Craniotomy Under Conditions of Quinidine-Protected Cardioplegia and Profound Hypothermia *

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IN A RETROSPECTIVE review of the principles of human refrigeration, Fay has stated, "Our failure to reach 67.5° F. (approximately 20° C.) by 7.5° (4° C.) still leaves the problem open for subsequent analysis, now that, with our present knowledge, this hypothermic level is potentially obtainable in the human being, and even lower levels are to be anticipated." [19] This report presents a further examination of the specific problem of avascular or bloodless craniotomy making use of further developments in the fields of induced hypothermia and the pharmacological control of cardiac arrhythmias. The goal of this continuing study envisages a feasible and relatively safe surgical approach to incapacitating arteriovenous anomalies of the brain, the early bleeding of potentially fatal episodes of acute subarachnoid hemorrhage and to tumors involving major vascular channels of the brain or its coverings. The study is an outgrowth of an examination of profound hypothermia in the isolated experimental and human brain,[45-47] and stems as well from the original observations made in this field by Heymans in 1921.[23]

Fay abandoned attempts to induce hypothermic levels below 24° C. because of "fibrillation and cardiac failure" and reported 11 deaths due to sudden cardiac failure among 19 deaths in 169 episodes of general body refrigeration in 124 patients. This early observation of the development of cardiac arrhythmias during induction of hypothermia or during the rewarming period has been confirmed repeatedly both in man and common laboratory mammals and has attained the stature of an accepted clinical observation. The interest in the many aspects of the physiology of hypothermia is reflected in the publication of at least four reviews [7, 18, 22, 24] and a mass of individual reports. Basic to the understanding of craniotomy under conditions of profound hypothermia and concomitant cardiac asystole is the fact that ventricular fibrillation poses an unacceptable threat to the neurosurgeon, whereas to the cardiac surgeon with an open chest, this cardiac arrhythmia may be virtually disregarded.

The experimental and clinical approaches designed to surmount that dangerous thermocline of body temperature below the commonly induced levels of 32° to 28° C. have followed two lines of study. The first accepts a considerable mass of experimental data that indicate that hibernating, the young of nonhibernating and even nonhibernating mammals can survive profound hypothermia as a matter of homeostasis and transfers this evidence to similar ventures in man. Laboratory animals (mice, rats, hamsters, dogs and monkeys) have been cooled to levels of 1° to − 5° C. with encouraging survival rates. Ventricular fibrillation, however, occurs in a high percentage

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of dogs in whom profound hypothermia has been induced either by external or core technics of cooling.[1, 14, 16, 20, 28-31, 38, 40, 43, 44] Survival from profound accidental hypothermia and induced hypothermia has been reported in man,[17, 31] strangely enough without an instance in the reported cases of cardiac arhythmia. Craniotomy under the conditions of this report would have the advantage of a normal heart, as compared to thoracotomy for repair of cardiac disease or abnormality. The operative procedure must be conducted, however, not only with an appreciation of pertinent cardiac physiology but also with a full knowledge of the metabolic alterations that may ensue with deepening hypothermia, particularly when cooling is induced by extracorporeal perfusion.[2-6, 8, 10, 11, 25, 34, 39, 41, 48]

The second line of study, of real significance to the purposes of the present report, has to do with the protective influence of quinidine upon the occurrence of ventricular fibrillation during cooling and rewarming. None of the substances tested for antifibrillatory action appear to be as effective as quinidine [12, 13, 15, 21, 22, 27, 37] and indeed, in the normothermic state, this influence of quinidine upon cardiac arrhythmias has been known since 1918. The most recent observations of this phenomenon give convincing evidence that in the dog, at least, the proper administration of quinidine in appropriate dosages during the cooling period will eradicate the usual appearance of ventricular fibrillation during rewarming.[37] Granted that the other physiological hazards of profound hypothermia were understood the virtue of the antifibrillatory action of quinidine, confirmed in several laboratories, gave substantial support to the problem at hand.

Case Report

W. V., a 39-year-old man (Duke Hospital No. E-91455) was admitted, January 8, 1959, with the presenting problem of bifrontal headache which had commenced three months earlier. This was associated with progressive decrease in mentation, anorexia and weakness, staggering gait and a weight loss of 20 pounds. He appeared chronically ill, disinterested but oriented. There were decreased breath sounds, dullness to percussion, and respiratory splinting over the right upper lung field. There was a hard supraclavicular lymph node. Pertinent neurological findings included a mild mixed aphasia, incomplete loss of cortical sensory modalities in the right hand, a right hemiparesis with preservation of walking, a partial right homonymous hemianopsia and intermittent right-left confusion. Roentgenogram of the chest showed a bronchogenic carcinoma of the right upper lobe; this was confirmed by the supraclavicular lymph node biopsy. Roentgenograms of the skull showed no evidence of a metastatic lesion; the electroencephalogram disclosed a slow wave focus in the left parietal lobe. A left arteriogram was characteristic of a single, large, mass close to the midline in the left parietal lobe possibly involving the falx. Although the pulmonary lesion was asymptomatic, his headache became severe with the appearance of papilledema. After appropriate consultation with the relatives of this patient, decisions were made to remove the apparent single metastatic lesion, to study the effect of deep hypothermia upon the inoperable pulmonary carcinoma, and to follow the operative procedure with chemotherapy.

Operative Procedure. Preoperative medication consisted of 0.6 mg. of atropine. Intratracheal controlled respiration anesthesia of nitrous oxide and oxygen, Fluothane, 50 cc., and anectine, 1,300 mg. was used. During the induction of anesthesia, preparations were completed for the measurement of cardiac and cortical electroactivity by extremity and scalp leads, of temperature by thermistors and thermo-couples in the cerebral cortex, esophagus, muscle, pharynx and rectum, of systemic venous pressure in a basilic vein and of systemic arterial pressure in a radial artery. Continuous spinal fluid pressure recording was also anticipated. A right fronto-occipital lead electroencephalogram and lead two of the electrocardiogram, venous and arterial pressures and temperature gradients, and the spinal fluid pressure were recorded during the entire operative procedure and for the first postoperative hour.

The method of achieving cardio-pulmonary bypass and profound hypothermia with a modified DeWall-Lillehei pump-oxygenator, containing two Harrison-Brown heat exchangers coupled in series, has been described previously.[9, 35] In this case, connection to the extracorporeal system was through a cannula placed into the left femoral artery. Venous return from the left internal jugular vein was obtained by a similar cannula and the

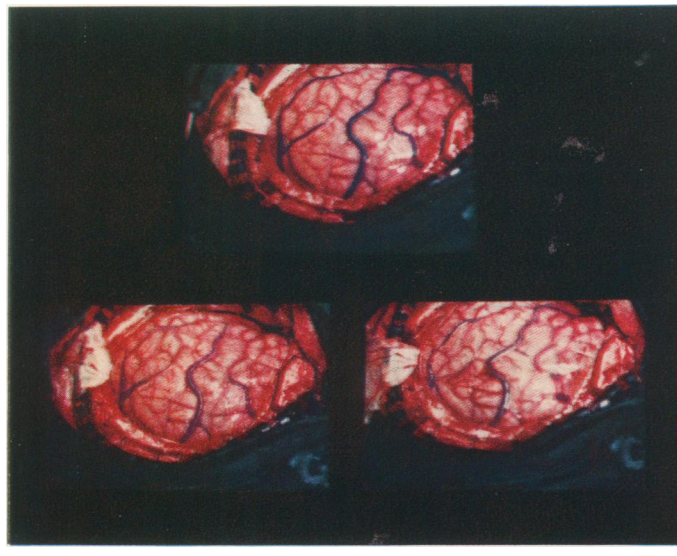

FIG. 1. A. (Top) Appearance of brain at esophageal temperature of 34° C., before beginning perfusion period. Convolutions are widened in the parietal lobe; the Sylvian vein shows a normal venous oxygen saturation. B. (Below left) Appearance of brain at an esophageal temperature of 5° C. and brain temperature of 15° C. Both cortical arteries and veins are fully oxygenated and the intracranial pressure has subsided with opening of the Sylvian fissure. Cardiac asystole is present and the extracorporeal perfusion is functioning at a flow rate of 1,200 cc./min. C. (Below right) Appearance of brain after 44 minutes of perfusion, at esophageal temperature of 4° C., and brain temperature of 11° C., during the period of cardiac asystole and cessation of perfusion. The brain is pallid, cortical arteries and veins remain fully oxygenated, the intracranial pressure has decreased further. An exploratory cortical incision is barely visible in the superior parietal lobule near the mid-line.

return from the body was withdrawn from a large cannula inserted through the sapho-femoral bulb into the inferior vena-cava. Temperatures of the inflow arterial blood and the outflow venous blood were recorded throughout the duration of the extracorporeal circulation. Arterial samples were obtained from the radial artery while mixed venous samples were obtained from the common venous outflow line. The oxygen saturation, pH and CO_2 content were determined by standard laboratory methods. The left side of the head was prepared for a large fronto-temporo-parietal craniotomy with the medial border of the bone flap close to the midline; the left anterio-cervical and left inguinal areas were prepared for the proposed extracorporeal circulation. The left chest wall was included in the operative drapings in case cardiac massage was necessary. Craniotomy was started at 9:30 a.m. and the area of tumor exposed fully at 11:00 a.m.

Observations. Intracranial pressure was high, the frontal and post-frontal convolutions were widened and the large area of paracentral tumor softening could be palpated (Fig. 1A). The brain was of good color with appropriate normal differences between large cortical arteries and veins. Quinidine hydrochloride in increments of 100 mg. every five minutes was given intravenously beginning at 11:00 a.m. and continued for a total dosage of 800 mg. (15 mg./kg.). The ECG was constantly monitored during the infusion using as criteria for toxicity a QRS spread of 50% or an increase in PR conduction to .30 seconds. During the infusion, the arterial pressure fell from a level of 120 to 80 to one of 100 to 78. Quinidine effect on the ECG as evidenced by a marked increase in the QT interval was noted, but a significant increase in QRS or PR conduction times did not occur with this dose. During the period of operative activity and quinidine dosage, heparinized cannulae were placed as indicated previously. At 11:46 a.m., 1 mg. of heparin/kg. of body weight (56 mg.) was given intravenously and the extracorporeal perfusion commenced at 12:08 p.m.

The arterial inflow blood temperature, begin-

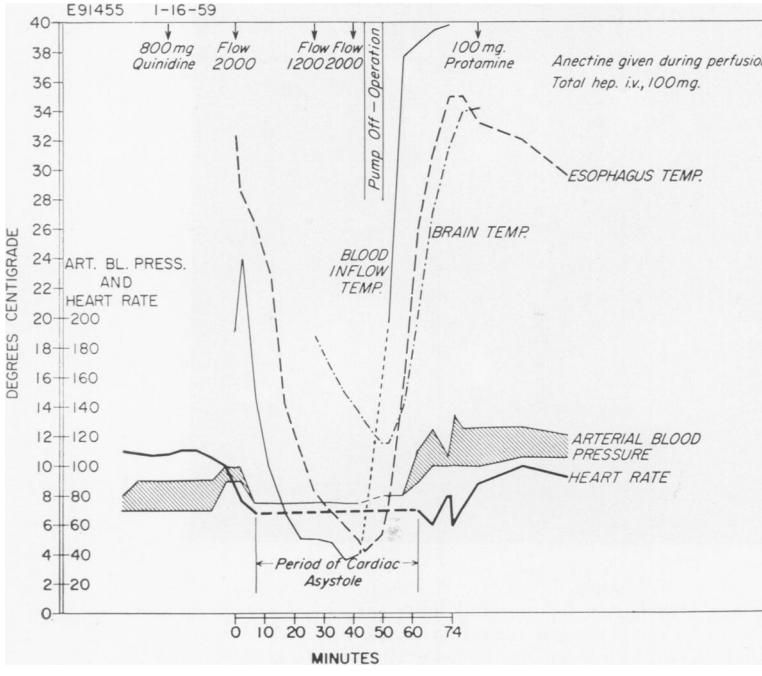

FIG. 2. See explanatory notes in text.

ning at 24° C., fell rapidly as the heat exchanger was irrigated with water at 2° C. Under a flow rate ranging between 2,000 and 1,200 cc. per minute, the inflow blood and esophageal temperatures reached a hypothermic level of 4° C. after 44 minutes of perfusion. The brain temperature, first recorded by direct insertion of a thermistor at a depth of 2 cm. below the cortex at 18° C., attained an eventual level of 11° C. (Fig. 2). At 15° C., the cortical arteries and veins were fully oxygenated (Fig. 1B).

Cortical electroactivity subsided under the influence of cooling and the cortex became isoelectric at 22° C., an observation made repeatedly in the experimental animal [46] and previously reported in the human.[47] In this particular case, conducted in an unprotected operating room, 60-cycle activity vitiated in part the accuracy of this observation (Fig. 3). At 23° C., normal cardiac rhythm was replaced by ventricular fibrillation 12 minutes after the start of the extracorporeal circulation. When effective heart action ceased, the flow rate was reduced to prevent overdistension of the heart. Cardiac asystole ensued at an esophageal temperature of 18.9° C., after 24 minutes of extracorporeal circulation. Controlled respirations were not given during the period of cardiac asystole to prevent overdistension of the left auricle by returning pulmonary blood. Adequate gas exchange was provided during the period by the pump oxygenator. At an esophageal temperature of 4° C. and a brain temperature of 11° C., after 44 minutes of extracorporeal circulation, the perfusion pump was stopped and remained off for the following 10 minutes. During this time, the brain was relaxed with bright arterial coloration in both arterial and venous cortical vessels (Fig. 1C). The brain was very cold to palpation as expected, soft and malleable, and the space between the Sylvian fissure and overlying dura became widened so that exposure of the fissure was expedited.

Only cadaveric bleeding developed during cortical incision, inspection, and drainage of a huge subcortical tumor cyst involving the left parietal lobe. The extracorporeal circulation was restarted and flow brought slowly up to 1,200 cc. per minute. A few cortical vessels were cauterized at this time. Reversal of the heat exchanger to irrigation with water at 42° C. caused a prompt rise in body and brain temperatures (Fig. 2), with these temperatures lagging behind the inflow blood temperature by a constant time interval of roughly 10 minutes. With several premonitory normal beats, cardiac asystole reverted to a normal cardiac rhythm at an esophageal temperature of 16° C., and the extracorporeal circulation was terminated at 1:22 p.m. Additional heparin, 40 mg., was injected intravenously and the perfused vessels sutured with fine arterial silk. The period of cardiac asystole lasted 30 minutes and the period of extracorporeal circulation measured at 74 minutes. The operative procedure was terminated at 2:30 p.m. and

TABLE 1. *Oxygen Saturation and Metabolic Studies*

Sample	O_2 Cap.	O_2 Content	O_2% Sat.	A-V Dif.	CO_2 Content mM./L.	Lactic Acid mg. %	Hemt.	pH at 37°C.	pH cor. to Body T (C.)
Arterial control 10:23	17.50	17.22	98.50		22.4	28	35	7.49	7.53(34.2°)
				Pump on 12:07					
Min.									
2 A	20.00	19.92	99.60						
V	20.00	15.10	75.50	4.82	16.88	53.10	40	7.21	7.30(30.8°)
11 A	20.00	19.79	99.00						
V	20.00	17.12	85.60	2.67	16.50	48.20	38	7.40	7.58(25°)
14 A	20.40	20.31	99.50						
V	20.40	17.46	85.50	2.85	—	47.80	40	7.31	7.59(18°)
16 A	20.00	20.00	100						
V	20.00	17.78	89.00	2.22	—	43.40	38	7.33	7.66(14.5°)
24 A	20.00	20.00	100						
V	20.00	18.50	92.50	1.50	17.14	42.90	40	7.24	7.64(10°)
45 A	19.45	19.36	99.50						
V	19.45	17.60	90.50	1.76	15.98	57.40	40	7.34	7.81(5°)
48 A	19.45	19.45	100						
V	19.45	18.13	93.40	1.32	17.54	75.10	38	7.25	7.65(10°)
51 A	23.40	23.40	100						
V	23.40	21.70	92.70	1.70	—	56.30	40	7.23	7.48(20°)
54 A	20.40	20.40	100						
V	20.40	18.28	89.60	2.12	17.70	49.20	41	7.23	7.40(25.6°)
58 A	20.60	20.60	100						
V	20.60	18.93	92.00	1.67	15.83	42.10	40	7.34	7.45(30°)
66 A	21.20	21.20	100						
V	21.20	16.89	79.60	4.31	—	36.90	40	7.36	7.39(35°)

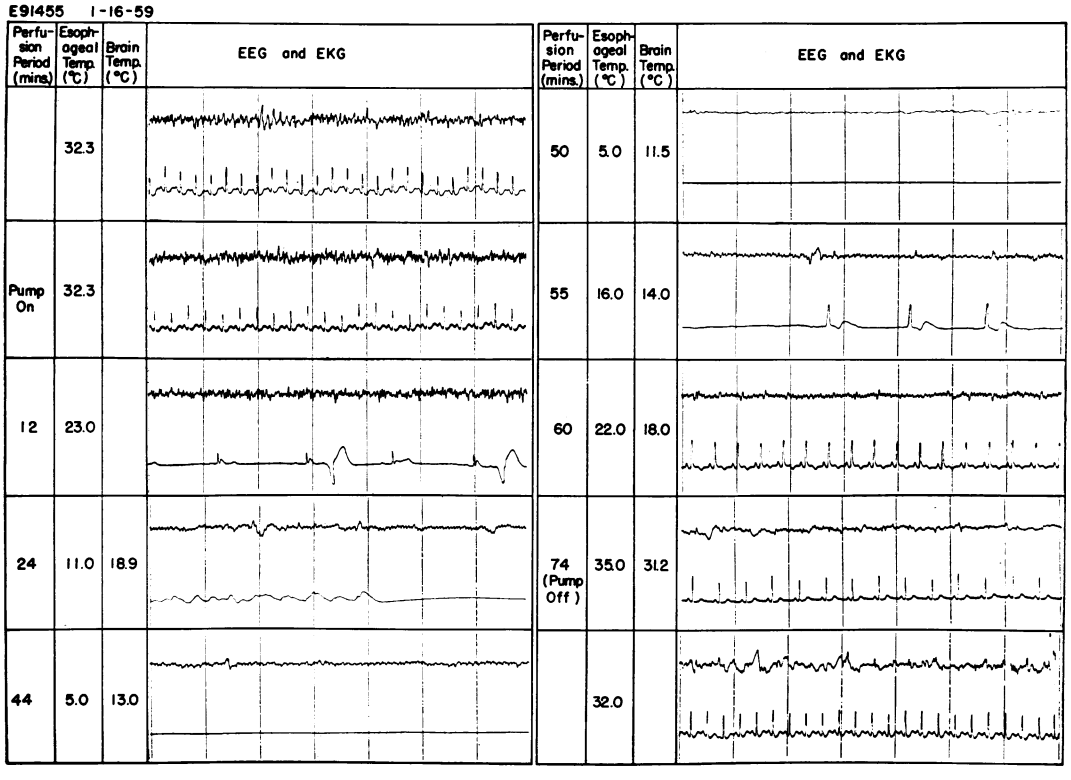

FIG. 3. See explanatory notes in text.

protamine, 100 mg., was given to counteract the state of heparinization. At 6:00 p.m., the rectal temperature was 34° C. and the patient stated that he felt "all right."

The immediate postoperative convalescence was smooth. Repeated electroencephalograms and electrocardiograms were unchanged as compared to the preoperative studies. Fluid collected beneath the craniotomy flap on two occasions and was aspirated. Headache relief was complete, the patient was conscious and oriented at all times, and the neurological picture remained unchanged. The patient was discharged to a convalescent home on February 15th and died late in May 1959 after a brief period of increased intracranial pressure. During the two-month period of observation, the pulmonary tumor slowly increased in size.

Control and operative observations of O_2 saturation, pCO_2, lactic acid, hematocrit and pH are noted (Table 1). Whole blood buffer base values were derived from these data using the nomagram of Singer and Hastings.[39] The pH values were corrected uniformly to a temperature of 37° C. before applying them to the nomagram.[34] Control buffer base value was determined as 50 mEq. per liter, well within the normal variation whereas at the end of the perfusion period, at 30° C., the value was determined at 40 mEq. per liter. This degree of metabolic acidosis may occur during any major surgical procedure [3] and a large amount of fixed acids in the blood used to prime the extracorporeal circuit may contribute to the decrease in buffer base observed during perfusion.[26] Lactacidosis has been noted in both dogs and humans under hypothermia and may be striking after periods of cardiac asystole.[6] It has its origin in an impaired circulation and a failure of body organs, in particular the liver, to metabolize lactate. Metabolic acidosis may be prevented by adequate flow rate and maintenance of a high venous oxygen saturation,[11] factors that were scrupulously pursued in this case.

The spinal subarachnoid fluid pressure remained high before and during the induction of anesthesia. With craniotomy, and with the onset of cooling, the pressure fell to virtually a base line level when the extracorporeal perfusion ceased. With closure of the dura and scalp and resumption of the circulation, intracranial pressure rose to a normal level. With the exception of the period of cadaveric pressure, these changes have been reported previously.[41]

Discussion

A review of the diverse technical factors that were assembled to effect a controlled bloodless craniotomy for extraordinary intracranial conditions suggests several potentially valuable refinements and areas for more detailed attention. Because of well-recognized body temperature gradients,[33] the venous outflow of the brain was directed to the extracorporeal circuit by cannulation of the internal jugular vein. This implies a possible obstruction of the venous circulation of the brain for a temporary period at least which would tend to increase intracranial pressure already elevated by tumor growth, hemorrhage or an anomaly. Cannulation of a subclavian vein reached by an infraclavicular approach would be preferable. Some reference has already been made to the importance of monitoring systemic arterial blood pressure during the administration of quinidine. The metabolism of quinidine during hypothermia is not known but it is evident from the report of Sealy *et al.*[36] that quinidine does metabolize rapidly during cooling since the antifibrillatory protection of quinidine given before a primary period of profound cooling was lost during repetitive periods. Maximal quinidine protection is gained therefore by injection of adequate amounts at a time period immediately adjacent to the onset of cardiac asystole. Long periods of cardiac asystole associated with cessation of extracorporeal perfusion, even in the presence of a high venous oxygen saturation, may be undesirable in terms of the possibility of minute tissue necrosis.[35] The incredible relief from operative hemorrhage would not be impaired by short intermittent periods of extracorporeal perfusion at flow rates giving a perfusion pressure of 25 to 30 mm. Hg. Such periods of perfusion are actually valuable to check hemostasis. Finally, the efficiency of the Harrison-Brown heat exchanger is such that very rapid rewarming is possible, and rapid rewarming is contraindicated for a number of physiological reasons, including increased peripheral tissue metabolic demand, threat to an existing low cardiac output and the development of cardiac muscle temperature gradients.

Rewarming should be conducted at initial low flow rates and less precipitously than demonstrated in this report. Further experience with this technic will be reported when appropriate cases present the opportunity.

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