HYPOTHERMIA: ITS USES IN MODERN CARDIOVASCULAR SURGERY

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Since hypothermia is now being used as an aid in cardiovascular surgery, it is appropriate at this time to review the extensive literature on the subject and present the relevant facts and opinions to the medical profession in South Africa. As this subject has not been reviewed previously in this country, I have quoted the authorities rather extensively.

The word 'hypothermia' is of course not synonymous with 'freezing', a word sometimes used for it in the lay press, but implies a cooling of body temperature by several degrees centigrade only.

PHYSIOLOGY

Cooling delays the onset of anoxia during interruption of oxygen supply and postpones secondary enzymatic changes that follow anoxia and lead ultimately to death of the cell. If an animal is placed in a cold environment it combats the tendency to a fall in body temperature by shivering. The adrenal and pituitary glands react as they would do under any severe stimulus, by an outpouring of their metabolic hormones. If these reactions are minimised or prevented by the use of drugs or by anaesthesia, then cooling occurs at a more or less even rate and *pari passu* there is a diminution in oxygen requirement. All the body reactions are slowed down. At first there may be very little evidence of physiological change, but around 32°C consciousness is lost and the breathing and heart rates slow down. At lower temperatures the activity of the various organs may cease. Cardiac arrhythmias are common between 28° and 30°C and ventricular fibrillation, which is one of the gravest complications, may develop. The lower the temperature the greater the chances of fibrillation occurring and around 25°C it is present in a high proportion of cases because the hypothermic heart still requires oxygen in order to function. Below 25°C the coronary flow is disproportionately high in spite of falling aortic pressure. Acceleration of the heart rate during hypothermia lessens coronary flow; an increase from 50 to 70 beats a minute at 20°C completely arrests coronary flow (Brock[1]). If the coronary flow can be maintained artificially and the work load on the heart reduced to a minimum, cardiac arrest may be postponed until a temperature of 14°C is reached. Very low temperature may cause tissue damage apart from the anoxic effect. At 25°C the circulation can be occluded safely for 15 minutes without there being any clinical evidence of tissue damage; at 28°C the period is about 10 minutes.

The metabolism of glucose ceases at 31°C and during hypothermia operations this must be remembered. The intravenous drip should contain half-normal saline or blood. Sodium citrate is also not metabolized and may reach concentration high enough to be toxic to the myocardium. Likewise, stored blood with its high potassium-ion concentration may produce cardiac arrest.[2]

The optimum temperature of tissue functioning is brought down by a drop of the potassium content in the extracellular medium and an increase in the calcium. The ultimate effect of hypothermia down to 30°C is hypometabolism (40%), bradycardia (60-80 per minute), hypotension (80-100 mm. Hg), bradypnoea (12 per minute), hypokalaemia, alkalosis and moderate hypercalcaemia, hypocoagulability (50-60% prothrombin index) and moderate hyperglycaemia. The ECG shows slowing of the heart rate, progressing to prolonged electrical systole and heart block. Auricular fibrillation is common around 32°C and ventricular fibrillation at 28°C. This is particularly apt to occur during the re-warming.

Breathing stops at varying temperatures. Muller[3] noted that two infants breathed when their temperatures were 19 and 19·5°C respectively and Kaplan[4] had a child cry at 24°C. In Glen's series,[5] spontaneous respiration ceased at 28°C but sometimes at 25°C. At 25°C no animal survived complete circulatory occlusion for 20 minutes. However, he clamped off both brachiocephalic arteries in dogs for 30-55 minutes and all recovered normally. He totally exsanguinated one dog and re-introduced the blood. This too recovered. With the depression of respiration an acidosis develops. Delorme[6] thinks that hypercapnia (excess CO_2) acts as an innocuous metabolic depressant enabling warm-blooded animals to survive temperatures far below the lethal level if oxygen is breathed. Likewise Holmdahl[7] showed that dogs exhibit some high tolerance to respiratory acidosis under hypothermia. He postulated that the sudden elimination of carbon dioxide may threaten cardiac action. However, most workers prefer an alkalosis to an acidosis. The hypocoagulability which in Lewis's experience may be manifest by an increased tendency to post-operative haemorrhage[8] is thought by Huguenard[9] to be due to sympathalase.

PRODUCTION OF HYPOTHERMIA

The following methods of lowering body temperature have been used: (*a*) Drugs, (*b*) surface cooling, (*c*) vascular cooling and (*d*) internal cooling and (*e*) a combination of two or more of these.

(*a*) *Drugs*

These have been pioneered by French workers (notably Laborit) to produce hypometabolism. The so-called 'lytic cocktails' produce multifocal inhibition of the autonomic nervous system, both central and peripheral (neuroplegia). The essential ingredients of such a cocktail should possess antiadrenergic (chlorpromazine), anticholinergic (pethedine, atropine), and antihistiminic (phenergan) properties. With these it is possible to obtain results as with a 'balanced anaesthetic' comprising barbiturate, a curarizing agent and a ganglion-blocking agent (vasoplegia). Bimar[10] used hydergine and diethazine in combination instead of chlorpromazine.

Hydergine is a vasoplegic with a central (medullary) effect. It inhibits the carotid-sinus and other presso-sensory reflexes. It induces latent adrenosympatholysis by inhibiting the effects of adrenalin in the case of sympathetic stimulation.

Diethazine has a vagolytic central action and hypnotic effect and is a depressor of the motor centres. It is also cholinergic and antihistaminic. These properties make its respiratory and circulatory effects marked.

Either of these drugs used separately is not satisfactory. The vagomimetic action on the tracheobronchial tree is marked when hydergine is used alone, and the adreno-sympatheticomimetic action on the myocardium or respiration and on the basal metabolism is marked when diethazine is used alone.

Adrenolytic drugs include chlorpromazine (Largactil), which has a central and peripheral neuroplegic effect. Regitine and the di-hydrogenated derivatives of rye ergot (hydergine) cannot be used in its place.

Ganglion-blocking agents include tetra-ethyl-ammonium, procaine amide, methonium and arfonad.

Parasympatholytics, opposing the action of acetylcholine, include pethidine, atropine and antrenyl.

Antihistaminic derivatives of phenothiazine (promethazine, phenergan) or others like benadryl hold the precapillary sphincter closed and also contribute their interesting secondary effects, viz. hypnotic, anti-emetic, anticholinergic, (slight), analgesic and antipyretic.

The result of neuroplegia is as follows:

1. Endocrine inhibition—hypophyseal and suprarenal (chlorpromazine is adrenolytic but not noradrenolytic). Neuroplegia diminishes post-operative eosinopenia and diminishes or prevents the loss of ascorbic acid in the suprarenal glands.

2. Direct cellular action—diminishing cellular activities.

3. Neuroplegia plus hibernation produces a hypocoagulability attributed to sympathalase. This is seen with chlorpromazine alone (Huguenard[9]).

The drop of body temperature seen in neuroplegia is entirely due to the temperature of the surrounding air (Delorme[6]). It is concluded that massive doses of chlorpromazine do not significantly lower the temperature or oxygen consumption; it has an adverse effect on the natural defensive reactions unless supplemented by transfusion or by lowering of the metabolism (the lowering is minimal with the drug alone). Dundee[11] found in animals that deep anaesthesia, curarization or lytic cocktails were equally effective in facilitating hypothermia, and chlorpromazine alone apparently as effective as lytic cocktails in potentiating surface cooling.

Other Methods of Cooling

(*b*) *Surface Cooling*. This is effected by a variety of methods, the commonest of which is the immersion of the patient in an iced bath. Other methods are the use of refrigeration blankets, cold fans, etc. All of these must be combined with an anaesthetic and neuroplegic agent.

(*c*) *Vascular Cooling*. The arterio-venous method is simple. An artery is cannulated and the blood circulated through a cooling coil and returned to a vein. This, however, leads to undesirable side-effects, and veno-venous cooling is better. For this a pump is required.

(*d*) *Internal Cooling*—by circulating iced water through plastic bags in the stomach, or by pouring cold saline into the open thorax. These methods have not been used to any great extent.

Comparison of Methods of Cooling

1. *Extracorporeal venous cooling* is rapid. This method was devised by Delorme[6] in 1949 and by Boerema.[12] Later it was much used clinically by Brock and Ross.[1] These latter recommend rapid cooling and re-warming. They did not commence the cooling process until the chest had been opened, and then any cardiac irregularity could be rapidly dealt with. One advantage of venous cooling is that it allows of differential hypothermia, the cooled blood being returned to the proximal aorta and shunted mainly to the heart and brain. Thus the vital organs can be cooled rapidly to a sufficient degree to permit circulatory arrest for the allotted time. Re-warming then occurs equally rapidly. Whatever method of cooling is employed, the blood returning to the heart will be cooler than that of the rest of the body except the skin; hence the need for oesophageal temperatures, as giving a reasonably accurate index of the temperature of the heart itself.

The great disadvantage of this method is that cooling of the heart may occur too rapidly, which increases the risk of ventricular fibrillation, especially if instituted before thoracotomy has been done. Dangerous side-effects also arise from circulating the blood outside the body.

Hypothermia augmented by an assisted circulation of low or high flow (heart-lung machine) is much safer, prolonging the time of safe circulatory arrest. Cannulation of vessels will be necessary and when extra-corporeal venous cooling has been employed the stage will be set for assisted circulation. In the future perhaps this will prove to be the greatest advantage of this method of cooling.

Surface Cooling by bath immersion is simple, the equipment is readily obtained, and cooling can be well controlled. It is the method that has been most generally employed up till the present, particularly in the USA.

Helmsworth,[13] in a comparative study of hypothermia induction in dogs, found that surface cooling with iced water produced more profound haematological changes than extracorporeal cooling (Table I).

TABLE I. COMPARISON OF METHODS OF COOLING

	Extracorporeal circuit without cooling (90 min.)	*Water immersion to 23°C (60 min.)*	*Extrocorporeal cooling*
Haematocrit ..	15·8% increase	27·2% increase	20·4% increase
Platelet	9·6% decrease	80·7% decrease	24·8% decrease
Leucocyte ..	25·1% decrease	88·5% decrease	51·2% decrease
Total Eosinophil	13·2% decrease	85·0% decrease	33·1% decrease
Mean Corpusc. Hb. Content. ..	5·2% decrease	6·1% decrease	4·7% decrease

An advantage of the venous cooling method is that in the doubtful case cooling need not be commenced until a diagnosis to justify hypothermia is established at thoracotomy. However, in the majority of cases the decision to use hypothermia can be made beforehand. A disadvantage of extracorporeal venous cooling is the employment of a mechanical pump and the circulation of the blood through coils of plastic tubing which in themselves may lead to complications of blood clotting and destruction. After 300 experiments with dogs Delorme[6] concluded that cooling from 38° to 25°C by the vascular method, and re-warming, was nnocuous *per se*.

Control of Temperature

The control of temperature is of the greatest importance because at too low a temperature there is a danger that cardiac irregularity will develop. Cooling is actively employed down to a temperature of about 31°C according to the end temperature desired. After active cooling has ceased, the body temperature continues to drop a further 2-4°C. This drop is more marked where surface cooling is employed, because the surface tissues are colder than those at a depth. In a fat patient this 'after drop' will be greater. Surface temperatures would then be misleading. Oesophageal or rectal temperatures are awkward to take with the conventional thermometer. An oesophageal thermocouple with galvanometric recordings, though it entails special equipment, is desirable both for safety and convenience.

The rate of cooling is also important; too rapid cooling is dangerous. Children tolerate hypothermia better than adults and can have their temperature lowered faster and lower. It needs

30-40 minutes to reduce an infant's temperature from 37° to 31°C (about 1°C for each 5 minutes). An adult will cool less rapidly and will probably have to be immersed in the bath for fully an hour. Refrigeration blankets, although less cumbersome and more aesthetic than bath immersion, require 2-3 hours to achieve the same effect. Constant electrocardiographic monitoring is necessary throughout this period. The best instrument for this is the cathode-ray oscillograph.

The re-warming period is just as dangerous and important. It should take about as long as the cooling. When the oesophageal temperature has reached 35°C the patient will be sufficiently 'round' for the intratracheal tube to be removed and the anaesthetist to leave. Spontaneous respiration should then be sufficient. It is to be realized, however, that apart from the anaesthetic used for induction and a long-acting muscle paralysant, no anaesthetic agent is needed throughout the major part of this procedure. The lowered temperature is sufficient anaesthetic for all surgical procedures. However, there is an individual variation in the patient's response and in a few cases a little anaesthetic will be required.

Re-warming is done in various ways. If left alone at room temperature the patient will gradually warm up once the effect of the drugs has worn off. Glen[5] cooled dogs to 25°C; without any artificial respiration or supervision they were returned to their kennels, and all were well the next morning. However, it is generally desirable to start warming the patient as soon as the need for hypothermia is over. This stage is reached when the definitive procedure is completed. This re-warming is commenced while the operation is still in progress, and is effected by means of electrically warmed blankets or, better still, specialy constructed rubber blankets through which warm water is circulated. These are put into place at the commencement of the operation. Other methods are to use a diathermy coil or radio-frequency (Bigelow[14]), which has the advantage of warming the deeper tissues. Warm saline in the chest before closure will also help. At the end of the operation the patient's temperature may hardly have started to rise. The warm-blanket treatment can be continued or the patient may be immersed in a warm bath until the temperature has risen to 35°C. In some of our patients consciousness has returned at a lower temperature; one child was returned to the ward while the oesophageal temperature was 33°C.

METHODS OF AUGMENTING HYPOTHERMIA

Various authors indicate what they think is the safe period of venous occlusion at different levels of hypothermia. The temperatures most surgeons prefer are 28°-31°C. Below this the risks of ventricular fibrillation are greatly increased. At 28°C the circulation can safely be occluded for 10 minutes without fear of ischaemic damage. Nevertheless, during circulatory occlusion the heart still contracts and is in need of a proportionately greater amount of oxygen. The following methods are used to supplement hypothermia.

(*a*) *Controlled Asystole*

Controlled asystole can readily be produced by perfusing acetylcholine or prostigmine through the coronary circulation. This prostigmine effect will be eliminated as soon as the blood-flow through the coronary arteries washes it out. Potassium chloride and magnesium sulphate can be similarly used (Young[15]). However, the cold heart frequently fibrillates after release from standstill induced by potassium.[15] Prostigmine slows the heart rate at the critical post-standstill period (Sealey[16]).

Swan[17] found defibrillation easier if potassium chloride was injected into the coronary circulation. A somewhat conflicting opinion is expressed by Reberi,[18] who found the standstill produced by perfusing the coronary arteries with potassium chloride difficult to convert to normal rhythm. Perfusion with calcium chloride at this time often produced fibrillation. Because of these conflicting views we have not used potassium chloride to produce cardiac arrest. Instead we have used prostigmine wherever necessary. Jordan[19] has found potassium chloride with glucose and insulin to be safe and effective.

(*b*) *Differential Hypothermia*

By circulating oxygenated and refrigerated venous blood in a gas-dispersion pump oxygenator, Gollam[20] was able to achieve survival of dogs after cardiac arrest for 1 hour at 0°C. In these experiments, in 40 minutes of blood cooling the temperature inside the right heart was lowered to 5°C and in 15 minutes of blood warming it was raised to 27°C. Differential hypothermia between upper and lower parts of the body reached 20°C. The last heart contraction was noted at 13°C. On re-warming, the pump was turned off at 28°C. Gollam gave quinidine and had no ventricular fibrillation, no anoxia of the central nervous system, heart or viscera, no CO_2 retention and no air embolus in asystole. Cortisone was used to prevent the high mortality that occurs after short circulatory cessation below 20°C. He gave his animals 100 mg. of cortisone acetate intramuscularly on the day before the operation, 100 mg. of hydrocortisone intravenously before cooling, and 50 mg. intramuscularly on that and the next 3 nights. At these low temperatures a low systemic blood pressure is adequate (20-30 mm. Hg), but by the time 21°C is reached a higher pressure is required and this is achieved by an intravenous drip of 20 mg. of L-arterenal (nor-adrenaline) in 500 c.c. of plasma expander (continued slowly throughout the re-warming period, 4-5 hours). Gentle cardiac massage is also necessary until 22-23°C is attained.

Delorme[6] produced differential hypothermia of 7-10°C by perfusing the pericardial sac with iced saline after the rest of the body temperature had reached 25°C and the inflow had been occluded.

In the presence of a septal defect, differential cooling may occur, causing the heart and lungs to be cooler than the rest of the body (Brock[1]).

(*c*) *Low-Flow Extra-Corporeal Circulation*

Battezzati[21] reported that 22 out of 26 dogs survived complete cardiac occlusion and right ventriculotomy for 13 to 56 minutes. He cannulated the vena cavae and cooled the blood through coils in ice and oxygenated it before returning it to the carotid artery. He contended that 40-50 c.c. per minute was sufficient for a dog at 28°C, 60-70 c.c. at 32°C, and 100 c.c. at normal temperature. The blood was heparinized and he advocated the use of an equal dose of protamine sulphate to counteract the effect of the heparin.

Using a low-flow extra-corporeal circulation, Sealey[16] has kept the cold heart in standstill and ischaemic for 31 minutes in a dog and for 17 minutes in a man. He considers cardiac standstill to be safe for 13-30 minutes at 30°-32°C, and that flow rates of as little as 15 c.c. per kg. per minute are probably safe for 10-15 minutes,, 30 c.c. per kg. for 15-20 minutes and 40 c.c. per kg. for 20-30 minutes. He has carried a 23 kg. patient through 21 minutes perfusion at 26 c.c. per kg. per minute.

Swan[17] found a flow rate of 50-85 c.c. per minute with pressure range of 25-85 mm. Hg adequate in dogs. He used plastic bags for oxygenation. For anticoagulation he used 0·5 mg. of heparin per kg. through the venous outflow catheter. To neutralize this, a 0·05% solution of protamine sulphate in 0·85% sodium chloride was given by slow drip. The estimated protamine dosage was mg. for mg. of heparin, including that given in the donor blood. The clotting time returned to normal ½ hour after starting protamine.

Ross[22] also advocated relief of the heart's work by the use of the heart-lung machine.

(*d*) *Coronary Perfusion*

Bahnson[23] used the ordinary intravenous blood-transfusion apparatus suspended from the ceiling to provide for coronary perfusion. For this purpose oxygenated heparinized blood was collected from donors by heating the arm in a bath for 15 minutes and collecting venous blood in the usual way.

Bailey[24] found that arterial transfusion to maintain high pressure in the aortic arch reduced the chance of coronary air embolus. For transfusion he advocated the use of red corpuscles suspended in gelatin-Ringer solution. The use of arterial transfusion prolongs the period at any given temperature during which the circulation can be clamped off. He has closed the circulation for 22 minutes for the repair of a septal defect.

Gollam[20] had only one dog survive 12·0°C, but by circulating oxygenated blood had one survive 0°C.

Shumway[25] used coronary perfusion to protect the heart. He used a Sigmamotor pump. The right heart was aspirated through either right cardiotomy or through an incision in the pulmonary artery. This blood was re-circulated. Thus only a reservoir of 500 c.c. of blood was needed. At 25°C he found that a flow rate of 50-85 c.c. per minute with pressure range of 25-85 mm. Hg was adequate. To prevent clotting he used 20 mg. of heparin in 500 c.c. No neurological defect was observed in any dog with circu-

latory occlusion for 20 minutes at 25°C, but it did occur in 2 out of 6 occluded for 30 minutes. He observed no ventricular fibrillation in 7 dogs in which the coronaries were perfused with oxygenated blood. He mentions 2 clinical cases of atrial septal defect in which unexplained post-operative bleeding took place. The flow rate was 100 c.c. per minute. Both fibrillated but this was easily reversed. On perfusion of the coronary arteries of 10 dogs with venous blood, all survived 20 minutes of occlusion; no post-perfusive transfusions were necessary, but two developed ventricular fibrillation. The flow rate was 50 c.c. per minute (a reservoir of 1,000 c.c. of heparinized blood was sufficient). The coronary drainage was discarded, and the oxygen content averaged 4·4. vols.% less than the perfusate, indicating that the myocardium extracted oxygen as readily from the venous blood as from arterial blood.

INDICATIONS FOR HYPOTHERMIA

Shock

Controlled hypothermia has been used as an aid in the treatment of severe shock and prophylactically for poor general condition before major procedures. Van Krankenanstalen[26] reported its use in over 70 such cases. Internal temperatures of 34-35°C should be maintained for 48-100 hours. He advocated this procedure in severe injuries, including head injuries, and in intoxication.

Controlled hypothermia for this purpose, particularly that induced by the administration of drugs, has received wide acclaim in France (artificial hibernation of Laborit).

Recently Lewis[27] advocated a 'technique for total body cooling of the febrile gravely ill patient'. The first case he had was one in whom an operation for atrial septal defect had just been completed. After the operation the patient could not maintain her condition. There was immediate improvement on cooling. Since then this method has been used on 24 other gravely ill patients.

Cardio-vascular Surgery

It is in this field that the greatest application of hypothermia will be made in this country at present. Later, when a safe method of maintaining an artificial circulation with pump oxygenator has been established*, the scope of operations performed under hypothermia will be restricted. At present it is the only real aid we have that will enable us to work on a vital organ in a completely bloodless field with the added safety of prevention of haemorrhage and lessened possibility of tissue death. At present the operations which we feel should be performed under hypothermia are the following*:

1. Those requiring cardiac arrest
   - (*a*) Open cardiotomy: (i) Atrial septal defect, (ii) intra-atrial lesions, (iii) mitral incompetence and recurrent mitral stenosis, (iv) ventricular septal defect, (v) right ventricular infundibular stenosis.
   - (*b*) Opening of aorta and pulmonary vessels: (1) Aortic stenosis, (ii) pulmonary stenosis, (iii) aortic pulmonary fistula.
   - (*c*) Other operations on the proximal aorta.
2. Those not requiring cardiac arrest
   - (*a*) Aneurysms of the distal thoracic and upper abdominal aorta,
   - (*b*) Various shunt operations on severely cyanotic patients (Blalock's and Pott's operations),
   - (*c*) other operations.

1. *Operations Requiring Cardiac Arrest*

(*a*) *Open Cardiotomy.* Lewis[8] is credited with first using hypothermia in the closure of an atrial septal defect. He considered the advantages of this method over the heart-lung machine were: (1) it is completely bloodless and there is no coronary flow; (2) the chance of air embolus is reduced if the inflow and outflow are shut; (3) it is simple. At the time of writing he had operated upon 11 atrial septal defects. It is interesting to note that as late as 1957 Lillehei,[28] who had performed over 200 operations using the pump oxygenator, recommended that atrial septal defect of the osteum secundum type be treated under hypothermia.

By 1957 Holmes Sellors[29] had closed 40 cases of atrial septal defect under hypothermia. Bigelow[30] advocated the use of hypothermia in adult atrial septal defects and in serious-risk cases, e.g. mitral stenosis with right ventricular failure and the cyanotic group of congenital heart diseases.

On the other hand Gross[31] was until recently still using his 'well technique' for the closure of atrial septal defect, while Kirklin[32] even though he has an elaborate and smoothly running pump-oxygenator, still repairs atrial septal defects by Gross's technique.

Our present experience of open cardiotomy has been in 2 cases of right ventricular infundibular stenosis and in 2 cases of atrial septal defect. There is a place for this technique in the removal of interatrial tumours, for the repair of mitral incompetence, and for the relief of mitral stenosis where previous attempts have failed. Ventricular septal defects are not commonly dealt with under hypothermia, for the time available for circulatory occlusion is not really adequate, although with differential hypothermia and coronary perfusion successful repair has been reported (Bahnson[23]).

(*b*) *Pulmonary and Aortic Stenosis.* The approach is retrograde through the opened aorta or pulmonary artery during circulatory arrest.

Swan,[33] who has had extensive personal experience of hypothermic operations, quotes 52 cases of the open relief of pulmonary stenosis without a death. By 1956 he had reported the use of hypothermia in 130 congenital cardiac cases.

In Johannesburg this approach has been used in 4 cases each of congenital aortic stenosis and pulmonary valvular stenosis and in 2 cases of common truncus arteriosus.

(*c*) *Other Operations.* Hypothermia is ideally suited to the repair of aneurysms of the aortic arch or innominate artery where cessation of circulation to the brain may be necessary.

2. *Operations not requiring Cardiac Arrest*

Thornton,[2] working in Professor Rob's clinic, has described 71 cases without death. Mostly these were the placement of aortic grafts in the descending aorta close to the renal vessels.

We have performed shunt operations (Blalock's and Pott's) in 4 severe cyanotic children, 2 for a Fallot's tetralogy and 2 for congenital tricuspid stenosis. We have also used hypothermia for the ligation of patent ductus in 2 children with pulmonary hypertension.

Uglov[34] has used hypothermia in a variety of other intrathoracic procedures, including pulmonary resection.

COMPLICATIONS OF HYPOTHERMIA

1. *Ventricular Fibrillation* (VF)

This complication is common in hypothermia below 28°C. It is produced in the main by the lowered temperatures, rough cardiac manipulation and coronary air embolus.

Shumway[25] reported it in one-third of his clinical cases, but found defibrillation successful in all but one case. Swan[17] reported VF in 100% of dogs not protected by prostigmine or acetylcholine in which right ventriculotomy was done, all cooled to 25°C. He recommended coronary perfusion with Sigmamotor pump at a coronary pressure of about 70 mm. Hg to prevent air embolism. He pointed out the danger of using citrate, which is toxic to the hypothermic myocardium. Cookson[35] reported that with hyperventilation at 20-25°C VF resulted in only 8% of cases. During cooling and hyperventilation, serum-potassium levels fell. He found defibrillation easier if potassium chloride was injected into the coronary circulation (air embolus is unlikely to occur if the heart is arrested). Reberi[18] and Young[15] expressed a contrary opinion. Delorme[6] thought VF was due to lowered potassium in the cells possibly due to sodium entering the cell or potassium leaving.

Battezzati[21] used extracorporeal circulation to lessen the VF of 26 dogs, of which 22 survived right ventriculotomy plus right and left auriculotomy for 13 to 56 minutes (venous cooling). He advocated the use of a pulsating flow.

Khalil[36] used internal cooling (gastric bag) and in 20 rabbits cooled to 20°C had no VF. The process took 2½ hours. He safely cooled one hyperpyrexial child to 23-24°C.

Brock[1] gave no preliminary intravenous procaine injection, and suggested rapid cooling and re-warming (venous cooling) to prevent VF. He also[37] recommended maintaining adequate coronary flow by (*a*) simple veno-arterial pump circuit, (*b*) clamping the aorta beyond the left subclavian, and (*c*) the heart-lung machine. To manage a VF he considers it is necessary first, if possible, to repair the defect and then restore myocardial tone by injecting 5-10 c.c. of 1/10,000 adrenaline in normal saline, or the same quantity of 1% calcium chloride, into the left ventricle; also to cross-clamp the aorta. A noradrenalin drip increases perfusion pressure and slows the heart. Factors increasing the heart rate

* We have had a Gross-type disc oxygenator in use since August 1958 and anticipate that this aid will be used in operations on most of the conditions listed under this heading.

must be avoided, such as unnecessary trauma, heat from the operating lamp and warm instruments; prostigmine may be used to slow the heart.

Thornton[2] re-warmed slowly, no faster than 1-1·5°C an hour. He is emphatic that one should release inflow clamps slowly to avoid VF (endogenous epinephrine stored up in the inferior vena cava acts on the sensitized myocardium (Covino[38]).

Glen[5] cooled dogs with the aid of an arteriovenous extracorporeal circuit. VF only occurred below 23°C.

Ross[22] has given up chemicals like prostigmine and advocates slow release of the vena cava after arrest. He has experienced no difficulty in defibrillating the hypothermic heart provided massage produced adequate tone. Venous pooling occurs and his aim is to under-transfuse and keep respiratory acidosis at a minimum.

Covino[38] advocated using ambonestyl intravenously or by mouth and artificial ventilation. To show this he performed

TABLE II. VENTRICULAR FIBRILLATION AFTER COOLING

Cooling without artificial ventilation	80% VF
Cooling with artificial ventilation	40% VF
Cooling with ambonestyl I.V. 40 mg./kg.	30% VF
Cooling with ambonestyl and artificial ventilation ..	0% VF

controlled experiments at 25°C (Table II). It was his opinion that the circulation could be stopped for 15 minutes at 20°C.

Radigan[39] infiltrated the superior atrio-caval junction (S.A. node) with procaine. Without this 18 out of 20 dogs developed VF. With procaine there was no VF. He suggested that there is a neural causal component. He has used this method in 11 patients without VF. We have used it in all but one of the cases where circulatory arrest was applied. Reberi[18] also used this method (1% procaine), and reported that the P wave disappeared or decreased, the pulse rate slowed, and the blood pressure fell moderately, these changes lasting 12-27 minutes at 25-28°C. All 12 controls fibrillated and the 11 treated did not. At lower temperatures only 1 of 16 treated animals fibrillated. Reberi listed the following procedures in dealing with established ventricular fibrillation. (1) If the myocardium is weak during fibrillation give intracardiac epinephrine (a few c.c. of 1 in 20,000). (2) Give the procaine injection both before and after. (3) Block the sympathetic supply to the heart either with arfonad or by stellate-ganglion block (upper 3 thoracic). (4) If the fibrillation is due to coronary air embolus, massage the heart to express the air from the vessels. (5) Defibrillate with high voltages (greater than 110 volts).

Kyle[40] in comparing the effectiveness of calcium chloride and electric shock in defibrillating hearts of hypothermic dogs stated: (1) Serial electric shocks after 4 minutes of fibrillation produced 100% defibrillation with effective heart beat in 100% of cases. (2) Calcium chloride after 4 minutes of fibrillation produced 100% defibrillation but only 57% effective beat. (3) Calcium chloride after 1½ to 2 minutes produced 100% defibrillation but only 87% effective beat.

Cookson[41] gave ACTH beforehand, injected procaine into the pericardium after unclamping the venae cavae, and injected benedaine (adrenolyte), 0·8 mg. per kg., into the right ventricle. VF has been much lessened since using this method. He cooled to 26°C in 2½-3½ hours.

Bigelow[42] tried an electrical pacemaker to control the heart beat. The prospects of such an apparatus are good.

Many experimenters have warned against the danger of transfusing cold blood. This, if given rapidly, sometimes causes a serious drop in the temperature of the heart. For this reason, and because there is a tendency for blood to pool on the venous side of the circulation, intra-arterial transfusions are often given.

Lewis[8] injected butocaine into the pericardium (4-8 c.c. of 10%) and passed tapes around both lung roots to occlude the pulmonary veins; he used procaine hydrochloride before and during cooling and VF did not occur.

2. *Tissue Anoxia*

There are conflicting reports on whether cooling alone will produce tissue anoxia. Probably artificial respiration will prevent the development of tissue necrosis.

Sarajas[43] found myocardial necrosis in animals cooled from 27·5°C to 20°C and kept thus for 1-4 hours. Glen[5] interrupted the cerebral circulation for 30 minutes in animals at 25°C, and all recovered normally.

Virtue[17] found that at 28°C 50% of cases showed auricular fibrillation of ECG. A disturbing feature was the high take-off of the S.T. segment half way down the R.S. segment indicating myocardial damage or hypoxia. This frequently preceded VF.

Ross[22] considered the main hazard in 70 patients with circulatory arrest for 5-10 minutes to be cerebral anoxia. There were 5 recoveries out of 8 in whom cerebral circulation was absent or poor for more than 10-12 minutes. He stated that increased notching or slurring of the QRS complex often preceded VF.

Cahn[44] stated that at 30°C the ECG showed curves similar to those of hypometabolism. He thought that prolonged anoxia resulted in myocardial failure but that cardiac resuscitation could be obtained with an injection of adenosine triphosphate plus cytochrome.

Edwards[45] showed that the oxygen consumption of the hypothermic heart muscles was reduced but there was no discrepancy between myocardial oxygen supply and demand. He did not think hypoxia was a factor in the production of VF. Bailey[24] clamped off the circulation in dogs for 40 minutes at 16°C without detectable brain damage. Delorme[6] found no renal changes (functional or anatomical) after clamping the kidney pedicle for 4 hours at 25°C; similarly with the liver. There were no nerve-cell changes after cerebral ischaemia for 1 hour at 25°C. Huguenard[9] found no histological lesion in hibernation, except at temperatures below 27°C.

The general conclusion from the available data is that within the temperature ranges used for hypothermia operations tissue damage is not likely to result from the lowered temperature alone.

Other Complications

3. *Air Embolism.* The greatest danger of air embolism is to the coronary circulation. If it occurs, manual systole must be used with the aorta clamped to propel the air bubbles out of the vessel. Because of the danger of coronary air embolus, some do not advocate open left cardiotomy. The danger could be diminished by cross-clamping the aorta at the level of the coronary arteries. When operating on septal defects one must be careful not to suck the blood out of the left side, and it is important to fill the chambers with saline before finally closing the heart. Cerebral air embolism has not been found troublesome. A veno-arterial shunt to maintain sufficient pressure to keep the aortic valves closed also helps. The use of asystole has eliminated the possibility of air being propelled along the coronary arteries while the heart is open.

4. *Acidosis.* Scurr[46] has drawn attention to the synergism between carbon dioxide and the neuromuscular blocking agents. He therefore warned against respiratory acidosis. It is thought that ventricular fibrillation is more likely to occur if acidosis has developed.

5. *Bleeding.* Swan[33] stated that the major cause of death in 105 cases was disturbance of the clotting mechanism. Shumway[25] could find very little cause experimentally for the post-operative bleeding (the clotting times, prothrombin index, plasma, haemoglobin and platelets were normal). Haemorrhage may be due to liver anoxia and citrate poisoning with severe calcium depletion. Osler Abbot[47] suggested that the calcium should be removed from the blood by a resin membrane so as to prevent its clotting, and thus obviate the need to use citrate or heparin.

6. *Pneumonia* has been reported in a number of patients who have been subjected to hypothermia.

7. *Curare Retention.* Thornton[2] has given a warning about the tendency to recurrence of neuromuscular block which previously has been reversed by neostigmine. Perhaps curare may persist in some depot during hypothermia, or if renal circulation has been interrupted there might perhaps be delay of curare excretion. However, Bigelow[48] attributed this effect to CO_2 build-up.

8. *Temperature Regulation Defect.* In certain cerebral conditions where there is a disturbance of the heat regulating centre, the 'after drop' in temperature may be excessive and difficult to overcome.

9. *Local Fat Necrosis.* Delorme[6] reported fat necrosis as having occurred after surface cooling in infants.

10. *Burning during Re-warming.* This has occurred with the use of diathermy coils.

OPTIMUM TEMPERATURES

On this point there is no unanimity of opinion, although most workers consider it inadvisable to reduce the internal temperature below 28°C.

Cookson[41] cooled to 26°C and Ciocatto[49] to 29°-28° for bloodless

open heart surgery. Swan[50] recommended reducing the temperature to 26°C, recorded by rectal thermocouple, for closure of atrial septal defect. By stopping the cooling process at 34°C and allowing the patient's temperature to drift to 30-31°C, and using extra-corporeal blood oxygenation, he[17] has maintained safe cardiac asystole for 17 minutes in man. He therefore contended that with hypothermia of 30°-32°C the safe period of standstill with ischaemia is between 15 and 30 minutes. (He has had no difficulty with post-operative bleeding.)

Gollam,[20] using pump oxygenation, had dogs survive cardiac arrest for 1 hour at a differential hypothermia at 0°C; at 15°C 2 dogs died after 15 minutes' inflow occlusion and 2 were not quite normal after 12 minutes occlusion. However, Shumway[25] found no neurological defects in any dog after circulatory occlusion for 20 minutes at 25°C, but he did find neurological defects in 2 out of 6 dogs occluded for 30 minutes. Lewis[8] operated upon 11 cases of atrial septal defect at 29°C. Holmes Sellors[51, 29] has performed the closure of atrial septal defect on 40 cases with one death; he cooled the patients to 29-30°C. Bailey[24] considered that the optimum temperature in severely cyanotic infants was 23·3-26·1°C and for surgery to the great vessels involving interruption of circulation to vital centres for prolonged periods 21·1-24·4°C; but that in adults the temperature should not be reduced below 26·1°C. Kaplan[4] reported 22 patients between the ages of 18 days and 4 years in whom the rectal temperature was reduced to 24°C.

We have tried to keep the oesophageal temperature above 29°C but in several it has fallen below this and in 2 patients reached 28·1°C without any ill effect.

HISTORICAL

In 1875 Reincke[52] wrote an article on 'Observations on accidental hypothermia in man'. In 1938 Temple Fay[53] described attempts to control malignant disease by hypothermia produced by surface cooling. This stimulated other workers and investigations into the effects of climatic cold followed.

As an aid to cardiac surgery hypothermia is directly the result of the experimental work done by Bigelow[42] of Toronto, in 1950. This was put to the clinical test by Cookson and Bailey (1952)[41] Lewis and Taufic[54] (1953), Swan and Zeavin[50] (1954), Bailey and Cookson[24] (1954). Bigelow[55] and Boerema[12] are credited with the conception of hypothermia to allow cessation of the circulation.

Lewis and Varco,[54] 1952, were the first people to close an atrial septal defect under hypothermia and direct vision. Cooling by the extracorporeal (arterio-venous) circuit was originated by Delorme[6] and Boerema[12] in 1951. Venous cooling was originated by Ross in 1954.

Hypothermia in South Africa

Many of the cardiovascular procedures that have been undertaken in this country under hypothermia would be more adequately performed with the use of an artificial oxygenator (heart-lung machine).

To date I have had experience with 24 clinical cases operated upon under hypothermia. These have included 2 cases of open right cardiotomy, where the right ventricle has been opened and an infundibular obstruction resected under direct vision, 2 cases of an atrial septal defect, and 4 cases each of pulmonary valvular stenosis and congenital aortic stenosis with retrograde approach to the valves *via* an incision in the respective arteries. All these 12 cases necessitated complete circulatory occlusion for 5-7 minutes. The remainder of the operations have been on the great vessels outside the heart, in only 2 of which was circulatory arrest needed.

The use of hypothermia is simple and safer than the artificial oxygenator and for some years yet it is likely to be employed in a variety of conditions. Against this is the disadvantage of limited time in which to work and the inability therefore to repair the more complicated intracardiac defects.

A review of the individual cases will be presented in the future. In the meantime we and the anaesthetists concerned have been fully convinced of the safety of the procedure as at present practised here.

This paper would not be complete without paying tribute to those anaesthetists who have so courageously undertaken this pioneering work in Johannesburg. I head the list with the name of Dr. F. W. Roberts, who administered the anaesthetic to the first group of patients, and add those of Drs. C. H. van Hasselt, K. B. Meaker, J. R. Duffield, H. Ginsberg, C. Frost and D. Jeffes. Also I must thank the theatre staff at the Children's Hospital, Johannesburg, who willingly coped with many teething difficulties presented by hypothermia, and Sister Tickner in particular. Dr. C. H. Wyndham and his team from the Chamber of Mines Research Laboratories devoted much time to galvanometric temperature recordings in our first four cases, and without their help this work may well have not commenced. I thank Dr. L. Braudo for his constant encouragement and help.

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