	67	156	101	91	135.0	72.5
	Caval and Aortic occlusion for 15 min. at 15°C cerebral temperature and 30°C rectal temperature			Caval and Aortic occlusion for 15 min. at 25°C rectal temperature			Circulatory occlusion for 5 min. at physiological temperature	

Note: B. Before the Cooling

C. Just before the circulatory occlusion (The cooling is proceeded)

A. Just before the release of occlusion

after cerebral circulatory occlusion for estimating carbohydrate and phosphorus metabolism²⁷⁾²⁸⁾²⁹⁾ remarkable changes are noted in five min. at physiological temperature. While under general hypothermia and selective brain cooling changes of similar grade are manifested for the first time after fifteen min. has elapsed being accompanied with appreciable rise of inorganic phosphorus and lactic acid, and a diminution of ATP and creatinephosphate. Notable changes are not recognized in pyruvate. These changes described here are less apparent in selective brain cooling than in general hypothermia (Table 22 and Fig. 18). When similar

Fig. 18 Carbohydrate and phosphor metabolism of the brain under circulatory occlusion.

investigation is carried out with liver tissue³⁰⁾, the changes are of less degree in general hypothermia than in the selective brain cooling, which is quite contrary to the state in the brain above mentioned (Table 23). All these consequent changes seem to be dependent on the temperature of the respective organ being investigated.

TABLE XXIII CARBOHYDRATE AND PHOSPHOR METABOLISM OF THE LIVER UNDER CIRCULATORY OCCLUSION (DOGS)

mg %	selective brain cooling by irrigation			general hypothermia			physiological temperature	
	B	C	A	B	C	A	B	A
Inorganic P	19.6	18.0	30.4	25.6	31.2	34.4	27.7	35.4
ATP	9.2	8.6	2.0	10.0	7.4	4.3	12.3	5.6
Total acid soluble P	106	116	120	88.0	96.5	95.8	113	118
Lactic acid	20.0	17.3	86.4	25.8	23.4	28.2	7.4	180.2
Pyruvic acid	6.4	4.1	5.5	5.2	4.2	4.1	4.0	2.3
L/P	3.1	4.2	15.7	3.2	5.5	6.9	1.8	78.3
Glycogen	1.9	1.4	1.2	1.7	1.3	0.8	3.6	5.4
	Caval and Aortic occlusion for 15 min. at 15°C cerebral temperature and 30°C rectal temperature			Caval and Aortic occlusion for 15 min. at 25°C rectal temperature			Circulatory occlusion for 5 min. at physiological temperature	

Note : B. -Before the cooling

C. -Just before the circulatory occlusion (The cooling has been proceeded)

A. -Just before the release of occlusion

Based on the standpoint that circulatory arrest is to be understood as a sort of severe anoxia of the tissues, the experimental animals (dogs), that inhaled pure nitrogen gas to drive out reserve oxygen

Fig. 19 Carbohydrate and phosphor metabolism of the liver under circulatory occlusion.

in the tissues, were examined. Under physiological body temperature, the animals' general condition deteriorates within a short time and becomes almost fatal in 3 min. (Fig. 20). Whereas at lower tem-

perature and the following increase of CMR_{O_2} are recognized, the circulatory condition gradually gets worse after more time has elapsed (Fig. 21 and 22). The lower the cerebral temperature, the slower

Fig. 20 Inhalation test of 100% Nitrogen under normal temperature by using dogs.

peratures, especially when the selective brain cooling by irrigation is employed, the rise of blood pressure, increasing CBF, cerebral arterial-venous oxygen

Fig. 22 Inhalation test of 100% Nitrogen under selective brain cooling by using dogs.

Fig. 21 Inhalation test of 100% Nitrogen under the general hypothermia.

the occurrence of these changes seem to proceed. But in any way the state of low oxygen in the brain holds such a strong influencing factor that the sufficient oxygen supply is necessary up to the onset of the occlusion for the purpose of prolonging the duration of circulatory arrest²⁴⁾.

PROBLEMS CONCERNING THE SELECTIVE BRAIN COOLING

In reference to the cerebral circulation, pathological physiology has been extensively investigated by our department, and the studies are briefly described.

a) Thyroid Function at Low Body Temperature.

When the function of the thyroid gland is examined by means of the quantity of uptake of I^{131} it decreases radically and the state of hypofunction remains unchanged even after 24 hours without any response to massive bleeding as a "stress" (Fig. 23).

b) Nucleic Acid Metabolism at Low Body Temperature

In order to understand the metabolism of nucleic acid³³⁾³⁴⁾ various features of this acid in those in-

Fig. 23 Rate of I^{131} intake in thyroid gland after 24 hours.

flicted with burns were investigated. When the general hypothermia is employed, RNA shows decrease in hypothalamic region and pituitary, contrary to the control, but no appreciable changes occurred in the liver. In other words, under the latter circumstances nucleic acid in the brain diminishes as a whole; its metabolism and protein synthesizing mechanism also seem to decline. The reactivity toward invasive stimuli is also inhibited (Fig. 24).

Fig. 24 Nucleic acids changes (Burn under general hypothermia).

When the selective brain cooling is adopted, changes in the hypothalamic region and pituitary are almost similar to those observed at the general hypothermia. RNA of the liver, however, appeared to increase which may indicate promoted synthesizing action of the liver (Fig. 25).

Fig. 25 Nucleic acid changes (Burn under selective brain cooling).

DNA has almost the same tendency both in general hypothermia and selective brain cooling showing diminution, and the reactivity to invasive stimuli stands subnormal on the occasion of selective brain cooling even an extreme invasion such as circulatory occlusion does show very little difference in reaction when compared with the reactions from burns (Fig. 26).

Fig. 26 Nucleic acid changes (Circulatory occlusion under selective brain cooling).

c) Changes of ADS-Level in Serum at Low Body Temperature

ADS-level⁽³⁵⁾⁽³⁶⁾⁽³⁷⁾⁽³⁸⁾ in serum shows hardly any changes under the simple employment of selective brain cooling by irrigation (Fig. 27). When a burn is produced at normal temperature, ADS-level shows an acute rise, whereas under the selective brain cooling hardly any changes are noted (Fig. 28). This fact implies that neurosecretion of pituitary has almost completely been inhibited. When the cooling is interrupted the cerebral temperature rises with restoring of the blood pressure, and it results in rapid neurosecretion of slight grade, but these changes are low when compared with those with general hypothermia.

As the after-effects of the circulatory arrest were empirically investigated, some of the control

Fig. 27 ADS-level in serum under selective brain cooling.

Fig. 28 ADS-level in serum at produced burn under selective brain cooling by irrigation.

group had a sudden rise of ADS, but under either general hypothermia or selective brain cooling ADS level does not show any notable change. This is explained as a reaction to invasive stimuli which has been inhibited by the cooling procedure. The ADS-level is lower in selective brain cooling than in general hypothermia, which seems ascribable to the state that in selective brain cooling the temperature of the liver is relatively high and its

Fig. 29 ADS-level in case of the circulatory occlusion under the general hypothermia.

Fig. 30 ADS-level in serum in case of the circulatory occlusion under selective brain cooling.

function is fairly well maintained (Fig. 29 and 30).

d) Action Potential of Posterior Pituitary at Low Body Temperature.

Action potential of posterior pituitary³⁹⁾⁴⁰⁾⁴¹⁾⁴²⁾ decreases rapidly in close parallel to the fall of the cerebral temperature and nearly vanishes at 20 degrees C suggesting interrupted function of posterior pituitary. The feature is almost the same with the declining course of centrifugal impulse of the vagus⁴³⁾ and also is in accord with the varying picture of the electroencephalogram (EEG) (Fig. 31). It

Fig. 31 Action potential under selective brain cooling.

Fig. 32 Action potential of posterior pituitary at produced burn under selective brain cooling.

may be said that almost all the functions come to a halt when the cerebral temperature approaches 20 degrees C. The action potential of the posterior pituitary is strengthened at varying invasions, but does hardly change under the selective brain cooling, even when a burn is produced (Fig. 32).

e) Peripheral Vascular Resistance at Low Body Temperature

As one of the reactions of the central nervous system against invasive stimuli, the peripheral vascular resistance is estimated with the perfusion method under constant pressure⁴⁴. The peripheral vascular resistance decreases nearly in parallel to the blood pressure as the selective brain cooling is carried out (Fig. 33). When a certain invasive

Fig. 33 Peripheral vascular resistance under selective brain cooling.

stimulus, for example, vigorous manipulation of the intestines is produced, in general the peripheral vascular resistance rapidly rises⁴⁵, while under the selective brain cooling such reaction is hardly observed (Fig. 34). From this observation it may be assumed that the innervation of the vasomotor

Fig. 34 Changes of peripheral vascular resistance under the selective brain cooling and vigorous manipulation of intestines.

center has probably been depressed by the selective brain cooling.

f) Electroencephalogram (EEG) at the Low Body Temperature and Circulatory Arrest.

Studies with the electroencephalogram (EEG) during the lowered body temperature and the circulatory occlusion were carried out with the cooperation of the Surgical Clinic directed by Prof. Shimizu and Noken (the research institute of the Brain), Tokyo University. There are several reports on EEG during hypothermia^{46,47} and on circulatory occlusion^{48,49}.

Under general hypothermia the EEG shows slow waves around 33 degrees C, 22 min. after the onset of cooling. Smaller amplitudes are noted at 28 degrees C, 54 min. after onset of cooling (Fig. 35 and 36). The waves are almost extinct at 20 degrees C, 2 hours after the beginning of cooling (Fig. 37). When warmed up again the waves reappear at around 28 degrees C, 1 hour after re-warming and return to the original condition around 30 degrees C, some 3 hours later (Fig. 38 and 39).

Under selective brain cooling by irrigation, slow waves are first recognized at cerebral tem-

Fig. 35 Slow waves at around 33°C under general hypothermia.

Fig. 36 Smaller amplitude at 28°C.

Fig. 37 The waves are almost extinct at 20°C.

Fig. 38 Warmed up again, the waves reappear at around 23°C.

Fig. 39 Return to original condition 3 hours after rewarming.

perature 30 degrees C, 6, min. after the cooling process has started (Fig. 40). From our experiment it can be said that since the side on which cooling is carried out stays at lower temperature, the changes of EEG on this side are stronger. Recovery from the after-effect of circulatory occlusion is more rapid

Fig. 40 Slow waves are recognized at 30°C (cerebral temperature) under brain cooling.

on the side of cooling. It is confirmed that a certain grade of reduction of cerebral temperature is necessary for successful survival of circulatory occlusion. When the cooling proceeds further to 25 degrees C, 17 min. after the beginning of cooling, the amplitude of the waves diminishes (Fig. 41).

Fig. 41 Amplitude of EEG diminishes at 25°C.

At around 20 degrees C, 26 min. later, the waves are almost extinct (Fig. 42). When the cooling process is interrupted, the cerebral temperature rises without rewarming and returns to the state where only slight slow waves are appreciable at 29 degrees C, 25 min. after the interruption of cooling process, which is a characteristic of the selective brain cooling (Fig. 43).

As so far mentioned, the EEG at low body temperature changes in close parallel to the cerebral temperature, both in general hypothermia and selective brain cooling, and it is almost extinguished around 20 degrees C cerebral temperature.

The effect of the circulatory occlusion on the EEG is investigated⁴⁹⁾. The effects are manifested

Fig. 42 The waves are almost extinct at around 20°C.

Fig. 43 EEG is almost recovered at 29°C without rewarming.

quite rapidly at normal cerebral temperature and the EEG becomes extinct at $1\frac{1}{2}$ min. (Fig. 44). When the occlusion lasts for $2\frac{1}{2}$ min. before release almost normal condition is restored 1 min. later. While with occlusion for 5 min. a normal state does not return ever after $1\frac{1}{2}$ hours has elapsed (Fig. 45

Fig. 44 EEG of circulatory arrest at normal temperature becomes extinct $1\frac{1}{2}$ min. later.

Fig. 45 After occlusion for $2\frac{1}{2}$ min., EEG is almost restored 1 min. after release.

Fig. 46 After the occlusion for 5 min. original EEG does never come back even $1\frac{1}{2}$ hrs after release.

and 46).

Under general hypothermia the circulatory occlusion is started at 26.5 degrees C rectal temperature. One min. and 40 sec. after the occlusion the EEG extinguishes itself (Fig. 47). Ten min. later the occlusion is released. After rewarming for 30 min., slight waves reappear again for the first time at around 29 degrees C. The original state is

Fig. 47 EEG in case of circulatory occlusion at 26.5°C extinguishes itself $1\frac{1}{2}$ min. later.

Fig. 48 After occlusion for 10 min. dog is rewarmed. Slight waves reappear again at 29°C and the original EEG recovered itself at around 35°C.

recovered at around 35 degrees C, 4 hours later (Fig. 48).

In applying the selective brain cooling on clinical cases, at around 18 degrees C cerebral temperature (after cooling procedure for 30 min.), the waves

Fig. 49 After cooling for 30 min. at 34.5°C rectal temperature and 18.2°C cerebral temperature, EEG disappears, and does not reappear during occlusion.

Fig. 50 EEG reappears and distinguishes itself at 26°C, and 6 min. after release.

get extinct and do not reappear during circulatory occlusion (Fig. 49). It is released 9 min. later and the EEG reappears in 4-5 min. and clearly distinguishes itself at around 26 degrees C, 6 min. after release (Fig. 50). Original state is restored 1 hour after release (Fig. 51).

Fig. 51 Original EEG recovered itself 1 hour after release. Rectal temperature 31°C. Cerebral temperature 31°C.

As described so far the EEG wave is influenced delicately by circulatory arrest. Especially in selective brain cooling is it desirable that the waves of EEG completely disappear just before the circulatory occlusion, since the complete disappearance of the waves causes the prompt reappearance (a few minutes after release of occlusion) even at relatively prolonged occlusion and rapid recovery with favorable clinical course without exception.

CEREBRAL CIRCULATION UNDER EXTRACORPORAL CIRCULATION

The artificial heart and lung may become indispensable in open heart surgery. We have studied and investigated in this field, and succeeded empirically to produce high rate of lasting survival after the dry heart operation for more than 30 min. There are, however, many problems to be solved. Cerebral circulation is one of these problems.

Even when the volume flow of the pump is dropped down to 20 ml per kg., inspite of reducing arterial blood pressure the CBF hardly shows any appreciable changes because of the reducing CVR, and CMR_{O_2} almost keeps its normal level. But when the flow of the pump comes down to 15-10 ml per kg., the CBF diminishes together with the fall of CMR_{O_2} (Fig. 52).

The general outline of problem of cerebral

Fig. 52 Cerebral circulation under extracorporeal circulation by the dye dilution method using dogs.

circulation in the surgical field has been presented. Recently open heart surgery has especially drawn our attention and under these circumstances we have had a great deal of interest on the reacting attitude of the brain which is most sensitive to the influence of circulatory disturbance.

Further studies in this field are expected.

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