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EXPERIMENTAL APPROACH TO VISUAL INTRACARDIAC SURGERY, USING AN EXTRACORPOREAL CIRCULATION

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The possibility of temporary by-pass of the heart to facilitate visual intracardiac surgery has stimulated world-wide interest and investigation during the past twenty years. To achieve this objective it is necessary to continue the functions of the lungs as well as the heart by mechanical means—removing blood as it returns to the right atrium and returning it to the aorta after passage through an oxygenator. Pioneers in this work (Björk, Gibbon, Jongbloed, Dennis, Melrose, Dodrill, Dogliotti, and Mustard) devised ingenious but complicated machines, designed to imitate basal cardio-pulmonary function. Despite the use of heparin and its subsequent antagonization by protamine, it was at first difficult to achieve adequate oxygenation of the large volumes of blood involved without haemolysis or alteration of the clotting mechanisms. An even greater obstacle was the difficulty of obtaining the expected venous return during cardio-pulmonary by-pass and the consequent inability to obtain normal blood flow and arterial pressure. This problem is still unsolved.

Andreasen (Andreasen and Watson, 1952, 1953a, 1953b), working at the Buckston Browne Farm of the Royal College of Surgeons of England, showed that, if the venae cavae in dogs were temporarily clamped for 30 minutes and venous return to the heart was reduced to that flowing through the vena azygos, survival could be expected. He postulated that during cardiac by-pass it might be possible to obtain satisfactory results with much lower flows than were hitherto thought to be necessary. He confirmed this by donor-circulation experiments in which one animal carried out cardio-pulmonary function on its own behalf and that of a recipient dog undergoing cardiac by-pass. Cohen and Lillehei (1954) later repeated this work, and Warden *et al.* (1954) showed that in dogs a flow rate of three times the vena azygos flow obtained by using donor animals in a cross-circulation study was sufficient to achieve a very high survival rate. As a result of this Lillehei was able to use a similar technique in cases of congenital heart disease in young children, one of the parents providing the donor circulation during cardiac by-pass.

Obvious difficulties arise from a surgical operation carried out on two people in order to benefit one of

them. The next logical step was to devise a pump-oxygenator simple enough to deal with relatively small blood flows. Using a finger-pump already in commercial use and a simple oxygenator in which bubbles of oxygen are passed through a moving column of blood, Lillehei was able to achieve comparable results in the experimental laboratory and in human cases. Although he (personal communication) achieved unqualified success in animal experiments before his apparatus was used in human cases, many groups have used this technique with less satisfactory results. So far little has been published concerning the difficulties encountered in the laboratory. This paper describes the methods we have used and the problems encountered in obtaining animal survivors.

At the beginning of 1956 there were only two types of heart-lung machine available which had proved successful by continued clinical use. The Gibbon (Gibbon *et al.*, 1954) apparatus, used most successfully by Kirklin at the Mayo Clinic, was the only one of its kind available, whereas the Lillehei-DeWall apparatus was easily copied and more simple to use. It was because of this that our own work was directed towards constructing such an apparatus and using it in the experimental laboratory.

Our objectives were twofold. First, to train a team who would later be using an identical apparatus in the treatment of intracardiac lesions in children, and, secondly, to achieve survivals in animals. Although it was known that such an apparatus was being used successfully in human cases it was felt that animal survivals were essential before the technique could be used with confidence in the human.

It was also desirable to obtain as much information as possible about physiological changes which occurred and to obtain experience in the use of apparatus designed to record them.

Apparatus

The apparatus (Fig. 1) has been well described by DeWall *et al.* (1956). Precise details of our version of this apparatus are as follows.

The "sigmamotor" pump is model T-6S with a rated output of 2,000 ml. a minute.

Blood from the venae cavae passes through one pump-head and upwards through a vertical column (48 by 1 in.; 122 by 2.5 cm.) through which oxygen is also bubbled via a single opening $\frac{1}{4}$ in. (6 mm.) internal diameter. The top of this oxygenator joins an inclined debubbler (18 by 2 in.; 46 by 5 cm.), which leads to a reservoir coil (120 by 1 in.; 300 by 2.5 cm.) and then to the arterial line via a filter of stainless-steel gauze. The coil is maintained at 38° C. in a thermostatically controlled water-bath. The coil serves a fourfold purpose: (1) It allows small bubbles to separate from the blood on its spiral descent. (2) It acts as a reservoir. (3) It allows the temperature of the blood to be maintained at approximately body temperature. (4) It acts as a level indicator. During perfusion the pumps are adjusted as required to ensure a constant blood level in the coil. The inflow/outflow balance to the patient is thereby maintained.

The column, debubbler, coil, and arterial and venous lines ($\frac{1}{4}$ in. (6 mm.) internal diameter) are of clear P.V.C. tubing with polished "perspex" connectors. Short tubes passing

FIG. 1.—The apparatus.

through the pump-heads are of translucent rubber ($\frac{1}{4}$ in. (1.3 cm.) internal diameter and $\frac{1}{2}$ in. (1.9 cm.) outside diameter), which gives more satisfactory results than plastic materials in this situation.

The debubbler, pump tubes, and filter are siliconed with an ethereal solution of M 430 (I.C.I.) and allowed to dry before sterilization.

The P.V.C. components are sterilized by autoclaving at a pressure of 5 lb./sq. in. (0.5 kg./sq. cm.) for 30 minutes. The lid of the container is then propped open and the contents are subjected to dry heat for a further 45 minutes. This prevents or reverses opacification due to absorption of water.

The behaviour of the apparatus was investigated before its use in any animal experiments. It was found that the pumps were sensitive to the inflow pressure but substantially independent of the outflow pressure up to 130 mm. Hg. Accordingly, the pumps were calibrated with various paired venous cannulae of different sizes connected to a suitable length of "venous line" tubing. Curves were drawn of the reading of the pump speed control dial against the flow in ml./min. Any required flow for given cannulae could be subsequently set on the pumps and checked at the time if required.

Operation of the Machine

The objects in operating the perfusion apparatus were: (1) To balance the arterial and venous pumps prior to perfusion. (2) To maintain a balance during the perfusion between blood volumes held in the animal and the apparatus. (3) To ensure that any adjustments in flow rate did not reduce the arterial flow below the minimal requirements. (4) To provide adequate oxygenation of the blood.

The dog was weighed before operation and a minimal requirement of 35 ml./kg. body weight/min. was assumed (Warden *et al.*, 1954). The perfusion rates usually ranged between 40 and 65 ml./kg./min., with extremes of 35 and 80 ml./kg./min., the higher flows being used for smaller animals. After circulation of normal saline through the apparatus, about 1,200 ml. of fresh blood (500 ml. containing 18 mg. of heparin in 20 ml. of 5% glucose) was used to prime it.

The end of the arterial line and the cannulae attached to the venous line were inserted into a 100-ml. polythene measuring cylinder. The arterial pump was set at the required rate and the venous pump was adjusted for constant level in the cylinder. During this stage the blood in the machine was oxygenated and the level of blood in the coil was noted.

During perfusion the blood level was maintained constant in the reservoir coil by adjusting the venous pump. Occasionally, if too great a perfusion rate was attempted, the venous pressure would fall and the cavae would tend to be sucked flat. It was then necessary to reduce the arterial flow to effect a balance, but never to less than 35 ml./kg./min. During these adjustments the positive or negative balance need not exceed 50 ml. of blood. The highest total flow rate used has been 900 ml./min.

Oxygenation was obtained by bubbling oxygen directly through a single opening into the bottom of the column and not through multiple tubes or holes. The oxygen/blood flow ratio was 15/1, which, although higher than reported elsewhere, assured oxygenation of 95% or more with acceptable haemolysis.

Coronary Sinus Flow Regulator

This apparatus was designed to allow blood from the open heart (this includes blood from coronary sinus, Thebesian veins, and bronchial circulation) to be returned

FIG. 2.—Coronary sinus flow regulator.

to the machine or to be discarded (Fig. 2). In the latter event an equivalent volume is returned to the venous line from a reservoir of fresh heparinized blood.

Blood is sucked out from the heart via a pump (P). In practice a second rubber tube is inserted through the venous

pump-head. The sinus blood passes to one side of the U-tube (T), and hence to the other side, which contains electrodes A, B, and C. These are connected to a cold cathode trigger device ("Iondex"), which causes the two magnetic valves, M1 and M2, to open when electrodes A and B are bridged by blood. The valves clip around latex rubber tubes, which are closed in the quiescent state. R is a reservoir of fresh blood connected via M2 to the venous line from the patient.

In operation, when blood reaches A the valves M1 and M2 open. Blood then flows from the U-tube until electrode B is uncovered, when the valves M1 and M2 close. The flow through M1 goes to a measuring cylinder, while the equal flow through M2 returns to the machine. Any residual inequalities can be adjusted manually as the volumes entering the cylinder and leaving the reservoir are known.

By the means described an overall balance may be achieved to within about 10 ml. of blood.

The Cannulae

It was felt that both arterial and venous cannulae should have the following characteristics. (1) They should be flexible enough to avoid damage to the vessel being cannulated, yet be rigid enough to avoid kinking or compression. (2) It should be possible to stiffen and shape the cannula to facilitate insertion. (3) The proximal end should have an adaptor to make connexion to the venous and arterial lines easy but certain. (4) The cannulae should be long enough to extend outside the chest but short enough for the connexion to be made by the surgeon. (5) Connexions between the cannulae and the arterial and venous lines should be made with minimal internal ridging to ensure a smooth flow. (6) A range of sizes should be available. The largest possible arterial cannula should be used, while the venous cannulae should be large enough to carry the expected venous return without obstructing the veins before starting cardiac by-pass.

FIG. 3.—A, venous cannula. B, arterial cannula.

venous cannulae should be large enough to carry the expected venous return without obstructing the veins before starting cardiac by-pass.

Venous Cannulae (Fig. 3 A).—Those designed to meet these requirements are of soft vinyl tubing* about 6 in. (15 cm.) in length, having perspex adapters fused to the proximal end. The distal ends are cut square with four small terminal side holes, to avoid obstruction by the wall of a collapsing vein. Malleable stylets are used during insertion to stiffen the tubing and to allow bending to a convenient shape. Reflux of blood is prevented by the ends of the stylets, which fit into the adapters. After the stylets have been withdrawn the tubes are temporarily clamped by a haemostat whose opposing surfaces are ground flat.

Arterial Cannula (Fig. 3 B).—During arterial cannulation, especially when the artery was small, a soft tube was difficult to insert and was liable to be occluded by the retaining ligature. The cannula consists of two parts. The intra-

arterial portion is of polythene, the proximal end of which is heat-softened and expanded over a conical metal former. This is tied into one end of a short length of vinyl tubing, the other end of which is cemented to a perspex adapter. The arterial end is cut to a short bevel, but there are no side holes. A stylet is passed and the surgeon bends the tube to the appropriate shape. The polythene end is dipped in boiling water and becomes rigid on cooling. The stylet is then removed, when the cannula retains the correct shape and is ready for insertion, a haemostat having been applied to the proximal vinyl portion to prevent reflux. When the carotid artery is used only 1 in. (2.5 cm.) of polythene is required, but the terminal 3 in. (7.5 cm.) should be of this material when the cannulation is made within the chest into the left brachial artery.

Methods

During each experiment, and for a variable time post-operatively, records of the following have been made. (1) Electroencephalograph. (2) Electrocardiograph. (3) Central arterial pressure. (4) Central venous pressure. (5) Venous oxygen saturation. (6) Venous pH. (7) Body temperature. (8) Time.

The E.E.G., E.C.G., arterial and venous pressures, and time are recorded simultaneously and continuously on an Ediswan four-channel pen recorder (Fig. 4).

Electroencephalograph and Electrocardiograph.—In applying the E.E.G. leads the head is shaved unilaterally

FIG. 4.—Simultaneous recordings of E.E.G., E.C.G., and venous and arterial pressures.

and the skin cleaned with ether. Silver electrodes smeared with electrode jelly are held in place with strapping. This is sprayed with "nobecutane" and bandaged into place to prevent drying out and mechanical disturbance. The E.C.G. electrodes are subcutaneous needles which, although satisfactory for a cardiograph, tend to produce polarization effects when used for E.E.G. recording over long periods. E.C.G. standard lead I has been employed routinely in the present work. Difficulty was experienced in the early stages if attempts were made to record the electroencephalogram during diathermy coagulation, as the recorder pens were violently disturbed. Accordingly, the diathermy pedal switch was arranged to operate a relay system which switched the recorder amplifiers to a resistive load at a time 0.2 second prior to the completion of the diathermy circuit by another relay. In this way the pens were switched off during coagulation. On release of the switch pedal the diathermy circuit was broken in less than 0.1 second but the recorder relays were held for several seconds and then switched on the pens. Amplifier blocking was much reduced by this procedure and the pens were automatically protected. To avoid 50 c/s interference the usual mains earth was discarded and all the electrical equipment was connected via a single earth lead to a water-pipe. This includes the neutral leads of the

*"Portex" tubing, manufactured by Portland Plastics Ltd., grade H.D.

E.E.G. and E.C.G., the diathermy plate, and the earth leads of the various instruments and motors simultaneously in use.

Arterial and Venous Pressures.—Arterial pressures were recorded through a cardiac catheter inserted via the femoral artery into the thoracic aorta. The catheter is connected to a capacitance manometer (Southern Instruments) through a specially designed system of taps. These provide for a slow pressurized saline or dextrose drip through the catheter, while allowing recalibration of the manometer without interruption of the flow. Blood-clotting in the catheter is thus prevented, whilst accuracy of recording can be checked at will. The venous pressure manometer is of the variable inductance type (New Electronic Products). Errors in pressure scales due to slow drift are less than 0.5 mm./hour arterial and about 0.25 mm./hour venous pressure.

Oxygen Saturation.—This was measured by the Kipp haemoreflexor on the mixed venous blood of the dog during thoracotomy and at three-minute intervals during perfusion. Arterial samples were examined as required.

pH of Blood.—This was determined on the samples withdrawn for oxygen saturation. The necessity for accurate pH values within the restricted range in blood has prompted the use of an electrometer rather than a standard commercial pH meter. A glass-calomel electrode system is connected to a "vibron" electrometer (Electronic Instruments) adjusted so that full-scale deflection corresponds with a pH change from 7 to 8. Further, as facilities are provided to reverse the input, the instrument reads pH 6–7 when the scale is read backwards. Measurements are made at 37° C. and are reproducible to 0.01 pH. There are indications that if enough care is taken with the blood KCl boundary the errors in the method may be reduced to the order of 0.002–3 pH.

Body Temperature.—Rectal temperature was measured with a thermistor thermometer constructed for the purpose. It is read at intervals of 0.1° C.

Anaesthesia

After comparing unpremedicated dogs with those receiving various drug combinations—for example, morphine, pethidine, and chlorpromazine—we found that the best results were achieved by morphine and atropine given intramuscularly one hour before operation. Dogs are tolerant of opiates, and morphine, 16 mg., usually produced effective sedation in a dog of 11 kg. body weight—the average weight in this series. Side-effects of morphine were vomiting, salivation, and defaecation. Atropine, 0.6 mg., was given to diminish secretions.

A 2.5% solution of sodium thiopentone was injected into the anterior subcutaneous vein of the forelimb, the average "sleep-dose" of thiopentone used being 18 mg. per kg. When the jaw was sufficiently relaxed the tongue was pulled out and intubation under vision was performed, using a Magill laryngoscope with an adult blade and a cuffed endotracheal tube. Care was taken to ensure that both sides of the chest were being ventilated.

Many anaesthetic variations have been used: these include thiopentone and air, thiopentone/nitrous-oxide/oxygen, thiopentone/pethidine/nitrous-oxide/oxygen, and thiopentone/nitrous-oxide/oxygen/ether. The most satisfactory results were obtained by thiopentone induction followed by 50:50 nitrous oxide and oxygen with an initial trace of ether, using a Waters canister for carbon dioxide absorption. Following induction spontaneous respiration began after a variable period, and was maintained until the start of operation unless panting occurred. Then the ether was discontinued and anaesthesia maintained with 50:50 nitrous oxide and oxygen and a muscle relaxant. Originally, D-tubocurarine chloride was used, but often this caused a profound fall in blood pressure, presumably due to histamine release or ganglion block. Suxamethonium chloride, however, was free from these side-effects. A dose of 1 mg. may produce apnoea, and throughout operation intermittent doses of 0.45

mg. per kg. were used as required, with controlled respiration. A Guest cannula was inserted into a forelimb vein for the administration of fluids and drugs.

During cardiopulmonary by-pass the lungs were gently inflated with oxygen to diminish post-operative pulmonary collapse and to minimize mediastinal displacement. Extubation was performed only when the endotracheal tube could no longer be tolerated and respirations were adequate. The intravenous drip was maintained for a further 12–18 hours to provide fluids and for the administration of pethidine to control pain and restlessness.

Experimental Procedures and Results

The series includes experiments on 39 dogs, and may be divided into four groups.

Group 1

The purpose of the first eight acute experiments was to gain experience in anaesthesia, surgery, methods of cannulation, operation of the by-pass, and to establish methods of recording data.

Group 2

In this group 21 experiments were carried out with a view to survival.

After shaving and skin preparation, with the animal supine and the forelimbs extended, a trans-sternal bilateral thoracotomy was made in the fourth interspaces (Andreassen and Watson, 1953a, 1953b). The vena azygos was tied or temporarily clamped and the venae cavae were encircled by tapes, avoiding the phrenic nerve. The left brachial artery was mobilized with distal ligation. Heparin (1.5 mg./kg.) was given and the brachial artery cannulated.

The pericardium was opened parallel to the right phrenic nerve. The caval cannulae were inserted through an incision in the right atrial appendage, with temporary control by a Rumel snare. This was removed when the tips of the cannulae were judged to be in the correct position well into the great veins. Bleeding around the cannulae was controlled by two Dunhill haemostats placed between them on the lips of the incision. The arterial line was attached to the arterial cannula with care, so that no air bubbles were included. The venous catheters were then attached to the clamped venous line. Small gas bubbles in this situation are unimportant.

As the pump was started the venous clamp was removed. The caval tapes were tightened around the cannulae to divert returning blood into the oxygenator.

Right atriotomy or ventriculotomy was then performed. Blood from the coronary sinus was removed by suction and discarded or returned to the oxygenator. If discarded an equivalent volume of fresh heparinized blood was automatically provided. After open cardiectomy lasting 15–40 minutes the incision was closed. The caval tapes were released and the venous cannulae removed, with ligation of the atrial appendage. An arterial transfusion was then given if required and the cannula removed, with ligation of the left brachial artery.

Protamine sulphate (3 mg./kg.) was given slowly over a period of 10 minutes, preceded by chlorpheniramine hydrogen maleate ("piriton"), 1–1.5 mg., to lessen the hypotensive effect of histamine release. The pericardium was loosely sutured, drainage tubes were inserted in both pleural cavities, and the chest was closed after complete haemostasis had been achieved.

The predetermined flow rates in these animals varied between 35 and 65 ml./kg.

In this group none failed to survive the period of operation, but all were dead within six hours. During the course of this series certain factors were investigated which may have contributed to the deaths.

Haemorrhage.—Three animals sustained severe haemorrhage, one from a tear at the base of the left brachial artery. In other animals there was enough blood loss to suggest interference with clotting mechanisms. In six

experiments protamine titration was performed (Hurt *et al.*, 1956). This was discontinued for the following reasons: (1) canine blood clot is ill-formed and difficult to recognize, consequently the end-point is sometimes distributed between several tubes; (2) the test took up to 20 minutes at 37° C. at a time when it seemed urgent to antagonize the effect of heparin; (3) on two occasions when the end-point was fairly well defined the clotting-time remained grossly abnormal for several hours. On no occasion was there evidence of fibrinogen lack as judged by the addition of thrombin, which produced immediate clotting. Further experience in human cases as well as animal experiments may modify present practice. On only one occasion were fibrin deposits noticed in the filter.

Sepsis.—Because of reference to fulminating septicaemia with rapid death in a few hours (Nelson, 1951), associated with bacterial contamination in the machine, a clean technique was replaced by a sterile one early in the series. Blood cultures consistently failed to show contamination, so that death from this cause was unlikely.

Anaesthesia.—This underwent frequent modification, as related elsewhere, without apparent effect on mortality.

Lung Complications.—Post-mortem examinations showed pulmonary collapse and haemorrhage of varying degree in many animals in the series, and it seems that the highly elastic lungs of the dog would be more prone to this complication than those in man. Handling of the lungs during the heparinized state and prolonged ventilation during vain attempts at resuscitation were obviously responsible for some of the appearances, and the finding was not constant. Drinker (1945) noted a similar finding in dogs anaesthetized for experimental purposes.

Low pH of Donor Blood.—The pH of blood used to prime the apparatus was constantly 6.8–7. Buffering this acidity with sodium bicarbonate did not achieve survival.

Method of Obtaining Donor Blood.—It seemed that this might have some bearing on our unsatisfactory results. Blood taken by complete exsanguination might contain substances which would prejudice chances of survival after perfusion with it. The result of using several donor animals, each contributing small amounts of blood, was unchanged.

Recirculation of Coronary Sinus Flow.—Replacement of discarded coronary sinus blood did not produce a more successful outcome.

Inadequate Cerebral Blood Flow.—Analysis of the post-operative course demonstrated a fairly constant clinical picture. The animals recommenced spontaneous respiration during the first hour. At first they showed increasing consciousness, but in no case was the improvement maintained. Within a period of two to four hours spontaneous respiration became weaker and gasping in character and eventually ceased, and reflex responses (eyelash, swallowing, tracheal, etc.) which had returned also gradually disappeared. With controlled respiration the blood pressure could in most instances be maintained, and the E.C.G. showed few abnormalities. Just before death occurred twitching movements of the limbs were seen and sometimes generalized convulsions. Evidence of cerebral anoxia was obtained from the encephalograms, but satisfactory tracings were obtained only in the later cases. Having developed the technique already described, we found that the records during perfusion usually showed a rapid and considerable decrease in frequency and amplitude. Occasionally this state was preceded by an increase in amplitude up to 300 μ V with a frequency below 1 cycle per second. Such a change is consistent with a slow onset of anoxia (Wilson, 1957). It was concluded that low flow perfusion via the left brachial artery might not provide an adequate cerebral blood flow, and on this account the animals failed to survive.

Group 3

The surgical approach was modified as follows.

1. Arterial cannulation was carried out via the left carotid artery. The anatomy of the carotid system in the dog differs

from that in man in that both carotid arteries arise from a common trunk, which in turn arises from the aorta. The cannula was inserted proximally along the vessel towards the bifurcation but not past this point. In this way blood flowing along the cannula perfused the right carotid and brachial arteries and the aorta (Fig. 5). It seems probable that cerebral blood flow is greater with this technique than when the left brachial is used.

These observations do not apply to the human, where in a number of cases perfusion via the left subclavian artery has been carried out by us without any evidence of deterioration in the E.E.G. recording or with any clinical evidence of brain damage post-operatively.

2. Only a right-sided thoracotomy was necessary. This resulted in the incision of a much smaller muscle mass, and manipulations were confined to the right pleural cavity.

In this series there were three survivors out of five experiments involving cardiectomy lasting 20–30 minutes. One of the two non-survivors was hypertensive at the beginning of the operation, with a blood pressure ranging from 170/120 to 230/165. It appeared to be an old animal and unlikely to do well.

This demonstrates the difficulties which arise from experimental work when the age and fitness of the subjects are unknown quantities. The other non-survivor, although hypertensive (180/125), did not appear to be either old or in bad condition. Haemorrhage persisted post-operatively and insufficient blood was available for transfusion purposes. In spite of the eventual result it regained sufficient consciousness to raise its head and limbs, the clinical picture being that of blood loss rather than cerebral damage. During perfusion the blood pressure varied between 70 and 80 mm. Hg, the E.C.G. recording was satisfactory throughout, and the E.C.G. was normal.

The blood pressure of the survivors returned to normal one to two hours post-operatively. Consciousness was regained over a period of one to four hours, when the drainage tubes were removed. One animal was able to drink water within four and a half hours of insertion of the skin sutures.

The survivors were watched continuously for 24 hours post-operatively and pethidine was given to control pain and restlessness. They were encouraged to take water and food, and change of posture was made at frequent intervals.

During the period of cardiectomy blood from the beating heart, mainly from the coronary sinus, was aspirated and discarded. An equivalent amount of fresh, heparinized blood was returned to the venous line, using the coronary sinus blood flow regulator. This practice required a large amount of reserve blood.

The volume of venous blood returning from the heart muscle during the by-pass was 10–30% of the aortic inflow. During a flow of 500 ml. a minute, suitable for an animal of 9–10 kg. body weight, at least 50 ml. a minute would be lost. During cardiectomy lasting for 30 minutes 1,500 ml. of blood would be discarded, requiring replacement of the same amount of fresh blood. This was one reason why

FIG. 5.—Carotid system in dog and man. Showing surgical approach.

in the next group of experiments it was decided to produce cardiac arrest using potassium citrate (Melrose *et al.*, 1955).

Group 4

This resembled group 3 in all respects except that at the beginning of the by-pass the heart was stopped by means of potassium citrate solution—2 ml. of 25% solution mixed with 18 ml. of blood. Enough of this mixture (7–12 ml.) to produce cardiac arrest was injected between a clamp placed on the ascending aorta and the coronary ostia.

The subsequent cardiectomy period occupied some 20–40 minutes. The ventricular wall was partly repaired, the aortic clamp was removed, and with the restoration of the coronary circulation the heart beat recommenced after a variable period. In some instances this took as long as 10 minutes, after which ventricular suture was completed. Occasional ventricular fibrillation was treated by means of an electrical defibrillator. In each animal of this series the heart eventually regained a normal beat. The E.C.G. showed diverse changes; the main feature in the initial stages of recovery consisted of high T waves.

A further difficulty experienced in the dog was the liability for bleeding to occur from the site of injection in the aorta. In two out of five experiments this was the cause of death, as the bleeding persisted in the post-operative period. Our experience with potassium-induced arrest contrasts sharply with our findings in human cases; in these the heart stopped almost immediately after the potassium injection, and the recommencement of normal rhythm was rapidly re-established at the end of the perfusion. Furthermore, no complications arose from bleeding from the injection site. The wall of the aorta in the dog is thin and sometimes splits on insertion of the needle. Even a small puncture may produce uncontrollable bleeding, often made worse by attempts at suture.

Biochemistry

Apart from the measurements of the pH and oxygen saturation during perfusion, full biochemical investigations have not been carried out for each experiment.

Serum Electrolytes

On several occasions serum or plasma sodium, potassium chloride, and alkali reserve have been estimated during the perfusion and for several hours afterwards. Typical results are shown in Tables I and II. Each refers to a 30-minute perfusion in which the heart was not arrested. Table I refers to a survivor and Table II to an animal which

TABLE I

Sample	Time (min.)	pH	Na (mEq/l.)	K (mEq/l.)	HCO ₃ (mEq/l.)	Protein (g.%)
Machine balanced	0	6.91	137	3.6	—	6.1
I.V.C.	0	7.19	132	3.2	25	5.2
Machine	94	7.02	143	3.9	—	5.4
"	21½	7.01	152	4.5	—	5.0
"	30	7.04	147	4.1	18	5.0
S.V.C.	30	6.96	144	3.5	—	—
I.V.C.	30	7.02	—	—	—	5.0

TABLE II

Sample	Time (min.)	pH	Na (mEq/l.)	K (mEq/l.)	HCO ₃ (mEq/l.)	Protein (g.%)
Machine balanced	0	7.06	147	4.7	12	5.4
I.V.C.	0	7.30	140	3.0	20	<4.5
Machine venous	8	7.10	151	2.9	21	5.2
I.V.C.	32	7.06	185	4.0	19	4.5
Machine venous	30	7.10	138	3.0	19	<4.5
I.V.C.	120	7.29	132	2.8	22	<4.5
"	180	7.30	136	2.8	20	4.5
"	210	—	138	3.2	15	4.7

ultimately died of haemorrhage. Carotid cannulation was used for each experiment. The serum Na and K levels were well maintained for three and a half hours post-perfusion. Haemolysis in canine blood does not produce a significant increase in serum K; this contrasts with human red-cell haemolysis, because K is not concentrated in canine red

cells (Kerr, 1937). However, inadequate perfusion leads to increased serum K levels owing to escape of the intracellular ion.

Typical electrolyte changes in a survivor, in which the heart was arrested with K, are shown in Table III. The plasma K level in the inferior vena cava was only 4.8 mEq/l.

TABLE III

Sample	Time (min.)	pH	Venous O ₂ %	Na (mEq/l.)	K (mEq/l.)	Alkali Reserve (mEq/l.)	Chlorides (mEq/l.)
S.V.C.	0	7.30	62	134	3.0	23	94
Machine	2	7.14	65	144	4.2	—	—
"	3	—	—	1.5 ml. 25% K citrate—aortic injection	—	—	—
"	13	7.18	63	137	3.9	21	—
"	23	—	—	Clamp removed from aorta	—	—	—
Coronary sinus blood	23	—	—	154	15.2	—	105
S.V.C.	28	7.20	—	137	4.8	22	—
Femoral artery	79	—	—	145	3.2	—	—

five minutes after removal of the aortic clamp, although the concentration in the first blood sample from the coronary sinus following arrest was 15.2 mEq/l. The relatively small amount of K injected is itself insufficient to cause any significant change in plasma K when distributed throughout the circulation.

pH of Blood

The pH has been measured serially before and during perfusion in each experiment. The pH and alkali reserve of the donor blood was consistently lower than that of the animal, values being pH 6.8–7.2 and alkali reserve 14–20 mEq/l.

FIG. 6.—Blood pH in surviving dogs.

FIG. 7.—Blood pH in non-surviving dogs.

Typical results during perfusion are shown in Figs. 6 and 7. Fig. 6 shows the variation of pH with time for six survivors. In three of these the heart was arrested and in three it was not. Fig. 7 shows corresponding results for six non-survivors. For all these animals carotid perfusion was employed. The first point on each curve represents a sample from the S.V.C. or I.V.C. at the start of perfusion, while subsequent points represent samples drawn from the venous line. Clearly there is no obvious difference between Figs. 6 and 7. Each curve shows an initial fall in pH, presumably due to the rapid introduction of relatively acid donor blood. As perfusion continues the pH usually remains within about 0.1 pH and the majority of perfusion levels lie between 7 and 7.2. These results appear to be independent of either K arrest or survival. Furthermore, when left brachial perfusion was performed the majority of pH values were within the present range.

However, no attempt has been made to separate the various factors contributing to a given blood pH. It is hoped in future experiments to extend pH measurements to include determination of carbon dioxide tension during perfusion (Astrup, 1956).

Oxygen Saturation

Arterial oxygen saturations have been consistently 95–100% during the perfusion. Venous oxygen saturation levels have shown some variation, but the majority of values were 50–80%, depending on the flow rate per kg. body weight. For the largest animal of the series, 25 kg., the flow rate was 35 ml./kg./min., and the venous oxygen saturation fell from 52 to 33% after 18 minutes' carotid perfusion. This animal made a rapid recovery, and in spite of the low oxygenation the E.E.G. on perfusion was well maintained. In a 10-kg. animal which survived a flow of 50 ml./kg./min. maintained a venous saturation between 70 and 84% during a 30-minute perfusion via the carotid artery. When sub-clavian perfusion was used the E.E.G. showed evidence of cerebral anoxia, even though venous oxygen saturation remained between 65 and 80%.

Other biochemical determinations have included calcium phosphate, urea, and blood sugar. These have shown no significant change from normal.

Summary and Conclusions

This paper describes our experimental approach to the use of an extracorporeal circulation. The Lillehei-DeWall apparatus was chosen because of its simplicity and clinical success. Our version of this, with a coronary sinus flow regulator, is described in detail together with plastic arterial and venous cannulae which have proved satisfactory.

A description is given of recording apparatus used to observe physiological changes.

In the first group of experiments there were 21 successive deaths when trans-sternal thoracotomy and left brachial perfusion was performed.

Factors which might have been partly or wholly responsible for these failures were investigated. Study of the E.E.G. tracings suggested that low flow perfusion via the left brachial artery gave insufficient cerebral blood flow to achieve survival and was the most important cause of failure. When the left carotid artery was used for perfusion there were three survivors in the next five experiments, and identical results were obtained under similar experimental conditions when cardiac arrest was induced with potassium citrate.

Flow rates ranged between 40 and 65 ml./kg./min., cardiomy lasted 15–40 minutes, and the largest total flow used was 900 ml. per minute.

The routine and continuous recording of physiological variables was well justified in enabling all stages of each experiment to be carefully monitored and subsequently analysed. The use of the E.E.G. must be especially emphasized, particularly during the period of cardiac bypass when low flows are used. A method of eliminating the effect of electrical interference due to the use of diathermy is described.

It is obvious that success in complex experimental work such as this depends upon a multitude of factors, many small and easily overlooked. From the beginning we have tried to reproduce so far as is possible in the laboratory the conditions prevailing in the operating theatre.

Asepsis was observed both in the apparatus and during the experiment, and the post-operative care was intensive and followed similar lines to those in the wards.

Finally, all those who eventually worked together with human patients, including our theatre sister, did so in the laboratory. The transition from experimental to clinical work was carried out with minimal disturbance due to strange apparatus, colleagues, or technique.

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