IN THE PAST DECADE hypothermia has been a subject of intense experimental and clinical study.\textsuperscript{1-6} After initial experiences showed its severe limitations for intracardiac surgery, many technics of hypothermia were gladly discarded as pump-oxygenators were developed. Subsequently, the combination of hypothermia and extracorporeal circulation has permitted degrees of hypothermia previously incompatible with survival and has made possible elective use of long periods of complete circulatory arrest. These possibilities have prompted many experimental and clinical studies to determine the safety and advantages of surgical procedures performed during circulatory arrest and "deep" hypothermia. This review describes the current status of hypothermia in this changing field of cardiac surgery.

Three broad areas of current use of hypothermia can be defined. Two of these, intracardiac surgery performed with hypothermia and circulatory occlusion and hypothermia for neurologic injury from cardiac arrest, are limited in scope and are briefly presented. By far the largest of the three is the combination of hypothermia with extracorporeal circulation. Three subdivisions can be recognized in this broad category and are considered individually: (1) moderate hypothermia with extracorporeal circulation; (2) deep hypothermia with extracorporeal circulation and periods of circulatory arrest; and (3) selective cardiac hypothermia during extracorporeal circulation.

\textbf{Intracardiac Surgery Performed with Hypothermia and Circulatory Occlusion}

The increasing safety of pump-oxygenators has progressively shortened the number of intracardiac disorders operated upon under hypothermia alone. At present, we use this method only for uncomplicated atrial septal defects in children.\textsuperscript{1} For adults a pump-oxygenator is preferred both because the atrial defects are often larger, and because longer periods of time are required to cool and warm large patients. Hypothermia is no longer used for pulmonic valvular stenosis because two deaths occurred in our series from intractable ventricular fibrillation in patients who were thought to have stenosis limited to the pulmonic valve, but were found to have a diffuse hypoplasia of the entire valve ring. In young patients with pulmonic stenosis a transventricular valvulotomy is usually performed. In older patients in whom a densely fibroed valve is often found a pump-oxygenator is used. An additional reason for using a pump-oxygenator is the frequency of high pressure gradients across the pulmonic valve after simple valvulotomy (five of 20 patients in one series), not all of which have disappeared with subsequent regression of muscular hypertrophy.\textsuperscript{1}

\textbf{Physiologic Changes}

The most significant physiologic effects of hypothermia at 29 to 31 C. are a decrease in oxygen consumption, some increase in cardiac irritability, and a decrease in spontaneous respiratory activity. At 29 C. oxygen consumption is about 50 per cent of that at 37 C.\textsuperscript{2-6} Cardiac ischemia for 6 minutes is tolerated readily, but longer periods cause...
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Myocardial failure or ventricular fibrillation. The time limitation of myocardial ischemia can be avoided by perfusion of the coronary arteries via the ascending aorta during circulatory interruption. The limit of safe circulatory interruption then becomes that of the tolerance of the brain for ischemia, which is probably near 15 minutes at 29 C. In seven patients we have occluded the circulation for 10 to 12 minutes without evident neurologic injury. Experimentally, Brockman and Fonkalsrud found periods of circulatory interruption for 15 to 17 minutes well tolerated in dogs at 28 C, but periods longer than 20 minutes always caused gross neurologic injury.

Some increase in cardiac irritability occurs with mild hypothermia (30 to 34 C.). This is reflected in the frequency of atrial fibrillation which often appears below 33 C and later spontaneously reverts as the temperature is raised. Above 32 C. ventricular fibrillation is rare, but it becomes more frequent with lower temperatures. It is so common below 28 C. that we no longer use this degree of hypothermia except in conjunction with extracorporeal circulation. Below 32 C. assisted ventilation is needed because of depression of the respiratory center from hypothermia. Otherwise a respiratory acidosis will develop, both from decreased rate of respiration and from increased solubility of carbon dioxide in body fluids.

Operative Technic and Results

The technic of operation with hypothermia has changed little in the past 4 years. Surface cooling with chipped ice is used to lower the temperature to 32 or 33 C. in 5 to 15 minutes, after which it “drifts” to 29 to 31 C. During circulatory occlusion the coronary arteries are perfused with oxygenated blood at a pressure of 100 mm. Hg through a needle in the ascending aorta. The rate of perfusion has varied from zero to 70 ml. per minute, the flow rate varying with the amount of blood in the pulmonary circulation. Most operations for atrial septal defects, which are simply closed with a continuous suture, can be completed within 6 minutes, but in one series of 75 operations occlusion times between 8 and 12 minutes were needed in 18 patients. After the operative incision is closed, rewarming is done by immersion in a tub of water at 40 C.

With the use of hypothermia at 30 C. as described, ventricular fibrillation is the most significant complication, occurring in about 5 per cent of the patients. It probably results from the increased myocardial irritability associated with hypothermia. The best evidence for this etiology is the rare occurrence of fibrillation during palpation of the heart before the circulation has been interrupted, and in the presence of a normal pH of the arterial blood. Electrical defibrillation can be accomplished easily, especially if performed quickly; more complicated methods of chemical defibrillation are not needed. If electrical shock is not effective, cardiac massage can be used while warm saline is poured about the heart to raise the temperature 1 to 3 C., after which defibrillation is usually successful.

An important reason for continued use of hypothermia is the notable lack of complications following operation. Rewarming shock, severe metabolic acidosis, or a bleeding tendency has not occurred, and convalescence has usually been uncomplicated. The last death following operation for an uncomplicated atrial septal defect in a child in our series occurred almost 5 years ago. A recurrence of the defect has been found in one patient, but most have not had a postoperative cardiac catheterization because clinical signs indicated complete closure of the defect. Some residual shunts cannot be excluded, however, as Morrow and associates found residual defects by detailed catheterization studies in seven of 28 patients operated upon under hypothermia, and for this reason they have subsequently used a pump-oxygenator. Recurrences were more frequent in adults with large defects, and hence a dehiscence of the suture line was suspected.

A similar low operative mortality has been reported by others. Swan and associates re-
ported one death in their last 125 operations, and Johnson and co-workers recently reported no deaths in a series of 41 cases. Postoperative catheterization studies by Swan's group did not show a high incidence of residual defects.

In the future, hypothermia for the closure of atrial septal defects will probably be gradually replaced by pump-oxygenators as they become simplified and better understood. At present, however, there is an impressive amount of data supporting continued use of hypothermia alone as a safe and effective method.

**Hypothermia for Neurologic Injury Following Resuscitation from Cardiac Arrest**

Hypothermia was first used in 1957 for neurologic injury following resuscitation from cardiac arrest because signs of increasing neurologic injury in the first few hours after resuscitation were associated with signs of increasing intracranial pressure. It had been observed during neurosurgical procedures that hypothermia decreased brain volume; so it was hoped that hypothermia following cardiac arrest might prevent or decrease cerebral edema. The initial trial of hypothermia was so encouraging it has since been regularly used at the Johns Hopkins Hospital for such neurologic injuries. Control studies are difficult or impossible to obtain in man because of uncertainty of the exact time of onset of cardiac arrest as well as the time of restoration of an effective heart beat. The frequency of recovery of patients with neurologic injury, however, has been much increased. In experimental studies neurologic injury following 10 minutes of circulatory occlusion is greatly lessened by the immediate institution of hypothermia; in one study 79 per cent of cooled animals recovered from neurologic injury, but only 17 per cent recovered when hypothermia was not used. Recently similar experimental findings were reported by Wolfe.

The technic of hypothermia for this purpose has not been changed significantly since 1958. If the patient does not awaken promptly after cardiac resuscitation, the temperature is lowered to 32 or 34 C. by placing a water mattress beneath the patient and surrounding the extremities with chipped ice. Chlorpromazine is given if shivering occurs. Unless spontaneous recovery of neurologic function occurs, the temperature is kept at 32 to 34 C. for 3 or 4 days. Although we have not seen benefit from hypothermia used longer than 4 days, adequate data are not available to be certain of the maximum time that hypothermia should be maintained. Other therapeutic measures include restriction of fluid intake to one liter per square meter of body surface per day, and the use of osmotic diuretics (urea or mannitol) to lessen cerebral edema.

Serious complications have not resulted from this mild degree of hypothermia. Temperatures below 32 C. have been avoided because experimental studies have not shown benefit, and deeper hypothermia seriously risks ventricular fibrillation. Fortunately, surviving patients have had little residual neurologic injury. The mechanism by which hypothermia benefits neurologic injury is still not certain. Kaupp and Starzl and Rosomoff and associates have reported studies indicating that the benefit is due to factors other than reduction in cerebral edema.

**Combined Hypothermia and Extracorporeal Circulation**

With the disappointing finding that hypothermia below 25 C. was associated with a prohibitive frequency of ventricular fibrillation or cardiac failure, the combination of extracorporeal circulation with hypothermia of this degree became necessary for safety. Gollan, who was one of the first to use this combination, has summarized many of the early experimental studies in his monograph in 1959. The clinical combination of the two methods was stimulated greatly by the development of a simple, efficient heat exchanger by Brown in 1958. The following year Drew and Anderson and Shields and Lewis each reported experimental observations of operations performed with circulatory standstill under deep hypothermia. Subsequently,
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Much experimental and clinical data have been reported; but the advantages and limitations of hypothermia are still far from clear. Three broad categories of usage of the combination of hypothermia and extracorporeal circulation exist at present: (1) moderate hypothermia (25 to 32 C.); (2) deep hypothermia (5 to 20 C.) often with periods of circulatory standstill; and (3) selective hypothermia of the heart. The current status of each of these combinations is briefly considered.

Moderate Hypothermia with Extracorporeal Circulation

If hypothermia of 26 to 32 C. is combined with extracorporeal circulation, a lower perfusion rate is required because of the decreased rate of oxygen consumption. Except for the decreased oxygen consumption, the physiologic changes associated with this degree of hypothermia for short periods of time are not significant. As the decreased rate of perfusion results in less blood flow through the bronchial and coronary circulations, less aspiration of blood from within the heart is required during intracardiac surgery. Hence, both from the decreased rate of perfusion and from the decreased amount of intracardiac aspiration there is less trauma to the blood during bypass. If intermittent aortic occlusion is needed, the tolerance of the heart for ischemia is also significantly increased.

Sealy and Gerbode and their associates have each enthusiastically reported extensive experiences with this technic after observing that the postoperative course of patients seemed better than those operated upon under normothermic conditions. Obviously these observations cannot be quantitatively measured; so the value of mild hypothermia cannot be more precisely determined. The most obvious indication for its use is when occlusion of the aorta with associated interruption of coronary blood flow is planned for more than a few minutes. Such circumstances occur during operations for congenital aortic stenosis or during operation for tetralogy of Fallot with extensive bronchial circulation.

Deep Hypothermia (5 to 25 C.) with Extracorporeal Circulation

Physiologic Changes

In contrast to the slight physiologic alterations that occur with mild hypothermia, deep hypothermia results in many radical physiologic changes. The more important of these are summarized.

Oxygen Consumption and Temperatures Gradients. As the temperature is lowered, the oxygen consumption decreases at a varying rate. The rate of decrease is not linear but more closely resembles an exponential function, with the rate of change below 20 C. being more gradual than that at higher temperatures. Much interest has been focused on the oxygen consumption at different temperatures in order to estimate how long the circulation can be safely arrested. Though the findings of different investigators are not in complete agreement, in general oxygen consumption at 18 to 20 C. is 20 to 28 per cent of that at 37 C., and at 10 to 12 C. it is 5 to 17 per cent. Bjork and Holm-dahl have reported one of the few studies in man, finding a total body oxygen consumption of about 5 per cent at 10 C.

The principal reason for the variation in oxygen consumption found by different investigators is the development with cooling of large temperature gradients between different tissues in the body. These gradients, which may be 10 C. or greater, result from different perfusion rates in different organs. The most vascular organs, such as the heart, esophagus, and kidneys, have temperatures near that of the perfusing blood. By contrast, the highest temperatures are found in the skeletal muscle and subcutaneous tissues, where blood flow is minimal, apparently because of spasm of arterioles and sludging of blood in the capillaries. The brain and rectal temperatures are intermediate between these two extremes.

The size of the gradients varies with many factors. They are greater with “core” cool-

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ing by perfusion of cold blood than with surface cooling by applying cold to the skin. They also vary with the rate at which body temperature is lowered, the perfusion rate with cooling, and possibly with the use of low molecular weight dextran, which tends to lessen the degree of capillary sludging.\textsuperscript{37} Gradients up to 5 C. may even be found in the same organ;\textsuperscript{35} in tissues highly vulnerable to anoxia, such as the heart and brain, this is of obvious importance. The development of these gradients not only makes comparison of data from different investigators difficult, but also should make one cautious against too liberal interpretation of individual temperatures obtained only from one area.

As mentioned earlier, oxygen consumption at different temperatures has been used to indicate how long the circulation could be safely arrested. In recent analyses of the causes of neurologic injury following periods of circulatory interruption under deep hypothermia, Bjork and Hulpquist\textsuperscript{38} and Drew\textsuperscript{39} have suggested that factors other than anoxia were present. Bjork concluded that neurologic injury probably resulted from intravascular accumulations of platelets and white blood cells, while Drew found a correlation between the frequency of neurologic injury and the type of heat exchanger used, suggesting that bubbles formed in the perfusing blood could have been the cause of injury.

Cardiac Changes. Below 28 C. there is progressive myocardial failure with bradycardia and distention unless the heart is decompressed. Ventricular fibrillation commonly occurs at this time, but experimentally can often be prevented with quinidine, 30 mg./Kg.\textsuperscript{2, 40} With lower temperatures (10 to 15 C.) fibrillation is replaced by cardiac asystole. On rewarming, ventricular fibrillation usually reappears, requiring electrical defibrillation after the temperature has reached 32 to 34 C. An interesting correlation has been found by Osborn and associates\textsuperscript{41} between the frequency of spontaneous defibrillation in man at warmer temperatures and the presence of a mild acidosis. By infusing small amounts of hydrochloric acid to produce an arterial blood pH near 7.20, spontaneous defibrillation occurred in 69 per cent of their patients; but without the deliberate production of an acidosis, it occurred in only 14 per cent.

Effects upon the Central Nervous System. Below 20 C. the electrical activity in the electroencephalogram decreases and soon disappears completely. Cerebral oxygen consumption decreases to about 25 per cent of normal at 25 C., but unfortunately adequate data are not yet available for oxygen consumption at deeper levels of hypothermia.\textsuperscript{1,3,36,42} This information is sorely needed in determining whether the brain injury occurring in some patients with periods of circulatory arrest under deep hypothermia is due to anoxia or some more obscure metabolic cause.

Perfusion Flow Rates. As the temperature is lowered, the rate of venous return to the pump-oxygenator usually decreases so that the rate of perfusion has to be decreased from around 100 ml./Kg./min. at 37 C. to 50 to 60 ml./Kg./min. at 10 C. unless additional fluid is added to the perfusion system. This decreased venous return apparently results from trapping of blood in areas of capillary stasis. It can be lessened by adding low molecular weight dextran to the perfusion fluid.\textsuperscript{37} These circulatory changes during deep hypothermia are associated with increasing viscosity of the blood, a rising hematocrit level, a decreasing white blood cell count, and almost complete disappearance of circulating platelets.\textsuperscript{4}

The variation in flow rate raises the yet incompletely answered question as to what rate of perfusion is needed at different body temperatures. Theoretically a low rate of perfusion should be adequate at 10 C., but two different experimental studies have shown that perfusion rates of 50 ml./Kg./min. at 10 C. are required to prevent completely tissue anoxia and metabolic acidosis.\textsuperscript{35, 37}

Acid-Base Changes. The reported frequency of metabolic acidosis with hypothermia varies widely in different studies, probably reflecting the different rates of perfusion used.\textsuperscript{3, 24-27, 30}
With high perfusion rates at low temperatures (50 to 60 ml./Kg./min. at 10 C.) a metabolic acidosis may not develop. An additional consideration is that data from some reports are not comparable because of differences in the method of pH determination at different temperatures. The best method for obtaining comparable data is probably to measure the blood pH at the same temperature that existed when the sample was obtained.43

Cold changes the oxygen dissociation curve of hemoglobin so that hemoglobin remains over 90 per cent saturated at very low oxygen tensions (below 20 mm. at 15 C.). This effect varies directly with the pH of the blood and can be altered accordingly. Theoretically, tissue anoxia can exist despite a high oxygen saturation of the returning venous blood because oxygen cannot be easily released from hemoglobin. If the arterial blood pH is lowered, oxygen can be released at a higher partial pressure, and in such experiments an increased oxygen consumption has been measured.41,44 The importance of this interesting type of tissue anoxia is not yet clear, but it may be related to the findings of Lewis3 that long-term survivals of animals cooled to very low temperatures could not be obtained without adding carbon dioxide to the system.

Morphologic Changes with Deep Hypothermia. Whether hypothermia per se of short duration produces specific histologic changes is yet unknown. Scattered foci of necrosis in different organs have been found by several investigators, but not consistently enough to be accepted as characteristic of hypothermia.2,3,20,22,25,31,38 As similar histologic changes occur with endotoxin and hemorrhagic shock, they may result from inadequate circulation during hypothermia rather than from hypothermia itself. The high mortality of dogs kept at 20 to 25 C. for 20 hours by Connaughton, Holt, and Lewis21 (85 of 98 dogs) is impressive. After the first few hours of hypothermia there was a gradual rise in the hematocrit level, a progressive metabolic acidosis, and a gradual fall in oxygen concentration of the mixed venous blood to low levels—all suggestive of progressive circulatory failure.

Bjork and Hulpquist38 have described in detail the histologic changes in the brains of children dying from neurologic injury following deep hypothermia and circulatory arrest. They interpreted the findings as resulting from diffuse capillary obstruction from agglutination of white blood cells and platelets. Another possible mode of injury is the formation of bubbles of gas in the blood during warming or cooling, because gas solubility varies greatly with temperature. The physical factors influencing the formation of bubbles during hypothermic perfusions have been recently evaluated by Donald and Fellow,45 who concluded that temperature gradients of 15 C. or greater might easily result in the release of bubbles.

Clinical Experiences and Future Considerations

The important physiologic changes with deep hypothermia have been described in detail in order to define the considerations encountered when the technic is used clinically.22,33,39,46,47 Several reports of large groups of patients operated upon show that intracardiac surgery can be performed with a high percentage of good results. Survival alone, however, is an inadequate criterion for the safety of the technic. Particularly disturbing are the incompletely explained episodes of neurologic injury encountered by three different surgeons.28,39,47 Fortunately, these have been infrequent, but they warn of potential hazards not yet well understood.

For certain cardiac defects, such as transposition of the great vessels or tetralogy of Fallot with a previously constructed aortopulmonary anastomosis, circulatory arrest offers advantages greater than any other technic. With most other defects, however, caution is indicated in using circulatory arrest for long periods in preference to other methods. The recent suggestions of Kirklin and associates47 concerning the safe duration of circulatory arrest at different temperatures (15 min. at 22 C., 30 min. at 12 to 14 C.) are
consistent with the best physiologic data now available.

Selective Cardiac Hypothermia during Extracorporeal Circulation

Selective cardiac hypothermia during extracorporeal circulation at mild or normothermic temperatures has been carefully studied as a method of myocardial protection from anoxia during operations upon the aortic valve or operations for other conditions when the coronary blood flow must be interrupted for long periods. Among the first to use local cardiac cooling were Shumway and associates, who irrigated the pericardium with cold saline, and Gott and associates, who perfused the coronary arteries with cold blood. Detailed experimental studies have been reported from several other sources. These have shown a decrease in myocardial oxygen consumption to 20 to 25 per cent of normal at 18 to 20°C., and 12 to 18 per cent at 10 to 12°C. Left ventricular function studies following different periods of ischemia have shown little loss of function, and no histologic signs of injury from cold have been found. In a recent summary of their experimental findings, Greenberg and Edmunds concluded that myocardial ischemia was well tolerated for 30 min. at 18°C. and for 60 min. at 10°C.

Recently, Hufnagel and associates described good results with over 100 aortic valve operations, using continuous pericardial irrigation with iced saline during periods of aortic occlusion for 1 hour or longer. When this technic is used, the use of large amounts of iced saline, as emphasized by them, is essential. Otherwise rewarming of different areas of the heart may occur with resulting myocardial injury from ischemia.

Current experimental and clinical data are in agreement that local hypothermia is a useful and safe technic when cardiac arrest is needed. If myocardial ischemia is limited to 30 min. at 10 to 12°C., a wide margin of safety is present.

Summary

A survey of the current use of hypothermia during cardiac surgery has been presented. Hypothermia remains a simple and safe method to permit the surgical correction of uncomplicated atrial septal defects, although it is gradually being displaced by pump-oxygenators as they become better understood.

In conjunction with extracorporeal circulation moderate and extreme ('deep') hypothermia has been employed. Moderate hypothermia is without any known deleterious effects and may be of benefit by lowering perfusion rates and decreasing intracardiac aspiration of blood. The role of deep hypothermia with circulatory arrest remains uncertain. It is a condition associated with extreme physiologic alterations, many of which are poorly understood, and the safe limits are not yet clearly defined.

Finally, hypothermia remains a beneficial technic for neurologic injury following resuscitation from cardiac arrest. Recent evidence indicates that the mechanism of benefit involves considerably more than simple reduction of cerebral edema.

References

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Yet in his (Harvey's) need of a motor for his machine he was not able to divest himself of the language nor even of the philosophy of his day; he referred the cause of the motion of the blood, and therefore of the heart, to innate heat.—THOMAS CLIFFORD ALLBUTT, M.A., M.D. Science and Medieval Thought. London, C. J. Clay & Sons, 1901, p. 43.