EXPERIMENTAL AND CLINICAL STUDIES ON PROFOUND HYPOTHERMIA
——PREVENTION FROM VENTRICULAR FIBRILLATION——

by

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PART I. EXPERIMENTAL STUDIES

I. Introduction

The recent development of cardiovascular surgery has been quite remarkable with an aid of hypothermia which has proved to be favorable to the surgical operations for the infants or poor risk patients. On the other hand, it has been pointed out that hypothermia may produce fatality with cardio-pulmonary complications. It is the purpose of this paper to investigate how to prevent cardiovascular complication particularly ventricular fibrillation and to prevent pulmonary complication under hypothermia in order to introduce a unique technique of hypothermic anesthesia.

II. General concepts of ventricular fibrillation in hypothermia and it's prevention.

It has already been stated that one of the most serious and dangerous complications under hypothermia was ventricular fibrillation. To this day, it has been accepted that the lowest body temperature at above which no ventricular fibrillation occurs was 28°C. Today, heart surgery is carried out at a body temperature of 30° to 32°C for the purpose of prevention of ventricular fibrillation which occurs frequently when the mechanical stimuli are delivered to the heart. However, as our collaborator TOMIOKA has stated, the time limit for circulatory occlusion in such mild hypothermia is too short to perform the intracardiac operation safely and securely. In order to perform complete intracardiac operation securely, profound hypothermia below 25°C must be considered. However, since the incidence of the ventricular fibrillation in such profound hypothermia is very high, one must consider the prevention of the fibrillation in order to perform safe profound hypothermia. Many authors have presented the following procedures as the prevention of the fibrillation : Coronary perfusion with KCl or neostigmine, infiltration of HCl-procaine around the sinus node, YOUNG's solution as a cardioplegic solution and so on. However, it is generally known that these procedures do not always inhibit the fibrillation. The prevention of the fibrillation means ideally to completely inhibit the fibrillation which is almost impossible. Clinically, it is of use to produce the condition to be easily defibrillated. However, it is meaningless to take time or to carry out cardiac massage forcefully

for defibrillation, because cardiac massage for a long period of time may produces injury of the heart muscle.

Hypothermia which reduces metabolic rate being able to permit the cardiac arrest for the adequate time to perform the intracardiac operation is similar to the hibernant state in the nature. It is well known that the animals become in the hibernated state after they store the lipid sufficiently in their body. It has been taken for the reason of the fat storage that the animals would keep their body temperature unchanged by the subcutaneous storation of the sufficient fat or an anticonductor of heat and that they use the dépot fat as a caloric source effectively. It is suggested that the R. Q. 0.7 in the hibernated state of the animals shows that they use the fat effectively as a caloric source.

Moreover, recent development of the lipid chemistry has thrown light upon the many specific nutritional significance of essential fatty acid (E. F. A.). On this point of view, it is suggested that the animals store the fat before they go into the hibernated state not only because of the above mentioned reasons, but also because of this specific nutritional significance of E. F. A.. Out of the specific nutritional effects of E. F. A. that have been known to this day, the facts that is able to explain the reason for the physiologic phenomenon that the animals store the sufficient fat before they go into the hibernated state will be described as follows.

1) As our collaborator TOMIOKA, NAGASE and KOBAYASHI have reported, E. F. A. which is contained in the capillary wall or the cell membrane have an effect to make the permeability of the capillaries and cell membrane normal.

2) Deficit of E. F. A. causes the dissociation of oxidative phosphorylation that impedes the synthesis of A. T. P., energic source, to make the muscle contract. Consequently, this dissociation of oxidative phosphorylation disturbs the cardiac contraction. In facts, active heart muscle contains far much more amount of E. F. A. than the other muscles and comes after the adrenal glands and liver in the content of E. F. A..

3) Heart muscle consumes usually a large amount of higher fatty acids, which is illustrated by the fact that A-V difference of fatty acids is greatest in the coronary artery and vein, and hepatic artery and vein.

4) It has been stated that animals in E. F. A. deficiency had reduced resistance to cold stress.

5) On the concepts of the active transportation of electrolytes, lipids have an important significance on the in- or out-wards movement of electrolytes in the cell membrane.

Since it is believed that the changes in concentration of K-ion in the heart muscle is one of the causes of the fibrillation, it is suggested that the heart of the animals in E. F. A. deficiency may be fibrillated easily because of the abnormal permeability of the cell membrane of electrolytes.

The present study was performed with the idea in mind that the administration of E. F. A. makes hypothermic anesthesia safer.

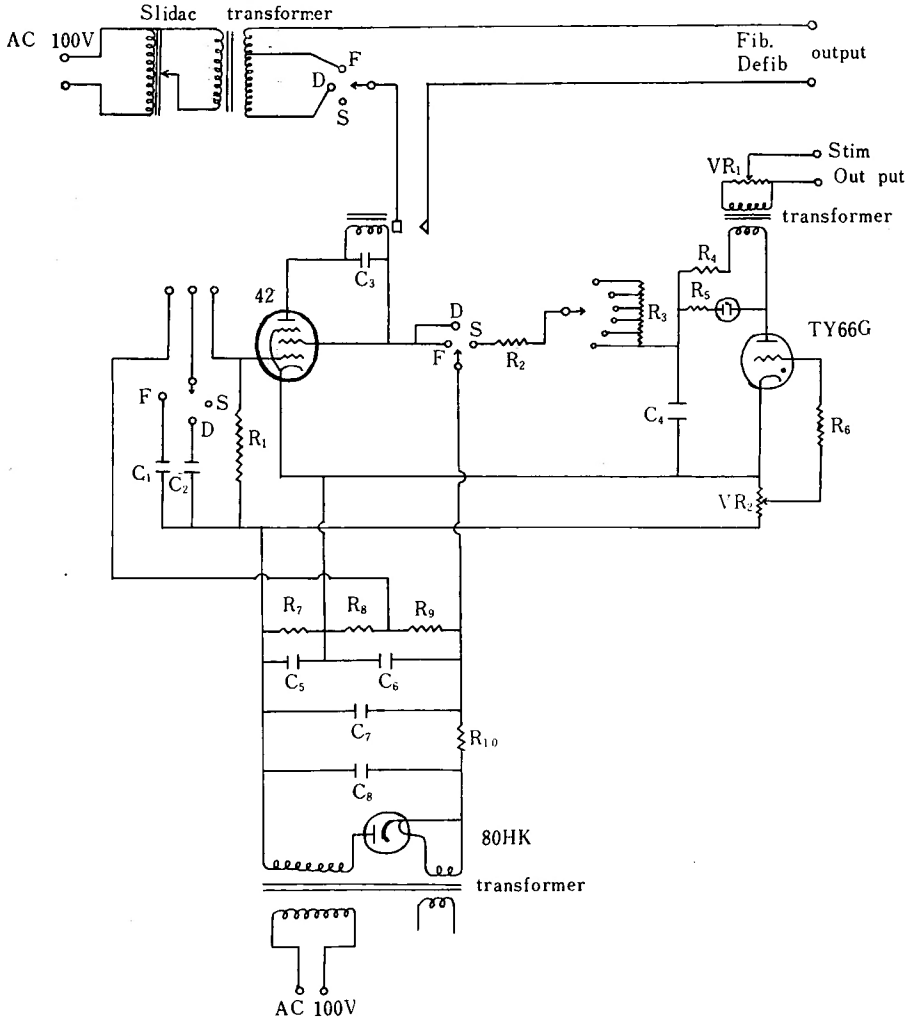
Ⅲ. Experimental animals and methods

1) Experimental animals:

Infant mongrel dogs weighing 6 to 12 kg were used. Because, most of the adult dogs have filarias in the right ventricle, which eventually become pulmonary emboli unfortunately after open heart surgery. The author selected the animals carefully from a point of the growth of teeth and only two dogs had filarias throughout the experiments. One of them died of pulmonary emboli of filarias after the operation, the other survived because filarias were successfully removed from the right ventricle.

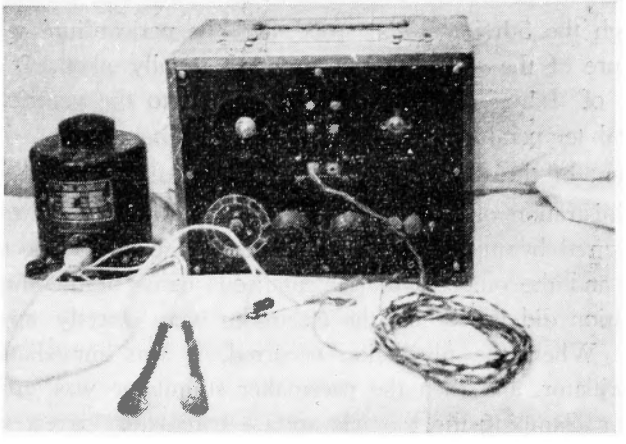
2) Fibrillator, defibrillator and pacemaker stimulator :

Fig. 1 Circuit diagram of the Fibrillator-Defibrillator-Pacemaker stimulator



The author designed the apparatus of fibrillator, defibrillator and pacemaker stimulator. The structures are given in Figs. 1 and 2. An electronic circuit of the fibrillator provides an impuls of alternating current of 60 cycles, in duration of 2 seconds and variable from 0 to 13 volts. One of the electrodes was applied to the anterior wall of the left ventricle, and the other to the subcutaneous tissue of the anterior thoracic wall

Fig. 2 Photograph of the Fibrillator-Defibrillator-Pacemaker stimulator



(usually at the height of the third rib.) The threshold value to the fibrillation was expressed as the lowest voltage of which the stimuli in duration of 2 seconds containing the WEGRIA's vulnerable period produce the fibrillation.

The electronic circuit of the defibrillator provides an impuls of alternating currents of 60 cycles, in duration of 0.1 seconds and variable from 0 to 200 volts. The electrodes were applied at the longest axis of the heart.

The electronic circuit of the pacemaker stimulator provides an impuls of a saw-tooth current variable from 0 to 20 volts and in duration from 0 to 0 05 seconds. The points of the electrodes were 4 mm apart. The electrodes were applied to the sino-auricular node under temporary clamping the thoracic aorta after the conversion of the ventricular fibrillation produced at the measurement of the fibrillatory threshold value. By doing so, the color of the heart changed from cyanotic to normal or red color by defibrillation. And then, ventriculotomy was carried out following circulatory occlusion. Besides, the pacemaker stimulator was used with the object of holding the pulse rate and the blood pressure when the heart beat was not satisfactory yet after release of occlusion. However, the animals whose threshold value to the fibrillation was not measured were not applied.

3) Premedication :

Atropine-sulfate 0.25 mg were given subcutaneously as premedication, the autonomic nerve blocking agents being not given.

4) Anesthesia :

Anesthesia was induced with intravenous administration of thiopental. An endotracheal tube was inserted. An anesthetic gas mixture of oxygen-ether was then administered through the complete rebreathing system and the anesthetic level was maintained deep enough to control shivering while the animals were in ice water to induce hypothermia.

Throughout the procedure, the rectal temperature and heart rate were recorded. The action of the heart was monitored by electrocardiogram (Ⅱ lead). The arterial pressure was measured by the electromanometer through the femoral artery.

5) Cooling method :

The dogs were cooled by the immersion method. Neostigmine 0.25 mg were given

subcutaneously at 25°C rectal temperature. The dogs were removed from the ice bath at 19° to 24°C rectal temperature. Then left thoracotomy was performed, the left chest being entered through the 5th intercostal space, and the pericardium was opened widely. The rectal temperature of the dogs further dropped usually about 2°C by after drop. Heparin in a dose of 1.5mg per kg was administered to the ventricles of the dogs, at which time the rectal temperature was from 17° to 22°C.

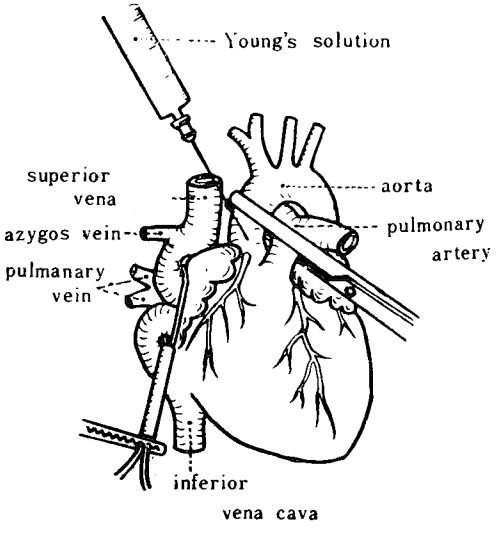
6) Measurement of the threshold value to ventricular fibrillation :

After the administration of heparin into the left ventricle, the threshold value to the fibrillation was measured by means of the fibrillator. One of the electrodes was applied to the left ventricle and the other to the subcutaneous tissue of the anterior thoracic wall. If ventricular fibrillation did not occur, the electrodes were directly applied to the right and left ventricles. When the fibrillation occurred, it was immediately defibrillated by the use of the defibrillator, and then the pacemaker stimulator was applied to the sino-auricular node under clamping the thoracic aorta. Circulatory arrest was produced after the heart was well oxygenated. All the heart which ventricular fibrillation did not occur was arrested immediately after heparin was administered into the left ventricle.

7) Circulatory occlusion and right ventriculotomy :

Firstly inflow occlusion was done by the ligation of the venae cavae with the use of polyethylene tube and then the aorta and pulmonary artery were cross clamped by the SATYNSKI's clamp. As is given in Fig. 3, YOUNG's solution (0.54 g potassium citrate and 2.47g magnesium sulfate per 100 ml ; adjusted to pH 7.4 with sodium bicarbonate) was injected rapidly into aorta proximally to the clamp without additional administration of neostigmine. By doing so, coronary blood is removed and the heart becomes edematous. Finally the heart action stops. 1.5 to 3 cc per kg of YOUNG's solution was sufficient to make the heart arrested.

Fig. 3 Circulatory occlusion and injection of YOUNG's solution



Immediately after the cardiac arrest, right ventriculotomy was performed about 3 cm in length at the area free from blood vessels. Venous blood and YOUNG's solution in right ventricle were washed out by physiologic saline solution. If filarias were seen, they were removed and then right ventricle was sutured and closed after being filled with physiologic saline solution.

8) Release of occlusion :

After ventriculotomy was performed under circulatory occlusion for about 18 to 50 minutes, coronary perfusion with physiologic saline solution 15 cc was carried out in order

to wash out YOUNG's solution from the heart. Outflow occlusion was first released followed by release of inflow occlusion. In order to make the cerebral and coronary blood flow increase and to make the heart action strong, cardiac massage was carried out under the condition which the thoracic aorta was clamped. By doing so, the flaccid heart muscle became to have its tonus. In dogs of E. F. A. group and E. F. A. plus dimethylaminoethanol (D. A. E.) group, normal heart beat was obtained within 1 to 2 minutes after release of occlusion. On the contrary, in the controls cardiac massage for a long period of time was necessary to convert to the normal rhythm.

In dogs of E. F. A. plus D. A. E. group, observing the cardiac action after normal heart beat was obtained, intrathoracic rewarming was carefully carried out. Pressing the thoracic aorta was discontinued when the dog was rewarmed to 22° to 23°C rectal temperature. Immersion rewarming method was employed at above 24° to 25°C rectal temperature.

According to our collaborator KUWANA, applying pressure to the thoracic aorta for a long period of time may cause pulmonary edema because of the high pulmonary arterial pressure. Therefore, at above 22° to 23°C rectal temperature (heart beat is relatively strong) this procedure is contraindicated. As mentioned above, most dogs in E. F. A. group or E. F. A. plus D. A. E. group resuscitated without fibrillation. Few of them incurred the fibrillation at the change of body position. Even in these cases, defibrillation was successfully carried out with the use of defibrillator and all resuscitated.

However, most dogs in the controls incurred the fibrillation which was not easily converted to the normal rhythm below 25°C rectal temperature with the use of defibrillator. Therefore, the dogs were rewarmed to 25°C rectal temperature by intrathoracic rewarming under long cardiac massage, and then defibrillatory procedure was carried out. However, most of the dogs died of the fibrillation.

9) Rewarming method

Intrathoracic rewarming method was carried out as follows. RINGER's solution as warm as 30°C was infused into thoracic cavity through polyethylene tube. As the heart beat became stronger, the temperature of the solution was gradually elevated to about 43°C. After the body was rewarmed to 24° to 25°C rectal temperature by the intrathoracic rewarming, the body was immersed into the hot water as warm as about 43°C. The intrathoracic rewarming was discontinued at 28°C rectal temperature, and the chest was closed under immersion rewarming. The immersion rewarming was continued until 33°C rectal temperature. After the discontinuation of the immersion rewarming, dog's skin was dried and electric heat blanket was applied in order to maintain the body temperature.

10) Neutralization of heparin :

When the heart beat became strong enough after release of occlusion, heparin which has been given intravenously in order to prevent blood coagulation was neutralized as follows, protamine sulfate 1.5 times volume of heparin, being diluted with 20 cc of physiologic saline solution, were slowly infused intravenously.

11) Administration of E. F. A. :

Linoleic acid (9, 12-Octadecadienoic acid), linolenic acid (9, 12, 15-Octadecatrienoic

acid) and arachidonic acid (5, 8, 11, 14-Eicosatetraenoid acid) are known as E. F. A. today. Particularly arachidonic acid which is synthesized in vivo from linoleic acid with action of Vit. B_6 should have the specific physiologic effect as E. F. A.. Therefore, in order to correct the E. F. A. deficient state, administration of sufficient amount of linoleic and linolenic acids takes place of arachidonic acid. Clinically, sesame oil or soya lecithin are to be administered. However, as these are easily decomposed by the heat treatment, diet which contains E. F. A. must not be treated with the heat.

Since plant oil without heat treatment seems to be difficult in administration to the patients and in digestion and absorption, soya lecithin which is easily digested and absorbed and easily dispersed as microglobule in warm milk is advantageous for administration of E. F. A.. Moreover, administration of soya lecithin by mouth is advantageous, because rapid load of a large amount of fluid may cause detrimental effects to the heart of the severely ill patients.

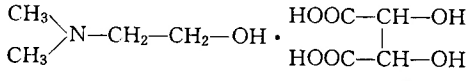
In the present study, administration of soya lecithin by mouth was mostly applied as a method of administration of E. F. A., partially sesame oil emulsion being given intravenously. The present study was done with the mind not to be different in effect between in intravenous administration of E. F. A. and in administration of E. F. A. by mouth. Soya lecithin in a dose of 5 g by mouth or intravenous 25 cc of 20% sesame oil emulsion were administered to the dogs one week prior to the experiment.

12) Other premedication :

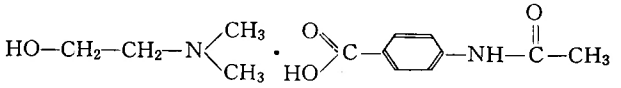
Dimethylaminoethanol (D. A. E.……Eason, Recrein), precursor of acethylcholine, was given to the dogs (Fig 4). Eason and Recrein which are acidic tartaric soda of D. A. E. and paraamino benzoic soda were given to the dogs by mouth in a dose of 10mg with administration of E. F. A. daily one week prior to the experiments. The effects were sufficient and equal between them.

Fig. 4 The formula of dimethylaminoethanol.

Recrein (Yoshitomi)



Eazon (Dainihon)



Vitamine E (dl-α-Tocopherol) was administered by mouth in a dose of 200 mg daily one week prior to the experiments.

Prométhazine (Pyrethiazine) 0.5mg per kg was injected subcutaneously after resuscitation.

Ⅳ. Experimental results and discussion

1) Simple resuscitation experiment

Our collaborator TOMIOKA has reported that blood viscosity and hematocrit value were increased at low body temperature, but if E. F. A. was administered to the dogs before hypothermia these were maintained within normal limits. From this fact, he sug-

gested that the load to the heart was reduced because of the reduced blood concentration, the reduction of the increased peripheral resistence and maintenance of the hemodynamics in hypothermia in the fat group. He also stated that this is attributed to the reduction of the abnormal increase in the permeability of the capillaries in hypothermia in the fat group. From this TOMIOKA's results and the several specific nutritional effects of essential fatty acids, it is suggested that administration of fat is effective to inhibit ventricular fibrillation.

The author measured the electrical fibrillation threshold value at 17° to 19°C rectal temperature in the fat group and the controls, and investigated whether they survive or not after right ventriculotomy under circulatory occlusion for 18 to 30 minutes.

A) The measurement of the electrical threshold value for the fibrillation:

The dogs were removed from ice bath at 19° to 20°C rectal temperature and the right chest was entered in the 5th intercostal space. The rectal temperature was lowered to 17° to 19°C when the pericardium was opened widely so as to expose the heart. After heparin was injected into the left ventricle, the electrical threshold for ventricular fibrillation was measured with use of the fibrillator applying the electrodes at the anterior wall of the left ventricle and the other at the subcutaneous tissue of the thoracic wall.

The threshold value in the fat group was 11 25 volts in the average of 8 dogs, and in the controls 3.9 volts in the average of 7 dogs. There were significant differences in the threshold value between the fat group and the controls (Table 1).

In summer the dogs showed the low fibrillation threshold value. This seems to be attributed to the abnormal state of water and acid-base balance in summer because of the absence of the sweat glands in dogs. Since the present study has the purpose to apply the hypothermia clinically, the experiments were carried out in winter (in Oct. to Jun.) in which the absence of sweat glands was of no significance.

Why were there significant differences in the threshold for the fibrillation between

Table 1

(E) given 25cc of 20% sesame oil emulsion intravenously daily for one week preoperatively.
1) Fat group: (L) given soya lecithin 5g by mouth daily for one week preoperatively.

Dog No.	Wt. of dog(kg)	Sex	Lowest rectal temperature (°C)	Ventricular fibrillation threshold(V)	Occlusion time(min.)	Ventricular fibrillation	Recovery
1(E)	6.2	우	18.2	10	20	no	yes
3(E)	6.2	우	18.2	13	40	yes	yes
4(E)	6.7	우	20.0	13	31	no	yes
5(E)	6.6	우	19.0	13	30	no	yes
7(E)	8.5	숫	18.0	7	20	no	yes
10(E)	9.5	우	18.0	8	21	no	yes
12(L)	7.0	우	18.5	13	31	no	yes
14(L)	9.2	숫	19.0	13	20	yes	yes
mean	7.5		18.6	11.25	27		

Ventricular fibrillation in dog No. 3 immediately after intrathoracic rewarming and in dog No. 14 after release of occlusion occurred.
K-citrate as cardioplegica was given in dog No. 14.

2) Control :

Dog No.	Wt. of dog(kg)	Sex	Lowest rectal temperature (°C)	Ventricular fibrillation threshold(V)	Occlusion time(min.)	Ventricular fibrillation	Recovery
2	6.7	♀	20.0	6	20	yes	no
6	12.0	♀	18.0	4	18	yes	yes
8	8.0	♀	17.2	6	20	no	no
9	12.7	♂	18.0	2	25	yes	yes
11	11.6	♀	19.0	3	25	yes	no
13	6.8	♀	18.0	1.5	22	yes	yes
15	6.8	♂	19.0	5	20	yes	no
mean	9.2		18.5	3.9	21		

Ventricular fibrillation in dogs No. 2 and 6 at occlusion and after release of occlusion, in dog No. 9 at occlusion, in dog No. 11 at occlusion and during rewarming and in dogs No. 13 and 15 during rewarming occurred.

the fat group and the controls who were fed with the natural diet? This seems to be attributed to the absence of E. F. A.. Dogs in the controls were fed with the diet deficient in E. F. A., because E. F. A. or polyunsaturated fatty acids in the diet were destroyed easily by the heat treatment of diet.

B) When did ventricular fibrillation occur?

In both groups, ventricular fibrillation did not occur until the induction of artificial ventricular fibrillation by the fibrillator. As TOMIOKA has stated, this fact shows that the fibrillation rarely occur in hypothermia at such rectal temperature as 17° to 19°C if anesthesia and respiration are carefully managed and blood pH is maintained within normal limits. However, if neostigmine was not given in dogs at 25°C rectal temperature, ventricular fibrillation often occurred.

During circulatory occlusion or after release of occlusion, ventricular fibrillation occurred in 4 out of 7 dogs in the controls. On the other hand, the fibrillation did not occur in any dogs in the fat group.

It has been reported that the incidence of the fibrillation was high after release of occlusion. In the present study, YOUNG's solution was used as a cardioplegica. Ventricular fibrillation occurred in 4 out of 7 dogs in the controls, but as mentioned above, none occurred in the fat group except one dog which incurred the fibrillation when k-citrate was used as a cardioplegica.

During rewarming, fibrillation occurred in 3 out of 7 dogs in the controls and in only one out of 7 dogs in the fat group who was given YOUNG's solution as a cardioplegica and was easily converted to the normal rhythm by means of the defibrillator.

Thus, when E. F. A. was administered to the dogs prior to hypothermia and YOUNG's solution was used as a cardioplegica, all 7 dogs survived, being easily defibrillated. On the other hand, it was difficult to defibrillate in one dog in the fat group was given K-citrate as a cardioplegica and cardiac massage had to be carried out for about 23 minutes. From this result, it is suggested that YOUNG's solution which is composed of K-citrate and $MgSO_4$ is much better than K-citrate alone as a cardioplegica. However, in the controls the incidence of ventricular fibrillation was high and it took a long time

to defibrillate.

C) Administration of E. F. A. and dimethylaminoethanol :

It has been stated that one of the factors of frozen death was vagal palsy, the vagus did not react even by the strong electrical stimulus at 20° to 21°C, and that hypothermia inhibited the vagal activity more than the sympathetic activity. It has been reported that sympatholytic drugs prevent ventricular fibrillation in hypothermia. SWAN and PREVEDEL have devised the coronary perfusion method of prostigmine or acetylcholine in order to prevent ventricular fibrillation. However, this method seems to disturb the recovery of the cardiac action after release of occlusion. Therefore, in the present study, neostigmine was given subcutaneously in a dose of 0.25mg at 25°C rectal temperature. Moreover, both E. F. A. and D. A. E., precursor of acetylcholine, were administered prior to the experiments.

The fibrillation threshold value in this E. F. A. plus D. A. E. group was above 13 volts and much higher than in the group with fat alone. In this group, the electrodes were applied at the ventricle and subcutaneous tissue, and at the left and right ventricle. As the impulse range of this fibrillator was from 0 to 13 volts, the fibrillation threshold value above 13 volts could not be measured. In the fat plus D. A. E. group, heart was arrested immediately after the measurement of the fibrillation threshold value because of the absence of ventricular fibrillation. And all of the dogs were successfully resuscitated without fibrillation (Table 2).

Table 2

Fat plus D. A. E. group :

Dog No.	Wt. of dog(kg)	Sex	Lowest rectal temperature (°C)	Ventricular fibrillation threshold(V) (1)	(2)	Occlusion time(min.)	Ventricular fibrillation	Recovery
16(L)	5.8	♂	19.5	>13	(>13)	30	no	yes
17(L)	11.0	♀	18.0	>13	(>13)	20	no	yes
18(L)	6.3	♂	17.0	>13	(>13)	21	no	yes
21(L)	8.2	♂	19.0	>13	(>13)	30	no	yes
mean	7.8		18.4	>13	(>13)	25		

1) The electrodes were applied to the left venticle and the anterior thoracic wall.
2) The electrodes were applied to the left and right ventricle.

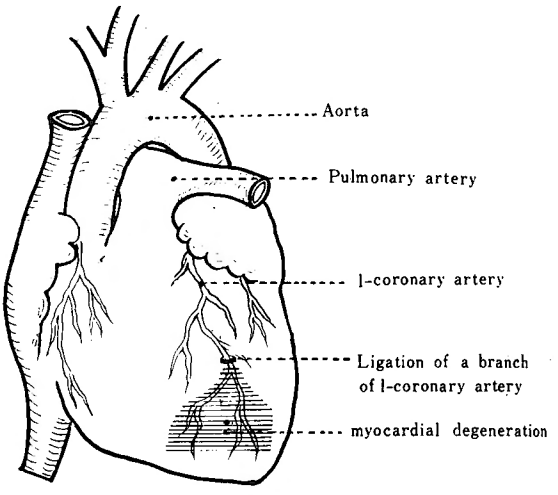
This fact seems to be attributed to the condition of the administration of D. A. E.. It is suggested that no ventricular fibrillation occur because the sympathetic active condition caused by hypothermia is corrected by the administration of D. A. E..

2) Long survival experiments

Thus, it is obvious that the administration of E. F. A. and D. A. E. prevents ventricular fibrillation in hypothermia and the dogs are successfully resuscitated after ventriculotomy under circulatory occlusion. Furthermore, YOUNG's solution proved to be an excellent cardioplegica. However, as to the clinical application of hypothermia, other complications in hypothermia have to be considered. Can the dogs suffered from ventriculotomy under hypothermia survive for a long time ? The author investigated whether

the ventriculotomised dogs who were not sacrificed or not measured the fibrillation threshold value survived for a long time or not. The dogs were divided into the following groups, 5 dogs of E. F. A. group, 2 dogs of E. F. A. plus D. A. E. group, 6 dogs of the controls. Anterior descending branches of the left coronary artery of 2 dogs in E. F. A. plus D. A. E. group were ligated one month prior to the experiments (Fig. 5).

Fig. 5 Ligation of a branch of left coronary artery



Ventriculotomy was performed in all dogs under circulatory arrest in hypothermia. As the heart were adhesive to the pericardium and the right lung in the dogs with myocardial insufficiency, the dissection had to be considered. However, even in hypothermia of 19°C, ventricular fibrillation did not occur. The dogs in E. F. A. group and E. F. A. plus D. A. E. group to whom YOUNG's solution was given as a cardioplegica survived for about 2 weeks after the experiments except one dog who died of pyothorax and asphyxia 5 days after the experiment (Table 3). However, in the dog of E. F. A. group to whom K-citrate was given as cardioplegica, cardiac massage for 23 minutes had to be carried out during fibrillation which was not easily defibrillated by means of defibrillator, but resuscitated after defibrillation and survived for a long time. On the contrary, ventricular fibrillation occurred in 5 out of 6 dogs in the controls and 3 of them were died of unsuccessful defibrillation. The cooling and rewar-

Table 3

1) Fat group: (D) given D. A. E. 10mg by mouth daily for one week preoperatively.

Dog No.	Wt. of dog (kg)	Sex	Lowest rectal temperature (℃)	Occlusion time (min.)	Ventricular fibrillation	Period of cardiac massage (min.)	Result
1(E)	6.2	♀	18.2	20	no	<3	survived
7(E)	8.5	♂	18.0	20	no	<3	survived
10(E)	9.5	♀	18.0	21	no	<3	survived
12(L)	7.0	♀	18.5	31	no	<3	survived
14(L)	9.2	♂	19.0	20	yes	23	survived
19(L/D)	6.7	♀	19.0	24	no	<3	died after 5 days post-operatively
20(L/D)	10.0	♂	19.0	26	no	<3	survived

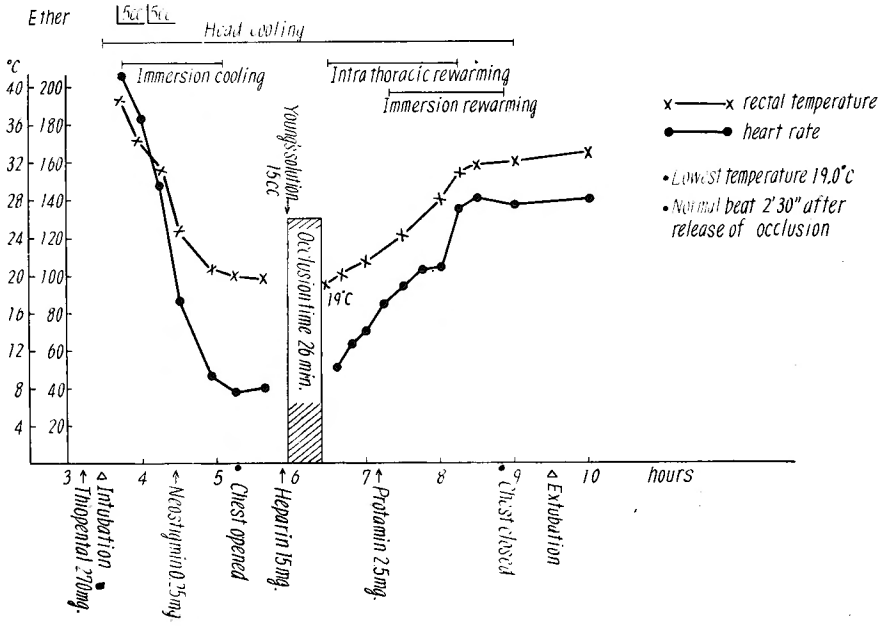
K-citrate as cardioplegica was given in dog No. 14. Anterior descending branches of coronary arteries of dogs No. 19 and No. 20 were ligated one month prior to the experiment.
Dog No. 19 died of pyothorax and asphyxia.

2) Control :

Dog No.	Wt. of dog (kg)	Sex	Lowest rectal temperature (°C)	Occlusion time (min.)	Ventricular fibrillation	Period of cardiac massage (min.)	Result
6	12.0	우	18.0	18	yes	58	survived
8	8.0	우	17.2	20	no	40	died
9	12.7	숫	18.0	25	yes	<3	survived
11	11.6	우	19.0	25	yes	7	died
13	6.8	우	18.0	22	yes	<3	survived
15	6.8	숫	19.0	20	yes	25	died

Dog No. 8 died of emboli of filarias in pulmonary artery.

Fig. 6 Dog No. 20 Weight : 10.0kg L-Coronary artery was ligated one month prior to the experiment. Preoperative administration ; soya lecithin 5 g and D. A. E. 10mg by mouth daily for one week.



ming course of the dogs with myocardial insufficiency was given in Fig. 6. The electrocardiograms during cooling and rewarming were given in Fig. 7.

3) Circulatory occlusion time

As mentioned above, dogs whose circulation was occluded for 18 to 40 minutes under hypothermia at rectal temperature of 17° to 19°C were resuscitated without pulmonary complications and survived even for 2 weeks after experiments. However, in an ambient temperature of 10°C, animals declined to die of pulmonary complications particularly pulmonary edema.

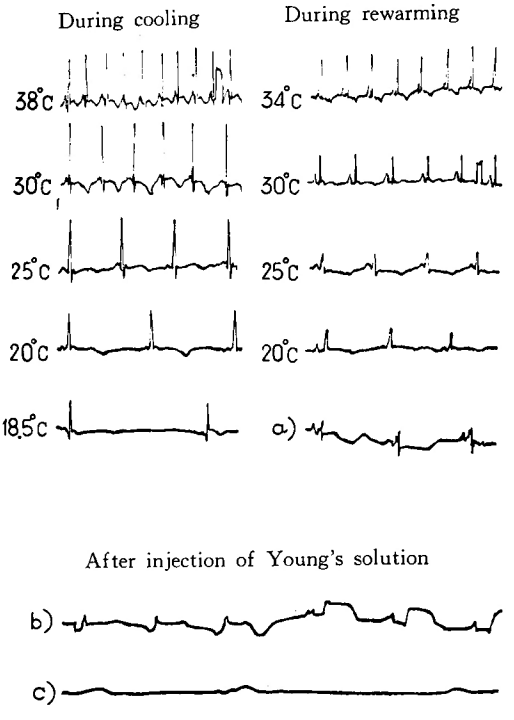
It is pointed out that hypothermic animals suffer frequently from pulmonary complications. In hypothermia, pulmonary temperature is lower than rectal temperature, therefore, pulmonary congestion should be produced.

According to our collaborator KUWANA, pulmonary edema was prevented by the administrations of sufficient amount of Vit. E and promethazine during rewarming or immediately after the resuscitation. From the results, the author examined the dogs who were given E. F. A., D. A. E. and Vit. E before the experiment.

According to TOMIOKA, circulatory occlusion time is 50 minutes at 20°C rectal temperature and 25 minutes at 25°C. The author investigated whether the animals whose circulation was arrested for 50 minutes at 18° to 22°C survive or not for 2 weeks after the experiments. Because it is the author's hope to determine the most suitable rectal temperature at which the open heart surgery is safely carried out.

In order to occlude circulation for the adequate time to perform the intracardiac procedure and to resuscitate safely and surely, how far the body temperature should be lowered? Since the radical operation of A. S. D. is carried out through left thoracotomy, it is technically difficult to apply pressure to the thoracic aorta. As mentioned above, in open heart surgery under hypothermia at 17° to 19°C rectal temperature, application of pressure to the thoracic aorta until the body is rewarmed to 22° or 23°C rectal temperature is the necessary procedure. However, according to KUWANA, this procedure may lead to pulmonary edema. Therefore, in hypothermia open heart surgery should be carried out under the condition which the heart can be resuscitated safely and surely without applying pressure to the thoracic aorta. Therefore, intracardiac operation should be carried out under hypothermia at 22° to 23°C rectal temperature.

Fig. 7 Electrocardiogram (Lead II)



a) 10 min. after release of occlusion
b) immediately after injection of YOUNG's solution
c) 32 sec. after injection of YOUNG's solution

The author investigated that in dogs to whom E. F. A., D. A. E. and Vit. E were given in sufficient amounts open heart surgery could be carried out successfully with circulatory occlusion for 50 minutes at 18° to 22°C rectal temperature even in severe cold atmosphere (Table 4). The cooling and rewarming course in dogs who were suffered from ventriculotomy under circulatory occlusion for 50 minutes at 22°C rectal temperature is given in Fig. 8. This experiment clearly demonstrates that circulatory occlusion for the adequate time to perform the intracardiac operation safely and securely

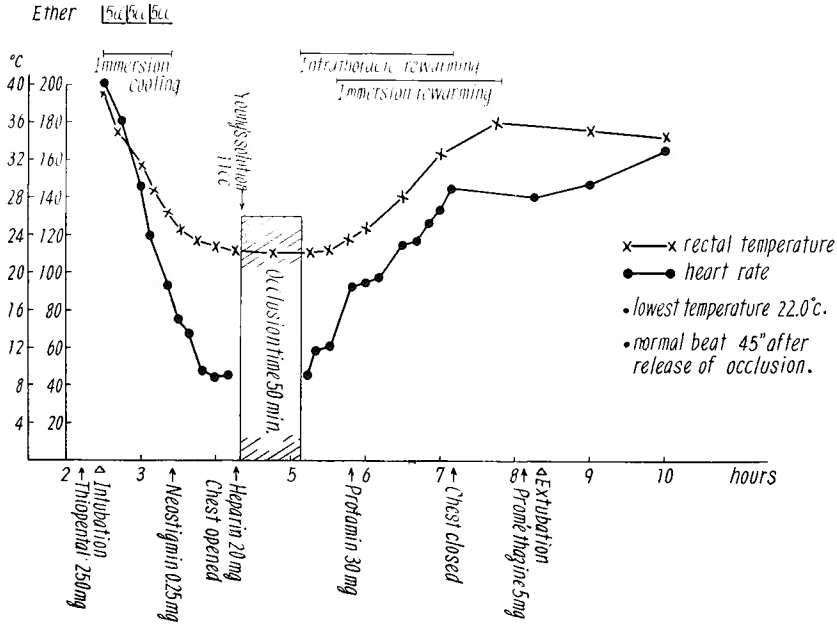
Table 4

Soya lecithin plus D. A. E. plus V. E group :

Dog No.	Wt. of dog(kg)	Sex	Lowest rectal temperature (°C)	Occlusion time(min.)	Ventricular fibrillation	Period of cardiac massage(min.)	Result
31	8.5	♂	18.3	50	no	<3	survived
32	7.5	♂	18.0	50	no	<3	survived
33	7.5	♂	19.5	50	yes	<3	survived
34	6.8	♂	21.0	50	no	<3	survived
35	8.0	♀	22.0	50	no	<3	survived

Long term survival experiment in winter (over 2 weeks)

Fig. 8 Dog No. 35 Weight: 8.0kg Preoperative administration; soya lecithin 5 g, D. A. E. 10mg and V. E 200mg by mouth daily for one week.



was carried out successfully at 22°C rectal temperature without applying pressure to the thoracic aorta. Furthermore, as KUWANA has reported, pulmonary complication was prevented by 2 doses of each 0.5 mg prométhazine per kg after rewarming.

From these results, open heart surgery has to be carried out at 22° to 23°C rectal temperature under our unique hypothermic anesthesia.

V. Conclusion

The author studied prevention of ventricular fibrillation during hypothermia. From this result and KUWANA's result, the author presented the unique hypothermic anesthesia as follows.

1) In order to prevent cardio-pulmonary complications during hypothermia, it is

necessary procedure to give sufficient amount of E. F. A. and Vit. E, or E. F. A., D. A. E. and Vit. E for one week prior to the operation. Furthermore, prométhazine 0.5 mg per kg has to be given 2 times after resuscitation at least.

2) At 25°C rectal temperature during cooling subcutaneous administration of neostigmine is necessary. Coronary perfusion of neostigmine is not considered.

3) As a cardioplegic agent in hypothermia, YOUNG's solution without neostigmine is excellent and K-citrate alone must not be given.

4) Complex intracardiac operation should be carried out in hypothermia at 22° to 23°C rectal temperature.

5) When the normal heart beat is obtained by cardiac massage after release of occlusion, intrathoracic rewarming must be carried out and immersion rewarming should be performed at above 24° to 25°C rectal temperature. In dogs to whom E. F. A. and D. A. E. are administered normal heart beat is obtained within 1 or 2 minutes after release of occlusion.

Hypothermic anesthesia can be carried out safely with the above procedure and intracardiac procedure is successfully performed. The author showed indirectly that E. F. A. had many specific nutritional effects and that in order to correct the E. F. A. deficient state intravenous administration of E. F. A. had equal efficiency to per os administration.

PART Ⅱ. CLINICAL STUDIES

Ⅰ. Introduction

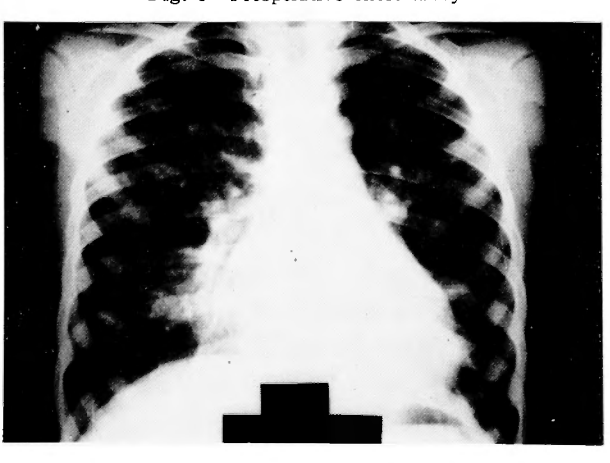
In the previous section, the author investigated prevention of ventricular fibrillation during hypothermia by means of animal experiments. From this result and our collaborator TOMIOKA's and KUWANA's experiments, the author presented our unique hypothermic anesthesia. In this section, the author investigated our unique hypothermic anesthesia on the clinical standpoint of view. Hypothermia has been markedly developed since LEWIS, SWAN and BIGELOW have performed successfully the intracardiac surgery under hypothermia. However, because of the danger ventricular fibrillation during hypothermia, they have applied mild or moderate hypothermia. The author carried out successful intracardiac operation experimentally under profound hypothermia without ventricular fibrillation. Out of the cases whom cardiac surgery was performed under direct vision with the help of hypothermia, representative 2 cases of A. S. D. (atrial septal defect) and P. V. S. (pulmonary valvular stenosis) will be discussed.

Ⅱ. Applications of hypothermia to the operation for congenital heart diseases.

1) Case of A. S. D.

The patient was 7 years old. From the preoperative roentgen picture (Fig. 9), electrocardiograms, cardiophonograms (Fig. 10), and cardiac catheterization (Fig. 11), it was suggested to be A. S. D. or shunt from pulmonary vein to the right atrium. The exceeding left to right shunt, high pulmonary arterial pressure and no sign of cardiac insufficiency show the indication of surgery. The patient was given Soya lecithin 10g and Vit. E 180 mg daily for 10 days prior to the operation. He was cooled by immersion method under G-O-E inhalation anesthesia without autonomic nerve blocking agents as premedication. Since application of pressure to the thoracic aorta after release of

Fig. 9 Preoperative chest X-ray.



occlusion is not necessary and the occlusion time is adequate to perform intracardiac operation under hypothermia at 22° to 23°C rectal temperature, cardiac surgery under hypothermia at 23°C rectal temperature was considered. At 28°C rectal temperature, neostigmine was injected subcutaneously 2 times separately at a dose of 0.1mg. Cooling was discontinued at 26.3°C rectal temperature, because rectal temperature usually lowered after the discontinuation of cooling (after drop). However, since there was no after drop in body temperature in this case, recooling was performed to lower the rectal temperature to 25.2°C and the lowest rectal temperature reached to 24.3°C at which time, neostigmine 0.1mg was administered. The right chest was entered through the 5th intercostal space and the pericardium was opened widely. The venae cavae were freed from the adjacent tissue within the pericardium so that tapes might be passed about them for inflow occlusion. Thereafter right auricle was incised and the lesion was recognized as secondary A. S. D. by finger research. At the closure of the auricle, the rectal temperature was lowered to 23.5°C. After administration of heparin 40mg into left ventricle, the inferior vena cava was occluded, followed by occlusion of the superior vena cava. Outflow occlusion was performed 5 heart beats after inflow occlusion. Immediately thereafter, YOUNG's solution was rapidly injected by the needle placed in the aorta between the clamp and the aortic valve. As the slender needle was applied with respect of bleeding from the stick wound, it took 2 minutes and 20 seconds to cardiac arrest. YOUNG's solution of 34 cc was sufficient to arrest the heart. Right atrium was incised under cardiac arrest without coronary perfusion. Under direct vision, the defect was closed with double continuous suture. The right atrium was closed with continuous suture after being filled with saline. YOUNG's solution was removed by the coronary perfusion

Fig. 10 A) Preoperative electrocardiograms
B) Preoperative cardiophonograms

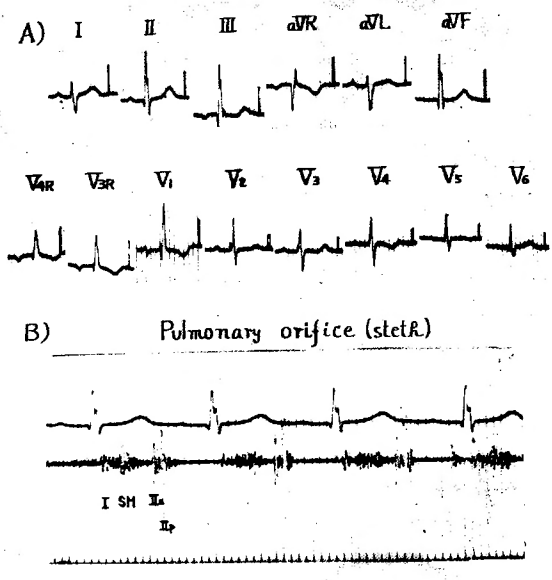
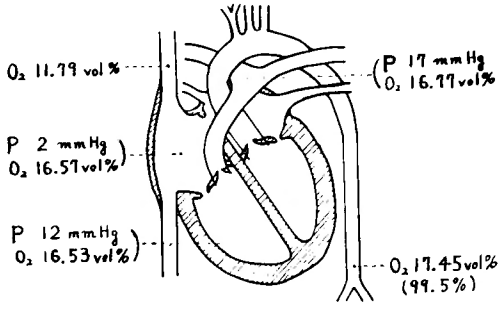


Fig. 11 Findings of cardiac catheterization



QS	1396	cc/min/m²
QPA	11618	
L to R shunt	10222	

of saline 30 cc. Thereafter, occlusion was released and cardiac massage was started. The circulatory occlusion time was 14 minutes and 13 seconds. The normal rhythm was obtained 30 seconds after the commencement of cardiac massage. However, as cardiac action was unsatisfactory, cardiac massage was continued. During cardiac massage, the transient ventricular fibrillation for about 30 seconds occurred. However, this was converted to normal rhythm by continuous massage without electric shock. Cardiac massage was continued for 2 minutes and 35 seconds till heart beat became satisfactory. Observing the cardiac action and the cardiac color, intrathoracic rewarming with warm saline was started 15 minutes after release of occlusion. Additional immersion rewarming was done at 25°C rectal temperature. Pericardium and chest were closed after intrathoracic rewarming was discontinued at 28°C rectal temperature. In this case, spontaneous respiration was present 20 minutes after release of occlusion (at 24.3°C rectal temperature). Blood loss was replaced by whole blood during the operation. Protamine sulfate was administered intravenously postoperatively for neutralizing heparin.

The patient was successfully resuscitated without ventricular fibrillation and or pulmonary complications. Fig. 12 shows the course of hypothermia during operation, and Fig. 13 electrocardiograms during cooling and rewarming and at the coronary perfusion of YOUNG's solution. Prométhazine 0.5 mg per kg were injected subcutaneously 2 times separately after closure of chest for the purpose of protection of pulmonary complications. The patient was fully awakened 7 hours postoperatively without pulmonary complications, neuro-cerebral damage, hepato-renal symptom, postoperative emboli and hemorrhage. He walked a week after operation and was taken back to pediatrics 2 weeks after operation. Fig. 14 shows the electrocardiograms and cardiophonograms 10 days after operation, and

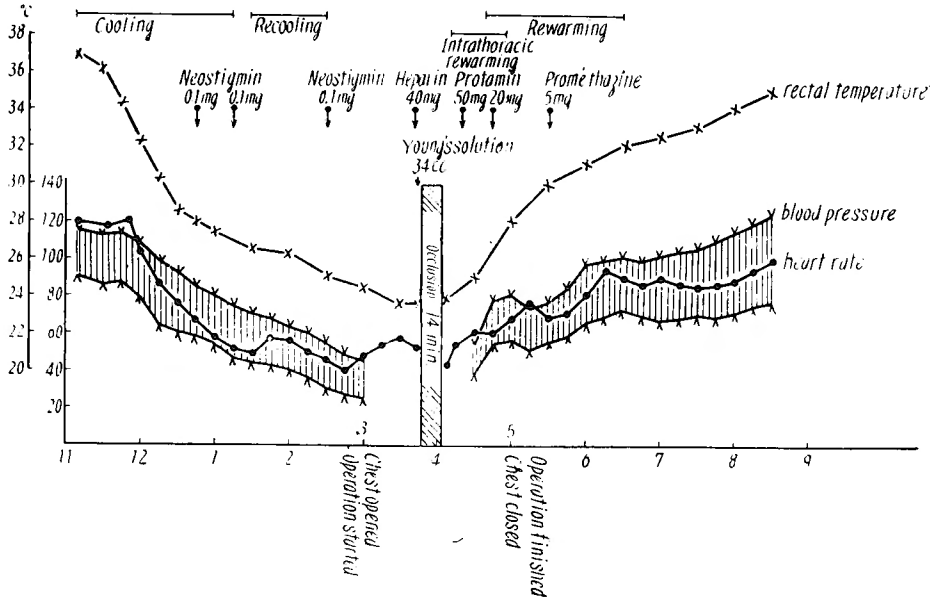
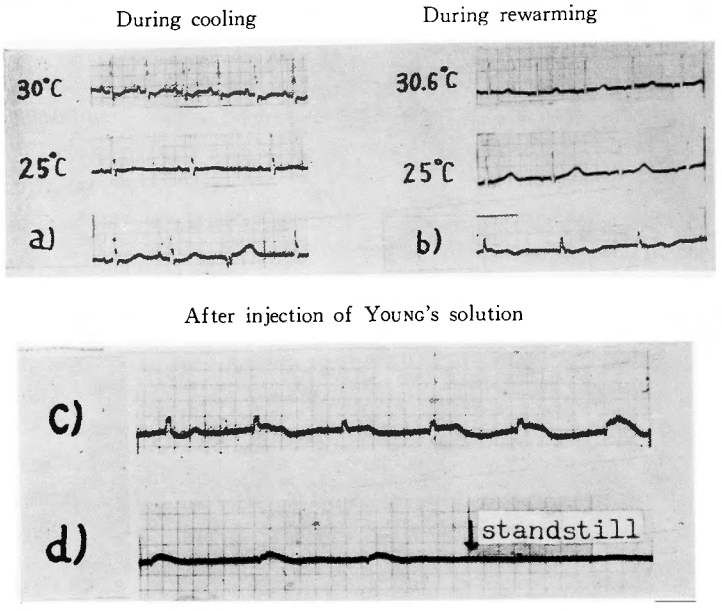


Fig. 12 (Correction of an A. S. D. under direct vision) ♁ 7 years old. Weight 17 kg. Duration of total circulatory occlusion 14 min. Lowest rectal temperature 23.5°C

Fig. 13 Electrocardiograms during hypothermia (Lead II)



a) immediately after circulatory occlusion (23.5°C)
b) immediately after start of normal beat (23.8°C)
c) 12 sec. after injection of YOUNG's solution
d) 70 sec. after injection of YOUNG's solution

Fig. 15 X-ray findings of chest at discharge from the hospital.

Our clinical experience confirms the value of administration of E. F. A. and Vit. E prior the to operation, subcutaneous injection of neostigmine at 28° to 25°C rectal temperature observing the pulse rate, application of YOUNG's solution as a cardioplegica and intrathoracic rewarming. Even if ventricular fibrillation occurred during cardiac massage, it was immediately converted to normal rhythm without electric shock. It was only 2 minutes for the period of cardiac massage. Therefore, there seems rarely to damage the intracardiac correction of the lesion. In fact, postoperative electrocardiograms and cardiophonograms was much satisfactory.

Fig. 14 A) Postoperative electrocardiograms
B) Postoperative cardiophonograms

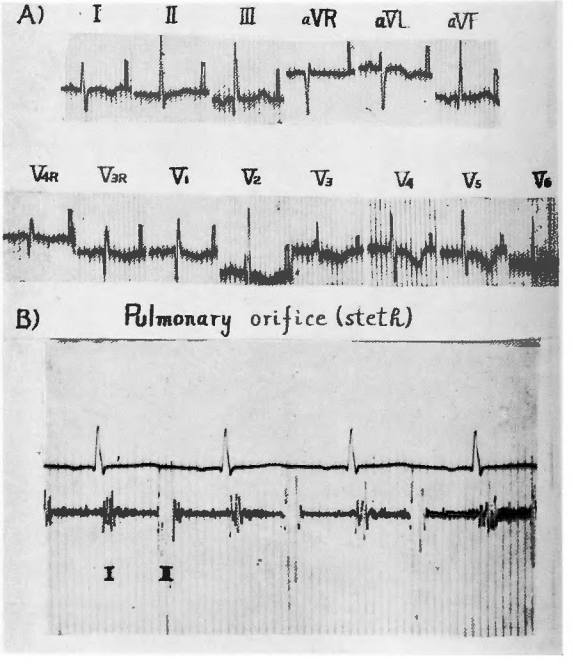
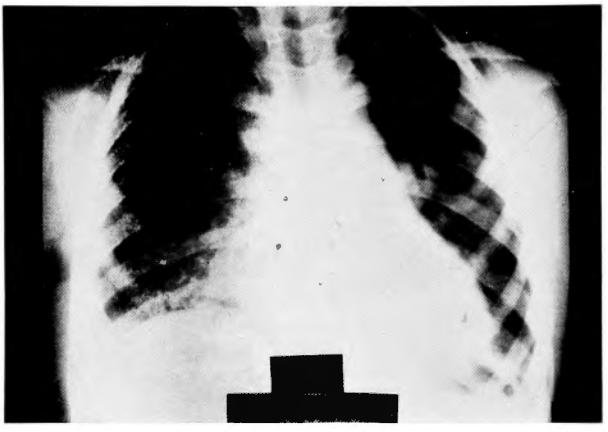


Fig. 15 Postoperative chest X-ray.



2) Case of P. V. S.

The patient was 17 years old. Since about 2 years, he began to have dyspnea on exercise, edema of the face and the legs, and arrhythmia. X-ray findings (Fig. 16), electrocardiographic findings (Fig. 17), cardiophonographic findings (Fig. 18) and cardiac catheterization findings (Fig. 19, 20) revealed the P. V. S..

Soya lecithin 20g and Vit. E 180mg were administered daily for 11 days prior to the operation. Under general anesthesia (Ether and Oxygen) without administration of autonomic nerve blocking agents as premedication, he was cooled by immersion method. Neostigmine 0.25 mg were injected subcutaneously at 27.5° and 26°C rectal temperature.

Fig. 16 Preoperative chest X-ray.

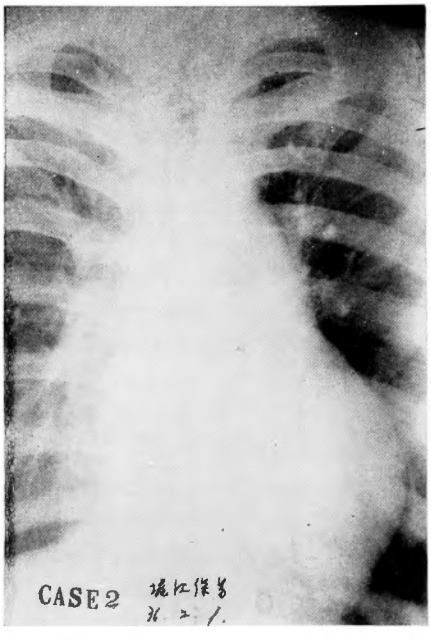


Fig. 17 Preoperative electrocardiograms.

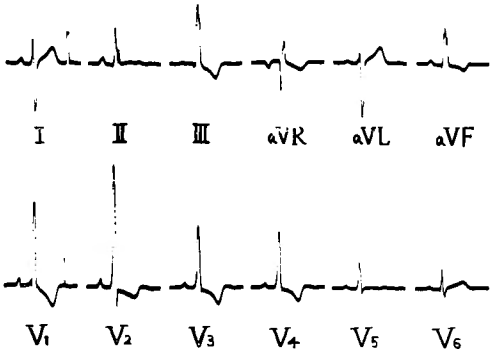


Fig. 18 Preoperative cardiophonograms

(Pulmonary orifice)

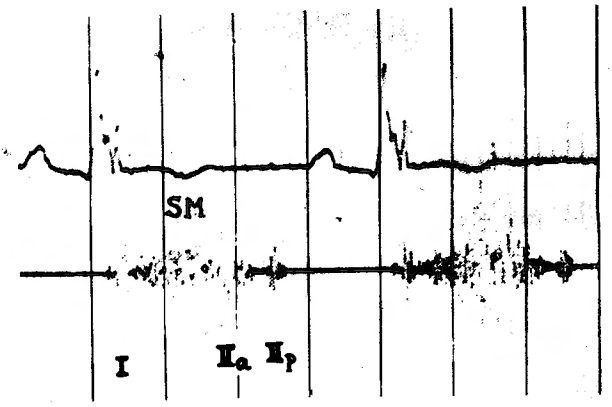


Fig. 19 Findings of cardiac catheterization.

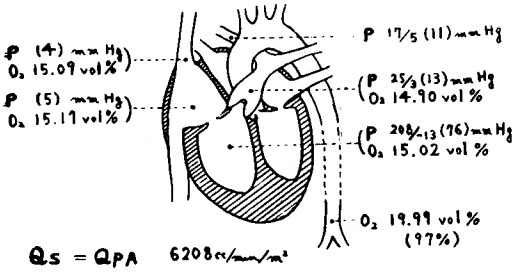
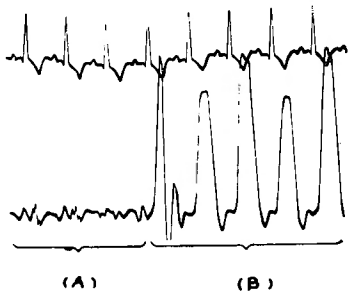


Fig. 20 Pressure curve changes from the pulmonary artery to the right atrium



(A) Pulmonary artery (B)Right atrium

Cooling was discontinued at 25.5°C rectal temperature. After subcutaneous injection of neostigmine 0.25 mg, the left chest was entered through the 3rd intercostal space and the pericardium was opened. The right ventricle was greatly enlarged and the pulmonary artery presented the post-stenotic dilatation. The thrill commenced at that point. The lowest rectal temperature was 24.7°C. After heparin being injected intravenously in a dose of 70mg, inflow occlusion was done with tape, outflow occlusion being followed. Immediately thereafter, 12 cc of YOUNG's solution without neostigmine was rapidly injected to the coronary system. It took 42 seconds for the heart to be arrested. The anterior wall of the pulmonary artery was incised and the fish mouth like valve was cut into three leaves. After being confirmed for infundibular stenosis not to be present by finger research, the pulmonary artery was sutured.

Circulation was occluded for 12 minutes and 3 seconds. The normal cardiac rhythm was seen 36 seconds after release of occlusion. However, the cardiac action was unsatisfactory so that the cardiac massage was necessary for about 3 minutes. Thereafter, intrathoracic rewarming and immersion rewarming were done in the usual manner. The pericardium and the chest were closed after the discontinuation of intrathoracic rewarming

Fig. 21 (Vulvulotomy of a pure pulmonary stenosis under direct vision) ♂ 17 years old. Weight 60kg. Duration of total circulatory occlusion 12 min. 3 sec. Lowest rectal temperature 24.7°C.

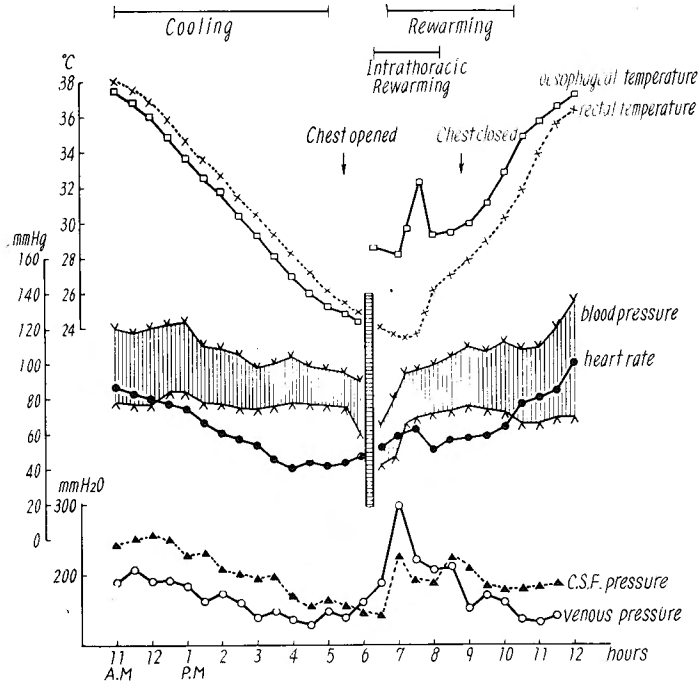
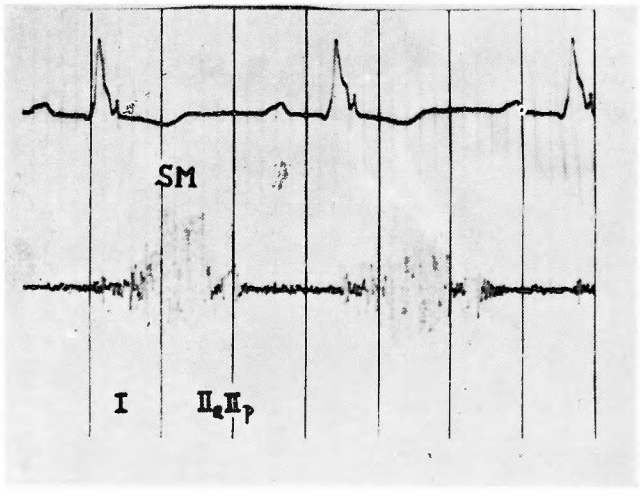
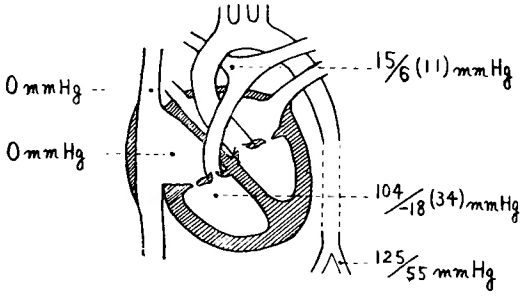


Fig. 22 Postoperative cardiophonograms.



at 26°C rectal temperature. In this case, spontaneous respiration was present 10 minutes after release of occlusion. The course of operation was uneventful without ventricular fibrillation and pulmonary complications. During operation, blood loss was replaced by whole blood and protamine sulfate was administered for neutralizing heparin. Fig. 21 shows the anesthetic course during operation. For the purpose of prevention of postoperative pulmonary complications, prométhazine 0.5mg per kg were injected subcutaneously 2 times separately after closure of chest. Recovery was uneventful. The patient was fully awakened 7 hours after operation. He began to walk 2 weeks after operation and left the hospital 7 weeks after operation. Fig. 22 shows the cardiophonographic findings and Fig. 23 shows cardiac catheterization findings 40 days postoperatively. This experience confirms the value of our unique hypothermic anesthesia for the operation of P. V. S..

Fig. 23 Postoperative findings of cardiac catheterization (40 days postoperatively)



Ⅲ. Summary

In this section, a review of the experience with representative 2 cases to whom intracardiac surgery was performed with the help of hypothermia was presented. Our clinical experiences revealed that the congenital heart defect as A. S. D. or P. V. S. can be corrected under direct vision only with the help of hypothermia.

Ⅳ. Conclusion

1) Our unique hypothermia is much advantageous clinically.

2) A. S. D. or P. V. S. are to be corrected under direct vision only with the help of hypothermia.

The author wishes to express his sincere gratitude to Dr. Y. HIKASA, the lecturer of our clinic, for his helpful suggestion and kind guidance in the course of the work.

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和文抄録

超低体温麻酔法の基礎的並びに臨床的研究

——特にその際の心室細動の発生防止対策について——

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心内直視下手術を行うに当つては，低体温麻酔法の応用が必要であるが，安全且つ確実に心内手術操作を行うに必要な心血流遮断を得るためには，25℃以下の所謂超低体温麻酔法が確立されなければならない．然るに，従来，斯る超低体温麻酔法を行う際には，必ずといつてよいほど心室細動という重篤な心合併症が招来され，この超低体温麻酔法の応用は危険視されて来た．

また他方，脂質の生化学的研究が飛躍的に進歩するにつれて，不可欠脂酸の有する数々の特殊的意義が解明され，即ち，(i)不可欠脂酸が生体内に欠乏すれば，Oxidative phosphorylation の Dissociationを来たすようになること，(ii)心筋は平素から不可欠脂酸を多量に含有していて，心筋機能の正常維持に大きく寄与していること，(iii)心筋活動のエネルギー源としても脂酸が大きな意義を有すること，(iv)脂質は細胞膜の構成に与つていて，細胞内外の水層を絶縁し，物質の細胞内外への移行を制限乃至選択していること，等の事実が明らかにされるに至つた．そこで，われわれは，以上の事実を観て，もし不可欠脂酸を予め充分に投与したならば，超低体温麻酔の施行に際して発生する心室細動を完全に防止し，これを安全に応用し得るのではないかと考え，まず実験的に犬を用いて本問題を追究した．即ち，

著者の考案，試作したFibrillatorを応用して，氷水浸漬法によつて，直腸温が17～19℃に至つた試獣の心室細動発生刺激閾値を電気的に測定してみた．然るに，対照犬に於ては，それが平均3.9 Voltsであつたのに対して，不可欠脂酸投与犬に於ては平均11.25 Voltsで，後者に於ては前者に較べて，その心室細動発生刺激閾値は明らかに上昇していた．即ち，不可欠脂酸が予め投与されていた試獣に於ては，斯る超低体

温麻酔下に於ても，著しく心室細動が発生し難いことを物語つている．事実，斯る超低体温麻酔下に20～30分間に亘る心血流遮断を施し，右心室切開術を行つた際にも，対照犬に於ては7例中6例に心室細動が発生し，4例が斃死したのに対して，不可欠脂酸投与犬に於ては，8例中2例に心室細動が発生したに過ぎず，仮令心室細動が発生した例に於ても容易に除細動され，その全例が順調に蘇生した．更に，不可欠脂酸と共にアセチール・コリンの前駆物質であるDimethylaminoethanol をも投与しておくと，更に一層心室細動発生刺激閾値を上昇させ得ることをも明らかにすることが出来た．但し，臨床例に於ては Dimethylaminoethanol を予め投与しておく必要はなく，不可欠脂酸の投与のみで充分である．

斯くして，協同研究者桑名の明らかにした超低体温麻酔時の肺合併症防止対策をも併せ講ずることによつて，直腸温18～22℃下に50分間に亘る心血流遮断を施し，右心室切開術を行つた試獣を何れも長期生存させ得ることが可能となつた．

以上，われわれは此処に，麻酔前に予め不可欠脂酸とビタミンEを充分に投与しておくと云うわれわれ独自の超低体温麻酔法を確立し得たと同時に，それが極めて安全な麻酔法であることを実験的に明らかにすることが出来たので，次いで，これを心房中隔欠損症や純型肺動脈弁狭窄症のような先天性心疾患に対する直視下手術にも応用し，それが極めて優秀な超低体温麻酔法であることを臨床的にも確認し得た．