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PHYSIOLOGIC REACTIONS DURING PROFOUND HYPOTHERMIA WITH CARDIOPLEGIA

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Numerous investigators have agreed that moderate hypothermia, (approximately 30 C.), can be of benefit during certain types of surgical procedures. At Duke Hospital, when "open heart" surgery was begun with extracorporeal circulation in 1956, moderate hypothermia, induced by external cooling, was utilized simultaneously. We believe that hypothermia, by reducing the metabolism of vital tissues, offers protection against the hazards of extracorporeal circulation, *viz.*, the difficulty in equalling cardiac output with mechanical pumps, the possibility of damage to cellular elements of the blood with high rates of perfusion, and the mechanical breakdowns in the pump or oxygenator. Clinical experience indicated that combining these techniques was feasible and was advantageous to the patient.[1]

It was not long before profound hypothermia (below 22 C.) during surgical procedures was explored. If metabolism of tissues could be reduced to near zero, then perfusion could likewise be reduced to a minimum or stopped completely, cardioplegia could be attained by hypothermia rather than by chemical mediators (potassium), and more complex surgical procedures could be carried out with minimal danger to the vital tissues.

It was obvious that low body temperatures could not be achieved practically with external cooling. A rapid, controllable, and reversible technique of core cooling was required.[2] A simple and effective blood heat exchanger was therefore designed.[3] This exchanger was placed in series with the extracorporeal circulation pump and oxygenator, interposed on the arterial side between pump and femoral artery catheter. The temperature of the water circulating around the tubes of the heat exchanger, through which the blood flowed, could be varied by an automatic thermo-regulated mixing valve. Body temperature, as measured in the mid-esophagus, could be lowered at a rate of approximately 1 degree centigrade per minute. The rewarming process was a little slower. This technique is referred to as "core" cooling because the organs that cool most rapidly are those with the largest blood flows, namely, the heart, liver, kidney and brain. These are the organs in which maximal cooling is desired during profound hypothermia.

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Procedure

Profound hypothermia, utilizing extracorporeal circulation and the heat exchanger, has now been utilized in 47 "open heart" and 3 neurosurgical procedures. Usually the patients have been anesthetized with an ultrashort-acting barbiturate, nitrous oxide and oxygen and succinylcholine. Controlled respiration with hyperventilation of the lungs has been practiced throughout the operation. No

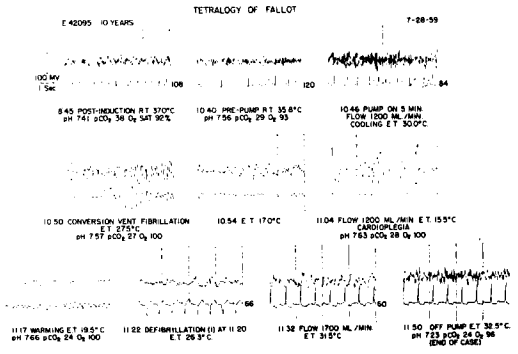

FIG. 1. Excerpts from continuous electroencephalographic and electrocardiographic recordings during open heart operation for correction of tetralogy of Fallot. Cardioplegia at 15.5 C.

attempt has been made to cool the patient until the extracorporeal circulation has begun. Then the patient has been cooled rapidly, cardioplegia produced if needed, the operation performed, and the patient rewarmed. Once cooling began only nitrous oxide and oxygen anesthesia was required.[4] The lungs were partially expanded during the period when the superior and inferior venae cavae were occluded.

Vital functions should be monitored during the procedures. We have recorded continuously esophageal and rectal temperatures, as well as the inflow and outflow blood temperatures, and have varied accordingly the rate of perfusion and temperature of the water in the heat exchanger. When the desired body temperature has been reached, only low perfusion flows, 25 mg./kg./minute or less, have been required to maintain the temperature at the desired level. The electroencephalogram and electrocardiogram have been monitored continuously, and records of the blood pressure have been recorded directly from the radial artery or from a large vessel within the field of operation by means of a Statham strain gauge. In many patients arterial blood samples have been obtained at regular intervals through an indwelling Cournand needle. From these samples the *p*H, P_{CO_2} and oxygen saturation have been determined. We believe that the most sensitive indicator of the status of the patient at any moment is the electroencephalogram. A sudden flattening of the electroencephalogram in the absence of a low body temperature is an indication that all is not well, as far as perfusion or oxygenation of the cerebral cortex is concerned.

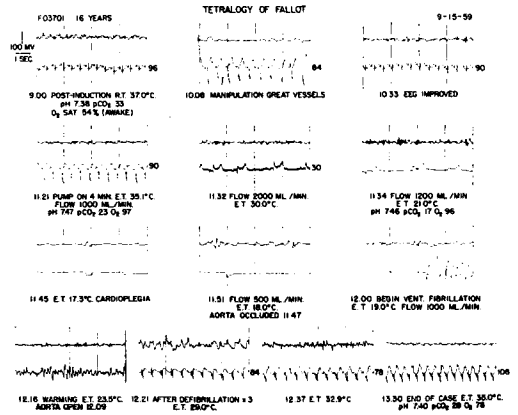

FIG. 2. Excerpts from continuous recordings of electroencephalogram and electrocardiogram during open heart procedure for correction of tetralogy of Fallot in 16 year old patient. Cardioplegia and electroencephalographic silence at 17.3 C.

PHYSIOLOGIC REACTIONS

The physiologic reactions due to the profound hypothermia induced in these patients are modified to an unknown extent by the state of anesthesia, the technical procedures involved in the operation, and the extracorporeal circulation. The following observations have been made with the realization that hypothermia per se may not be the only factor involved in the changes seen.

Respiration. Inasmuch as all patients subjected to profound hypothermia were maintained with controlled respiration, we obtained little information regarding respiratory activity at low temperatures. However, in a patient suffering from exposure to cold and admitted to our clinic with a rectal temperature of 24.0 C., the respirations were regular but shallow at a rate of 6 per minute. In another patient exposed similarly and with a rectal temperature of 21.6 C., a respiratory rate of 9 per minute was recorded.[5] There seems little doubt that, with progressive reduction in body temperature, depression of respiration occurs affecting both rate and tidal volume. This perhaps can be considered physiologic because of the reduced oxygen requirements and diminished

carbon dioxide production during hypothermia. At what body temperature spontaneous respirations cease in man is as yet unknown.

Cardiovascular System. During progressive hypothermia, the heart rate slows gradually until cardiac arrest occurs in asystole. Niazi and Lewis,[6] in a unique experience in which profound hypothermia to 9 C. was induced in an effort to abort carcinoma, report a cardiac rate of 4 per minute at 11.2 C. and asystole at 10.5 C. Arterial blood pressure declined from 130 mm. of mercury systolic at 37 C. to 12–16 mm. of mercury systolic at 11–13 C. In our patient with exposure and rectal temperature of 24 C., the cardiac rate was 26 per minute, peripheral pulses were not palpable and blood pressure was unobtainable by conventional means.

In the rapid hypothermia induced in patients in this series, the pulse rate slowed progressively with reduction in body temperature, with cardiac asystole occurring between 26 and 10 C. In the patient whose record is reproduced in figure 1, pulse rate slowed from a normal of 120 to 84 per minute at an esophageal temperature of 30.0 C. Ventricular fibrillation intervened at 27.5 C., but the fibrillatory movements became less active as the temperature decreased with asystole developing at 15.5 C. Electrical defibrillation applied once during rewarming established a regular rhythm. In another patient (fig. 2) a similar slowing of the heart rate was noted, but ventricular fibrillation did not occur during cooling: cardioplegia occurred at 17.3 C.

The esophageal temperatures at which ventricular fibrillation and/or asytole occurred in 37 patients during rapid core cooling are listed in table 1. In the first group of patients, the temperature was not reduced sufficiently to induce asystole; in the second group, asystole was preceded by ventricular fibrillation; in the third group, a normal beat persisted during cooling until asystole occurred.

The esophageal temperatures at which ventricular fibrillation and/or effective cardiac rhythm occurred in 37 patients during rewarming are noted in table 2. In 18 patients an effective cardiac beat returned spontaneously; in 19 patients electrical defibrillation applied 1 to 5 times was required to establish normal rhythm.

TABLE 1

TABULATION OF ESOPHAGEAL TEMPERATURES (DEGREES CENTIGRADE) IN 37 PATIENTS AT WHICH VENTRICULAR FIBRILLATION AND/OR ASYSTOLE OCCURRED DURING RAPID CORE COOLING

Cooling	
Ventricular Fibrillation	Asystole
28.0	—
24.7	—
25.5	—
31.0	—
29.5	—
27.0	—
22.7	—
20.0	—
19.5	—
31.0	—
25.0	—
16.3	—
26.0 Average 25.1	—
21.0	19.4
21.5	20.0
27.1	27.0
24.5	19.0
24.2	18.0
29.0	21.0
20.5	19.0
18.0	19.0
27.0	15.0
27.6	26.5
24.2	10.8
18.0	17.0
27.0	16.0
23.0	18.0
20.5	18.5
18.0 Average 23.2	15.0 Average 18.5
—	21.0
—	13.0
—	27.0
—	15.0
—	13.9
—	18.2
—	16.0
—	25.0 Average 18.6

The electrocardiogram reflects the reduction in conduction rate which occurs with progressive hypothermia. The P-R interval lengthens and the complexes widen. A nodal rhythm is seen frequently and the T wave, as noted in figures 1 and 2, becomes abnormally high; the significance of these developments is unknown.

The extracorporeal circulation associated with profound hypothermia in this series pre-

TABLE 2

TABULATION OF ESOPHAGEAL TEMPERATURES (DEGREES CENTIGRADE) IN 37 PATIENTS AT WHICH VENTRICULAR FIBRILLATION AND/OR EFFECTIVE CARDIAC RHYTHM WAS RESTORED DURING WARMING PERIOD

Warming			
Ventricular Fibrillation	Effective Beat	Spontaneous	Shocked
—	23.0	X	
—	26.7	X	
—	30.0	X	
—	29.5	X	
—	17.0	X	
—	21.5	X	
—	19.0	X	
—	17.0	X	
—	27.1	X	
—	21.0 Aver. 23.1	X	
18.2	24.0	X	
15.3	18.8	X	
20.0	26.0	X	
13.9	24.5	X	
14.0	28.9	X	
18.0	25.3	X	
24.5	27.0	X	
15.0 Aver. 17.3	26.5 Aver. 25.1	X	
16.0	30.0		X1
28.0	29.0		X1
20.0	27.5		X2
21.5	30.4		X1
19.5	28.5		X1
21.0	24.5		X1
24.0	29.0		X3
22.0	26.0		X1
19.2	29.8		X3
27.0	33.0		X2
13.9	14.5		X2
25.0	33.2		X1
15.2	29.3		X1
18.8 Aver. 20.8	29.0		X3
?	32.6		X1
?	30.0		X5
?	29.9		X2
?	32.3		X1
?	30.0 Aver. 28.8		X1

cluded an accurate evaluation of blood pressure changes due primarily to the cooling process.

Central Nervous System. Because the patients were anesthetized during cooling, an estimate of the reduction in cerebral activity caused by cooling could be obtained only indirectly by study of the electroencephalogram. A blood pressure of 60–80 mm. of mercury during perfusion appeared sufficient to maintain electroencephalographic patterns compatible with the recorded temperature. However, in the exposed patient whose body temperature was 24 C., unconsciousness was present and painful stimuli evoked no response. It appears significant also that under 32 C. only minimal concentrations of anesthetic drugs were required during operations. Under the conditions described, and as noted in figures 1 and 2, cerebral electric activity was not altered grossly until the esophageal temperature was in the low twenties. In this series cessation of electroencephalographic activity occurred between 20 and 14 C. and was preceded by slow, high voltage waves and sometimes by burst-suppression activity. It should be reiterated that at normal body temperatures slowing and flattening of the electroencephalogram can be associated with sudden blood loss, reduction of blood supply to the brain by manipulation of the great vessels (fig. 2), or be due to inadequate drainage of blood from the superior vena cava during perfusion. Occasionally one of these factors is operative at low body temperatures.

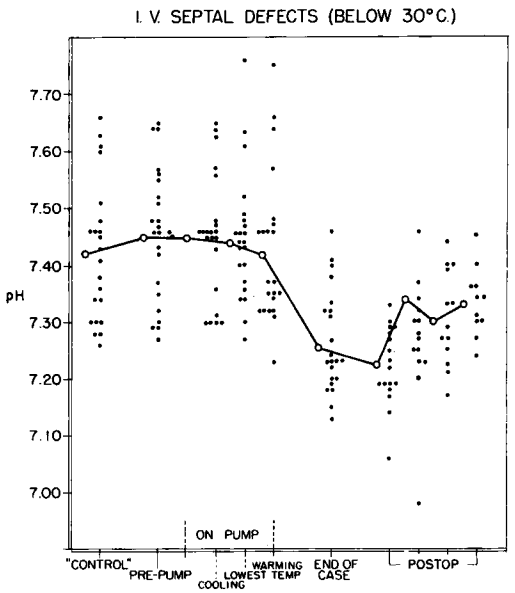

FIG. 3. Scattergraph to show *p*H changes of arterial blood in 22 patients subjected to profound hypothermia and extracorporeal circulation.

At present, one cannot infer that absence of electrical cortical activity implies cessation of cellular metabolism within the brain: such evidence is only presumptive and may reflect acute hypoxia as noted above.

Acid-Base Balance. In our patients subjected to extracorporeal perfusion and profound hypothermia, wide variations were found in the arterial *p*H and P_{CO_2} (figs. 3 and 4). During perfusion, and while the patient was cool, the *p*H tended to remain within normal limits, but the carbon dioxide tension decreased to low levels. This trend could be due to the increased solubility of carbon dioxide in blood at low temperatures; it could reflect the metabolic acidosis believed to be associated with both induced hypothermia [7] and extracorporeal circulation; [8] or it could result from excessive elimination of carbon dioxide through the oxygenator without metabolic replacement. After warming, and in the immediate postoperative period, the *p*H tended to decrease to low acidotic levels, while the P_{CO_2} rose to within normal ranges. In some patients respiratory acidosis was believed to be present, and could be corrected by adequate alveolar ventilation. In others a persistent metabolic acidosis appeared to be a logical explanation.

Our present lack of knowledge precludes a full explanation of the situation. The inadequate perfusion of certain organs, or the temperature gradients found in rapid core cooling (to be discussed below), may prevent the completion of metabolic reactions in certain areas and lead to the accumulation of intermediate metabolites which induce metabolic acidosis.

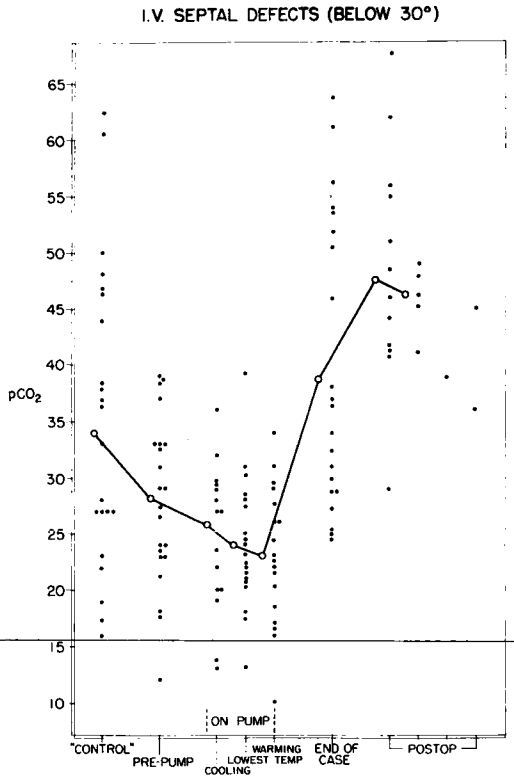

FIG. 4. Scattergraph to show changes in carbon dioxide tension of arterial blood in 22 patients subjected to profound hypothermia and extracorporeal circulation.

PROBLEMS OF PROFOUND HYPOTHERMIA

Ventricular fibrillation is encountered frequently during profound hypothermia. In 75 per cent of the patients in this series it occurred either during cooling or during rewarming. During the induction of hypothermia its onset was of no particular consequence because of the associated extracorporeal perfusion: when the myocardial temperature became low the fibrillation reverted into a slow regular rhythm or asystole occurred. When ventricular fibrillation developed during rewarming and did not revert spontaneously to a regular rhythm (table 2), electrical defibrillation was necessary before perfusion could be stopped. In every instance in this series it was possible to defibrillate the heart by electric shock when required: defibrillation appeared to be accomplished most readily at an esophageal temperature above 29 C.

In spite of the relative ease with which ventricular fibrillation was controlled in these patients, this complication remains a principal drawback to the wider clinical application of profound hypothermia. When a technique or drug is found which will prevent this arrhythmia, profound hypothermia will become a relatively safe procedure.

Rapid core cooling by extracorporeal perfusion produces marked temperature gradients between different regions of the body. With cold or warm blood entering the femoral artery, the outflow blood coming from the su-

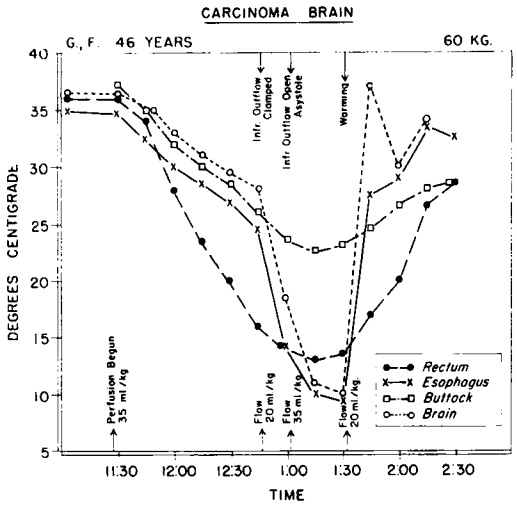

FIG. 5. Temperature graph to show changes during rapid cooling and warming as recorded in the rectum, esophagus, cerebral cortex and buttock. Temperature of blood flowing from heat exchanger also recorded.

perior and inferior venae cavae, one of two general patterns usually is seen. Figure 5 presents data for a patient showing at first a rapid fall in rectal temperature, with esophageal temperature lagging behind. When the inferior vena cava outflow tube was clamped, a rapid reduction in the esophageal temperature ensued. In the patient depicted by figure 6 the esophageal temperature decreased to more profound levels than did the rectal temperature; and it responded to temporary warming with alacrity, whereas the rectal temperature changed little. Rectal temperature measurements, in general, are unreliable as criteria of core temperatures during rapid cooling or warming. Depending upon the sites of cannulation of the central vascular system, and the technique of extracorporeal cooling, it appears in some patients that the blood circulates principally within the lower part of the body. In other patients the inflowing blood finds its way rapidly to the heart, producing a rapid decreases in the esophageal temperature. Closure of the inferior vena cava forces the cold inferior vena cava blood to the heart for recirculation in the superior half of the body. This variability in distribution of perfused blood can be correlated with the differences seen between temperatures monitored in the rectum and in the esophagus.

In both figures 5 and 6 it is seen that the recorded temperature of peripheral muscles (buttock and thigh) lagged markedly behind that of the rectum and esophagus. It is apparent that in core cooling the peripheral portions of the body are affected least by cooling.

From the standpoint of practical management, we believe that temperature measurements in the mid to lower esophagus reflect most accurately, but do not equal, the temperature of the brain cortex and the myocardium.[9] In figure 5 it is seen that the recorded temperature of the cortex rather closely followed that of the esophagus, and in figure 6 the recorded temperature of the heart muscle lay about midway between the rectal and esophageal temperatures.

The significance of these temperature gradients as they relate to the patients' over-all metabolism is difficult to assess. Obviously, in a vertebrate in which under normal circumstances the temperature of the "milieu interieur" is regulated within narrow limits, the sudden institution of varying temperatures in different portions of the body must upset normal metabolic relationships. The importance of these changes awaits further investigation.

Complications of Operation, Anesthesia and Hypothermia. Fifty patients have been sub-

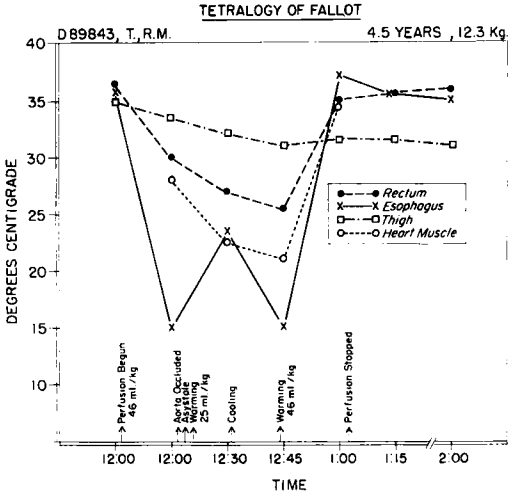

FIG. 6. Temperature graph to show changes during rapid cooling and warming as recorded in the rectum, esophagus, heart muscle and thigh. Temperature of blood flowing from heat exchanger also recorded.

TABLE 3

DATA FOR 50 PATIENTS SUBJECTED TO PROFOUND HYPOTHERMIA

Diagnosis	Age (years)	Lowest Temperature °C	Result
1. Tetralogy of Fallot	18	18.0	Satisfactory
2. Tetralogy of Fallot	14	18.6	Satisfactory
3. Tetralogy of Fallot	27	19.0	Satisfactory
4. Tetralogy of Fallot	3	16.0	Satisfactory
5. Tetralogy of Fallot	9	15.2	Satisfactory
6. Tetralogy of Fallot	17	18.0	Satisfactory
7. Tetralogy of Fallot	14	17.0	Satisfactory
8. Tetralogy of Fallot	17	17.8	Satisfactory
9. Tetralogy of Fallot	9	15.2	Satisfactory
10. Tetralogy of Fallot	5	10.3	Satisfactory
11. Tetralogy of Fallot	11	11.0	Satisfactory
12. Tetralogy of Fallot	15	10.2	Satisfactory
13. Tetralogy of Fallot	7	14.0	Satisfactory
14. Tetralogy of Fallot	8	17.0	Awakened Died 26 hours postoperatively Cardiac failure
15. Tetralogy of Fallot	5	15.5	Awakened Died 48 hours postoperatively Cardiac failure
16. Tetralogy of Fallot	13	15.2	~~Renal failure 26 hours postoperatively~~ Died 16 days later
17. Tetralogy of Fallot	7 weeks	16.5	Died on table. Cardiac failure
18. Tetralogy of Fallot	3	12.0	Awakened Died 15 hours postoperatively Cardiac failure
19. Tetralogy of Fallot	14	17.8	Awakened Died 3 days postoperatively Cardiac failure
20. Tetralogy of Fallot	10	15.5	Died suddenly 5 months after operation while playing
21. Tetralogy of Fallot	9	12.0	Awakened Died 12 hours postoperatively Cardiac failure
22. Interventricular Septal Defect	2	14.0	Satisfactory
23. Interventricular Septal Defect	1	20.5	Satisfactory
24. Interventricular Septal Defect	21	19.3	Satisfactory
25. Interventricular Septal Defect	14	20.0	Satisfactory
26. Interventricular Septal Defect	17	17.7	Satisfactory
27. Interventricular Septal Defect	7	12.0	Satisfactory
28. Interventricular Septal Defect	4	13.0	Satisfactory
29. Interventricular Septal Defect	3	16.0	Awakened Sudden cardiac failure 7 hours postoperatively
30. Interventricular Septal Defect	4	18.0	Did not awaken Died 14 hours postoperatively Cardiac failure
31. Atrial Septal Defect Ostium Primum	15	16.0	Satisfactory
32. Atrial Septal Defect Ostium Primum	21	21.3	Satisfactory

TABLE 3—*Continued*

Diagnosis	Age (years)	Lowest Temperature °C	Result
33. Atrial Septal Defect Ostium Prium	6	18.2	Satisfactory
34. Atrial Septal Defect Ostium Prium	6	20.3	Satisfactory
35. Atrial Septal Defect Ostium Primum	14	15.0	Satisfactory recovery Died 5 months later
36. Transposition Great Vessels	2 months	15.0	Died on table Cardiac failure
37. Transposition Great Vessels	3	16.0	Died on table Cardiac failure
38. Transposition Great Vessels	1½	20.5	Died on table Cardiac failure
39. Transposition Great Vessels	2 months	7.0	Died on table Cardiac failure
40. Atrial Septal Defect and Anomalous Pulmonary Venous Drainage	8	10.0	Satisfactory
41. Atrial Septal Defect and Anomalous Pulmonary Venous Drainage	7	14.0	Satisfactory
42. Atrial Septal Defect and Anomalous Pulmonary Venous Drainage	6	20.2	Did not awaken Possible air emboli Died 24 hours postoperatively
43. Aortic Stenosis	52	18.0	Awakened Cerebral embolus 24 hours postoperatively Died 17 days later
44. Aortic Stenosis	41	15.5	Did not awaken Question of cerebral embolus Died 24 hours postoperatively
45. Ruptured Sinus Valsalva	22	21.0	Satisfactory
46. A. V. Canal	4	9.5	Died on table Cardiac failure
47. Post Myocardial Infarction, Ruptured interventricular Septum	45	14.5	In shock preoperatively Died 7 hours postoperatively Did not recover consciousness
48. Carcinoma Lung with Metastasis to Brain. Subtotal Removal Brain Metastasis	39	4.2	Uneventful recovery Gradual deterioration due to recurrence brain tumors
49. Carcinoma Lung with Metastasis to Brain. Subtotal Removal Brain Metastasis	46	9.0	Did not awaken Died 4 months postoperatively
50. Severe A. V. Anomalies Left Occipital and Temporal Lobes Brain	52	6.0	Died on table Impossible to control bleeding from vascular anomalies

jected to profound hypothermia as described (table 3). Of 21 patients who had intracardiac correction of a tetralogy of Fallot, 7 (33 per cent) failed to survive the postoperative period. One critically ill infant 7 weeks old died in the operating room, 5 patients developed cardiac failure 12 to 72 hours following operation, and one went into renal failure, succumbing 16 days later. All patients who left the operating room awakened and showed no evidence of cerebral damage.

Of 9 patients who had closure of an interventricular septal defect, 2 (22 per cent) failed to survive the postoperative period. One

patient recovered consciousness completely, but developed sudden cardiac failure seven hours after operation. The second patient did not respond postoperatively and died 14 hours later in cardiac failure. None of the patients who recovered showed evidence of cerebral damage.

All 5 patients who had closure of an ostium primum atrial septal defect had satisfactory postoperative recoveries: no evidence of cerebral damage could be detected.

Three infants and one child with transposition of the great vessels failed to survive attempts to correct this condition. Two of 3 patients who were operated upon to correct an atrial septal defect and anomalous pulmonary venous drainage recovered without evidence of cerebral damage. The third patient did not recover consciousness and died 24 hours postoperatively. The electroencephalogram indicated that this child was exposed to cerebral air emboli during the operation.

Two older patients with acquired aortic stenosis failed to survive the postoperative period. Both these patients probably had a cerebral embolus.

Three neurosurgical patients with severe intracranial lesions were exposed to profound hypothermia.[10] One recovered satisfactorily from the procedure, one survived the operative procedure for 4 months, but never recovered consciousness: he probably suffered cerebral damage in excess of that caused by surgery. The third patient succumbed in the operationg room due to uncontrollable bleeding from vascular anomalies which connected directly into large venous sinuses.

Summary

Observations of physiologic changes recorded when profound hypothermia (4.2 to 21.0 C.) was induced in 50 patients by means of extracorporeal circulation have been presented. Cardiac asystole was produced easily by profound hypothermia, but this procedure is believed to be safe. The most sensitive indicator of the status of the patient during such procedures was the electroencephalogram. Ventricular fibrillation occurring during the cooling or warming periods was the principal problem limiting the utilization of profound hypothermia for purposes other than cardiac or thoracic vascular surgery. The temperature gradients noted in different parts of the body during rapid core cooling presumably alter the metabolic relationships within the body in unexplained ways.

Twenty-seven of the 50 patients recovered uneventfully from operation and anesthesia. Seven patients died during the operation; eleven patients awakened after operation but subsequently died. None of the latter patients showed evidence of cerebral brain damage. Five patients failed to recover consciousness after operation and subsequently died.

This paper was read at The Second World Congress of Anesthesiologists, Toronto, Canada, September 7, 1960.

References

1. Sealy, W. C., Brown, L. W., and Young.: Report on use of both extracorporeal circulation and hypothermia for open heart surgery, Ann. Surg. **147**: 603, 1958.
2. Gollan, F., Blos., P., and Shuman, H.: Studies on hypothermia by means of pump-oxygenator, Amer. J. Physiol. **171**: 331, 1952.
3. Brown, I. W., Jr., Smith, W. W., and Emmons, W. O.: Heat exchanger for control of body temperature during extracorporeal circulation, Surgery **44**: 372, 1958.
4. Stephen, C. R., Dent, S. J., Sealy, W. C., and Hall, K. D.: Anesthetic and metabolic factors associated with combined extracorporeal circulation and hypothermia, Amer. J. Cardiol., In Press.
5. Ehrmautraut, W. R., Ticktin, H. E., and Fazekas, J. F.: Cerebral hemodynamics and metabolism in accidental hypothermia, A. M. A. Arch. Int. Med. **99**: 57, 1957.
6. Niazi, S. A., and Lewis, F. J.: Profound hypothermia in man: report of case, Ann. Surg. **147**: 264, 1958.
7. Brewin, E. G., Gould, R. P., Nashat, F. S., and Neil, E.: Investigation of problems of acid-base equilibrium in hypothermia, Guy Hosp. Rep. **104**: 177, 1955.
8. Magovern, G. J., Cartwright, R. S., Neville, J. F., and Kent, E. M.: Metabolic acidosis and dissociation curve of hemoglobin during extracorporeal circulation, J. Thor. Cardiov. Surg. **38**: 561, 1959.
9. Hercus, V. Cohen, D., and Bouring, A. C.: Temperature gradients during hypothermia, Brit. Med. J., **1**: 1439, 1959.