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## Perfusion

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### Abstract

The value of perfusion is reasonably well established yet the field is still developing and the ultimate applications and potentialities of perfusion techniques are as yet undefined. It is a subject on which, as I am sharply aware, my knowledge is very incomplete, and I will discuss, in the main, work being carried out in my department in Glasgow Royal Infirmary and the University of Glasgow.

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# PERFUSION

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The value of perfusion is reasonably well established yet the field is still developing and the ultimate applications and potentialities of perfusion techniques are as yet undefined. It is a subject on which, as I am sharply aware, my knowledge is very incomplete, and I will discuss, in the main, work being carried out in my department in Glasgow Royal Infirmary and the University of Glasgow.

Perfusion means, as you know, literally "through pouring"—a pouring through a part or all of the body by artificial means, of blood or an equivalent fluid capable of sustaining at least for a time some or all of the vital functions of the parts concerned. It is a technique which has, of course, long been familiar to physiologists, and much of our knowledge of the function of individual organs and their components has been built up by its use in recent years. The scope and complexity of the techniques available has been greatly increased, and if to-day one uses the word without qualification the concept implied is whole-body perfusion with blood, by-passing the heart and lungs. At the present time there exists in surgery, that is to say clinical surgery and related laboratory work, five main practical applications of the technique of perfusion.

1. Exclusion of the heart and usually the lungs from the blood circuit (which is meantime maintained by artificial means) in order to permit operation in a precise and orderly fashion on the heart.
2. The extension of this technique to include profound hypothermia, the circulation being maintained artificially until the temperature of the body is reduced to levels much below those at which efficient cardiac action is possible, after which it may be allowed to stop for quite long periods.
3. Maintenance or support of the circulation which is being acutely impeded either by recoverable cardiac embarrassment or modifiable obstruction to the vascular channels, usually in the lungs.
4. The introduction of powerful chemotherapeutic agents into an isolated sector of the vascular bed in concentrations that would be intolerable or even lethal if generally distributed.
5. The perfusion of organs such as the heart, the adrenal gland, the mammary gland, the kidney and so forth in order to study problems in their physiology and in particular their response to hormones.

Imaginative experimentalists of every age since the circulation and functions of the blood were first determined must have dreamed of the possibilities that would be opened up if one could substitute a machine, a pump, for the heart. The present-day reasonably satisfactory solution of the problems involved is based upon many years of dedicated work on animals by John Gibbon of Philadelphia, a surgeon and physiologist. The clinical develop-

ment was probably due in the main to De Wall, Lillehei and Varco in Minneapolis, Kirklin in the Mayo Clinic, Clowes in Cleveland and after them a great host of others. The requirements for an efficient whole-body perfusion are :

- a pump
- an oxygenator
- an abundant supply of heparinised blood
- and efficient connections to the patient.

The pump needless to say replaces the heart. Initially there was an impression that possibly there was some inherent merit in a pulsatile circulation and some pumps, especially the earliest of those designed by Denis Melrose in this country, were designed to provide an intermittent systolic ejection. It soon became apparent, however, that the technical requirements were simply adequate output and minimal trauma to the blood. In normothermic or near-normothermic conditions the output of the pump should come fairly close to that of the heart under basal conditions. It is found that this relates in a more linear fashion to the surface area of the subject than to his weight—about 2.4 litres per square metre of surface area per minute. It is easier to maintain this rate of pumping in children than in adults for whom a pump output of 5 litres per minute may be required. To circulate rapidly this amount of blood through tubes of modest calibre demands forces which, applied even by the most efficient sort of pump, tend to be rather violent and to inflict physical damage on the blood, especially on fibrinogen and platelets but to some extent on all the cellular components and on the plasma proteins. Many kinds of pump are available, all reasonably satisfactory. The most widely used is a roller pump running over a loop of elastic plastic tubing which refills by gravity and by recoil. This sort of pump gives a fairly continuous non-pulsatile output.

The oxygenator represents the lung of the apparatus. Its function is to expose blood to an atmosphere consisting largely of oxygen over as wide a surface as possible. This surface may be provided by bubbling oxygen through blood, filming blood in oxygen or exposing it to oxygen across a fine membrane; but at their best and most ambitious oxygenators can provide only a fraction of the area for gaseous interchange represented by the alveolar surface of the lungs and in practice the factor which limits the output of the heart-lung machine is the capacity of the oxygenator to maintain adequate oxygenation and removal of carbon dioxide for the volume of blood passing through. If the speed of the blood flow is increased beyond a certain point, oxygenation falls off rather steeply. The massive oxygenator of the Melrose machine has a filming area of 1.3 square metres. This has been somewhat increased in the most recent modification by Gerbode. The total area of the pulmonary alveoli in a human adult is about 90 square metres!

To carry out efficiently a total body perfusion a large volume of blood is required and this must be by all known tests identical in group with that of the recipient. The blood must be as nearly freshly drawn as possible, preferably within a few hours of perfusion and its clotting mechanism must be held in suspense by the use of heparin. The amount of blood required is often large and a perfusion of an adult may require 10 litres. If many perfusions are being carried out, it is difficult repeatedly to obtain so much accurately cross-matched blood and this problem is obviously likely to increase rather than diminish. At the present time I have to give 3 weeks' notice in order that arrangements can be made for the supply of blood for a perfusion. Attempts are being made to ease some of the difficulties involved and in particular to make blood more swiftly available for perfusion, and to permit

of the use for other purposes of blood drawn primarily for perfusion. For example blood preserved in "ACD mixture" or "Edglugate Mg." is found to store fairly well, and if it is to be used for perfusion it may be heparinised and recalcified just before use. Finally some evidence is accumulating that blood cells may be preserved deep-frozen in a water-glycerol mixture, and that after very long periods they may be thawed, washed and re-suspended in plasma and used as if they were fresh. This rather elaborate technique could make possible the establishment of a true blood bank containing blood of all conceivable groups in a quickly-available state.

At the end of the operation, the clotting mechanism of the blood must be restored as fully as possible by the administration of an appropriate dose of an antagonist to heparin. The substance originally used in this way was protamine sulphate. This is reasonably effective, but has certain disadvantages such as a troublesome hypotensive action, and Polybrene (hexadimethrene bromide) is probably superior. After a prolonged perfusion the blood remaining in the patient will be found to be significantly deficient in fibrinogen and this also may require to be added. Sometimes—fortunately rarely—the terrifying complication of fibrinolysis may follow any major bodily trauma, especially if associated with hypotension or haemolysis. It is due to activation of the plasmin mechanism in the blood, and it is liable to result in a progressive and hardly controllable haemorrhagic state. The platelet count also is markedly reduced to about 25 per cent of its original value. This appears not to be a desperately serious matter and at most the infusion, at the end of the operation, of a modest amount of fresh carefully-drawn citrated blood, will restore adequate platelet action.

TABLE 1.

<b>Indications for Whole Body Perfusion</b>	
<b>Clear :</b>	
V.S.D. ....	Foramen primum type of A.S.D.
Fallot's Tetralogy .....	Other severe developmental lesions
<b>Conditional :</b>	
Aortic stenosis .....	Myocardial infarct and aneurysm
Complicated mitral disease ...	Coronary artery disease
<b>Borderline :</b>	
A.S.D. ....	Pulmonic valvular stenosis

The heart-lung machine is coupled to the patient's circulation on the venous and on the arterial side. The venous connections usually consist of two plastic cannulae introduced into the cavac via the right atrium. In some techniques the atrium itself is cannulated and sometimes, as in Drew's double perfusion technique both atria are cannulated. The blood may be re-introduced on the arterial side at almost any convenient point, usually in the femoral or the external iliac artery, or occasionally the aorta itself. The blood moves freely and swiftly throughout the arterial tree and it is best simply to introduce a cannula of as wide a bore as possible into the most accessible capacious artery available.

#### INDICATIONS FOR WHOLE-BODY PERFUSION (Table 1).

At the present moment the primary indication and probably the only one is the intention to carry out upon the heart major operations demanding more than a few minutes of interruption of the circulation (in conditions of

moderate hypothermia—between 28°C. and 30°C.—the circulation of the blood may be stopped by caval compression for as long as 8 minutes without irreparable damage to the brain). The clearest indications are ventricular septal defect, Fallot's tetralogy and the most complicated types of atrial septal defect—persistent foramen primum and persistent atrioventricular canal. Conditional indications for by-pass are aortic stenosis, complicated cases of mitral valve disease, myocardial infarct or aneurysm and coronary arterial disease. If facilities for efficient by-pass are freely available, some surgeons would use by-pass for such easily treated lesions as foramen secundum type of A.S.D. and pulmonic valvular stenosis, which the majority would still treat by inflow occlusion under hypothermia.

### CARDIOPLEGIA

The continuous activity of the heart makes it difficult to stitch and patch moving parts with accuracy and the field tends to be obscured by ejected blood, coming ultimately in the main from coronary return and bronchial return, the latter being very large in many cases of cyanotic heart disease. The principal danger is injury to important vital structures and in particular to the atrio-ventricular bundle which in all cases of ventricular septal defect, whether simple or associated with other lesions, runs very close to the posterior and inferior margins of the septal opening. It lies in the main to the left side of the septum, and careful stitching may avoid it but damage to the bundle leads to heart block and if this persists it is usually fatal after a time. Cardioplegia is, however, a two-edged weapon. On the one hand it facilitates operation and therefore renders the bundle of His less liable to casual injury, on the other the effect of encroachment on the bundle is not so immediately perceptible as it is when the heart is beating. The heart may be arrested by a variety of methods. Possibly the most physiological is to use parasympathomimetic substances such as acetylcholine or acetylcholine and prostigmine. Introduced into the coronary circulation these will exercise an intense vagal action and stop the heart. On the other hand the heart may be stopped chemically. Cardiac action is depressed and conduction slowed by potassium ions while conduction is supported and accelerated by calcium ions. Infusion of potassium citrate has a double effect of adding potassium ions to the extracellular fluid and diminishing the ionisation of calcium by virtue of the citrate content. A third chemical which has been used either alone or in combination with others is adenosine triphosphate.

In Scandinavia anoxic arrest is widely used by cross-clamping the aorta and so cutting off the coronary circulation. After a time the heart slows and finally it stops with or without passing through a phase of ventricular fibrillation. When the coronary circulation is restored by removal of the aortic clamp, the heart re-starts, commonly with ventricular fibrillation, but this arrhythmia is easily converted electrically.

The newest method of producing cardiac arrest is by local hypothermia, perfusing the coronary vessels with ice-cold oxygenated blood. This is probably the best method of all because it is reliable, it produces no chemical disturbance and it permits the heart to be arrested with safety for quite long periods—probably 30 minutes to an hour—and it is immediately reversible without impairment of the efficiency of muscular contraction by re-infusion of warm blood from the general by-pass circulation.

### COMPLICATIONS OF BY-PASS

The general complications of by-pass surgery are as for any major surgery. The special ones are myocardial insufficiency, infection, bleeding and

pneumonitis.

Myocardial insufficiency may be temporary or permanent, temporary related, for example, to chemical upset, electrolyte imbalance, too slow recovery from a period of asphyxia or the traumatic injury inevitable in a cardiotomy and suture. The insufficiency may be more permanent and irrecoverable if, for example, the bundle of His has been interrupted or if the heart has been so deformed pre-operatively that its chambers are incapable of doing the work demanded of them following anatomical "cure" of the defect.

Infection is particularly dangerous, of course, in that it may settle upon the operation area in the heart and be very difficult to eradicate. Particularly troublesome organisms have been the now ubiquitous and unregenerate *Staphylococcus aureus* and *Pseudomonas pyocyanea*.

Possibly the most characteristic complication of by-pass is bleeding related to thrombocytopenia, fibrinogenopenia and sometimes fibrinolysis. It is insured against by meticulous haemostasis before closing, restoration of normothermic conditions (hypothermia slows the clotting mechanism), the administration of fresh blood or fibrinogen solutions.

Finally, a characteristic type of complication is the post-perfusion pneumonitis, a rather diffuse process involving both the vascular tree and alveoli of the lungs. Its aetiology is obscure. It is not known whether it is in part embolic due to emboli of, for example, fibrin, minute globules of anti-foam, or fat or what you will. The alveolar pathology may be related to the rather long period of hypoventilation.

## RESULTS

With a well-trained and practised team a very low mortality and a high success rate is nowadays attainable with correctable lesions. It must be remembered that some lesions are anatomically incorrigible. For example, there may be no pulmonary artery. An only slightly less daunting problem is offered by cases of complete transposition of the great vessels with wide septal defects. These represent a technical challenge which is unlikely ever to be immediately met and even following a successful operation there must inevitably be a very long period of re-education of the heart, for redeployment and development of myocardial forces to cope with a circulation that has been abruptly brought up to the normal post-natal pattern with a high-pressure and a low-pressure circuit.

## RELIEF OF CONGESTIVE FAILURE

Some ten years ago I talked with Professor Ian Aird at the Postgraduate Medical School in London, where he had recently gone from Edinburgh. He told me of work being done by Denis Mcrose to develop a heart-lung machine. Asked how he would propose to use it, he said with one of his highly characteristic sharply perceptive flashes of inspiration: "I should like to try it first of all on cases of congestive cardiac failure to take blood from the overloaded venous side, oxygenate it and inject it on the arterial side."

It is surprising that the perfusion technique has not been used more extensively in this frequently-met problem. There may be many instances in which a temporary but potentially lethal cardiac embarrassment could be relieved by the use of a machine which would supplement the propulsive power of the heart and the oxygenating power of the lungs over a period of one or two hours and permit them to resume their task refreshed. Never-

theless I believe that heart-lung by-pass has been little used clinically in this field.

However, in my laboratory, William Bain has been working over the past year on the relief of acute pulmonary hypertension by heart-lung by-pass. The pulmonary hypertension is produced by the injection of a suspension of small glass beads into the pulmonary artery of animals. In appropriate doses this leads to a sharp rise in pulmonary vascular resistance, severe overloading and overstrain of the right heart and cardiac failure culminating in death. If, however, the blood in the right atrium is allowed to flow out, is oxygenated and pumped back on the arterial side, the congestion is relieved and normal blood pressure and haemodynamics can be restored.

There are surely many cases in clinical medicine in which patients suffering from congestive failure or *cor pulmonale* could be markedly helped by a period on by-pass if the latter could be instituted without too great inconvenience and at a very low risk. A benefit comparable to those conferred by haemodialysis in acute renal failure, or assisted respiration and oxygenation in respiratory failure with carbon-dioxide narcosis, should be within reach.

#### HYPOTHERMIA WITH CARDIAC BY-PASS -

As indicated above it is possible by lowering the general temperature of the body to prolong the period during which the circulation even to the brain may safely be arrested, up to as long as eight minutes. This process cannot be extended indefinitely downwards, however, because at about 28°C. the myocardium of the ventricles becomes irritable, ventricular fibrillation occurs and effective cardiac action therefore ceases. Ventricular fibrillation cannot be reversed easily at these low temperatures. Consequently it has become customary to use some technique of by-pass or perfusion if it is desired to take the temperature down below 28°C. The circulation of the blood is maintained independently of the cardiac action and when the temperature is sufficiently low the pumping is stopped, the circulation of the blood ceases and the necessary operative procedure, usually on the heart but occasionally on the brain, may proceed in a virtually bloodless field under greatly simplified operating conditions.

When the operation is finished the pump is started once more and the blood is now re-heated relatively quickly, with fluid in the jacket of the heat-exchanger at about 45°C. As the temperature of the heart rises its electrical action is resumed, usually in ventricular fibrillation, but this is easily reversed with a single electric shock when the temperature reaches about 30°C.

One of the most important steps forward in this field was made by Drew of the Westminster Hospital in London using a double by-pass technique, one circuit containing the heat-exchanger by-passing the left heart and the other the right, the blood being pumped through the patient's own lungs for its oxygenation. The lungs are, of course, more efficient than any conceivable artificial oxygenator and the blood is less traumatized. However, it is not always convenient to cannulate the patient's pulmonary artery and most surgeons prefer to use a heat-exchanger in association with a heart-lung machine providing total body by-pass.

Murray Harper in my department is studying the effect on general and cerebral metabolism of profound hypothermia and circulatory arrest. He has found, as have others, that the oxygen consumption falls as the temperature falls and that, for example, at a muscle temperature of 30°C. the oxygen consumption is about 58 per cent. of the original value. At 15°C. it has

fallen to only 12 per cent. Thereafter the saving in oxygen consumption appears to diminish. In fact there is not a great deal to be gained by reducing the temperature below about 10°C.

During the subsequent phase of re-heating and restoration of the circulation there is a considerable release of lactic acid, presumably formed by anaerobic glycolysis during the phase of circulatory arrest. This produces a metabolic acidosis which, however, can readily be relieved by the administration of sodium bicarbonate and the whole complex process seems to be reasonably well tolerated. The main technical difficulty which may arise in association with this method is sludging of the blood, which may occur in small vessels at low temperatures. In the clinical field Drew has used the method with notable success, producing cardiac arrest of up to 45 minutes at temperatures below 15°C. This time is certainly adequate for most intra-cardiac surgical procedures. The technical limits of the technique have not yet, however, been fully determined.

This consideration applies in some degree to all methods of perfusion—of the whole body, with or without hypothermia, of regions, with cancericidal drugs or of organs, with active drugs or hormones. These afford an unusually good opportunity of seeing and learning more about human physiology.

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