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PROFOUND HYPOTHERMIA USING EXTRACORPOREAL CIRCULATION WITHOUT AN ARTIFICIAL OXYGENATOR

AN EXPERIMENTAL STUDY

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Since the time of Aristotle in the fourth century B.C. man has realized the importance of body temperature and has observed the response of animals to the changes in temperature of their environment.[1] Many observers were intrigued by the phenomenon of hibernation, where certain warm-blooded animals are able to reduce their body temperatures during winter and withdraw into a state of sleep.[2] In this condition all vital physiological processes are at a minimum and the animals can thus survive the privations of winter. Experimental work which followed showed that artificial hibernation could be induced in non-hibernating animals by body cooling, with little ill effect if the natural reactions of the body to cold are prevented by drugs.[3]

The potential value of this method of reducing body metabolism was recognized by pioneers in cardiac surgery (Bigelow,[4,5] Boerema,[6] Gollan,[7] and others [8,9]). It was shown that at temperatures of 29 - 30°C. the circulation through the heart could be interrupted for 8 - 10 minutes without damaging oxygen-sensitive organs such as the brain and kidneys. Lewis and Taufic[10] were the first to take advantage of these experimental observations, and in 1952 they performed the first successful operation on the heart under direct vision utilizing hypothermia and venous inflow stasis. Variants of this procedure, mainly using body-surface cooling, have been successfully employed in many hundreds of cardiac operations at temperatures that are not hazardous to the patient.

Hypothermia allowed the maximum period of 8 - 10 minutes inside the heart, and the more complex cardiac defects remained beyond the reach of the surgeon. Meanwhile, a number of investigators had been working on the development of a mechanical substitute for the heart and lungs to allow more time for the surgeon to correct defects such as ventricular septal defects and tetralogy of Fallot malformations. This eventually led to the development of the heart-lung machine, which makes it possible to bypass the heart and lungs for some hours.[11-14] Investigators were quick to combine the two methods, viz. the heart-lung machine and hypothermia, both for moderate[7-9,15-22] and later for profound degrees of hypothermia.[23-32]

Oxygenation of venous blood outside the body has dangers and difficulties, and the possibility of autogenous oxygenation (the use of the patient's own lungs for oxygenation), which dispenses with the artificial oxygenator, was studied by workers such as Wesolowski and Welch,[33] Cohen and Lillehei,[34,35] Mustard,[36] and Cooley *et al.*[37] These studies were carried out at normal temperatures and were not received with much enthusiasm.

In 1959 two separate groups of workers, Shields and Lewis[38] and Drew *et al.*,[39] published their experimental results of combining profound hypothermia *via* an extracorporeal circulation with autogenous oxygenation. This technique appeared to offer a number of distinct advantages, and Shields and Lewis state[38] that it is close to their ideal of obtaining a short period of cooling, a long bloodless period, rapid rewarming, an uncomplicated mechanical system, a low priming blood volume, and no oxygenator. To this may be added the advantage, where the more complicated cardiac defects are concerned, of the almost postmortem conditions for diagnosis, planning, and execution of cardiac-repair procedures.

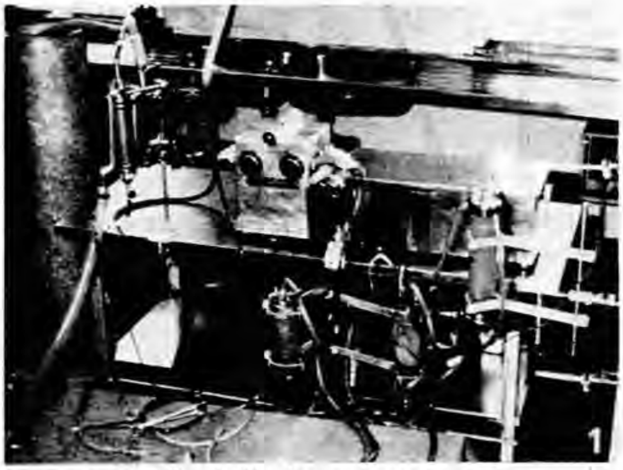

Fig. 1. The bypass apparatus.

We set out to investigate experimentally the possibilities of a procedure of this nature, along the lines described by Drew *et al.*,[39] with a view to its use in cardiac and aortic surgery.

METHOD AND APPARATUS

1. *Circuit (Figs. 1 and 2)*

(*a*) *Right bypass.* The venous blood is drained from the right auricle into a plastic well, by gravity. From here it is pumped by one head of a sigmamotor pump back to the patient's own lungs *via* his main pulmonary artery.

(*b*) *Left bypass.* The oxygenated blood returning from the lungs is drained from the left atrium into a second well and pumped by the second head of the sigmamotor pump through a heat exchanger back into the arterial system, through a catheter inserted into the right common femoral artery.

The left and right ventricles are thus bypassed, and the body can be perfused with oxygenated blood and cooled

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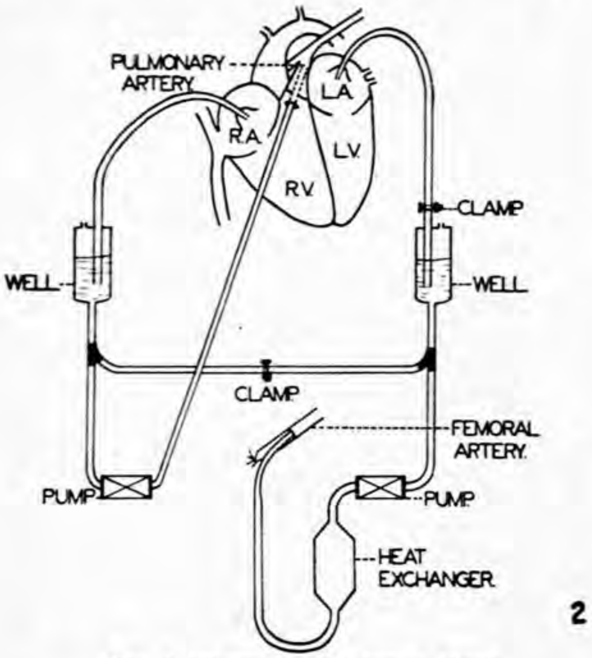

Fig. 2. Diagram of the bypass circuit.

or warmed after the ventricles fail as a result of the hypothermia.

2. *Apparatus and Preliminary Preparations*

The equipment, such as the sigmamotor pump, plastic tubing, metal connectors, catheters, etc., and preliminary preparation of these, are similar to those described for the bubble oxygenator system.[40,41,11]

The Bennington heat-exchange unit* is now employed (Fig. 3). This heat exchanger works on the principle that the blood entering it is spread in a thin film over the highly polished inner component, and so comes into contact with the similarly polished inner wall of the jacket carrying the heat-exchange fluid. Water from a tank containing melting ice is at present used for cooling, and water between 40 and 45°C. for rewarming. The water is pumped through the jacket at a rate of 12 gallons per minute. This heat exchanger has the advantage of having a low priming volume; it is efficient and we have used it with great success both in experimental and clinical work.[42] Various temperatures were recorded during the experiments using the Electric Universal thermometer,** Type TE3, with leads Types R-7, K-8 and OSG-1.

3. *Operative Procedure*

On the morning of surgery the apparatus is assembled,[40] first primed with warm saline to dispel the air, and then with freshly-drawn heparinized donor-blood.[43] In priming the 2 circuits, a connection between the 2 wells is used, but this is clamped off during the actual bypass (Fig. 2).

Adult mongrel dogs (in our cases weighing between 11 and 19 kg. each) are used for the experimental work. For induction of anaesthesia thiopentone sodium is used and, after intubation, anaesthesia is maintained with nitrous oxide and oxygen.

During the experiment the venous and arterial pressures are recorded by means of cannulae placed in the left femoral vein and artery and connected to a 2-channel Sanborn apparatus. The electrocardiogram is also recorded.

A thoracotomy through the fourth left interspace is performed, paying particular attention to haemostasis. The heart is exposed by widely opening the pericardium (Fig. 4A). The right common femoral artery is next exposed and encircled with a cotton tape. The dog is heparinized, using 1·5 mg. of heparin per kg. of bodyweight, and the largest possible metal catheter is inserted in a retrograde fashion for about 2 inches and secured in position. This catheter is connected to the left circuit in such a way as not to introduce any air into the line. A no. 32 Bardic catheter is inserted through the left auricular appendage into the cavity of the left atrium and secured in position. A purse-string suture of 0 silk is placed around the base of the auricular appendage. This catheter is connected by means of a piece of Mayon tubing to the well in the left circuit, flow in the circuit being prevented by clamping the line. The right atrium is cannulated in a similar manner through the right auricular appendage, and connected to the well in the right circuit (Fig. 4B). The clamp on the left circuit is now removed and left partial bypass commenced with cooling. Due to cooling of the myocardium, the heart soon slows. Before it fails the right circuit is completed by cannulating the pulmonary artery with a no. 22 Bardic catheter through a purse-string suture in the infundibulum of the right ventricle, and securing it in position (Fig. 4C). This catheter is connected to the right circuit and right bypass commenced, the pulmonary valves preventing blood leaking back into the right ventricle.

The lungs are continuously ventilated, and bilateral bypass with cooling is continued until the oesophageal temperature is in the vicinity of 9 - 15°C. Both sigmamotor pumps are then stopped, so that there is no circulation through the animal, and ventilation of the lungs is also suspended. The catheters can be removed at this stage, if desired, to facilitate operative procedures (Fig. 4D).

In order to evaluate the dangers of complete circulatory arrest at low temperatures, the animals are left in this

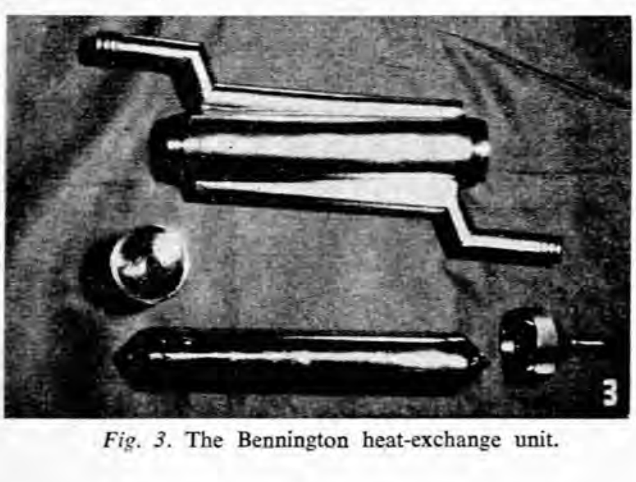

Fig. 3. The Bennington heat-exchange unit.

* Kindly lent by Messrs. Westdene Products (Pty.) Ltd., from whom it is commercially available.

** Manufactured by Messrs. Elektrolaboratoriet, Copenhagen.

state for periods varying from 2 to 60 minutes before their circulations are recommenced by warming.

To rewarm the dog the pumps are switched on again and ventilation of the lungs restarted. Warm water is now pumped through the jacket of the heat exchanger. When the mid-oesophageal temperature reaches 35°C., sodium bicarbonate is added to the system to counteract any metabolic acidosis, and the heart is defibrillated with electric shocks. When the heart beat seems satisfactory, the right bypass is discontinued, the catheters are removed from the right atrium and pulmonary artery, and the previously placed purse-string sutures are tied. The left bypass is next discontinued and the catheter in the left atrium is similarly removed. Protamine sulphate is administered and any blood deficit is replaced by way of the arterial catheter using the systemic blood-pressure and operative blood-loss measurements as monitors. The arterial catheter in the right femoral artery and the cannula in the left femoral artery are removed, and the arteriotomies are repaired with 6-0 silk. The venous cannula is left in the vein for the administration of blood and intravenous fluids in the postoperative period. After careful haemostasis a drain is placed in the left chest and attached to a suction apparatus, and finally the thoracotomy is closed in layers.

The dog is returned to a warmed recovery cage and initial blood loss is replaced as required. The chest drain is removed the same evening or the following morning. A small amount of sodium bicarbonate is added to the intravenous drip for the night and in some dogs antibiotics are given for a few days after surgery. Postoperative plasma-haemoglobin studies are performed as a routine and are measured by the method described by Crosby.[44]

RESULTS

The results of the first 13 consecutive experiments performed in our laboratory, making use of autogenous oxygenation and the Bennington heat exchanger, are summarized in Table I. They confirm the conclusions of other workers in this field: that this technique is safe and may have certain advantages over total cardiopulmonary bypass with an artificial oxygenator.[38,39]

Both cooling and rewarming were rapid. The myocardium and brain invariably cooled more quickly than the skeletal muscles and there was a close correlation between the temperatures of the former and those of the low mid-oesophagus, but not with the rectal temperature (Fig. 5). Close correlation was also shown between brain temperature, that recorded in the low mid-oesophagus, and

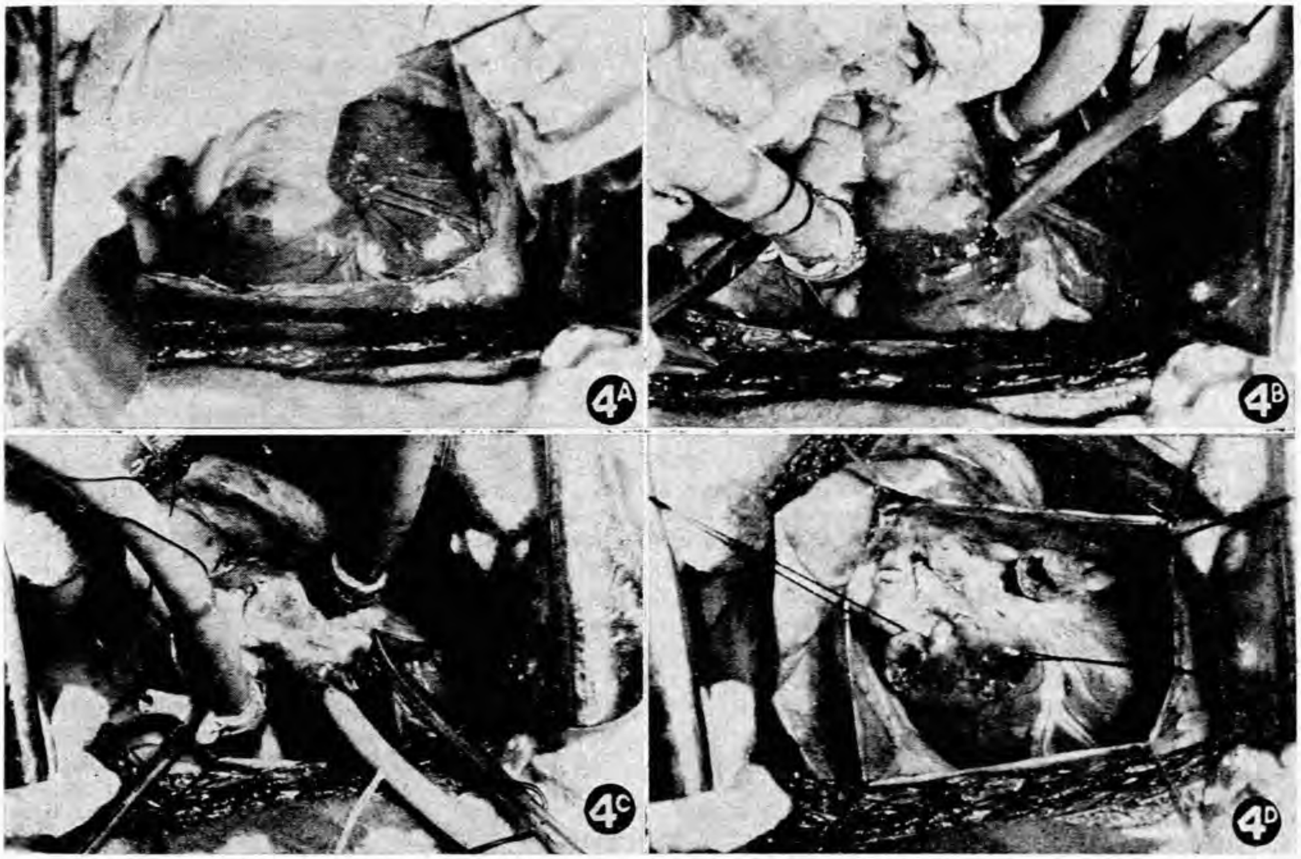

Fig. 4. The heart shown at various stages: (A) the exposed heart — note that both auricular appendages are visible. (B) The atrial catheters fixed in position. (C) All catheters, including pulmonary artery, inserted and secured. (D) Catheters removed to facilitate operative procedure.

TABLE I. RESULTS OF THE FIRST 13 CONSECUTIVE EXPERIMENTS

Dog No.	*Weight*	*Flow rate in c.c./min.*	*Method*	*Period of no circulation in mins.*	*Lowest temp. °C*	*Plasma Hb. mg. per 100 ml.*	*Antibiotics*	*Behaviour of cold heart in period of no circ.*	*Survived 24 hours*
1	14 kg.	980	A	2	11·4 - V	37	—	Arrest	Yes
2	19 kg.	1,330	A	4	14·2 - O 11·8 - V	30	—	Slow sinus rhythm	Yes
3	15 kg.	1,050	A	4	12·6 - O 13·0 - V	372	—	Arrest	Died 3½ hours due to haem.
4	18 kg.	1,260	A	4	12·6 - O 13·2 - V	57	Chloromycetin after 1 day	Slow fibrillation	Yes
5	15 kg.	1,050	A	5	11·3 - O 12·9 - V	32	Chloromycetin	Arrest	Died 24 hours, spastic
6	14 kg.	980	B	5½	9·4 - O 9·4 - V	61	Chloromycetin	Arrest	Yes
7	16 kg.	1,120	B	6	15·0 - O 10·4 - V	—	Chloromycetin	Arrest	Yes
8	14 kg.	980	B	22	12·6 - O 13·0 - V	44	Chloromycetin	Arrest	Yes
9	14 kg.	980	C	30	10·8 - O	42	Penicillin and streptomycin	Arrest	Yes
10	17 kg.	1,190	C	49	13·4 - O	74	Penicillin and streptomycin	Slow beat then fibrillating	Yes
11	11 kg.	770	C	60	9·6 - O	44	Penicillin and streptomycin	Arrest	Yes
12	16 kg.	1,120	D	35	9·7 - O 9·7 - Br	121	—	Arrest	Sacrificed postop.
13	15 kg.	1,050	E	34	8·9 - O	98	—	Arrest	Died 12 hours due to haem.

A–E = Minor variations in technique which are beyond the scope of this article.
V = Lowest ventricular temperature in °C.
O = Lowest oesophageal temperature in °C.
Br = Lowest brain temperature in °C.

blood temperature (Fig. 6). During the period of complete circulatory arrest, the rectal and muscle temperatures often continue to drop (e.g. the after drop of surface cooling) while the heart and oesophageal temperatures rise, equilibration taking place to some extent. (Note that in experiment no. 12, Fig. 6, this did not occur.)

During cooling there was an initial slowing of the heart rate, but ventricular fibrillation usually ensued as the oesophageal temperature passed the twenties. At the lower temperatures fibrillation was sluggish but continued until circulation was stopped when, as a rule, myocardial activity ceased.

On rewarming, events occurred in the reverse order. Soon after commencement of rewarming, myocardial activity returned in the form of slow fibrillation, which became more vigorous as the myocardial temperature rose. In our clinical cases and other experimental work using the bubble oxygenator, spontaneous rhythm often started at about 36°C.; in this experimental work, on the other hand, electrical defibrillation was always required, but only 1 or 2 shocks were necessary.

Postoperative plasma-haemoglobin tests indicated that trauma to blood is slight, provided there is no undue resistance in the arterial line or excessive heating of the blood in the heat exchanger,[42] as in our experiments nos. 3 and 12.

From Table I it can be seen that in the 12 survival experiments 9 dogs were alive and well 24 hours after completion of the bypass procedure. Two of the remaining 3 died of postoperative haemorrhage, but this cannot be attributed to the bypass technique used (dogs 3 and 13). The third death may have been due to faulty technique during bypass, such as air embolism. It is of great interest to note that dog no. 11 had complete circulatory arrest for 60 minutes and is doing well months after the experiment. Of the survivors, dogs nos. 1, 2 and 4 died during the first week. They were found to have marked sepsis. Once antibiotic therapy had been instituted, and was commenced as soon as the operation was completed deaths from infection were avoided. The reason for infection was probably due to the fact that asepsis and antisepsis are not practised as rigidly in the laboratory as they are in our patients, in whom infection is very rare.

DISCUSSION

Blood-stream cooling induced by any method, when associated with an efficient heat exchanger, has a number of advantages over either hypothermia or bypass alone.[15,21,23,27,38,39,45,46] With this technique, cooling and rewarming is rapid and control over temperature is possible. The dangers of cardiac arrythmias during cooling, the great fear of earlier days, do not exist, since the body can be adequately perfused after effective heart beat has stopped.[15] The vast literature which is accumulating on this subject at present contains discussions of other advantages, both practical and theoretical.[4-9,15-32,45-50]

Autogenous oxygenation dispenses with the use of an artificial oxygenator and its drawbacks and allows a less complicated and less expensive bypass to be used, with a much smaller priming blood volume.

Hypothermia with extracorporeal circulation and some form of oxygenation, whether it be autogenous or artificial, allows for much lower levels of cooling. There is doubt, however, whether anything is gained by continuing cooling below 15°C. Bigelow,[51] in his early work, showed that there is a steady decrease in oxygen consumption as the body cools down to approximately 20°C. It was wrongly concluded that this drop would continue at the same rate as the temperature is lowered further. Sealy *et al.*[25] have shown that between 20 and 10°C. there is little drop in oxygen consumption. It would thus appear that cooling to temperatures between 15 and 20°C. is adequate[25], since oxygen consumption and, by inference, tissue metabolism, is sufficiently reduced at these temperatures (about 75% of normal). Other factors may, however, come to light later to suggest that the lower temperatures are in fact better.

It has been suggested that profound cooling is not feasible, because oxygen dissociation of haemoglobin diminishes with cooling. This disturbance, however, is more than compensated for by the increase of direct solubility of oxygen in cooled serum.[28,45]

The different rates of cooling of various organs[21,23,27,30,39] is clearly shown in Figs. 5 and 6. This differential hypothermia also occurs, though somewhat differently, in surface cooling.[52] There is a close correlation between brain, oesophageal, and blood temperatures (Fig. 6).[25,26,38,42] This observation is further confirmed by the finding that EEG activity disappears at temperatures between 16 and 20°C., both in man and in animals.[25]

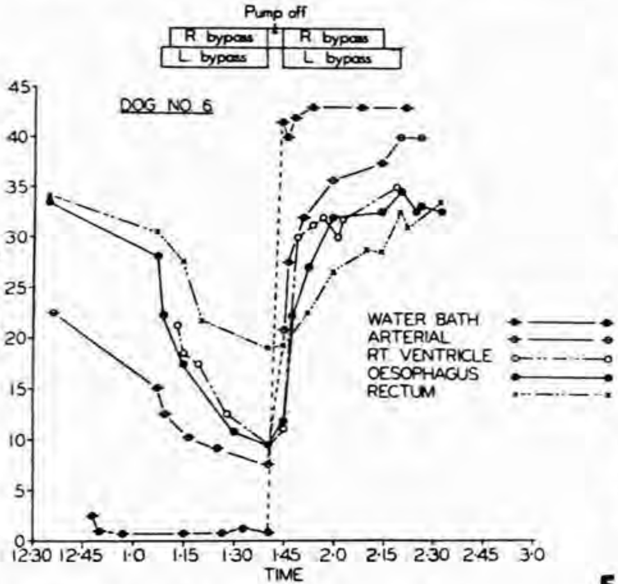

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Fig. 5. Graph of the temperatures recorded in experiment no. 6.

It is important to recognize the fallacy of using temperatures such as rectal, muscle, or oral as a guide to vital organ temperatures. The low mid-oesophageal temperature has been shown to be most easily recordable and the most accurate guide to the temperatures of vital organs.[42,52]

It is fortunate that with blood-stream hypothermia those organs with the richest blood supply, and hence the greatest metabolic activity, cool the quickest. At the end of cooling, when circulation is discontinued, a certain degree of equilibration of temperature takes place, and during this period one must expect a rise in the temperature of the vital organs.

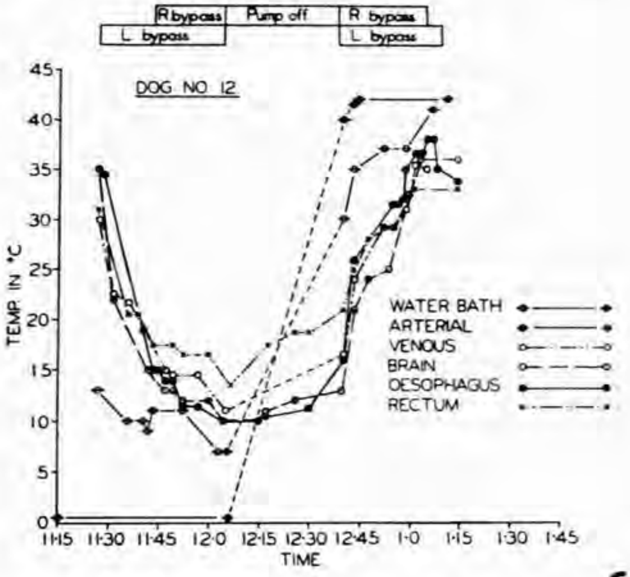

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Fig. 6. Graph of the temperatures recorded in experiment no. 12, including the brain temperature.

Although we place the heat exchanger in the arterial line without a bubble trap, oxygen bubbles have not troubled us. It is stated by Sealy *et al.*[25] that oxygen embolism has never occurred in their clinical studies nor in their laboratory experiments.[26,53]

Reports on the behaviour of the myocardium of dogs during cooling differ. Shields and Lewis state that arrest occurs between 18 and 13°C.[38] Heimbecker *et al.*[27] found fibrillation between 20 and 16°C. and arrest at from 12 to 10°C.[27] In our series ventricular fibrillation always continued until circulation through the coronary vessels was stopped. On rewarming, there was not a single case in this series in which the heart reverted spontaneously to sinus rhythm, but shock defibrillation was invariably successful.

Blood destruction, as judged by plasma-haemoglobin estimations, was usually well below the usual figure of 1 mg. per minute of bypass, which we have noted when using the bubble oxygenator.[42] This diminution in blood destruction is probably due to the removal of the artificial oxygenator from the bypass circuit, and is a definite advantage of autogenous oxygenation.

In our animal experiments all except 1 dog were awake and alert with no obvious neurological changes a few hours after the bypass, indicating that when accurately carried out this procedure is not inherently dangerous.

A fairly high flow rate of 70 ml. per kg. of bodyweight per minute was used throughout all experiments to obtain uniformity. Obviously, at lower temperatures a much lower flow is quite adequate.[15,21,22,24-26] There is, however, a disadvantage in cutting the flow rate as the temperature drops — cooling becomes less efficient.[42]

Only a left thoracotomy was used in this series, because the opening of both sides of the chest, with or without cutting through the sternum, in itself gives rise to trouble. In addition, the left atrial and pulmonary arterial cannulations are best done from the left side, and the right auricular appendage can also be seen and cannulated from there (Fig. 4). We feel that our good results are in part attributable to the use of this approach.

CONCLUSIONS

This experimental work has shown that the technique described above is safe, and could therefore be applied to patients, both for cardiac[45,54-56] and for aortic surgery. It is of considerable advantage in correcting the more complicated cardiac defects to stop the circulation completely at the lower temperatures, and to remove any catheters in the way. Thus the diagnosis and the repair of the heart can be made in an almost 'postmortem' condition. There appears to be a definite place for this technique in thoracic aortic-aneurysm repair, especially those involving the ascending aorta and arch, and there may even be a place for this technique in extensive surgery on the liver and brain.

Whether this technique will ultimately replace bypass with artificial oxygenation is a matter that future experience will decide. It is important to know that autogenous oxygenation becomes difficult, even impossible, in patients with severe pulmonary stenosis and atresia of the pulmonary artery. We feel, however, that the future of cardiac surgery lies in a combination of bypass with hypothermia. Whether the technique described in this paper, that is, the use of autogenous oxygenation, or the employment of an artificial oxygenator is the best, remains to be seen.

SUMMARY

The events leading to the development of the technique of extracorporeal circulation without an artificial oxygenator, to produce profound hypothermia, are briefly discussed and the apparatus and operative procedure are dealt with in some detail.

The results of our first 13 consecutive experiments are enumerated, and the more important findings are discussed with reference to the literature. The advantages of bloodstream cooling are shown, as well as the marked reduction of body metabolism which occurs between 15 and 20°C. The differential rate of cooling in the various organs and the use of the low mid-oesophageal temperature as a guide to the temperatures of the vital organs are discussed. The minimal blood destruction which usually occurs during this procedure, as compared with the bubble oxygenator system, is felt to be due to the removal of an artificial oxygenator from the bypass circuit. Our good survival rate is felt to be partly due to the use of a unilateral thoracotomy.

Finally, the safety of this method and its applicability in cardiac, and certain aortic, hepatic, and neurosurgical procedures, are discussed.

We wish to express our appreciation to Prof. J. H. Louw of the Department of Surgery, University of Cape Town, for his encouragement. The work would have been impossible without the able assistance of the technical staff of the J. S. Marais Laboratory: Mr. C. C. Goosen, Mrs. V. M. Connell, and Mr. C. J. Lockett. We also wish to thank Mr. J. Rees for plasma-haemoglobin estimations and Mrs. E. P. Kottler and Mr. G. McManus for diagrams and for some of the photography. Finally, our acknowledgments are due to the Dr. C. L. Herman Research Fund, which financed this work.

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