THE PHYSIOLOGICAL ASPECTS OF EXTRACORPOREAL CIRCULATION

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INTRODUCTION

PROBLEMS in the development and establishment of extracorporeal circulation as a safe technique permitting deliberate open heart surgery are essentially physiological. O'Shaughnessy (1939) thought that the real key to advance in cardiac surgery required the provision of an adequate cerebral circulation while the heart was out of action. The anatomy of the pulmonary veins makes cardiac by-pass a difficult technical procedure and extracorporeal circulation is now achieved by total cardiopulmonary by-pass. The systemic venous return is diverted from the right heart by cannulae in the great veins and passed to an artificial oxygenator, whence it is returned by a pump, the artificial heart, to the systemic arterial system through a cannula in a branch of the aorta. Ideal cardiopulmonary by-pass, implying the delivery of the correct amount of appropriately oxygenated blood to the tissues of the whole body without any attendant or ensuing adverse physiological effects, does not exist. The important observed effects of total cardiopulmonary by-pass are metabolic changes, especially relating to acid-base balance, damage to the blood, and anatomical or functional damage to vital organs. Before these changes are discussed, the factors involved in developing safe cardiopulmonary by-pass will be considered, and a short historical account of the early work of pioneers in the field will be given.

Problems innate in total cardiopulmonary by-pass.

(1) An extracorporeal circulation necessitates an extravascular route for the blood. Accidents due to bacterial contamination, cessation of flow and air and particulate embolism must be prevented. Blood clots outside its natural intravascular environment and extracorporeal circulation was never feasible until a reversible physiological anticoagulant had been discovered. Heparin, discovered by Maclean in 1916, is now universally used. Despite adequate heparinization, denaturing of the blood occurs, with damage to cellular constituents and changes in blood chemistry. To avoid change in intracorporeal blood volume, the extracorporeal circulation must be charged with donor blood. Blood compatibility is essential. An early difficulty was to provide adequate extracorporeal circulation without using an excessive priming volume for the extracorporeal system.

(2) An artificial heart cannot precisely mimic the action of a normal heart. Delivery of blood to the systemic system is abnormal whether the blood is returned to the body by the subclavian or the femoral artery. This may interfere with regional distribution of blood. No pump has been devised which can simulate the pulse of a normal heart, though it appears that, for periods during which by-pass is at present required, this is not essential. Even non-pulsatile flow is compatible with apparently adequate perfusion. An artificial heart causes more mechanical trauma to the blood than the normal heart.

(3) Similarly, no artificial lung performs the precise function of normal lungs. The difficulty of achieving by-pass without incorporating the patient's own lungs in the extracorporeal circuit has already been mentioned. The filtering properties of normal lung are lost and a suitable filter must be inserted in the extracorporeal circulation. It is difficult to simulate the gaseous exchange of normal lung with the artificial lung. Oxygenation can be adequately achieved if the oxygen is allowed to come into direct contact with the blood. Under these conditions, carbon dioxide is easily removed. Artificial lungs, incorporating a membrane separating blood and gas which simulates the alveolar membrane of normal lungs are being developed, but rapid gaseous exchange is difficult.

(4) Finally, an extracorporeal circulation has no homeostatic mechanisms. The homeostatic mechanisms in the intracorporeal circulation are deranged, and those still functioning may not cope
with the changes induced by an extracorporeal circulation. For this reason, monitoring techniques have been developed, so that deviations from normal physiology can be recognized and corrected.

The fact that these problems have been overcome to such degree that safe extracorporeal circulation is now possible is an indication of the immense advances made by experimental and clinical workers in this field in the last few years.

Historical

Gibson (1939) described the first total cardio-pulmonary by-pass with survival. He occluded the pulmonary artery of cats, maintaining the circulation with a pump-oxygenator. He continued to develop this machine and performed the first successful operation in man in 1953, when repair of an atrial septal defect was effected using total cardiopulmonary by-pass (Gibbon, 1954). Most workers at that time were preoccupied with heart-lung machines designed to deliver flow rates approaching the resting cardiac output, but the work of Andreason and Watson (1953) demonstrated the survival of dogs after a period of limited flow to the brain. After 8 minutes of total circulatory arrest, control dogs all showed signs of irreversible cerebral damage, Dogs could, however, survive clamping of both venae cavae for 30 minutes, the cardiac output being limited to the return through the vena azygos which, under these conditions, represented about 10 per cent of the normal cardiac output. This work was confirmed by Cohen and Lillehei (1954), and subsequently Lillehei (Warden et al., 1954) demonstrated that this limited flow could be supplied by a donor dog without prejudice to its own vascular equilibrium. In 1954, the first controlled cross-circulation perfusion for repair of ventricular septal defect was performed, the patient surviving (Lillehei, 1955). Forty-five operations were performed, using this technique, by which time the Lillehei-de Wall helix-reservoir bubble-oxygenator had been sufficiently developed in the laboratory to merit its clinical use for extracorporeal circulation in open heart surgery. Initially (de Wall et al., 1956) flow rates of 26-60 ml/kg/minute—less than half the resting cardiac output—were used. Survival rates were excellent, but physiological studies during operation demonstrated the development of metabolic acidosis, probably associated with inadequate flow rates, and a later report from the same centre (de Wall et al., 1957) described an increase in flow rate to 50-75 ml/kg/minute. At this flow rate, still considerably less than the resting cardiac output, it was reported that the acidosis produced was no more severe than that accompanying thoracotomy under general anaesthesia. Meanwhile, Kirklin (Jones et al., 1955; DuShane et al., 1956) had begun open heart surgery using a modification of the Gibbon-type stationary vertical screen pump-oxygenator. He originally perfused at 75 ml/kg/minute but, becoming aware that total oxygen requirements were more closely related to surface area than to body weight, later perfused at approximately 2.3 l./sq.m./minute. This approaches the resting cardiac output of an anaesthetized patient, and perfusion at this level is not attended by the development of metabolic acidosis.

Experience gained in the centres mentioned, and in other centres in the U.S.A. and now throughout the world has allowed definition of the criteria for adequate extracorporeal circulation. Adequate perfusion has been defined by Kirklin (Kirklin et al., 1958a) as that which allows accurate unburied operation and recovery of the patient. This may be achieved, of course, in different centres by different methods. Reports on the experimental and clinical experience of these different centres have provided a considerable fund of knowledge about the physiological effects of extracorporeal circulation. In general terms these are effects on metabolism and effects on the blood. The most important aspect of metabolism during and after extracorporeal circulation is acid-base balance. Changes in electrolytes are insignificant and have not been investigated extensively. The effects of extracorporeal circulation on the blood are trauma to its particulate components and disorders in coagulation. The effect of extracorporeal circulation on vital organs—the brain, the lungs, the kidneys and the heart—will be described.

THE EFFECT OF EXTRACORPOREAL CIRCULATION ON ACID-BASE BALANCE

The most important effect of extracorporeal circulation on metabolism is the development of acidosis, which, if not prevented or corrected,
may be severe enough to increase the morbidity and mortality of open heart surgery.

Before cardiopulmonary by-pass, a respiratory alkalosis is usually induced by controlled respiration with manual hyperventilation. During cardiopulmonary by-pass, a metabolic acidosis, characterized by a primary decrease in bicarbonate, with an increase in fixed acid, may develop. This may remain compensated, with no fall in blood pH, because of the pre-existing respiratory alkalosis and because most oxygenators are efficient in removing carbon dioxide. The most important cause of this metabolic acidosis is hypoxia due to inadequate flow rates. Other contributory causes will be discussed. After cardiopulmonary by-pass, providing a satisfactory circulation has been re-established, fixed acid metabolites are excreted and the acid-base balance tends to return to normal. If a satisfactory circulation has not been re-established, the metabolic acidosis may become more severe, and may be complicated postoperatively by an added respiratory acidosis due to pulmonary hypoventilation, with failure to remove carbon dioxide. The acidosis becomes uncompensated and the blood pH falls.

*Experimental and clinical observations.*

Miller et al. (1951), while developing a film-oxygenator reported falls in pH to as low as 7.25 during extracorporeal circulation at flow rates averaging 88 ml/kg of body weight/minute. Dennis et al. (1951), quoted by Callaghan et al. (1958), using a different film-oxygenator, reported a fall in pH to 7.2 in the hour following perfusion, with a return to normal values within 48 hours.

De Wall et al. (1956) stated that pH alone was an unreliable index of acid-base balance because of blood buffer compensating mechanisms, and used plasma bicarbonate estimations as an index of increase in fixed acid. Reporting studies on 60 of their first 80 human perfusions using the helix-reservoir bubble-oxygenator at flow rates between 26 and 60 ml/kg of body weight/minute, they found moderate plasma bicarbonate depression in acyanotic subjects, associated, in a few studied, with an increase in lactate levels to twice pre-perfusion values although the arterial pH remained substantially normal. In cyanotic subjects they demonstrated an uncompensated metabolic acidosis under ambulatory conditions before perfusion, with a great depression of plasma bicarbonate after perfusions. Later, de Wall et al. (1957) described the results of investigations of 120 patients undergoing open heart surgery. The perfusion rates were higher—between 50 and 75 ml/kg of body weight/minute in acyanotic and up to 100 ml/kg of body weight/minute in cyanotic patients. Flow rates were adjusted to give an adequate arterial perfusion pressure and a satisfactory electroencephalogram. They concluded that at these flow rates the depression of plasma bicarbonate was no greater than that found after general anaesthesia for minor surgical procedures. They demonstrated an uncompensated metabolic acidosis in cyanotic patients prior to perfusion, with return of pH and plasma bicarbonate to normal levels within 18 hours if the defect had been adequately repaired. They pointed out that a metabolic acidosis due to anaerobic oxidation of glucose was present in the donor blood in the machine prior to total cardiopulmonary by-pass.

Paneth et al. (1957) confirmed the development of a metabolic acidosis in control dogs undergoing general anaesthesia and thoracotomy only. They perfused 48 dogs for 1 hour at flows varying between 0.22 l./sq.m. of body surface/minute and 2.6 l./sq.m. of body surface/minute. They demonstrated uncompensated metabolic acidosis with a low pH, plasma bicarbonate deficit and raised lactic acid levels at flow rates of 0.4-0.8 l./sq.m. of body surface/minute. At perfusion rates of 1.2 l./sq.m. of body surface/minute the rate of excess lactic acid production, plasma bicarbonate deficit and fall in pH was reduced. At and above this perfusion rate the arterio-venous oxygen difference remained constant, suggesting that oxygenation was adequate. At higher rates (2.6 l./sq.m. of body surface/minute) the bicarbonate deficit after perfusion for 1 hour was less than in the control dogs undergoing only thoracotomy under general anaesthesia.

Clowes et al. (1958) perfused three groups of dogs at varying flow rates for 1 hour, using a membrane-oxygenator. They found that at flow rates of 26-36 ml/kg/minute, the oxygen consumption was only 47 per cent of controls. At 70-110 ml/kg of body weight/minute, it was 85 per cent of controls. Acidosis and lactic acid accumulation was inversely proportional to the perfusion rate despite maintenance of normal carbon dioxide
tensions. After perfusion, acidosis increased in all dogs, but to a greater degree in those which subsequently died. These developed an uncompensated acidosis due to an inability to maintain a normal carbon dioxide tension postoperatively—in other words, a superimposed respiratory acidosis on a metabolic acidosis.

Mendelsohn et al. (1957) reporting their results on 37 patients, using a multiple disc-oxygenator, also noted a fall in pH and a bicarbonate deficit, which they suggested was due to circulatory stasis. They too remarked on the metabolic acidosis present in the donor blood in the oxygenator prior to total cardiopulmonary by-pass.

Callaghan et al. (1958) investigated acid-base aspects in 35 patients subjected to extracorporeal circulation using the Lillehei–de Wall bubble-oxygenator. They found that pH remained fairly constant during perfusions of up to thirty minutes and was then followed by a slight fall. Bicarbonate was often reduced, the acidosis being compensated by low carbon dioxide levels thus demonstrating the efficiency of the oxygenator in removing excess carbon dioxide. After total cardiopulmonary bypass, however, in five patients out of twelve studied, a fall in arterial pH was observed. This was associated in three patients, who subsequently died, with a raised carbon dioxide tension, indicating a superimposed respiratory acidosis.

Several workers have been struck by the similarity between the acidosis of extracorporeal circulation and that of haemorrhagic or hypovolaemic shock. Beatty (1945) reported a rapid return of lactate levels to normal values in dogs surviving severe haemorrhage. Allison et al. (1949) demonstrated that high lactate levels in hypovolaemic dogs rapidly fell to normal values in survivors, but did not decrease in dogs that died. Bicarbonate levels fell and remained low in non-survivors.

**Acidosis during total cardiopulmonary by-pass.**

Uncompensated metabolic acidosis occurs in cyanotic subjects under ambulatory conditions before total cardiopulmonary by-pass (de Wall et al., 1956).

General anaesthesia and surgery lead to mild metabolic acidosis (de Wall et al., 1957). Paneth et al. (1957) emphasised that this occurred despite a marked respiratory alkalosis produced by hyperventilation.

Metabolic acidosis accompanying extracorporeal circulation might in part be due to the acidity of the priming blood in the extracorporeal system. Callaghan et al. (1958) found that the actual mean pH of eleven samples of donor blood fell from 7.53 to 7.42 at the end of 4 hours. They remarked, quoting Bird (1947) that, small as this pH fall may be, the accumulation of lactic acid due to anaerobic glycolysis was in the order of 16.5 mg per 100 ml of blood per hour at 37.5°C. This acidosis of the priming blood is obviously a considerable factor in small children, when the priming volume of the extracorporeal system may be three or four times the patient's blood volume. To correct this, Kolf et al. (1956) routinely gave 4.5 m.equiv./kg of sodium bicarbonate during total cardiopulmonary by-pass, repeating the dose 3 hours postoperatively.

The most important cause of metabolic acidosis during total cardiopulmonary by-pass is hypoxia. Hypoxia due to inadequate external respiration is not a significant factor. With established pump-oxygenators, full arterial oxygen saturation is achieved, though adequate oxygenation has been a problem with membrane-oxygenators. Excessive removal of carbon dioxide in the oxygenator may lead to respiratory alkalosis. The rise in blood pH may influence the dissociation curve of oxyhaemoglobin, so that, even in the presence of fully saturated haemoglobin, poor oxygen release may lead to tissue anoxia (Eiseman, 1958). The cardinal cause of hypoxia during total cardiopulmonary by-pass is a flow rate inadequate to meet the oxygen requirements of the body. Kirklin et al. (1958b) stated that the flow rate should approximate to the resting cardiac output of the anaesthetized patient and considered this to be approximately 2.3 l./sq.m. of body surface/minute. At these flow rates, metabolic acidosis did not occur. Lillehei (Paneth et al., 1957) considered that at flow rates of 1.2 l./sq.m. of body surface/minute, oxygen requirements, as assessed by arterio-venous oxygen saturation differences, are met without the attendant disadvantages of high flow rates.

**Acidosis following total cardiopulmonary by-pass.**

The acidosis occurring after total cardiopulmonary by-pass may be metabolic, respiratory or both. Progressive metabolic acidosis leading to death occurs when the body's homeostatic mechanisms
are impaired. It is observed when a satisfactory circulation has not been established after total cardiopulmonary by-pass, and is likely to occur when surgical cure of the circulatory defect has not been achieved. Under such circumstances, the compensatory mechanisms of the body do not function, and in the presence of an impaired circulation, progressive hypotension with further hypoxic acidosis ensues. Hypovolaemia following total cardiopulmonary by-pass produces hypotensive hypoxic acidosis, and for this reason great care must be taken after total cardiopulmonary by-pass to ensure that the pre-existing blood volume is restored and that any postoperative fall in blood volume due to haemorrhage is corrected. Hypotensive hypoxic acidosis may be due to myocardial damage. It has been emphasised (Ross et al., 1958) that stretching of the myocardium due to ventricular distension during elective cardiac arrest may result in hypotension following total cardiopulmonary by-pass. To avoid this, ventriculotomy or atrial venting should be performed before elective cardiac arrest is instituted, and no attempt should be made to end total cardiopulmonary by-pass until evidence is available that the myocardium has recovered its tone and left ventricular ejection is satisfactory following recovery from elective cardiac arrest. Hypotensive hypoxic acidosis may also follow depression of the medullary centres resulting from anoxia, from air, fibrin or silicone emboli, or from oxygen intoxication (Clowes et al., 1958).

A superimposed respiratory acidosis may result from postoperative hypoventilation. The pain due to the thoracotomy wound may inhibit adequate respiratory movements, and analgesic drugs may improve ventilation. The airways of infants are relatively narrow and airway obstruction may necessitate tracheotomy, either electively prior to operation, or in the immediate postoperative period. Assisted respiration with a mechanical ventilator may be indicated.

Changes in the pulmonary parenchyma following total cardiopulmonary by-pass have been described (Kirklin et al., 1958b). At autopsy, multiple areas of collapse, haemorrhage and oedema were seen. Alveolar gaseous exchange was impaired, leading to anoxia and hypercarbia with the development of a respiratory acidosis.

The role of the kidneys in regulating acid-base balance remains to be discussed. Renal hypotension during or after total cardiopulmonary by-pass, renal embolism and renal damage due to the breakdown products of excessive haemolysis may impair the ability of the kidneys to excrete an acid urine and dispose of the fixed acid metabolites.

**EFFECTS OF EXTRACORPOREAL CIRCULATION ON THE BLOOD**

Despite adequate heparinization, and improved pump-oxygenators designed to minimise turbulence and direct trauma to the blood, changes in the cellular and non-cellular elements of the blood are observed during and after extracorporeal circulation. The important effect on the red cells is traumatic haemolysis. The white cell count may fall during total cardiopulmonary by-pass, but a leucocytosis in the absence of overt infection may develop after total cardiopulmonary by-pass and may persist for seven to ten days. The platelet count falls at the onset of cardiopulmonary by-pass and may remain below normal levels for the next 24 hours. Important effects of changes in the non-cellular elements of the blood following extracorporeal circulation are disorders of coagulation.

**Haemolysis.**

Haemolysis due to pyrogens, bacterial contamination or incompatibility of pooled donor blood is avoidable.

Traumatic haemolysis occurs to some extent in any form of extracorporeal circulation. The blood factors involved in traumatic haemolysis include the age of the blood, cohesion of red cells, sphericity of red cells, innate fragility of red cell membranes and temperature, haemolysis being more rapid above 55°C (Ferbers and Kirklin, 1958). Extracorporeal haemoglobin resulting from red cell destruction is immediately bound by haptoglobin present in normal plasma which is capable of combining with 60 to 200 mg of haemoglobin per 100 ml of plasma. This haemoglobin-haptoglobin complex is removed by the reticulo-endothelial system and the breakdown products are probably excreted as bile pigments. With plasma haemoglobin levels exceeding the figures stated, the haptoglobin is saturated, and free haemoglobin is excreted by the kidneys. This mechanism explains the observed findings that
haemoglobinuria does not occur until high levels of free plasma haemoglobin are reached, but, once established, haemoglobinuria continues until the plasma haemoglobin has fallen to insignificant levels.

Under the conditions of total cardiopulmonary by-pass, plasma haemoglobin concentrations are used as an index of haemolysis. Because of the body mechanisms which remove circulating plasma haemoglobin, studies of traumatic haemolysis are best performed during circulation of blood through a closed system of pump and/or oxygenator without a patient or experimental animal in the circuit. Ferbers and Kirklin (1958) demonstrated that with a plastic sheet bubble-oxygenator, after closed circulation for one hour, the plasma haemoglobin was more than ten times higher than after circulation for 1 hour incorporating a dog in the circuit.

Traumatic haemolysis occurs in the extracorporeal circuit and at the site of arterial cannulation. Direct mechanical trauma to the blood by pumps and tubing is less important than turbulence. Turbulence is produced in the extracorporeal circuit or in the artery receiving the arterial flow, when changes in internal diameter of tubing or changes in direction of flow cause pressure gradients. One of the problems associated with high flow rates is the difficulty of delivering this large flow through a relatively narrow arterial cannula. Dodrill et al. (1957) suggested the suturing of an arterial graft to the descending aorta to take a large arterial cannula, but most centres find left subclavian or common femoral arterial cannulation satisfactory. Kirklin et al. (1958a) compared traumatic haemolysis after comparable perfusions, using the Gibbon type vertical stationary screen-oxygenator and a plastic-sheet bubble-type oxygenator. Concentrations of plasma haemoglobin were measured during circulation for one hour using the pumps and oxygenators, followed by circulation for one hour using the pumps only. Using the screen-oxygenator, after 2 hours total circulation, the plasma haemoglobin concentration was negligible. Using the bubble-oxygenator, there was a rise of plasma haemoglobin to 280 mg/100 ml in the first hour when both pumps and oxygenator were in the circuit but an insignificant further rise in the second hour, using only the pump. They concluded that, in this instance, the haemolysis was caused by the bubble-oxygenator, and thought that this was the result of turbulent flow induced by the oxygen jets and was not due to foaming (Ferbers and Kirklin, 1958). Excess foaming, nevertheless, indicates the deposition of fibrin (probably associated with inadequate heparinization) and may cause mechanical haemolysis. Powerful coronary suction with return of this blood to the extracorporeal circuit may also be a factor in mechanical haemolysis.

A raised plasma haemoglobin concentration may give rise to chills, fevers, cramps and vomiting. With severe haemolysis anuria may occur, due either to severe renal vasoconstriction (Ferbers and Kirklin, 1958) or to the blockage of renal tubules by casts of haemoglobin or its breakdown products.

Patients may develop anaemia three weeks after extracorporeal circulation. Though survival studies with tagged red cells suggest an antigen-antibody reaction, it is possible that premature death of red cells damaged during extracorporeal circulation has occurred.

Disorders of coagulation.

Extracorporeal circulation is associated with a degree of extravascular, and possibly intravascular, clotting which, if severe, depletes the body of factors essential to prevent abnormal bleeding, and may give rise to a severe or fatal postoperative state. This abnormal coagulation is diminished, but not prevented, by heparin.

Extravascular clotting occurs if the blood comes into contact with rough, dirty or wettable surfaces in the extracorporeal system. Direct trauma to platelets by the pump or by oxygen bubbles, and trauma due to turbulence increase extravascular clotting. With improved design of pump-oxygenators, the degree of extravascular clotting due to these causes has been reduced.

Adequate heparinization inhibits extravascular clotting. Until recently, the occurrence of post-operation haemorrhagic states was thought to be due to over-heparinization. It was stated that protamine neutralization postoperatively was difficult to achieve, or was followed by a phenomenon of "heparin rebound", where a clotting time, originally restored to normal, became again prolonged with attendant haemorrhage due to the more rapid inactivation of protamine than heparin. This
theory is now refuted (Perkins et al., 1958) and an accepted amount of heparin is considered to be 3 mg/kg of body weight. Heparin is neutralized in vitro by an equal amount of protamine. In vivo protamine is more effective and one might expect that a smaller dose would be required. In fact, after extracorporeal circulation a larger dose is needed (up to 5 mg of protamine per kg of body weight) because in the presence of thrombocytopenia, the anti-heparin effect of platelets is diminished and because the donor blood used to prime the extracorporeal circuit is heavily heparinized. Protamine in excessive doses, however, has an anticoagulant effect. A method of protamine titration has been described by Perkins et al. (1956).

Inadequate heparinization may lead to intravascular coagulation. Heparin affects surface tension, and excessive foaming, indicating impending coagulation and defibrination, is an index of inadequate heparinization. Fibrin emboli or thromboses may be a cause of the syndrome of sudden death, attended by cyanosis, hypotension, skin mottling and coma, described after extracorporeal circulation (Nyhus, 1958). Intravascular clotting may also lead to the production of fibrinolysins with the occasional depletion of fibrinogen levels, attended by postoperative bleeding. Von Kaulla and Swan (1958) reported an increased fibrinolytic activity during total cardiopulmonary by-pass due to inadequate flow rates and acidosis. Release of adrenaline during by-pass may lead to production of fibrinolysins. Excess circulating fibrinolysins have been described in patients with cyanotic congenital heart disease. The fibrinolysins produced during total cardiopulmonary by-pass remain active for up to four hours, and can be demonstrated by an in vitro clot lysis test (Allen, 1958). Prothrombin activity and its utilization are not affected by extracorporeal circulation unless fibrinolytic mechanisms are accelerated.

Haemorrhage after extracorporeal circulation may be due to lack of surgical haemostasis, inadequate neutralization of heparin, severe thrombocytopenia or fibrinogen depletion. Surgical bleeding is suspected if bleeding from or into the chest occurs in the absence of purpura or bleeding from the small cannulation wounds. It demands re-exploration of the chest to secure haemostasis. Allen (1958) describes simple laboratory procedures to distinguish the causes of bleeding due to coagulation defects. Inadequate neutralization of heparin is treated by administering more protamine. Thrombocytopenia is treated by infusion of platelet concentrates, if available. Depletion of fibrinogen is demonstrated by high fibrinolysin titres and is corrected by the intravenous injection of 6–12 g fibrinogen in 200 ml, repeated once in 4 hours if continued lysis of the transfused fibrinogen occurs.

EFFECTS OF EXTRACORPOREAL CIRCULATION ON THE BRAIN

Cerebral circulatory arrest for 3 to 4 minutes at normal temperatures causes irreversible ischaemic damage, and it is reasonable to assume that inadequate cerebral circulation for a longer period of time may have similar effects. Adequate cerebral circulation during extracorporeal circulation demands the delivery to the brain of an adequate flow of blood, containing adequate constituents.

Cerebral blood flow depends on the arterial blood pressure and the cerebral vascular resistance. The systemic arterial blood pressure during total cardiopulmonary by-pass depends on the flow rate and the total peripheral resistance. If the flow rate is inadequate, cerebral blood flow may be maintained by reflex systemic vasoconstriction, the vasomotor tone of the cerebral circulation remaining unchanged. (It is possible to maintain the systemic arterial pressure by increasing the systemic blood volume, but this is associated with a raised venous pressure, which may lead to raised intracranial pressure and cerebral oedema.) Halley et al. (1958) demonstrated experimentally the importance of the systemic peripheral resistance in maintaining cerebral blood flow when they found that, in dogs, the cerebral blood flow is proportional to the mean systemic arterial pressure achieved during total cardiopulmonary by-pass and bears no direct relation to the flow rate.

The cerebrovascular resistance tends not to alter during systemic vasoconstriction, but is sensitive to changes in oxygen and carbon dioxide tension. Low oxygen tension and high carbon dioxide tension cause vasodilatation, with a reduction in resistance, and thus an increased cerebral blood flow. To a lesser extent, high oxygen tensions and low carbon dioxide tensions cause vasoconstriction,
and thus a reduced flow. Cerebrovascular resistance is also sensitive to temperature changes, increasing as the temperature falls.

The normal oxygen tension of arterial blood is about 100 mm Hg. Oxygen tensions greatly in excess of this figure are produced by most oxygenators, and unless steps are taken to prevent this, oxygen poisoning (Stadie et al., 1944) may occur. If the blood in the oxygenator at less than body temperature is exposed to pure oxygen, the oxygen tension may become greater than atmospheric when introduced into the warmer intracorporeal circulation, due to the decrease in oxygen solubility at a higher temperature. This potential hazard may be overcome either by maintaining the oxygenator at body temperature or by reducing the partial pressure of oxygen in the oxygenator.

The normal carbon dioxide tension of the tissues exceeds 40 mm Hg and therefore the arterial carbon dioxide tension should be less than this figure, otherwise carbon dioxide will not be removed from the tissues. Oxygenators are efficient carbon dioxide eliminators, and the carbon dioxide tension of blood in the arterial line may approach zero so that normal cerebral vasodilatation may not be achieved. Some workers add three per cent carbon dioxide to the oxygen to maintain the carbon dioxide tension in the arterial line between 30 and 40 mm Hg at body temperature. Continuous monitoring of the partial pressure of both oxygen and carbon dioxide in the arterial line offers a more satisfactory control over these factors.

Lobpreis (1959) pointed out the dangers of hypoglycaemia during total cardiopulmonary bypass. Heparinized donor blood on standing undergoes anaerobic glycolysis by the red cells with a fall in the blood sugar level of 10.5 mg per cent per hour, for the first 4 hours. Frank hypoglycaemia may thus occur, especially in infants whose total blood volume is a fraction of the priming volume of the machine. To prevent this, donor blood should be received into a heparin-glucose solution.

Studies of the effect on the brain of circulating metabolites have not been documented, but there is clinical evidence that acidosis has an adverse effect on the brain.

An obvious hazard of extracorporeal circulation is embolism. Massive air embolism may follow an accident during total cardiopulmonary by-pass, when air gets into the arterial hose. Less obvious embolism may be due to microscopic gas bubbles or particulate matter, and will occur to a greater extent at high flow rates and during prolonged cardiopulmonary by-pass.

Fries et al. (1957) suggested that gas embolism was a cause of death after extracorporeal circulation using an oxygenator, and later simulated the picture of neurological damage by deliberate injection of air or oxygen into the carotid artery of dogs. Gas embolism due to microscopic bubbles is not confined to bubble-oxygenators, but can occur in any oxygenator where blood and gas are brought into direct contact with each other. Membrane-oxygenators do not have this disadvantage. The danger of oxygen embolism due to high oxygen tensions has already been discussed.

Particulate emboli may be fibrin or silicone. Fibrin particles due to denaturing of the blood, possibly related to inadequate heparinization, may be seen adhering to the filter and tubing of the heart-lung machine after total cardiopulmonary by-pass, and have already been mentioned as an intravascular cause of fibrinolysin production. Cerebral lesions due to fibrin emboli have not been observed histologically.

Silicone antifoam is used in some pump-oxygenators to prevent foaming of the blood. In the bubble-oxygenator it is also used in the "debubbler" to break up the bubbles produced in the oxygenating column. Gianelli et al. (1957), comparing the effects of various types of pump-oxygenator in dog perfusions, reported neurological abnormalities which they suspected were due to silicone embolism. These occurred with bubble-oxygenators but not with screen or rotating disc-oxygenators. Taylor (1958) described similar neurological damage and Yates et al. (1959) demonstrated silicone emboli histologically. Smith (1959) examined the brains of 39 dogs subjected to extracorporeal circulation in Birmingham using a bubble-oxygenator. He found histological evidence of extensive silicone embolism in 28 animals (72 per cent) including lesions in 18 dogs which survived for 14 days after total cardiopulmonary by-pass without obvious clinical neurological damage. He also described similar lesions in patients who died shortly after open heart surgery, and speculated that these lesions in
patients surviving open heart surgery using a bubble-oxygenator were potentially epileptogenic. In our experience, neurological sequelae of extracorporeal circulation using a bubble-oxygenator, occur 6 hours to 3 days after operation. Failure to regain consciousness after the operation is exceptional. After a period of 6 hours, during which the patient is quite alert, drowsiness or cerebral irritation may appear. The “sudden death” due to rapid respiratory failure (Kirklin et al., 1958b) has been observed. This may be a cerebral episode. In other patients, transient focal neurological signs, Jacksonian epilepsy, or generalised convulsions may occur. This state has been considered to be due to cerebral oedema and has not so far proved fatal. Our present knowledge

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**Fig. 1**

Grades of electroencephalogram during total cardiopulmonary by-pass. Grade a is a waking record. Grades 1 and 2 show a satisfactory e.e.g. in a patient during nitrous oxide and oxygen anaesthesia. Grades 3 and 4 denote unsatisfactory perfusion. Grades 5 and 6 show progressive loss of cortical electrical activity.
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does not permit us to point to a single causal factor, though embolism rather than inadequate cerebral blood flow seems more likely in that these neurological abnormalities seem to occur more frequently after total cardiopulmonary by-pass at high flow rates.

The electroencephalogram (e.e.g.) is a valuable monitor of cerebral function during extracorporeal circulation (Theye et al., 1957; Hodges et al., 1958). Hudson (1958) described a technique for recording the e.e.g. in dogs undergoing experimental extracorporeal circulation and described six grades of e.e.g. denoting progressive deterioration of cerebral function.

This technique has been transferred to the operating theatre and figure 1 shows the six grades of e.e.g. in human subjects. The top tracing, showing a rhythm is a waking record. Grades 1 and 2 are satisfactory and represent the e.e.g. under light nitrous oxide and oxygen anaesthesia. Grades 3 and 4 are slow, wide amplitude patterns, indicating moderate depression of cerebral function. Grades 5 and 6 show progressive loss of cortical electrical activity. Progressive deterioration in e.e.g. grade is a rapid and sensitive sign of unsatisfactory cerebral perfusion, and can usually be demonstrated to be caused by cerebral venous congestion, arterial hypotension or hypoxia. Correction of the cause is followed by rapid return of the e.e.g. to Grade 1 or 2. There is, as yet, no quantitative correlation between these causes and the e.e.g. grade, and the technique remains empirical. Its limitation is that moderate damage due to cerebral embolism can occur without apparent e.e.g. change.

EFFECTS OF EXTRACORPOREAL CIRCULATION ON THE KIDNEYS AND THE BODY ELECTROLYTES

Extracorporeal circulation is well tolerated by the kidneys, producing only transient depression of renal function, due to a diminished volume of blood passing through the kidneys at a reduced pressure. Beall et al. (1957) reported the results of studies on seven patients undergoing open heart surgery, using a bubble-oxygenator. A “low flow” rate of only 25 per cent of the cardiac output was used. The mean blood pressure, though variable, was largely in the range of 35 to 50 mm Hg. There was no significant depression of renal function during anaesthesia, thoracotomy and preparation for total cardiopulmonary by-pass. During total cardiopulmonary by-pass glomerular filtration rate and renal blood flow fell to 29 per cent and 23 per cent respectively of pre-operative control values. Urinary output fell to 33 per cent and urinary sodium and potassium excretion fell to 50 per cent and 48 per cent respectively of control levels. After total cardiopulmonary by-pass, the glomerular filtration rate was 92 per cent and the renal blood flow 73 per cent of pre-operative controls. Urinary sodium was not significantly abnormal though urinary potassium levels exceeded control values. There was no change in haematocrit or serum sodium levels during the studies though the serum potassium fell, (probably due to intravenous infusion of glucose and saline) returning to normal within 24 hours. Andersen (1958) performed comparative experimental studies of renal function during extracorporeal circulation, using low and high flow rates. At flow rates of 40 ml/kg/minute, glomerular filtration rate, renal blood flow, urine and electrolyte excretion demonstrated almost complete cessation of function, whereas at flow rates of 100 ml/kg/minute, measurements remained at control levels. Morris et al. (1958) investigated renal function during aortic by-pass and total cardiopulmonary by-pass. During aortic by-pass renal function was suppressed when the mean distal aortic pressures were less than the filtration pressure (about 32 mm Hg) but measurable renal blood flow was produced if the mean distal aortic pressure was 40 mm Hg. In their view, perfusion rates of 35 ml/Hg/minute were sufficient to prevent ischaemic damage to the kidneys.

Ashton, quoted by Smith (1959) noted circular capillary “holes” in the renal glomeruli of dogs subjected to total cardiopulmonary by-pass using a bubble-oxygenator. He assumed that these were embolic silicone lesions. There was no inflammatory reaction around them, and, at the present time, we have no knowledge about the significance of these lesions in man.

EFFECTS OF EXTRACORPOREAL CIRCULATION ON THE LUNGS

An important and frequent cause of death following extracorporeal circulation is respiratory insufficiency. Kirklin et al. (1958b) reporting the results of open heart surgery in 245 patients, found
that pulmonary complications were the most frequent cause of death and morbidity early in their series. Dodrill (1958) thought that the average incidence of pulmonary complications in different centres was as high as 15–25 per cent. A comparable incidence is not seen in cardiac surgery without total cardiopulmonary by-pass, and it is reasonable to suggest that extracorporeal circulation is a causal factor. The clinical picture is variable. After apparently adequate extracorporeal circulation and repair, the patient may develop frothy, sometimes blood-stained or thick tenacious sputum with progressive respiratory insufficiency leading to death within a few hours or a few days of operation. At autopsy, pulmonary oedema, pulmonary parenchymal haemorrhage and alveolar collapse are seen. A more insidious picture is a rapid respiratory rate and slight cyanosis postoperatively with progressive respiratory insufficiency leading to death. At autopsy, extensive alveolar collapse which is not segmental in distribution is seen. The cause of these pulmonary changes after perfusion is not understood. A discussion of the physiology of the lungs during total cardiopulmonary by-pass and of factors which may have been implicated may clarify the problem.

The lungs have a pulmonary arterial and a bronchial arterial circulation. The bronchial arteries arise from the aorta and pass to the lungs along the bronchi. Their function in health is unknown. They form precapillary and capillary anastomoses with the pulmonary circulation, and then drain both into the systemic venous system via the azygos, hemiazygos or intercostal veins, and also into the pulmonary vein. In Fallot's tetralogy and possibly in septal defects with raised pulmonary vascular resistances, the bronchial circulation is increased.

During total cardiopulmonary by-pass, the entire pulmonary circulation is excluded from the extracorporeal system. The bronchial arteries, however, continue to receive oxygenated blood from the pump-oxygenator via the aorta. A proportion of this blood returns to the superior vena cava and thus to the extracorporeal circuit. The remainder passes through collateral vessels into the left atrium via the pulmonary veins and also into the pulmonary artery.

In most centres, the lungs during total cardio-

pulmonary by-pass are held motionless but gently inflated with air or an oxygen-helium mixture. This procedure ensures alveolar patency during the time of total cardiopulmonary by-pass, and prevents alveolar damage which may occur if lungs without a pulmonary circulation are exposed to high oxygen concentrations.

Anoxia and retention of carbon dioxide in the lungs have been suggested as causes of alveolar damage during total cardiopulmonary by-pass. Hypervolaemia following total cardiopulmonary by-pass may cause pulmonary oedema or haemorrhage. A fall in the osmotic pressure due to dilution of the intracorporeal blood may result in exudation into lung tissues and alveoli. (Kirklin adds concentrated serum albumin to the system to compensate for the haemodilution in the donor blood caused by the normal saline used in initial priming of the machine and as the vehicle for the heparin.) Transient cardiac failure after by-pass may cause pulmonary oedema. Muller et al. (1958) considered that the pulmonary complications of extracorporeal circulation were related to increased pressures in the pulmonary circulation during total cardiopulmonary by-pass, arising from bronchial flow through the collateral anastomoses. They demonstrated experimentally that the pulmonary artery pressures of dogs, with a surgically-induced high bronchial arterial blood flow, rose during total cardiopulmonary by-pass with elective potassium arrest to levels compatible with pulmonary exudation and haemorrhage. An increased left atrial pressure was also observed. At autopsy, gross and microscopic pulmonary haemorrhage was seen. They suggested early ventriculotomy and left atrial venting as remedies. Ross et al. (1958) observed these findings in dogs with normal bronchial flows.

Respiratory insufficiency after by-pass occurs more frequently in infants. A bilateral thoracotomy or even a midline sternotomy may cause such pain that coughing is inhibited, with retention of secretion in the alveoli producing alveolar collapse. Early tracheotomy with repeated aspiration of secretions is then indicated.

EFFECTS OF EXTRACORPOREAL CIRCULATION ON THE HEART

The coronary flow of the normal heart in sinus rhythm is approximately 5 per cent of the resting
cardiac output. The myocardium can metabolize carbohydrate, lactate, pyruvate, ketone bodies and amino-acids. The oxygen consumption of the empty normal heart in sinus rhythm is between 20 and 30 per cent of the normal heart, beating in sinus rhythm. This suggests that 70 to 80 per cent of the oxygen consumption of the normal heart is concerned with external work (Bing, 1958).

During total cardiopulmonary by-pass, the coronary arteries are filled by retrograde flow of oxygenated blood in the ascending aorta delivered by the arterial cannula. Before ventriculotomy the coronary sinus return enters the right atrium, passes to the right ventricle and is pumped through the pulmonary circulation into the left heart, whence it is returned via the aortic valve into the aorta. The normal coronary flow and the anastomotic bronchial return represent only a small fraction of the normal cardiac output and the amount of work performed by the heart during total cardiopulmonary by-pass is negligible. After ventriculotomy the heart performs no external work. The oxygen requirements of the heart are thus greatly reduced. During adequate by-pass, coronary flow is probably normal, providing the aortic valve is competent. If by-pass is inadequate, coronary vasodilatation occurs. Read et al. (1957) showed that large coronary flows occurred with inadequate perfusion. Glenn et al. (1958) reported that the coronary circulation of dogs subjected to right heart by-pass was only slightly elevated when the arterial oxygen saturation of the perfusing blood was over 70 per cent. If this was reduced to 10 per cent, the coronary artery flow was increased sevenfold, falling to a lower but still increased level after adequate arterial oxygen saturation had been resumed. Coronary arterio-venous saturations were diminished during high coronary flow suggesting coronary vasodilatation of such a degree that a virtual coronary arterio-venous fistula existed. This may be associated with a fall in the systemic arterial pressure and thus a diminished flow to non-cardiac tissues, both during and after by-pass.

**Elective cardiac arrest.**

Elective cardiac arrest allows the surgeon to operate on a stationary heart. The methods used for achieving this are ischaemic arrest, potassium arrest and acetylcholine arrest. Each involves cross-clamping of the ascending aorta distal to the coronary ostia, interrupting the coronary circulation. Coronary sinus return is negligible and the only blood entering the heart is from the bronchial anastomotic circulation. Ischaemic arrest occurs after a period of about 5 minutes, during which time the heart continues to beat, though less vigorously and progressively more slowly. Ventricular fibrillation may occur. When the aortic clamp is released, the coronary circulation is re-established, and the heart begins to beat again, at first slowly, irregularly and weakly, but gradually returning to a vigorous sinus rhythm. Experimental studies of the coronary sinus effluent immediately after release of the aortic clamp show a metabolic acidosis due to anaerobic respiration during arrest, and gross coronary vasodilatation, with coronary flow reaching up to 80 per cent of the total flow, may occur (Glenn et al., 1958).

Melrose et al. (1955) advocated the use of potassium citrate for inducing cardiac arrest, believing that the energy requirements of the arrested heart were a fraction only of the energy requirements of the beating heart, and that, under these conditions, coronary stasis for a limited period of time was compatible with recovery of normal cardiac action. Provided the potassium citrate is injected rapidly, arrest occurs within a few seconds. After release of the aortic clamp, re-establishment of the coronary circulation flushes out the potassium citrate and the heart begins to beat and again. Bentall and Melrose (Bentall, 1958) observed that the lactic acid accumulation in the heart arrested by potassium was less than a third of that occurring when the ischaemic heart continued to beat. Elective cardiac arrest is a safe adjunct to open heart surgery (Effler et al., 1956; Gerbode and Melrose, 1958). Ross et al. (1958), however, described elevated intracardiac pressures during elective potassium arrest, producing stretching of the flaccid myocardial fibres and pulmonary haemorrhage. They advocated early ventriculotomy and atrial venting. Helmsworth et al. (1958a, b) produced experimental evidence that potassium salts may cause myocarditis or myocardial necrosis. Acetylcholine arrest (Lam et al., 1957) is used in some centres. Arrest is not so constantly achieved though an advantage may be its lack of toxicity to cardiac muscle.
The conduct of elective cardiac arrest includes monitoring by continuous recordings of the electrocardiogram and the systemic arterial pressure. During the onset of arrest, the electrocardiogram shows bradycardia, absence of atrial activity and broadening of the QRS component of the ventricular complex. Ventricular tachycardia and ventricular fibrillation may occur due to an insufficient or too slow injection of arresting agent. During arrest, the heart is in diastole, and overfilling must be prevented by early ventriculotomy or atrial venting. During recovery, the ventriculotomy should not be closed until vigorous heart action has been re-established. Following a few isolated weak ventricular beats, a regular rhythm returns, and sinus rhythm is confirmed by the electrocardiogram. This may be preceded by varying grades of heart block, ventricular tachycardia or ventricular fibrillation. Electrical defibrillation is applied to the fibrillating heart and to the heart in ventricular tachycardia, since if this latter arrhythmia is not stopped, it usually increases in rate and changes to ventricular fibrillation. When sinus rhythm has returned and the aortic pressure shows evidence of left ventricular ejection of coronary and bronchial anastomotic return, bypass may be discontinued, but if the systemic arterial pressure falls or the heart is seen to dilate due to inability to eject its contents, the by-pass should be temporarily re-established until myocardial tone has improved.

The electrocardiogram.

Permanent changes in the electrocardiogram may be observed after total cardiopulmonary bypass with ventriculotomy. Experimental and clinical studies by Zimmerman et al. (1958) report postoperative right bundle branch block, due to section of the right bundle branch during repair of low ventricular septal defects, and unavoidable surgical trauma to the right ventricular outflow tract and crista supraventricularis during right ventriculotomy and infundibular resection. Temporary or permanent complete heart block is a hazard of repair of high ventricular septal defects, the posterior sutures damaging the bundle of His. Postoperative artificial electrical pacemaking may provide an adequate heart rate in patients with complete heart block, either until sinus rhythm returns, or until idioventricular rate is rapid enough to maintain an adequate circulation.

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