# TECHNIQUES IN EXTRACORPOREAL CIRCULATION

*Second Edition*

*Edited by*

**Marian I. Ionescu, MD, FACS**

# TECHNIQUES IN EXTRACORPOREAL CIRCULATION

*Second Edition*

*Edited by*

**Marian I. Ionescu, MD, FACS**

*Consultant Cardiothoracic Surgeon,*
*The General Infirmary at Leeds,*

*Senior Clinical Lecturer in Cardiothoracic Surgery*
*at Leeds University, Leeds, England*



**Butterworths**

London Boston Sydney Wellington Durban Toronto

First published 1976
Second edition 1981



**British Library cataloguing in Publication Data**

Techniques in extracorporeal circulation. – 2nd ed.
1. Cardiovascular system – Surgery
2. Blood – Circulation, Artificial
I. Ionescu, Marian I.
617'.41 RD598

ISBN 0-407-00173-5

Typeset by Butterworths Litho Preparation Department
Printed in England by Butler & Tanner Ltd, London and Frome

# 1

# Physiology and Pathophysiology of Extracorporeal Circulation

Robert H. Bartlett and Alan B. Gazzaniga

*omnem movere lapidem*

# Introduction

The term 'physiology' was coined by the great Dutch physician Boerhaave to describe the study of interdependent organ function under normal conditions. Extracorporeal circulation (ECC) imposes several abnormal conditions which lead to a series of changes in normal organ function. The physiology of ECC, for purposes of this discussion, refers to interdependent organ function during conditions of venoarterial cardiopulmonary bypass with an extracorporeal device. Physiological function under these conditions differs considerably from normal physiology. The changes occurring with ECC are outlined in *Table 1.1*. The normal functions of blood flow, gas exchange, blood surface interface effects and reticuloendothelial function are the physiologic functions which are replaced in total or in part by the extracorporeal device. Subsequent changes in neurological, renal, hepatic and other functions are secondary to these substitutions. The mechanical and pharmacological factors which are inherent in the design of the device (and hence are responsible for physiologic changes) are also listed in *Table 1.1*.

Abnormal, deteriorating, or inadequate organ function associated with extracorporeal circulation is the pathophysiology of ECC. It is difficult, if not impossible, to separate uniform and ubiquitous changes in organ

**TABLE 1.1**
The physiology and pharmacology of extracorporeal circulation compared to normal circulation and pulmonary function

| *Normal function* | *Physiological changes with ECC* | *Mechanical factors* | *Pharmacological factors* |
|---|---|---|---|
| | ↓ Total flow<br>Negative venous P | Venous cannula size | Steroids |
| | ↑ Adrenergic response | | Adrenergic blockers |
| | ↑ Renin-angiotensin | Arterial cannula site | |
| | Abnormal distribution | | Diuretics |
| Blood flow | Non-pulsatile<br>Non-servo | Pump characteristics | Volume expanders |
| | ↓ Tissue washout<br>↓ Oxygen delivery<br>Acidosis | Heat exchanger | Hypothermia<br>Buffers-tris $HCO_3^-$ |
| Gas exchange | $O_2 - CO_2$ exchange requires large blood volume | Oxygenator<br>Disc<br>Bubble<br>Membrane | |
| | Microbubbles | | Defoamer |
| | Emboli and aggregates | Reservoirs, connectors, tubing | ? Platelet-active drugs |
| Blood-endothelial interface | Stagnant zones<br>Anticoagulation | Surface coating | Heparin |
| | ↑ Fibrinolytic activity | | Priming solutions |
| | ↓ Platelet function | Coronary suction | |
| Reticuloendothelial function | Blood dilution | | Haemodilution |
| | Tissue histiocytes loaded | Filters | |
| | Phagocytosis ↓ | | |

function associated with ECC from specific organ damage or deteriorating function due to our imperfect attempts to substitute devices for the heart and lungs. Hence, while some aspects of ECC can be clearly identified as pathophysiology (gross air embolism for example), in the current state of the art other aspects cannot be separated from normal function of the apparatus (platelet aggregate formation for example). In this sense *Table 1.1* represents both the physiology of ECC and the inherent pathophysiology.

## Haemodynamics, blood volume and endocrine response to cardiopulmonary bypass

With the blood heparinized and venous and arterial cannulae in place, venoarterial bypass is instituted by draining venous blood via siphon into the extracorporeal device and returning a like amount of blood into the arterial circulation. As heart-lung bypass is gradually begun, flow through the pulmonary artery falls off faster than bypass flow increases, hence total flow in the systemic circulation decreases. These phenomena are diagrammed in *Figure 1.1*. Peripheral and pulmonary hypotension occur, and the final flow on total bypass may be less than the original baseline flow at the same blood volume. Hypotension is probably due to the haemodilution of the oxygenator priming solution[82]. Haemodilution reduces blood viscosity and secondarily systemic vascular resistance. Hypotension may occur when

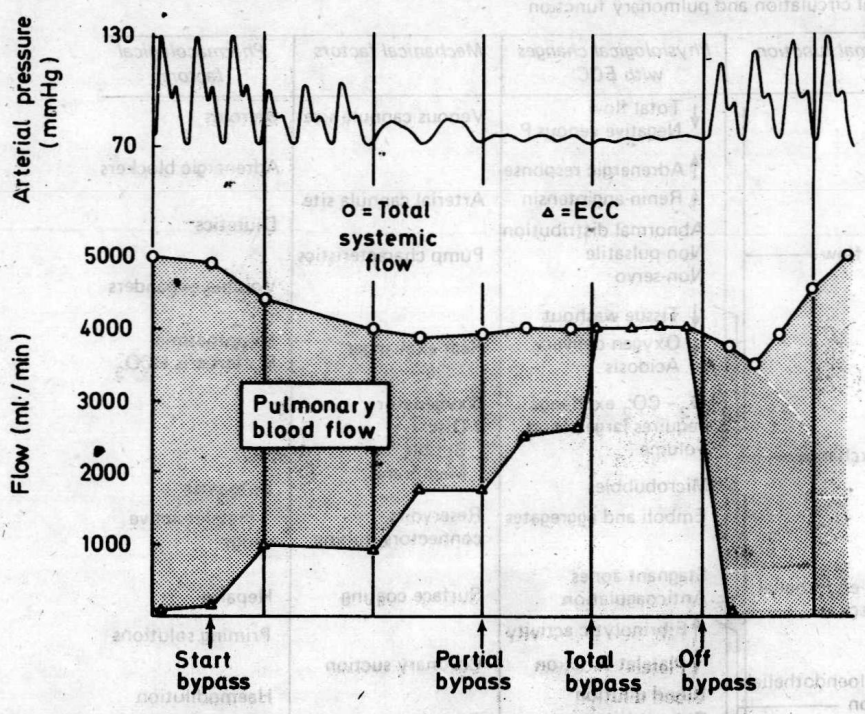


*Figure 1.1* Changes in pulmonary and systemic haemodynamics as cardiopulmonary bypass is instituted

whole blood prime is used and therefore changes in viscosity do not fully explain the phenomenon. Others have felt that release of vasoactive substances occurs when bypass is begun and this produces hypotension[118].

If blood flow is held constant during perfusion, there will be a gradual decrease in the venous reservoir which requires transfusion replacement. The loss in blood volume might be explained by loss at the surgical site as well as sequestration into dissected tissues. Another factor is that oxygenator-priming solutions are usually haemodiluted to a varying degree depending on the surgical team's preference and particular case involved. Breckenridge, Digerness and Kirklin[30] and Cohn, Angell and Shumway[39] noted as much as a 20 per cent increase in extracellular fluid space following cardiopulmonary bypass. During the early experience with clinical perfusion, it was felt that a 'hidden reduction' in blood volume was due to sequestration secondary to homologous transfusion reaction or due to stagnant areas in the circulation[116]. Studies by Giannelli *et al.*[70] seem to eliminate this as a cause for alterations in blood volume during ECC. Plasma volume loss may also result from diuresis induced by adding mannitol or a potent diuretic to the oxygenator-priming solution. If blood volume replacement does not occur, perfusion of tissues is not optimal and metabolic acidosis follows.

As bypass is continued, there is generalized increase in sympathetic tone due to release of epinephrine from the adrenal medulla and norepinephrine from sympathetic nerve endings[154, 181]. This release of catecholamines is a result of stimulation of both the carotid sinus and aortic baroreceptors[84]. These receptors appear to respond to low-pulse amplitude which occurs during non-pulsatile perfusion[176], when total flow is decreased. Renin secretion from the kidney is increased in response to the decrease in mean arterial pressure and reduction in left atrial pressure. The increase in sympathetic tone results in arteriolar constriction, returning the arterial pressure toward normal.

If total flow remains constant, with the increase in pressure blood is preferentially directed to organs which are more responsive to increased perfusion pressure and least dependent on arteriolar tone. This includes the two most important organs – the brain and the heart. At the same time blood flow is most decreased in organs in which the vasculature is sensitive to an increased arteriolar tone and least sensitive to increased perfusion pressure such as skin and skeletal muscle. The resulting redistribution of blood flow under these circumstances has been studied by several investigators[113, 160, 161]. The results indicate that during cardiopulmonary bypass there is a redistribution of blood flow that results from factors other than alterations in pulse pressure or the use of non-pulsatile perfusion. The factors include anaesthesia, peripheral emboli, amount of haemodilution, effects on blood elements, etc. This neuroendocrine response and redistribution phenomenon may be diminished by alpha-adrenergic blocking anaesthetic drugs, such as halothane, in which case the arterial pressure remains relatively low under conditions of constant flow. Adding to the blood volume causes an increase in perfusion pressure if flow is held constant. Occasionally the neuroendocrine sympathetic response will dominate the haemodynamics, creating the syndrome of hypertension at

constant flow with poor organ perfusion which may be serious enough to require definite alpha-adrenergic pharmacologic blockade[35, 65, 114, 122]. Usually at a constant but less than normal flow, the pressure will reflect a balance of increased sympathetic tone and alpha blockade induced by anaesthesia.

The haemodynamics of ECC have been evaluated by Gazzaniga *et al.*[64, 65] who utilized the method of skeletal muscle surface pH measurement to evaluate the perfusion metabolism relationship in that specific tissue. Since the arterial blood under conditions of anaesthesia or bypass is completely saturated with oxygen, decreasing muscle surface pH is a direct reflection of decreasing capillary flow. An initial decrease in muscle surface pH occurs with the induction of anaesthesia and its attendant minor myocardial depressant effects, demonstrating the sensitivity of the measurement. With the institution of cardiopulmonary bypass, muscle surface pH drops remarkably and then gradually continues to fall during the period of ECC, indicating inadequate tissue perfusion. The addition of blood volume results in an increase in arterial pressure at constant flow and minimizes to some extent the decreased organ perfusion resulting in a low plateau of muscle surface pH rather than a continuing fall. Preloading with volume can further minimize the low flow. The addition of alpha-adrenergic blockade reverses or nearly eliminates the muscle surface acidosis, indicating the major role of alpha-adrenergic stimulation during ECC[66]. Venous pH, as a more general and less sensitive measure of organ

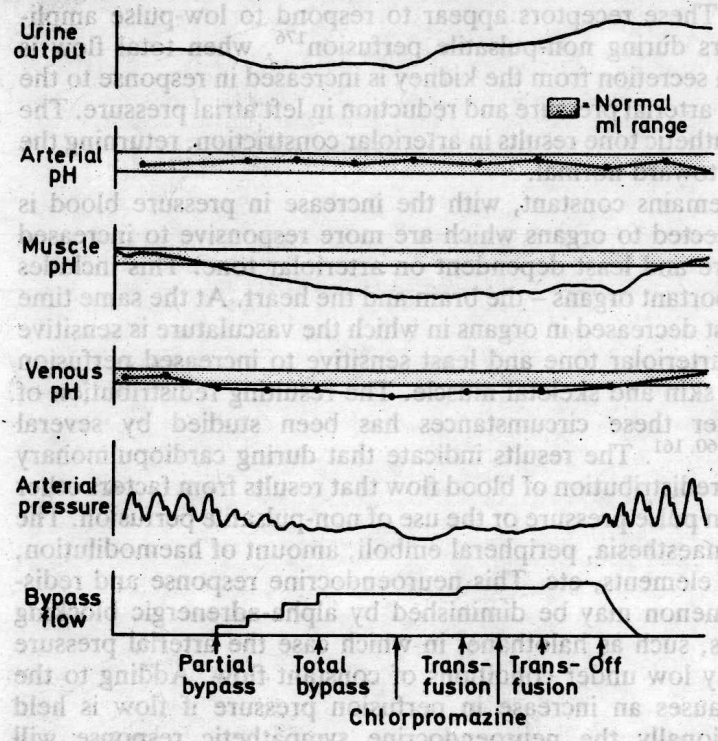


*Figure 1.2* Muscle surface pH during extracorporeal circulation, as a measure of the tissue perfusion. Increasing blood volume and decreasing arteriolar sympathetic tone resulted in improved perfusion

perfusion, falls during bypass at a constant $P_{CO_2}$. More specifically, a condition of metabolic acidosis can be detected by measurement of pH and $P_{CO_2}$[114]. Urine output usually falls during bypass, although the concomitant effects of antidiuretic endocrine stimuli and pharmacologically induced diuresis by haemodilution, mannitol, or diuretics, make observation of the urine output a questionable indicator of perfusion in a clinical situation. These effects are summarized in *Figure 1.2*.

**Mechanical limitations to physiological cardiopulmonary bypass**

Even with conditions of alpha-blockade and volume loading, can normal peripheral blood flow of 3.1 ℓ/min per $m^2$ be achieved with an artificial device? Probably so, but at the expense of somewhat increased risk due to increased flow in the extracorporeal circuit (i.e. high arterial line pressure, faster pumping rates, more surface exposure per minute, more chance of micro-air embolism, possibly greater chance of aggregate embolism). With the current state of the art, bypass flow of 2.2 to 2.4 ℓ/min per $m^2$ is generally considered an adequate and safe compromise[153, 182]. The resulting moderate flow state is well tolerated for the one to two hours required for most intracardiac operations and this does not result in any permanent sequelae. Hence flow levels of 2.4 ℓ/min per $m^2$ have come to be considered 'normal' physiology of extracorporeal circulation during condition of total cardiopulmonary bypass, although this need not necessarily be the case.

Mechanical factors affecting bypass flow rates include the size and position of venous and arterial cannulae, the nature of the pump and type of oxygenator. The flow obtained in total bypass is a function of the blood volume and the diameter of the venous lines. Assuming that 100 $cmH_2O$ of siphon suction is applied to the venous cannulae, the maximal possible flow increases linearly with tubing size until high flow rates are achieved[143]. Under conditions of inadequate venous return, whether due to low blood volume or low arterial perfusion with sequestration, the flow through the venous line is regulated by the collapsing of vena cavae around the venous cannulae. Under conditions of adequate venous return the bypass flow is limited by the size and length of the venous drainage lines. The resistance to flow is directly related to the length of tubing and inversely related to the fourth power of the radius of the tubing[18].

Under the conditions of non-pulsatile flow the size of the arterial cannula is not a major consideration. If 5 ℓ/min is pumped 5 ℓ/min will emanate from the cannula orifice. If the cannula is long and narrow, high pressure in the arterial perfusion line will result, with the possibility of tubing separation or rupture, but adequate flow is still delivered. The jet effects imposed by such an arterial constriction are generally not significant enough to cause blood damage and they become important only if the jet is directed at the left subclavian or carotid orifice, or at a specific atherosclerotic plaque[106]. Whether arterial perfusion is provided retrograde via a femoral or iliac artery or prograde via the aortic arch or subclavian artery, it appears to have no effect on the physiology of ECC under conditions of total bypass or under conditions of partial bypass when lung function is normal.

Resistance to flow in the arterial cannula does become an important factor if pulsatile flow is desired in the extracorporeal circuit. Under conditions of pulsatile pumping, flow rates during the systolic phase may be five to ten times the baseline minute flow rate. Resistance in a small arterial cannula may become a critical limiting factor by damping the pulse contour and reaching the point of significant jet effect, causing red cell damage.

Pulsatile flow during ECC has been a controversial subject. Since blood flow is normally pulsatile it would seem desirable to try to emulate this pulse contour with a mechanical device. There is universal agreement that the kidney 'interprets' non-pulsatile flow as inadequate flow, resulting in renin production and antidiuresis. This phenomenon, first described over 25 years ago, has been found by all investigators[76, 103, 121, 183, 196]. Several groups could find no other effects of non-pulsatile total body perfusion[28, 83, 161, 200]. However, equally competent researchers have reported a syndrome of high systemic vascular resistance, high blood catecholamine levels and poor tissue perfusion, resulting in cerebral changes, renal failure and severe lactic acidosis[50, 154, 165]. Trinkle *et al.* found this syndrome during non-pulsatile perfusion in animals[186], but found an equal incidence of the poor perfusion syndrome in both pulsatile and non-pulsatile flow during cardiac surgery in man[185]. These apparent contradictions can be resolved by careful examination of the experimental methods correlated with the classic studies of Harrison *et al.*[84, 85].

Normally, blood flow is approximately 110 ml/kg body weight with a pulse amplitude of 20–40 mmHg (with some species variations). The studies that demonstrated acidosis and organ failure during non-pulsatile flow were all conducted at flow rates ranging from 60 to 100 ml/kg[50, 154, 165, 172, 183, 186]. Those investigators who found no difference between pulsatile and non-pulsatile flow used total perfusion rates of 130–200 ml/kg[28, 83, 161, 200]. This relationship could have been predicted from the studies of Harrison *et al.*[84, 85] who showed that adrenal catecholamine secretion is regulated in part by carotid sinus baroreceptors. Decreased pulse amplitude caused maximal catecholamine output when total flow was less than normal, but minimal catecholamine output during normal and above normal flow rates. From Harrison's findings, one might expect no difference between normal flow, pulsatile perfusion and non-pulsatile perfusion at flow rates over 110 ml/kg. The high-resistance-acidosis syndrome would occur during non-pulsatile perfusion only at flow rates of 80–110 ml/kg, and the high-resistance-acidosis syndrome during both pulsatile and non-pulsatile perfusion at flow rates less than 70 ml/kg. This corresponds almost exactly to the reports listed above. Harrison's studies and most of the comparative studies listed above were carried out at 37°C. The effects of hypothermia and its relationship to normal blood flow requirement of the carotid sinus adrenal axis have not been thoroughly studied. This probably accounts for some of the variations seen during clinical cases[139, 185].

The implications of these studies for total cardiopulmonary bypass in cardiac surgery are significant as total perfusion is usually carried out at flow rates of 70–100 ml/kg. At this abnormally low flow rate the adrenal catecholamine secretion is increased by the decreased pulse amplitude,

hence pulsatile flow[31] or alpha-blockade should be used to ameliorate the systemic effects of the altered flow pattern. During partial cardiopulmonary bypass for life support, total flow should be maintained as near normal as possible, and should be regulated by whatever means necessary to assure a pulse amplitude of 15 mmHg or more.

## Gas exchange and oxygen delivery

Gas exchange has proved to be the easiest problem of ECC. Flowing blood is exposed to oxygen either directly or through a gas-permeable membrane. Oxygen diffuses into the blood plasma because of a gradient between high $P_{O_2}$ in the gas phase and the low $P_{O_2}$ in mixed venous blood. Oxygen then diffuses from the plasma through the red cell membrane to combine with unsaturated haemoglobin. The chemical binding of oxygen to haemoglobin proceeds very rapidly and the limiting factor in oxygenation of flowing blood is the rate of oxygen diffusion through plasma[15]. Hence, the thickness of the blood film between gas bubbles or surfaces, or between gas exchange membranes becomes the rate-limiting factor. $CO_2$ diffuses out of the flowing blood in the gas exchange device because of the gradient between the $P_{CO_2}$ in mixed venous blood and the partial pressure of $CO_2$ in the ventilating gas. Although the gradient for $CO_2$ exchange is relatively low and can never be greater than the mixed venous $P_{CO_2}$, the rate of diffusion of $CO_2$ through plasma is so rapid that $CO_2$ removal always proceeds more efficiently than oxygenation. Hence, to avoid excess $CO_2$ removal with its attendant alkalosis, the gradient is diminished by adding $CO_2$ to the ventilating gas or by reducing the gas flow.

### Oxygenator performance

The performance characteristics of the gas exchange device must be thoroughly documented to plan the best extracorporeal circuit for any given patient. Since $CO_2$ removal is almost invariably greater than oxygenation, it is sufficient to describe the performance of gas exchange devices in terms of their oxygenating efficiency. The following factors must be known about the gas exchange device. How much oxygen can actually be supplied per minute? How much oxygen can be supplied under conditions of variable blood flow and variable mixed venous saturation? How much $O_2$ can be supplied at flow rates which are compatible with adequate perfusion for the patient in question (i.e. at least 2.4 $\ell$/min per $m^2$)? What flow of ventilating gas is required? How much foreign surface is exposed to the flowing blood (this number is easy to derive for membrane oxygenators, but much more difficult for gas interface oxygenators)? What effects does the gas exchange device have on the components of flowing blood, if any?

Many of these factors have been conveniently combined into a single expression of oxygenator performance defined as *rated flow*[60]. The rated flow is the flow at which blood leaving the oxygenator is 95 per cent saturated, under the conditions of normal mixed venous blood inflow. In other words, when venous blood (haemoglobin 15 g/100 ml $P_{O_2}$, 40 mmHg,

saturation 65 per cent, $O_2$ content 15ml/100 ml) is pumped through a gas exchange device at 100 ml/min, the outflow blood will be 100 per cent saturated ($Po_2$ 150mmHg, $O_2$ content 20 ml/100 ml). The amount of $O_2$ actually delivered by the device is determined by the flow rate and the arteriovenous (AV) difference. In this example the $O_2$ delivery is 5 ml/100 ml blood × 100 ml/min = 5 ml $O_2$ delivery/min. As blood flow through the device is increased, a point is reached at which the limiting factor is the thickness of the blood film and the rate at which $O_2$ diffuses through that particular film. When that point is exceeded, the outflow blood will exit at less than 100 per cent saturation. The rated flow for a given device is that flow at which this limitation is reached. The *rated $O_2$ delivery* is the amount of $O_2$ that can be taken up by the blood at the rated flow. The upper limit of $O_2$ delivery is related to the flow and to the amount of unsaturated haemoglobin presented to the oxygenator per minute. If total bypass flow is decreased at a constant level of tissue oxygen consumption, venous saturation must decrease as more oxygen is extracted from the flowing blood. As long as this does not exceed the oxygenating capability of the gas exchange device, the oxygenator will compensate and function at a wider arteriovenous (AV) difference. Some of these variables are outlined in *Figure 1.3*, in which the oxygen delivery per minute is

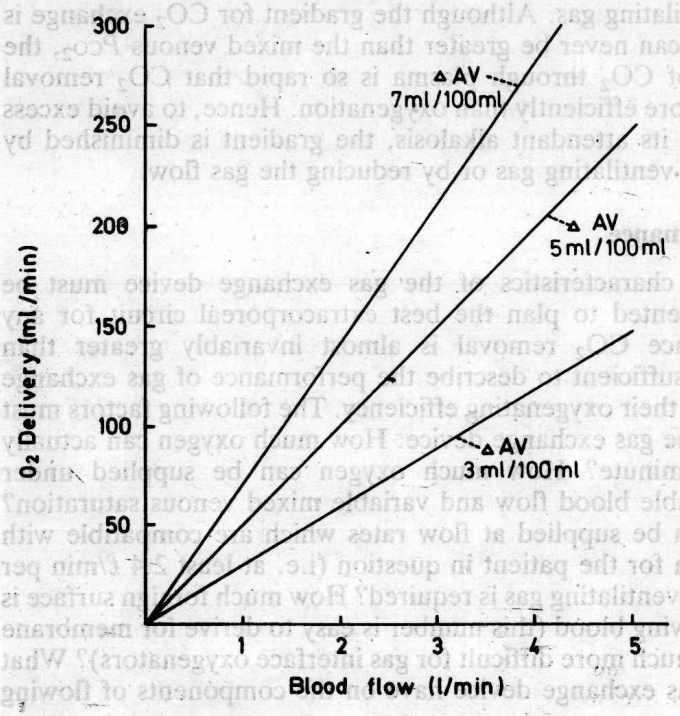


*Figure 1.3* Oxygen delivery is directly related to blood flow and arteriovenous difference. The maximum oxygen that can be delivered for a given blood flow at a given venous saturation is shown here. This represents the maximum amount of oxygen delivery that could be accomplished by a gas exchange device under a given set of flow and inlet conditions

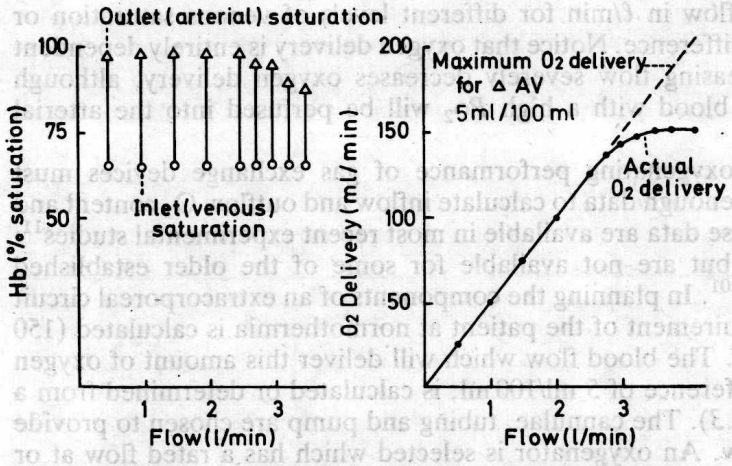


*Figure 1.4* The concept of rated flow. A hypothetical gas exchange device has a maximum oxygen transfer capability of 150 ml/min based on the surface area and blood flow characteristics. As long as the oxygen transport capability of flowing blood is less than 150 ml/min fully saturated blood leaves the oxygenator. When the oxygen transport capability of flowing blood exceeds this amount, desaturated blood results. Under normal venous blood conditions this occurs at a flow rate of 3 ℓ/min, the rated flow for this device. At flow rates in excess of 3 ℓ/min, the outlet blood is desaturated, the AV difference is narrow, and the actual oxygen transferred reaches a plateau

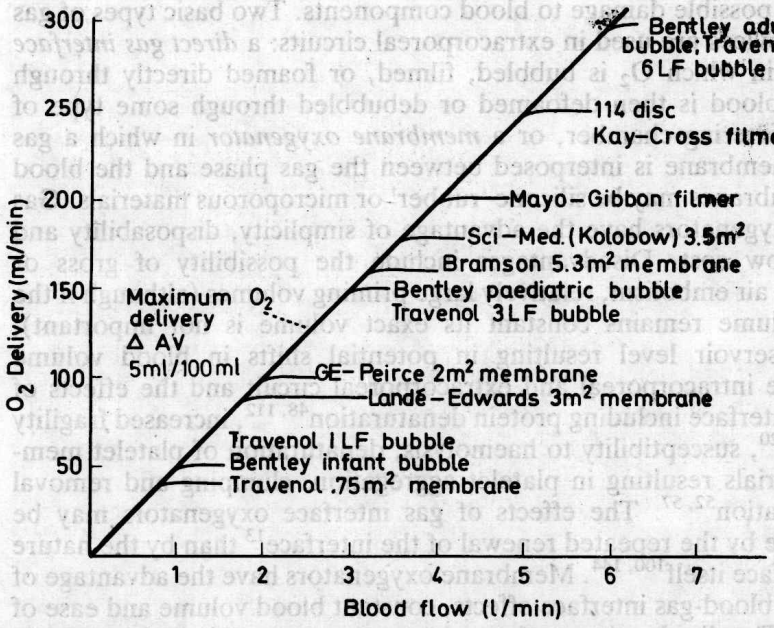


*Figure 1.5* Rated flow under normal venous inlet conditions for a variety of commercial oxygenators. (Data based on publications cited in text or manufacturer's data sheet.) When modular units are used in parallel the rated flow becomes the sum of rated flows of all units in the circuit

related to the flow in ℓ/min for different levels of venous saturation or arteriovenous difference. Notice that oxygen delivery is entirely dependent on flow. Decreasing flow severely decreases oxygen delivery, although fully saturated blood with a high $Po_2$ will be perfused into the arterial system.

Reports on oxygenating performance of gas exchange devices must include at least enough data to calculate inflow and outflow $O_2$ content and rated flow. These data are available in most recent experimental studies[11, 38, 53, 60, 130, 142] but are not available for some of the older established oxygenators[45, 201]. In planning the components of an extracorporeal circuit the oxygen requirement of the patient at normothermia is calculated (150 ml/min per $m^2$). The blood flow which will deliver this amount of oxygen with an AV difference of 5 ml/100 ml, is calculated or determined from a graph (*Figure 1.3*). The cannulae, tubing and pump are chosen to provide the desired flow. An oxygenator is selected which has a rated flow at or above the desired flow.

The concept of rated flow is demonstrated again in *Figure 1.4* and the rated flow for several oxygenators is outlined in *Figure 1.5*. If a gas exchange device is operated at flow rates higher than its rated flow, desaturated blood will be perfused and the actual $O_2$ delivery per minute reaches a fairly level plateau regardless of the flow rate.

## Types of oxygenators

Assuming that the oxygenator will be used at appropriate flow rates below the rated flow, the choice of an oxygenator must be related to the ease of use and the possible damage to blood components. Two basic types of gas exchange devices are used in extracorporeal circuits: a *direct gas interface oxygenator* in which $O_2$ is bubbled, filmed, or foamed directly through blood and blood is then defoamed or debubbled through some type of settling or filtering chamber, or a *membrane oxygenator* in which a gas exchange membrane is interposed between the gas phase and the blood phase. Membranes may be silicone 'rubber' or microporous materials. Gas interface oxygenators have the advantage of simplicity, disposability and relatively low cost. Disadvantages include the possibility of gross or microscopic air embolism, relatively large priming volumes (although if the priming volume remains constant its exact volume is not important), variable reservoir level resulting in potential shifts in blood volume between the intracorporeal and extracorporeal circuit and the effects of direct gas interface including protein denaturation[48, 112], increased fragility of red cells[20], susceptibility to haemolysis, denaturation of platelet membrane materials resulting in platelet aggregation, clumping and removal from circulation[52, 57]. The effects of gas interface oxygenators may be caused more by the repeated renewal of the interface[13] than by the nature of the interface itself[100, 144]. Membrane oxygenators have the advantage of eliminating blood-gas interface effects, constant blood volume and ease of operation. The disadvantages of membrane oxygenators include expense, potential difficulty in eliminating all bubbles during priming and moderately large, although constant, priming volumes in some instances. Changes in plasma proteins, lipoproteins and red cells surfaces, which occur with gas

interface oxygenators, appear not to occur with membrane oxygenators[48, 112]. However, some degree of platelet surface modification with resultant aggregation occurs with the membrane oxygenator[52, 57].

Many of the published reports on pump or membrane oxygenator characteristics have included an open gas interface reservoir in the experimental design[21, 52, 55]. Data from these studies are applicable to ECC for cardiac surgery, as coronary suction will always require some of the blood exposed to a direct gas interface. However, characterization of physiological changes of ECC or blood surface exposure should be done in experimental models which specifically exclude any gas interface to eliminate variables caused by that non-physiological condition.

*Microporous membranes* are made of non-wettable substances such as Teflon perforated with multiple small holes which permit gas transfer but preclude blood leakage because of surface tension effects. Laboratory and clinical results with microporous oxygenators are encouraging[55, 71, 131]. Oxygen and $CO_2$ transfer in a gas-to-gas test system are virtually unlimited with this type of membrane, but the plasma oxygen diffusion limitations still exist when blood is applied to the membrane. Hence, microporous membranes will have oxygen transfer characteristics similar to other membrane oxygenators of similar flow design. $CO_2$ transfer will be significantly better, however. The latter consideration is important only in oxygenators where mixing is intense[11] and $CO_2$ transfer is the limiting design variable. Haematologic studies indicate that the blood interface effects are more similar to a membrane device than a gas interface device[71]. Specific types of gas interface and membrane oxygenators and performance data are discussed in subsequent chapters of this book. Of the gas interface oxygenators, bubble oxygenators are most widely used because of the ease of assembly and priming and the low expense. Similar physiological effects are induced by all blood-gas interface oxygenators, whether of bubble, filming or foaming type. Membrane oxygenators can be characterized as sandwich type,[91, 104, 108, 166, 187] capillary type or induced mixing type[11]. Physiological effects on flowing blood appear to be the same between different types of membrane oxygenators. The reader interested in membrane oxygenator design, development and use is referred to an excellent review by Drinker[49]. Clinical use of membrane oxygenators for prolonged ECC has been reviewed by Peirce[141], Zapol and Qvist[205] and Bartlett and Gazzaniga[13].

## Blood surface interface effects

The effects of prolonged (more than 6 hours) direct gas exposure on plasma proteins and formed blood elements discussed above are so obvious and lethal that the more subtle changes due to the prosthetic vascular interface have been masked in many studies. This aspect of ECC is recently coming under more careful scrutiny. Normally flowing blood is continuously exposed to endothelial cells. Fibrin formation probably takes place continuously on the endothelial surface balanced exactly by plasmin

formation and concomitant fibrinolysis. Both of these reactions proceed at a very slow and balanced rate so that the end effect is a slow but definitely measurable gradual fibrinogen-to-fibrin conversion, an identical rate of fibrin degradation and elimination of fibrin degradation products. This delicate balance is abruptly upset by exposure of blood to collagen fibres underlying endothelial cells, tissue collagen, tissue thromboplastin, air, necrotic tissue or disrupted cells and to some extent foreign material in the bloodstream itself such as endotoxin. Under these circumstances the conversion of fibrinogen to fibrin is grossly exaggerated and proceeds to clotting much faster than fibrinolysis takes place. Concomitantly, platelet surfaces are altered, platelet adhesion and aggregation occur, platelets release platelet factor III, stimulating further formation of fibrin clot. The fact that this chain of events occurs results in normal haemostasis. If serious deficiencies occur in any of the various protein enzymes which constitute the coagulation mechanism, or if any of these enzyme steps are inhibited by a drug or by lack of a catalyst such as calcium, or if platelet numbers or function are severely decreased, then haemostasis is disordered. (Presumably a state of excess plasmin formation with fibrinolysis could also account for disordered coagulation, although the actual clinical occurrence of this phenomenon is rare.) The enzymes of the protein coagulation system (clotting factors) have received appropriate interest and study over the past two decades in relationship to ECC[12, 57]. The number and quality of platelets[44, 51, 88, 164] and the status of the plasminogen–plasmin system[62, 63] with the production of fibrin degradation products (FDP) are equally as important when considering surface interface effects.

**Fibrin formation and lysis**

In the process of ECC the blood is suddenly exposed to various types of plastic, glass, metal, cloth, direct gas bubble interfaces and a variety of foreign chemicals used for coating and priming the device. During cardiac surgery, blood is aspirated from the field ('coronary' suction) and mixed with the perfusate. This blood may include tissue thromboplastin, clots, lysed clots, serum, gross particles of fat and muscle and bone, suture and other foreign material all mixed together with large amounts of air to the point of being frothy[135, 137]. In addition to all these abnormal circumstances, the extracorporeal circuit contains innumerable flat edges, right-angle turns, totally stagnant zones, recirculating zones, jet zones—in short, flow characteristics unlike anything found in conditions of normal physiology. All of these factors have the effect of stimulating both the protein and the platelet arms of the clotting system. Considering the magnitude of forces which combine to stimulate clotting in the extracorporeal system, it seems incredible that this complex system can be held totally in abeyance by a single drug–heparin. Understanding and controlling coagulation and anticoagulants is the major thrust of research in prolonged ECC. However, for cardiac surgery it is apparent that effective total anticoagulation, presumably with heparin, will always be a central part of this technique because of the problems of coronary suction and low pulmonary and atrial flow.