The Past 50 Years of Cardiovascular Surgery

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Cardiovascular surgery has developed so rapidly that it is hard to believe that this specialty is little more than a half-century old. In fact, had it not been for World War II, the emergence of modern cardiac surgery may have been delayed further. In 1943 and 1944, Dwight Harken,[1] then a captain in the medical corps, successfully removed foreign bodies from in and around the hearts of >100 soldiers who had been injured in battle. Harken's work helped overcome the notion that the heart could not be surgically manipulated and, not only did it pave the way for the incredible progress of the last 50 years, it was a catalyst for the event that would mark the dawn of this era: the creation of the first Blalock-Taussig shunt for treating tetralogy of Fallot in 1944.[2] The striking results from this procedure, which increased the circulation through the pulmonary arterial system, caused much excitement in the surgical community.

In those early days at the midpoint of the 20th century, many warned about operating on children, particularly those with cardiovascular disease, severe cyanosis, and hypoxia. There was great concern that it would not be possible to anesthetize these young patients safely and to see them through an operation. Helen Taussig believed that one should not try to operate on a child younger than 4 years with tetralogy of Fallot or a child younger than 8 years with an aortic coarctation. Many pediatricians heeded these warnings, and it was with enormous trepidation that the anesthesia staff undertook the first congenital heart operations in very young patients. (In the earliest days of heart surgery, nurse-anesthetists usually administered anesthesia.) However, this did not deter those who believed that successful cardiac surgery could be undertaken in younger patients. By 1959, those at Texas Children's Hospital had successfully operated on 120 infants with congenital defects.[3]

Advent of Open Heart Surgery

Until the mid-1950s, most pediatric operations were "palliative" extracardiac procedures performed on the closed heart. The challenge was to operate inside the heart safely and to perform a definitive intracardiac repair. A number of ingenious techniques were proposed for this purpose. For instance, Elton Watkins, a medical student at Harvard, suggested a procedure to Robert Gross that became known as the Gross atrial well.[4] They showed that it was possible to operate inside of the beating heart, through a rubber funnel sutured to an incision in the atrial wall, as long as the patient was heparinized. This technique, however, was rather traumatic to the surgeon's index finger: the only way a surgeon knew when the suture was properly placed was to impale his finger with the needle. That resulted in many painful fingers.

What was definitely needed was a method for interrupting blood flow during an intracardiac operation. Hypothermia was one of the early methods tried, either by placing patients in a tub of ice water or by cooling them with ice packs. Once the patient's temperature was lowered to ≈26°F, blood flow to the heart could be interrupted rather easily by placing a snare on the inferior and superior vena cava. If the repair could be accomplished within 8 or 10 minutes, the patient was spared cerebral complications. Unfortunately, this technique had some serious drawbacks, including the possibility of air embolism, which was one of the greatest problems encountered by the developers of open heart techniques. In addition, the more complicated lesions, such as atrioventricular canal and large ventricular septal defects, could not be repaired at all. Thus, it became increasingly obvious that more dependable methods were needed.

For over a decade, John Gibbon[5] worked to design a device that would provide for the oxygenation and circulation of blood in an extracorporeal circuit. Finally, in 1953, his open heart technique with total cardiopulmonary bypass was tested in 4 patients with congenital heart disease, only one of whom survived. Although Gibbon called a personal halt to the clinical use of his technique, his efforts were a strong stimulus to other investigators.

The first truly successful open heart operations were performed by C. Walton Lillehei[6] using a cross-circulation technique; this method had been performed as a physiological experiment for ≈50 years before the first trial in a child. This approach worked very well. One of the parents, usually the mother, served as the oxygenator. By cross-circulating the parent's arterial blood into the recipient and controlling the amount of venous blood being returned, the surgeon had up to an hour in which to perform an intracardiac repair. Proponents of this technique soon determined that the patient could survive if less than full cardiac output was used and, therefore, only moderate stress was placed on the donor. Lillehei said that it was the only operation he knew of with a potential 200% mortality rate, because both the donor and the recipient could be lost. (In Lillehei's experience, only 1 donor

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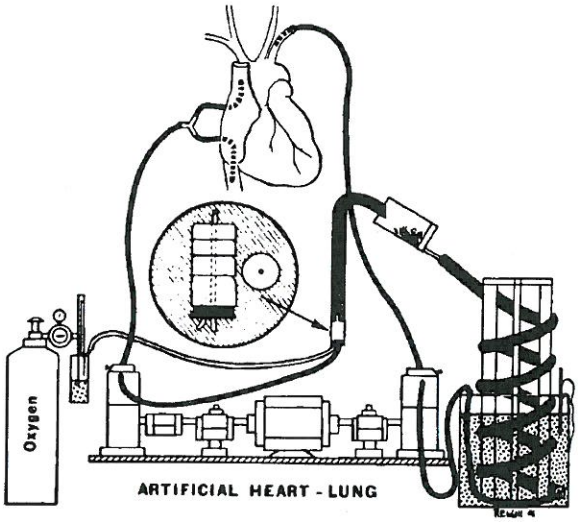

Figure 1. Drawing of the DeWall-Lillehei pump oxygenator. Reprinted with permission of the Texas Heart Institute.[7b]

ever suffered a serious complication—a stroke that probably resulted from an air embolism.) With this approach, Lillehei and his team were able to correct ventricular septal defects and even tetralogy of Fallot. With the success of this method, he became convinced that open heart surgery with temporary cardiopulmonary bypass was feasible.

Among the different types of oxygenators being investigated, the one devised by one of Lillehei's younger colleagues, Richard DeWall,[7a] proved the most practical (Figure 1). DeWall and his colleagues devised a simple bubble diffusion system, with a helical coil for defoaming the blood by means of a silicone antifoam substance. With this mechanical oxygenator and a pump in the circuit, open heart surgery finally became a reality. Many more complicated defects, such as tetralogy of Fallot, ventricular and atrial septal defects, and other intricate lesions, became amenable to surgical correction. Using the more complex Gibbon-type apparatus (Figure 2), John Kirklin at the Mayo Clinic also

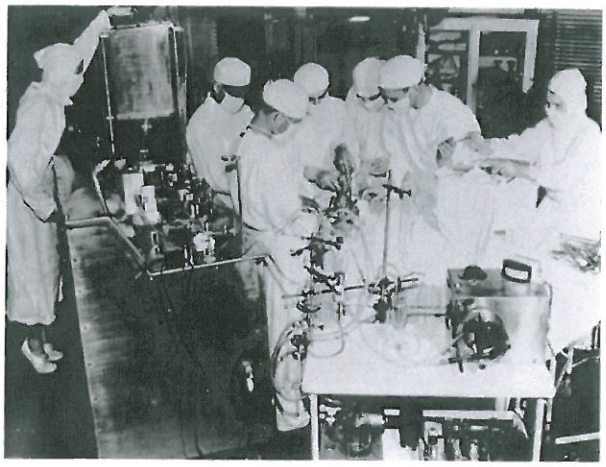

Figure 2. The Mayo-Gibbon heart lung machine. Reprinted with permission of the Texas Heart Institute.[7b]

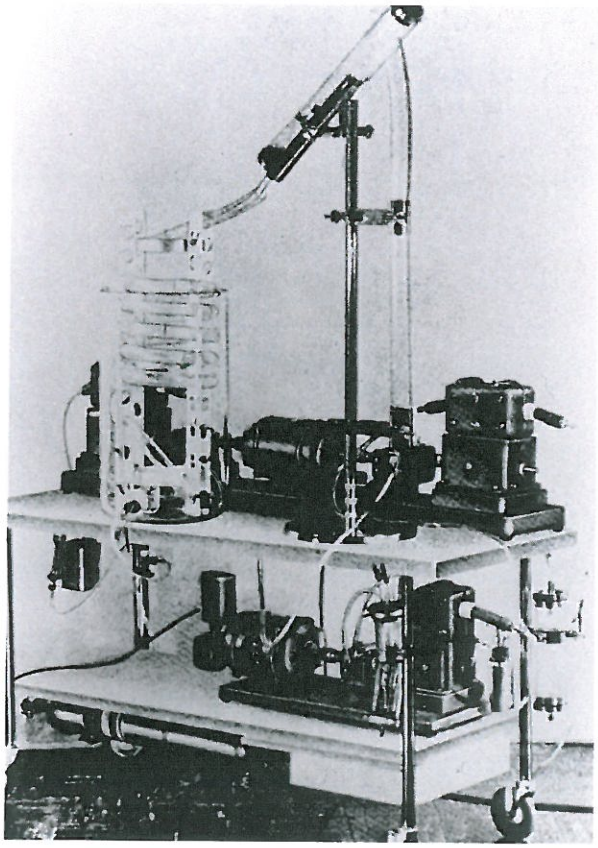

Figure 3. The modified DeWall-Lillehei pump oxygenator, which was first used at the Texas Heart Institute in 1956. Reprinted with permission of the Texas Heart Institute.[7b]

demonstrated that open repair of complicated defects could be accomplished with low risk.[8] Soon thereafter, our team at the Texas Heart Institute also adopted the DeWall-Lillehei device, which allowed us to establish an open heart program in 1955. We modified the DeWall device, however, by building a vertical stainless steel model that was easier to assemble and use (Figure 3). By the end of 1956, using this device and a roller pump (Figures 4 and 5), we had performed >100 open heart procedures, more than any other group in the world,[9] including the first repair of a postinfarction ventricular septal defect[10] (Figure 6).

One of the major problems associated with those early procedures was the need to prime the extracorporeal system with blood. Depending on the complexity of the system, up to 14 U of blood had to be collected on the morning of surgery, and the blood had to be freshly heparinized and kept at body temperature (Figure 7). With some of the larger extracorporeal systems, the operation could not be performed until 8 or 10 o'clock at night because it was difficult to collect so much blood. Eventually, we showed that blood could be stored overnight and that it could be citrated. Nonetheless, cardiac surgeons had become slaves of the blood bank with respect to the scheduling of open heart operations.

A major breakthrough came when Nazih Zudhi and colleagues[11] demonstrated that priming the extracorporeal circuit with blood was not only unnecessary, but potentially hazard-

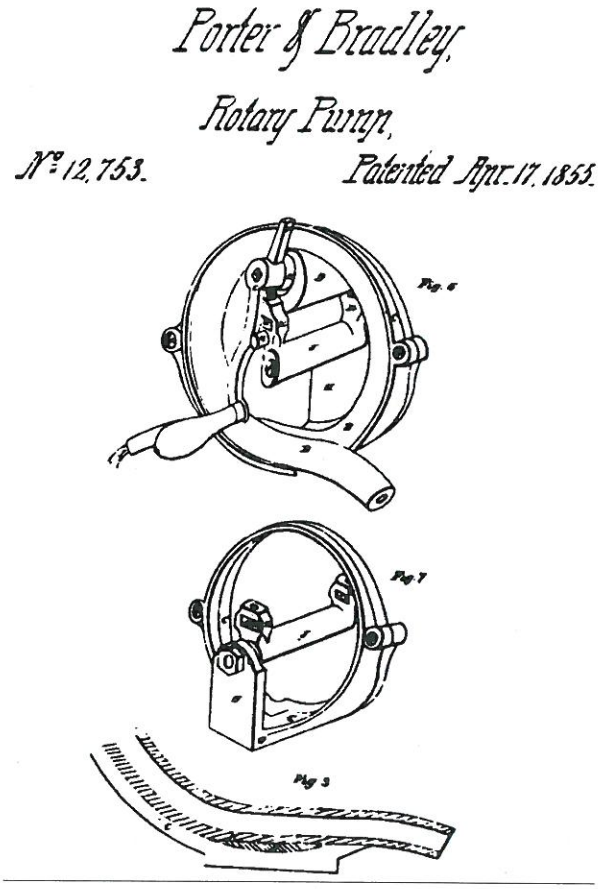

Figure 4. Drawing of an early roller pump, which was patented in 1855 by Porter and Bradley. Reprinted with permission of the Texas Heart Institute.[7b]

ous. Our team next promoted and popularized the concept of hemodilution with 5% dextrose solution[12] and, although we had many critics, the critics were proved wrong. In this technique, which is used almost universally today, a disposable oxygenator primed with 5% dextrose was used with normothermia. For the first time, open heart surgery became practical. It also became safer because, when 6 or 8 U of blood are mixed together in an extracorporeal circuit, patients end the procedure with more transfused blood than their original volume. Also, because each unit of blood had some basic incompatibility with the others, some patients developed homologous blood syndrome, which contributed to various postoperative complications. With the introduction of a non–blood-priming technique, these concerns became relatively unimportant.

With these simplified techniques, surgeons were quickly able to extend their use of open heart surgery and to repair almost every type of intracardiac abnormality.

Valvular Repair and Replacement

The earliest intracardiac operations had been performed for rheumatic heart disease and mitral stenosis. Several surgeons, including Lord Brock,[13] Charles Bailey,[14] and Dwight Harken and colleagues,[15] had shown that the stenotic mitral valve

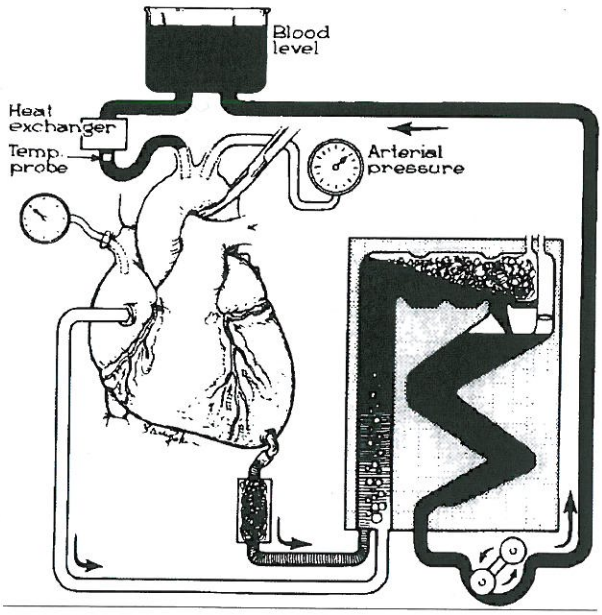

Figure 5. Drawing of the cardiopulmonary bypass circuit used with the heart-lung machine of the 1960s. Reprinted with permission of the Texas Heart Institute.[7b]

could be manipulated in a technique called "finger-fracture" valvuloplasty. However, those who performed such procedures realized that, in many instances, they were not really accomplishing much. Even with a knife on the fingertip, this technique was not very effective. In 1954, the treatment of mitral valve stenosis was revolutionized with the advent of the mechanical dilator, a relatively simple device that was designed and first used by Charles Dubost.[16] The dilator had 2 parallel blades that could be passed into the atrium and into the valve (Figure 8). Dilating the valve mechanically proved more effective than pulling it open manually. Today, cardiologists are using balloons, introduced through catheters in leg veins, for the same purpose. The approach seems to work well as a palliative measure.

Heart valve repair gave rise to a whole new field of possibilities, as well as a number of ingenious devices and techniques. In 1952, Hufnagel and Harvey[17] introduced a valve that they had placed in a patient's descending aorta to treat aortic regurgitation. Unfortunately, the silicone-type ball (methacrylate) was very resonant; if the patient opened his or her mouth, the clicking of the ball could be heard across a large room. Nevertheless, this valve did partially relieve aortic regurgitation by reducing left ventricular load by about one-third to one-half.

The real breakthrough was total valve replacement, which was introduced almost simultaneously by 2 surgeons: Dwight Harken,[18] who used a double-caged, ball-and-seat prosthesis, and Albert Starr,[19] who used a caged ball-and-seat valve. Both models incorporated a silastic ball within a metal cage. With the introduction of the ball-and-seat valve, surgeons could finally definitively treat aortic valve and mitral valve disease. Years of trial and error, however, were necessary before consistently durable, reliable valves would become available. Many of the pioneers of cardiac surgery worked to

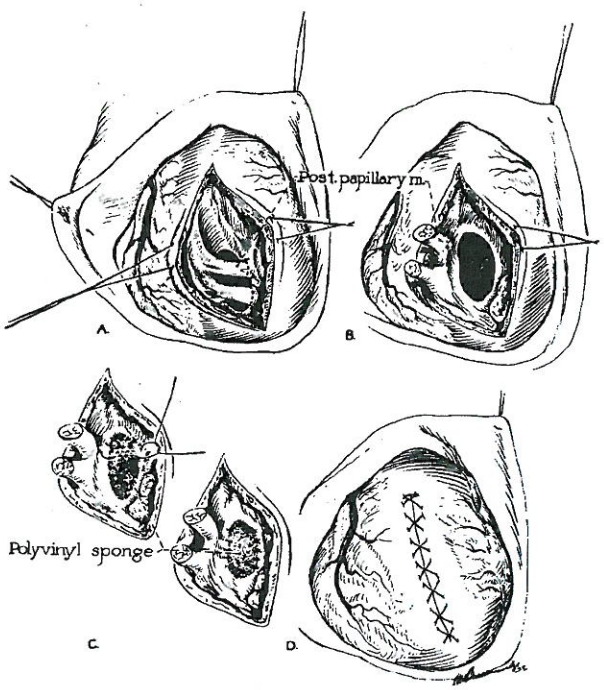

Figure 6. Technique used in the first repair of acute rupture of the interventricular septum. Reprinted with permission of the Texas Heart Institute.[7b]

develop reliable prostheses, and they gave their names to the products that they developed: Smeloff, Magovern, Cromie, Braunwald, DeBakey, Barnard, Beall, Cross, Jones, Conrad, Kay, Starr, Taber, Cooley, Lillehei, Wada, Stuckey, Pierce, Behrendt, Morrow, Williams, Bjork, Gott, Emery, and Nicoloff, among others (Figure 9).

Even in cardiac surgery, techniques and procedures lose and gain fashion. For example, today's surgeons are now using homograft valves in an increasing number of cases. In earlier years, homografts never had the popularity that their mechanical counterparts did, in part because of the problems of supply and demand and of storage and preservation. Some,

Figure 7. Early operating room scene, showing the cumbersome pump oxygenator equipment and the 14 units of freshly drawn blood needed to repair a simple atrial septal defect. Reprinted with permission of the Texas Heart Institute.[7b]

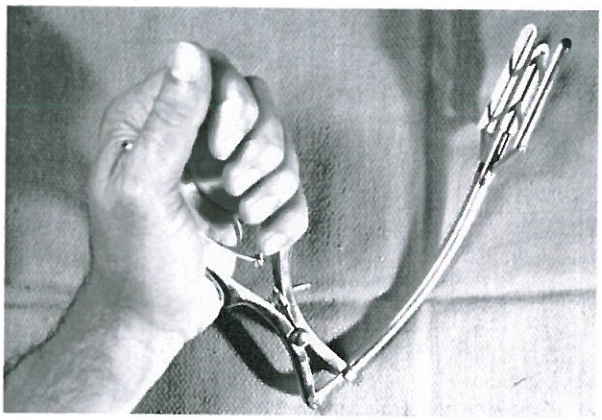

Figure 8. Dilator used in early commissurotomy procedures. Reprinted with permission of the Texas Heart Institute.[7b]

however, continued to use homografts, especially Donald Ross[20] and Brian Barratt-Boyes,[21] who were largely responsible for their development.

Even before valve prostheses became available, Ross[22] conceived the idea of implanting a patient's own pulmonary valve as an autograft into the aortic annulus; he then replaced the pulmonary valve with a homograft or some other kind of valve. Today, there is renewed interest in the Ross procedure, and surgeons are even considering the use of mitral homografts to mimic normal function and eliminate the need for anticoagulation. Nevertheless, the natural valve should be retained whenever possible.

Coronary Revascularization

Patients with coronary artery disease comprise another group that challenged early cardiac surgeons. Originally, the only option was to modify or palliate this condition. Early operations were designed to stimulate intercoronary anastomoses by producing a granulomatous response in the pericardium and epicardium. To achieve this goal, powdered asbestos, talc, silica, or phenol was insufflated into the pericardial space. Other approaches included abrading the epicardium, ligating the internal mammary artery or coronary vein,

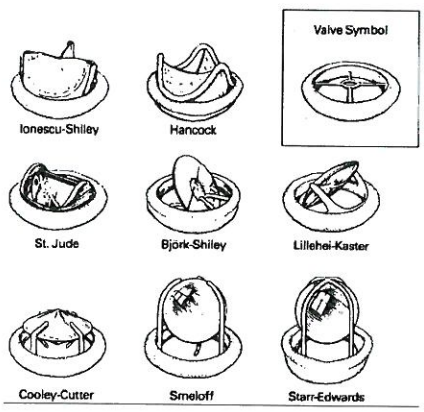

Figure 9. Examples of valves developed for valvular replacement operations.

arterializing the coronary sinus, or grafting vascular tissue into the epicardium.

A major breakthrough occurred with the advent of coronary arteriography, which allowed surgeons to visualize the coronary lesion for the first time. This breakthrough was brought about fortuitously in 1958 by Sones and Shirey,[23] who were attempting to perform a left ventriculogram in a patient and inadvertently injected a contrast agent into the patient's coronary circulation. Sones was terrified that the patient would not survive because, at that time, coronary injection was mistakenly considered dangerous. Sones subsequently designed and successfully used a specialized coronary catheter for selective coronary angiography.

Once surgeons could see where a coronary blockage was located, they could proceed with revascularization by means of a bypass graft technique. With cardiopulmonary bypass and cardioplegic arrest, surgeons were able to construct coronary bypass grafts in a quiet, bloodless field, originally by using saphenous vein grafts and later by including the internal mammary artery. The first coronary bypass was performed by Edward Garrett and colleagues[24] in 1964, when they encountered difficulties while performing an endarterectomy and were forced to bypass the left anterior descending artery. Much of the pioneering work in the area of coronary bypass was done by René Favaloro and Donald Effler and colleagues,[25] who were the first to report the procedure, and by Dudley Johnson and Derward Lepley and colleagues,[26] beginning in late 1968. The procedure soon became the world's most frequently performed cardiac operation.

After the introduction of percutaneous transluminal coronary angioplasty by Andreas Gruentzig and colleagues,[27] the use of interventional techniques increased, and the number of surgical revascularization procedures began to decline. At the Texas Heart Institute and at most other heart centers, patients with coronary artery disease now undergo more interventional procedures than direct surgical operations. However, the pendulum may swing the other way again. The results of simple beating-heart surgery are so satisfactory that surgeons can almost offer patients the same degree of comfort, and perhaps a better life expectancy, by performing an internal mammary artery bypass in a minimally invasive procedure rather than by an interventional procedure.

Many surgeons today are reverting to operating on the beating heart. Because coronary artery bypass grafting is done on the surface of the heart, cardiopulmonary bypass is not absolutely essential. Moreover, the extracorporeal circuit (particularly the oxygenators and suction devices) can induce a whole-body inflammatory response and other postoperative complications, which are eliminated by beating-heart surgery. One of the most difficult problems in developing this technique has been in finding methods to stabilize the arteries during grafting. New devices are being developed, however, to make such procedures safer and more reliable (Figure 10).

Despite the success of conventional myocardial revascularization techniques, some patients are not suitable candidates for these therapies, so researchers have continued to look for new options. Surgeons have begun to use lasers to perform a procedure called transmyocardial laser revascularization. The laser creates new channels through which oxygenated blood can enter the myocardium from the intracavitary region.[28] Controversy exists, however, regarding the mechanism of transmyocardial laser revascularization and the likelihood of the channels' remaining patent. Whatever its mechanism, this technique may stimulate angiogenesis, thereby revascularizing the ischemic myocardium. Thus far, it remains unclear whether the promising results are related to subjective factors or to actual myocardial revascularization.

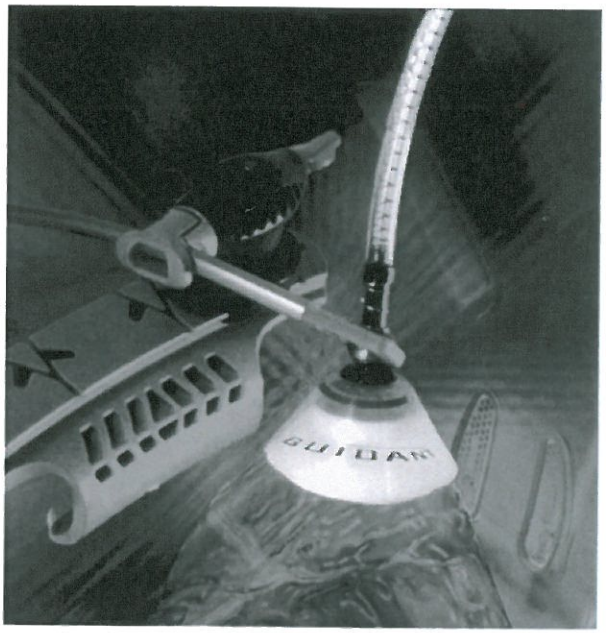

Figure 10. Example of a stabilizer used for beating heart surgical procedures. Reprinted with permission, Guidant Corp.

Aneurysm Repair

Aneurysm surgery has evolved in a fashion similar to coronary surgery, in that various indirect methods were used for some years until excision was undertaken and, later, repair became standard. In 1951, at the annual meeting of the Southern Surgical Society, Cooley and DeBakey became the first to recommend direct surgical removal of aortic aneurysms. Synthetic vascular grafts were not yet available, so the early operations were performed mainly on sacciform aneurysms, many of which were luetic in origin. After fabric vascular grafts became available in the late 1950s, the goal became to restore circulation without excision of the lesion.

Cardiac Support and Replacement

Probably the most exciting event in heart surgery occurred in 1967, when a South African surgeon named Christiaan Barnard[29] performed the first human heart transplant. The operation was only temporarily successful, but it was an important historic event. Although Barnard was roundly criticized at the time by ethicists and religious groups, both of whom opposed the very concept of heart transplantation, many surgeons around the world were searching for the means to perform a heart transplant. It was Barnard, however, who defined for the rest of the world the concept of brain

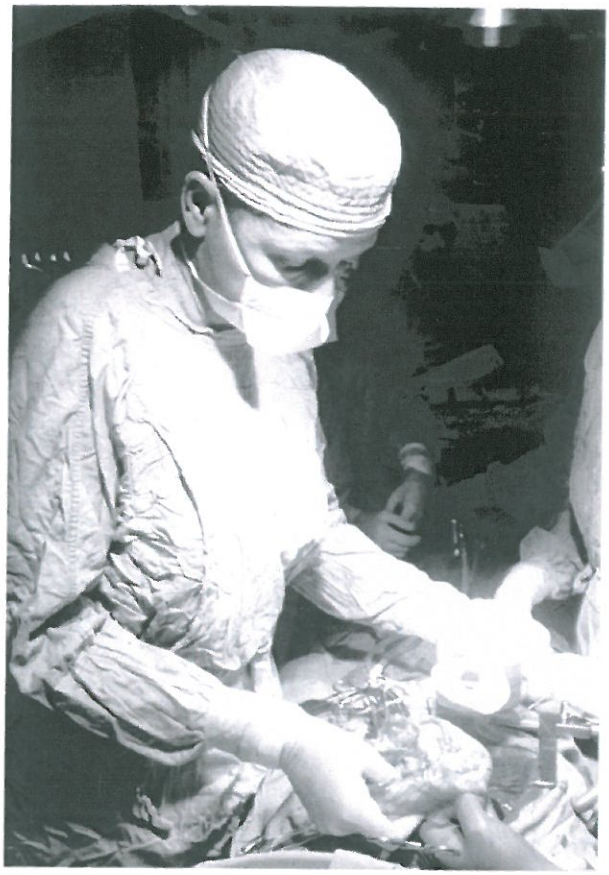

Figure 11. First bridge-to-transplant operation in 1969. The bridge used was the Liotta total artificial heart. Reprinted with permission of the Texas Heart Institute.[7b]

death and who deserves credit for making heart transplantation a reality.

Soon after Barnard's transplant, the Texas Heart Institute became actively involved in cardiac transplantation. Within a year, surgeons here had performed 20 transplant operations, which put the Institute in the forefront of cardiac transplantation in the world.[30] Unfortunately, none of those 20 patients lived more than 18 months: they all succumbed to rejection and infection. We, and others, became discouraged, and a moratorium was called on any further cardiac transplant procedures. In 1980, however, Barry Kahan[31] introduced the new immunosuppressant cyclosporine, which he used to prevent rejection in renal transplant patients. With his permission and encouragement, we began using cyclosporine to prevent rejection in heart transplant patients. The introduction of cyclosporine gave surgeons the tool they needed to re-enter the field of cardiac transplantation. Shumway and colleagues[32] maintained a determined interest in the field of cardiac transplantation during the precyclosporine era, and they demonstrated the logistics of organ procurement.

During this time, investigators were developing a mechanical means of supporting the failing heart. One possibility, a total artificial heart, was being developed by Domingo Liotta in our laboratory. In 1969, we[33] used this heart in the first bridge-to-transplant operation (Figure 11) for a patient who

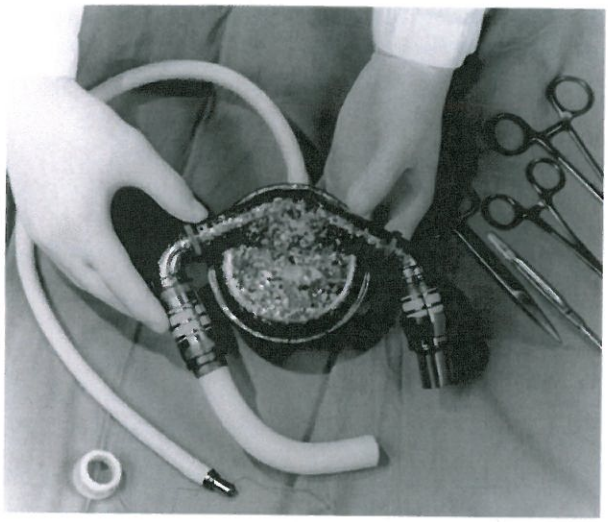

Figure 12. HeartMate left ventricular assist device. Reprinted with permission of the Texas Heart Institute.[7b]

could not be weaned from cardiopulmonary bypass after an extensive ventricular reduction procedure (what would be called the Batista[34] procedure today). Three days after the artificial heart was implanted (the first implantation of its kind in the world), a donor was found, and a heart transplant operation was performed. Today, the bridge-to-transplant operation has become a routine procedure, with a variety of circulatory support devices available for use as a bridge.

The left ventricular assist device is most commonly used today as a bridge to transplant. In a 1980 request for a proposal, the National Heart, Lung, and Blood Institute changed its focus from the total artificial heart program to support development of left ventricular assist devices. A number of devices resulted from that development program. One such device, the HeartMate left ventricular assist device (Thermo Cardiosystems, Woburn, MA), was the first fully implantable device to receive approval from the US Food and Drug Administration for implantation in humans as a bridge to transplant (Figure 12). The HeartMate connects the left ventricle to the ascending aorta. By unloading the left ventricle, the pump allows the heart to rest and is proven to help in the recovery of at least some left ventricular function in most patients.[35] Because of the possibility of recovery and its track record for reliability, the HeartMate device is now being tested in a controlled trial for long-term use.

Newer still are much smaller, continuous-flow pumps. One of several under investigation is the Jarvik 2000, which is being developed at the Texas Heart Institute with Robert Jarvik.[36] The device is implanted into the apex of the left ventricle and rests in an intracavitary position, which makes it very different from earlier left ventricular assist devices (Figure 13). The Jarvik 2000 shows promise as a bridge to transplant and as long-term support for the heart; however, in the United States, the Food and Drug Administration currently restricts its use to a bridge. The device has been implanted in 7 patients. Two of these patients have recently undergone transplant operations and are doing well. In

Figure 13. Jarvik 2000 continuous-flow left ventricular assist device. Reprinted with the permission of the Texas Heart Institute.[7b]

Oxford, England, the Jarvik system was implanted for long-term support in 2 nontransplant candidates.

Summary

Cardiac surgery has undergone a rapid and extraordinary development during the past 50 years. Many operations that were once considered experimental are now routine, and thousands of open heart procedures are performed each year. In 1997, in the United States alone, surgeons performed 197 000 cardiovascular procedures, including 2300 heart transplant operations. These statistics are astonishing to both Dr Cooley, who began practicing >50 years ago, and Dr Frazier, who began practicing 30 years ago. Even with this increased practice, cardiac surgery remains what it has always been: a profession where art and science mix and where skill and decisiveness rule; these qualities are unlikely to change any time soon. The use of robotics for minimally invasive procedures and the minimally invasive procedures themselves can challenge even the deftest of hands and may subject the patient to added risk. Technology has certainly provided a new dimension to the practice of cardiovascular surgery; in our haste to embrace the future, however, we must not forget that we should be building on our past.

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KEY WORDS: heart diseases ■ surgery ■ cardiopulmonary bypass

2

Principles of Oxygenator Function: Gas Exchange, Heat Transfer, and Blood-Artificial Surface Interaction

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Through common clinical usage, the term "oxygenator" has come to mean that portion of the perfusion apparatus that subserves the functions of the patient's natural lungs during the period of extracorporeal circulation. More correctly, the device should be called a gas exchanger, since it also transports carbon dioxide, anesthetics, and possibly other gases into and out of the circulation. In addition, most modern oxygenators have integral heat exchangers, and bubble oxygenators also serve as the main reservoir and as a filter for blood returned from the cardiotomy suction. Thus, the oxygenator performs all of the major functions of the natural lungs except for their endocrine function, which can be suspended for a short time without major ill effects.

As Chapter 1 indicated, designing a practical oxygenator constituted one of the major challenges faced by early pioneers of cardiopulmonary bypass (CPB), and it was only after disposable and relatively inexpensive oxygenators were developed that widespread practice of open heart surgery became possible. Table 2.1 shows the trends in the use of oxygenators over the past 8 years in the United States. The shift from bubble toward membrane oxygenators probably reflects progressive improvements in both performance and cost of membrane oxygenators, and a growing awareness of the theoretical advantages that they offer over bubble oxygenators for reducing blood trauma and the risk of embolization.

Oxygenator designers strive to maximize the amount of oxygen, carbon dioxide, and other gases that can be transferred at a given blood flow rate, to make gas transport easy for the perfusionist to regulate, to maximize heat-transfer efficiency, to minimize blood trauma, and to minimize the priming volume, i.e., the amount of liquid that must be added to fill the oxygenator prior to operation. Table 2.2 illustrates some of the reasons why engineers have such a formidable task in attempting to duplicate the functions of the natural lung. First, red blood cells pass through pulmonary capillaries one at a time, making the

Table 2.1. Comparison of Oxygenator Sales in the United States in 1983 and 1991[a]

Year	Bubble Oxygenators	Membrane Oxygenators
1983	150,000	50,000
1990	29,000	285,000

[a]Data obtained from Kurusz M. Gaseous microemboli: sources, causes, and clinical considerations. Medical Instrumentation 1985;19:73–76.

Table 2.2. Comparison of Physical Characteristics of a Membrane Lung and Natural Lung

Characteristic	Membrane Lung[a]	Natural Lung[b]
Surface area (m^2)	0.5–4	70
Blood path width (microns)	200	8
Blood path length (microns)	250,000	200
Membrane thickness (microns)	150	0.5
Maximum O_2 transfer (ml/min, STP)	400–600	2,000

[a]Data for a Sci-Med Spiral Coil Membrane Lung (Sci-Med Life Systems, Minneapolis, MN).
[b]Data obtained from Guyton AC. Textbook of medical physiology. Philadelphia: WB Saunders Co., 1976.

distance for O_2 diffusion much shorter than has ever been achieved in an artificial lung. The rate of oxygen transfer in natural lungs is not limited by diffusion, except in the case of severe lung disease or extreme exercise. Indeed, the difference between gas tensions measured in the natural alveoli and in the blood are mostly due to ventilation/perfusion mismatching. In contrast, in artificial lungs operating under normal conditions, a significant difference in partial pressures occurs between the gas and blood phases.

A second disadvantage to the artificial lung is a much smaller surface area over which to exchange gases (typically less than 10% of the natural lung's area). Current membrane lungs compensate for these shortcomings by increasing the blood path length (the distance that the blood travels past the gas exchange surface), thereby increasing the time available for blood exposure to the gas exchange surface (i.e., an increased dwell time). In addition, secondary flows are induced in artificial lungs to promote mixing and bring deoxygenated blood closer to the exchange surface (see "Enhancing Gas Transport with Secondary Flows"). Artificial lungs can be ventilated with 100% O_2 to maximize the driving pressure difference for O_2 diffusion, without the toxic effects that would occur in the natural lung, and the artificial lung can be ventilated with a high flow of fresh gas to keep the CO_2 fraction in the gas phase low. Even the best available artificial lungs are incapable of achieving anywhere near the gas exchange of the natural lung (Table 2.2). Fortunately, hypothermia, muscle paralysis, and anesthesia all reduce the patient's metabolic requirements to the point where gas exchange requirements can ordinarily be met by one of these devices.

In what follows, we review the physical principles that determine how gas and heat transfer occurs in oxygenators and how these principles are utilized in the design of generic bubble and membrane oxygenators. We also review studies examining interactions of blood with artificial surfaces and bubbles. Then we discuss how these considerations translate into the performance differences of membrane and bubble oxygenators. Finally, we discuss clinical considerations in the use of bubble and membrane oxygenators and techniques for safe practice.

PERTINENT PHYSICAL PRINCIPLES

Regardless of the type of oxygenator, gas transfer from the gas to the liquid phase (or the opposite direction) is driven by diffusion according to the partial pressure difference of the particular gas. Gas transfer is limited by the resistance to diffusion of the particular gas through the primary substance, whether it is a synthetic membrane, blood, or the gas phase itself. Other factors that come into play are the physical size and structure of the oxygenator and how the blood flow and gas flow affect these driving forces and resistances.

Determinants of the P_{O_2} and P_{CO_2} in Gas and Blood

The partial pressure of gases present in a mixture of gases occupying a volume acts as if each individual gas is occupying

the volume independently (Dalton's law), and the sum of the individual gas partial pressures equals the total gas pressure. This applies for gases occupying a space by themselves or dissolved in solution, i.e., blood. Thus, when blood equilibrates at atmospheric pressure, the partial pressures or gas tensions of all of the gases dissolved in blood must add up to 760 mm Hg at sea level. In the gas phase, the partial pressure (P), the concentration (C), and the mole fraction are equivalent.

The fact that CO_2 and O_2 blood content does not derive simply from these gases being dissolved in solution complicates analysis of gas transfer in oxygenators. The well-known oxyhemoglobin dissociation curve (1) shown in Figure 2.1 reflects the nonlinear binding of O_2 by hemoglobin. The CO_2 in the blood combines chemically with different moieties (Fig. 2.2) to form bicarbonate, the major carrier of CO_2 in blood, and to amino groups of proteins, primarily hemoglobin and is not linearly related to the partial pressure of CO_2 (2). Because of the chemical combination of CO_2 and O_2 to hemoglobin and the other moieties just described, both are present in much higher concentrations than would be possible simply by physical solution.

Diffusion of Gases Through Liquids and Solids

Diffusion is best considered at the molecular level. The random motion of the

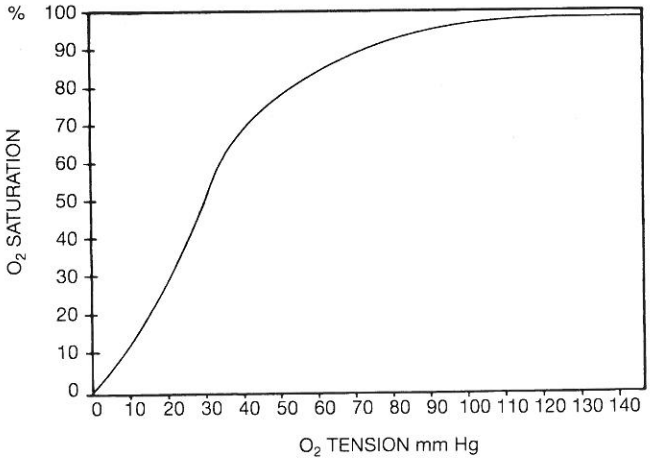

Figure 2.1. Oxyhemoglobin dissociation curve reflecting the nonlinear relationship between hemoglobin saturation and oxygen partial pressure.

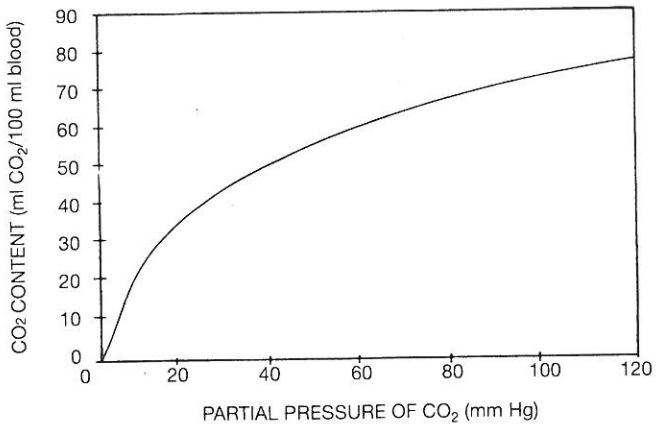

Figure 2.2. Carbon dioxide solubility in blood is not a linear function of the partial pressure of carbon dioxide because of its chemical combination to form carbonate and its binding to hemoglobin.

atoms or molecules of the diffusing gas move from regions of higher concentration to regions of lower concentration. Fick's law describes the rate at which gases diffuse through gases, liquids, and solids. This law states that the rate of diffusion is proportional to the partial pressure gradient of the gas in the direction of diffusion, i.e., the change in the partial pressure of the gas per unit distance. Mathematically, the rate of diffusion per unit area, J, at a particular location, x, along the diffusion path would be described as:

$$J = -D \cdot {}^{\delta P}/_{\delta x} \qquad (1)$$

where D = the diffusivity constant (a characteristic of the material and gas) and P = the partial pressure of the gas at any particular location, x. The negative sign in the equation is the result of the negative value of the partial pressure difference, a result of the decreasing pressure in the direction of increasing distance, x.

Several inferences can be made from this relationship. The rate of total gas transfer can be increased by increasing the partial pressure difference (represented by δP) or the surface area available for diffusion. The rate of gas transfer can also be increased by decreasing the distance through which the gas must diffuse (represented by δx). These important concepts will be discussed in the section on oxygenator function and design. Of course there are practical limits to how far these concepts can be taken, as they will lead to an increased oxygenator priming volume or increased pressure drop across the oxygenator as membranes are brought closer together.

The diffusivity, D, is constant for a particular gas and diffusion barrier material at a constant temperature. Kinetic theory dictates that the diffusivity is related to the molecular speed of the gas molecules and, according to Graham's law, is inversely proportional to the square root of the molecular weight of the gas. The diffusivity of a gas is related to the solubility of the gas, since increasing solubility enhances movement of the gas through a solid or liquid. This later factor complicates the analysis of gas transfer (3, 4).

Gas diffusion in blood, particularly oxygen diffusion, is somewhat more complicated than predicted by Fick's law. In addition to simple diffusion through the blood plasma, the absorption of oxygen by red blood cells must be considered. While detailed mathematical derivation of this process is beyond this scope of this book, if one assumes, as Marx et al. (3) have done, that local variations of O_2 around the red cell are small compared to the overall O_2 gradient, a second-order differential equation can be derived that describes diffusion of oxygen in blood as a nonlinear function of distance and time. It is not difficult to imagine that the O_2 concentration within a volume of blood will increase as the exposure time of blood to either a bubble or membrane interface increases. Thus, time, i.e., red cell dwell time within the oxygenator, becomes an important factor when considering gas transport in the blood phase. Furthermore, diffusion of O_2 within the red blood cell is not well-elucidated because the shape of the cell and the packing of the hemoglobin make this analysis difficult.

Diffusion of Momentum in a Flowing Fluid, and Generation of the Stagnant Boundary Layer

Blood or any other viscous fluid flowing past either a stationary surface or a bubble will have variations in velocity from zero at the interface surface to that of the free stream. This region in which this variation occurs is defined as the boundary layer. If the main stream of the fluid has a different velocity than the interface surface (a bubble could flow within the

blood flow),[a] a velocity gradient will be formed in which the fluid velocity varies from zero at the interface to V_S, the velocity in the main stream as shown in Figure 2.3A. This may be conceptualized as layers of fluid slipping or dragging over one another. Hence, as the distance from the wall increases, each subsequent layer has a greater velocity and momentum (momentum is the product of mass times velocity). Momentum thus varies from a maximum in the free stream to zero at the wall, which may be conceptualized as a momentum flux from the free stream through each layer to the surface. This is comparable to a flux of gas undergoing diffusion or heat transfer (see "The Analogs of Momentum, Mass, and Heat Transfer"). As Figure 2.3A shows, as the flow continues along a surface, the boundary layer widens (known as the developing boundary layer). If the boundary layer widens to the point that it meets the growing boundary layer from the other side of the flow channel, then the flow is said to be fully developed.

The contour of the velocity boundary layer is important because it determines the overall resistance to flow or the pressure drop that occurs. At any place within the boundary layer the shear stress, τ, is proportional to the rate of change of velocity in the direction perpendicular to the main flow (the partial derivative of velocity, $^{\delta u}/_{\delta x}$) with the proportionality constant being the viscosity, μ, or:

$$\tau = -\mu^{\delta u}/_{\delta x} \qquad (2)$$

Thus, as the velocity gradient increases, the shear stress increases.[b] The viscosity, μ, is constant for most fluids. Such fluids are referred to as Newtonian fluids. However, some fluids, including blood, do not have a constant viscosity, i.e., the viscosity changes depending on the nature of the flow; these are called non-Newtonian fluids. The primary determinant of blood viscosity is the concentration of red blood cells, i.e., the hematocrit, which tends to vary within boundary layers. At the wall, the shear stress, τ_w, is also related to the steepness of this velocity gradient, as shown in Figure 2.3A. The integral or summation of all of the wall shear stresses over the entire wall surface area is what determines the pressure drop of any viscous flow.

Velocity profiles vary with the nature of the flow stream to produce either laminar or turbulent flow. Turbulent flow generates spontaneous eddies from flow instabilities within the flow. Such a flow would have a high Reynolds number[c] (a nondimensional number used to predict the transition from laminar to turbulent flow). Turbulence can also result from an irregularity in the flow path, creating eddies within the flow (see "Enhancing Gas Transport with Secondary Flows"). Figure 2.3B shows how turbulence changes the boundary layer velocity profile by moving higher velocity fluid into the boundary layer closer to the surface, causing a steeper rise in the velocity profile (shear rate) and in shear stress.

[a] From a fluid mechanics viewpoint, it does not matter whether the blood is moving past the surface or the surface of a bubble past the blood. It is the relative velocity that affects the velocity boundary layer and possibly the diffusion boundary layer.

[b] Note that shear stress, τ, is a force applied to a unit area and thus has units of pressure. The force, however, is applied tangentially to or across the area, unlike pressure, in which the force is applied perpendicular to the area. Furthermore, note that the velocity gradient, $\delta u/\delta x$, is usually referred to as the shear rate.

[c] The Reynolds number is defined as the ratio of inertial to viscous forces, or $Re = \rho \cdot U \cdot d/\mu$.

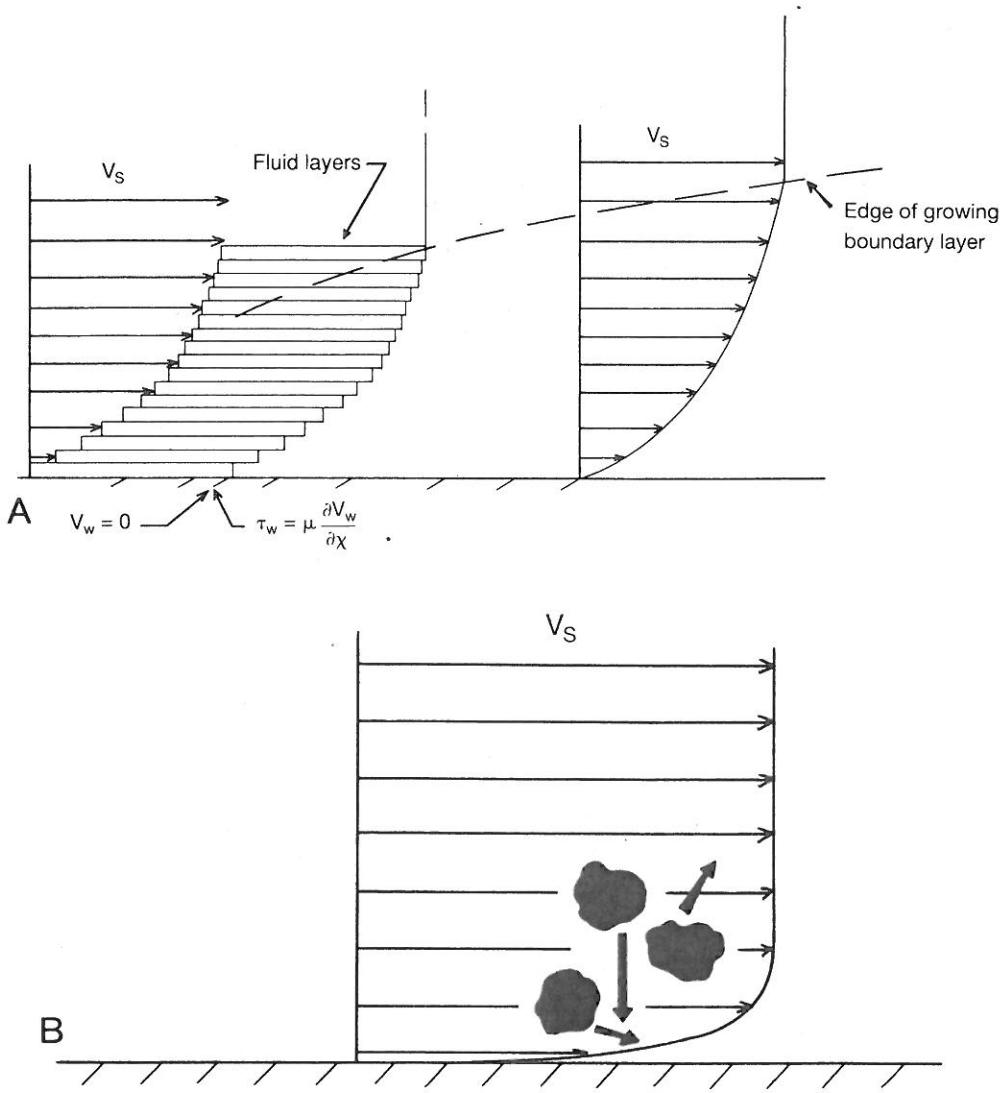

Figure 2.3. **A.** The laminar velocity boundary layer of fluid showing layers of fluid dragging each other along with greater velocity and momentum as the free stream velocity, V_s, is approached. Note the increasing thickness of the boundary layer as the flow continues along the surface from left to right. The wall shear stress, τ_w, is shown as equal to the product of the viscosity, μ, multiplied by the velocity gradient, $\delta Vw/\delta x$. **B.** Turbulent velocity profile, showing the steeper rise in velocity because of the movement of aliquots of fluid having a higher velocity into the boundary layer. Note that the velocity profile represents the *average velocity* throughout this turbulent flow.

As a fluid flows past a surface through which diffusion is occurring, a diffusion boundary is generated that is layer-similar to the velocity boundary and depends on Fick's law. For oxygen diffusion typical of a membrane lung, as shown in Figure 2.4, the oxygen partial pressure in the fluid varies from P_w, the partial pressure of oxygen at the interface with the blood, to P_s, the partial pressure within the stream not yet affected by the diffusion of gas to or from the wall. Note that in Figure 2.4, the o_2 partial

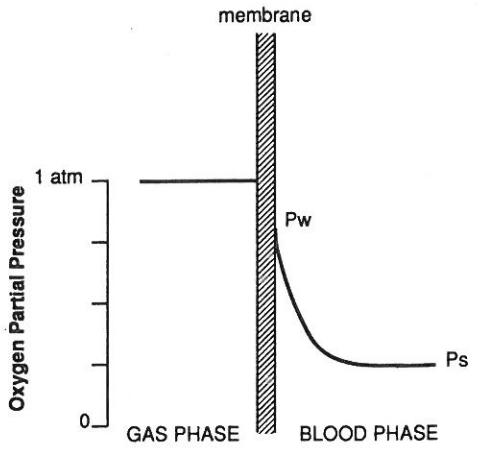

Figure 2.4. Typical variation of oxygen partial pressure from the membrane of an artificial lung to the free stream of blood. (See text for details.)

pressure decreases slightly in the membrane itself, but rapidly decreases in the blood. This graphically represents the actual physical condition. In modern membrane oxygenators, the majority of the resistance to O_2 diffusion occurs in the blood (estimates are >90%) due to the low diffusivity of O_2 in blood. As the blood stream flows along the interface, the boundary layer of O_2 grows in a manner similar to that described for the velocity boundary layer. As the width of this boundary layer increases, the diffusion distance increases and, hence, the rate of gas diffusion decreases because of the greater diffusion distance.

Principles of Heat Transfer

Discussion of heat transfer traditionally begins with consideration of the molecular basis of this form of energy transfer. Heat transfer represents the transfer of kinetic energy from molecules with a higher energy (higher temperature) to molecules with a lower energy (lower temperature). This transfer actually represents the transfer of kinetic energy from the higher energy source to the lower.

Heat transfer is possible in one of three forms: conduction (through solids), convection (from solids to liquids, with motion of the liquid carrying fluid away from the solid-liquid interface), and radiation (an electromagnetic mechanism). Within the CPB heat exchanger, the major forms of heat transfer are forced convection (the water and blood of the heat exchanger are actively pumped past the stainless steel interface; hence, the term forced) and conduction within the stainless steel.

The flow of energy or heat, Q, is related to the temperature difference by the thermal conductivity, K, a constitutive property of any material, such that:

$$Q = -K \cdot {}^{\delta T}/_{\delta x} \qquad (3)$$

where T = the temperature at any point and x = distance. This equation is the one-dimensional form of Fourier's law of heat conduction. In a similar manner to that already discussed for the other boundary layers, as blood flows past the heat exchanger surface, a thermal boundary layer is generated in which the temperature varies from the temperature of the wall to that of the free stream yet unaffected by the heat exchanger.

The Analogs of Momentum, Mass, and Heat Transfer

It provides insight to consider the similarities between the various forms of mass and energy transfer that have just been discussed: diffusion, momentum transfer, and heat transfer (5). Marked similarity exists between the apparent movement of momentum in the velocity boundary layer, gas diffusion, and heat transfer in the heat exchanger. Table 2.3 summarizes these similarities. The most striking feature is the resemblance of the defining equations as shown in the right column. While these equations are simpler than the actual equa-

Table 2.3. Comparison of Momentum Transfer, Heat Transfer, and Mass Transfer (Diffusion)

Transfer	Driving Force	Flow	Defining Equation[a]
Momentum	Velocity gradient	Momentum	$\tau = -\mu^{\delta u}/_{\delta x}$
Heat	Temperature gradient	Heat (energy)	$Q = -K^{\delta T}/_{\delta x}$
Mass (Diffusion)	Concentration gradient	Mass (diffusing gas)	$J = -D^{\delta P}/_{\delta x}$

[a]The negative signs in these equations are the result of standard conventions used in defining positive and negative directions.

tions needed to describe the physical situations, they provide insight into the nature of the equations.

Enhancing Gas Transport with Secondary Flows

The major resistance to gas diffusion occurs in the blood phase (6). Efforts to improve gas exchange have focused on reducing this diffusion barrier (7, 8). As mentioned earlier, the primary methods for enhancing gas diffusion are increasing the driving gradient and dwell time, or decreasing the diffusion path. Increasing the driving gradient is limited to 760 mm Hg minus the oxygen tension in the blood, because pressures above atmospheric pressure risk bulk gas transport across the membrane with resultant gas embolization. Increasing the dwell time is limited by the requirement for increased priming volume as the size of the oxygenator increases.

However, decreasing the diffusion path has been used very successfully to enhance gas transfer. First, the blood path thickness has been minimized as much as technically feasible by placing the membranes as close together as possible without causing an excessive pressure drop across the oxygenator. *The major advance has been the utilization of induced eddies or secondary flows of the blood (9) from the primary stream (Fig. 2.5) into the diffusion boundary layer, thus decreasing the thickness of this layer and increasing the gas transfer.* Eddies have been generated in several different ways. Some possible methods include making the surface of the membrane irregular, e.g., dimpled (10), or positioning the elements within the flow stream to disrupt the smooth flow.

This bulk movement of venous blood into the diffusion boundary layer also impacts on the blood velocity boundary layer, thus increasing the shear stresses within the boundary layer and at the wall. This has two negative effects. First, the increased shear stress within the boundary layer can lead to increased formed element destruction, as discussed later. Furthermore, increasing wall shear stresses (membrane oxygenators) increases the blood pressure drop across the oxygenator. These factors must be balanced in the design of the blood flow pattern within a membrane oxygenator.

BUBBLE OXYGENATORS

Standard Design

Although the concepts of both bubble and membrane oxygenation were well-appreciated by the early developers of CPB, the inherent simplicity of bubble oxygenation led to the earlier development of a practical device. Structurally, a typical bubble oxygenator is divided into two sections (Fig. 2.6). Venous blood first enters a mixing chamber, where fresh gas flows into the blood through a screen, which causes small bubbles to form. The blood and bubbles coalesce; sufficient time is allowed in this section for adequate gas exchange to occur prior to defoaming in the second section.

One of the major advantages of bubble oxygenators is their low pressure drop, which allows them to be placed upstream of the CPB pump where they can also act as the reservoir for the system. The flow

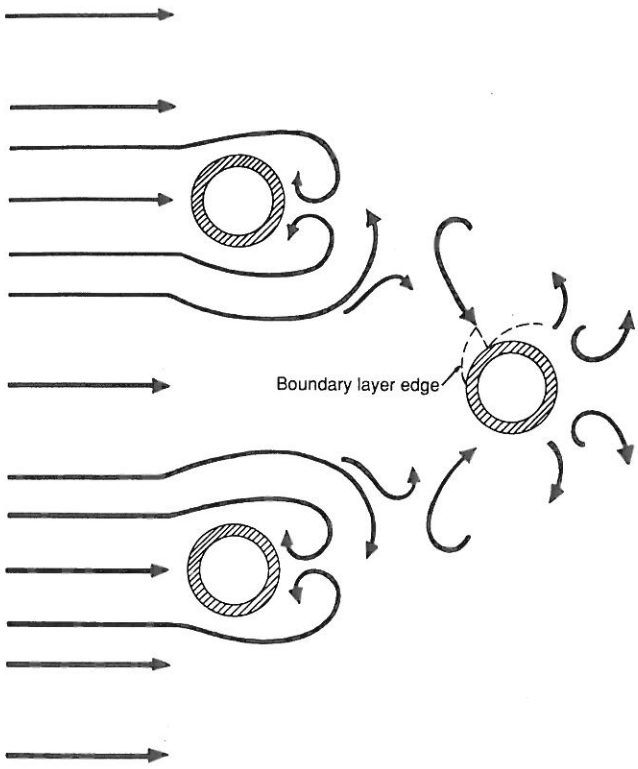

Figure 2.5. Conceptualization of the blood flow past hollow fibers, showing the effect of an eddy on the boundary layer (cross-section) of a downstream fiber. An eddy current impacts on the boundary layer of the fiber on the right, disrupting its development and reducing its thickness. This phenomenon occurs much more frequently and on a smaller scale than indicated here, causing continuous inhibition of the boundary layer development.

through a bubble oxygenator is driven primarily by the hydrostatic pressure head generated in the venous perfusion tubing (which explains why CPB machines are designed to stay close to the floor). However, the mixing chamber is designed so that the blood flows through it in an upward direction, exploiting the tendency of the rising bubbles to facilitate blood flow and reduce the pressure drop. Generally, the pressure drop through a bubble oxygenator is less than 30 cm of water, in contrast to the 100 cm of water pressure drop typically found in membrane oxygenators.

The hydrostatic pressure and drag from the bubbles carry the blood over the top of a separator and into the heat exchanger, bubble remover, and reservoir. As the heat exchanger functions similarly for both bubble and membrane oxygenators, it is described in a later section. An advantage to having the heat exchanger downstream from the bubble chamber is that gas exchange continues while heat transfer occurs. Blood is first defoamed by silicone antifoam-A, which consists of the liquid polymer dimethylpolysiloxane (96%) and particulate silica (4%). Dimethylpolysiloxane, the active defoaming agent, is mounted on the silica [which acts to disperse it in blood (11)] and destabilizes the bubbles, causing them to collapse. Bubbles are also mechanically restrained by the mesh net through which the blood and bubbles must pass.

The reservoir section has several purposes. First, it compensates for inevitable flow discrepancies between the passively flowing venous tubing and the pump-driven arterial tubing, and it allows the perfusionist some time to react to these changes. Unlike membrane oxygenators, bubble oxygenators do not require a separate venous or arterial reservoir. Second, the reservoir also serves a debubbling function by allowing time for the blood to briefly stagnate

and thus facilitate bubble elimination by allowing them to float to the top of the reservoir. Blood exits from the reservoir through the bottom, away from any bubbles floating to the top.

Bubble Considerations

Gas bubbles are eliminated from the oxygenated blood both by separation (as described above) and by absorption into the blood. The absorption of the gas in a bubble depends upon the difference in partial pressures between the gas in the bubble and the liquid. In the case of oxygen bubbles coming from the oxygenator, the net pressure difference tending to drive absorption is the sum of the ambient pressure of the blood and the surface tension of the bubble minus the sum of the partial pressure of CO_2 in the bubble and the oxygen partial pressure within the blood. This difference becomes more favorable for absorption when the bubbles are compressed by the high ambient pressure of the blood present in the arterial infusion tubing. Absorption of bubbles will be inhibited as the arterial P_{O_2} increases.

Bubble size also affects the rate of CO_2 and O_2 exchange. For a specified flow of oxygen into the mixing chamber, decreasing the size of the bubbles by injecting the gas through smaller holes will increase the total amount of surface area of the blood-gas interface. As Table 2.4 shows, for a given total gas volume, the total area available for gas transfer is inversely proportional to the bubble diameter (assuming all of the bubbles are the same diameter). Thus, as the bubble diameter decreases from 100 μm to 10 μm, the surface area per cubic centimeter of total gas increases 10-fold from 300 cm^2 to 3000 cm^2. However, as Galletti and Brecher (12) pointed out, there is a difficulty with smaller bubbles: the CO_2 tension within them will rise faster, limiting the total carbon dioxide transfer. One can imagine a limiting case where bubbles containing only a few oxygen molecules are injected, resulting in excellent blood oxygenation without any carbon dioxide diffusing into them whatsoever! Manufacturers have assessed this trade-off between oxygenation and carbon dioxide elimination and have selected bubble sizes that provide the best compromise, generally with a respiratory

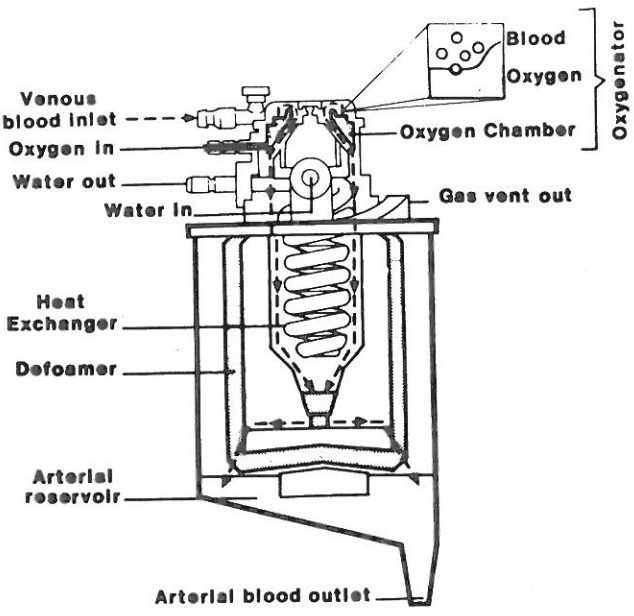

Figure 2.6. Schematic of a typical bubble oxygenator showing the mixing chamber, heat exchanger, defoamer, and arterial reservoir. (Reprinted with permission from High KM, Williams DR, Kurusz M. Cardiopulmonary bypass circuits and design. In: Hensley FA, Martin DE, eds. The practice of cardiac anesthesia. Boston: Little, Brown & Co., 1990.)

Table 2.4. Total Blood-Gas Interface for 1 cm³ of Gas Separated Into Various Blood Sizes[a]

Bubble Diameter (μm)	Number of Bubbles ($\times 10^{+3}$)	Total Surface Area (cm²)
10	238,700	3000
50	1,910	600
100	239	300
200	29.8	150
400	3.73	75

[a]Numbers calculated based on equations for volume of a sphere ($V = 4/3\pi r^3$) and surface areas of a sphere ($A = 4\pi r^2$).

quotient (ratio of CO_2 elimination to O_2 uptake) of 0.8 under standard operating conditions.

Operation and Control

Control of oxygenation in bubble oxygenators is made more complicated by the interaction between oxygenation and carbon dioxide removal. This situation contrasts with natural lungs or artificial membrane lungs, where independent change in carbon dioxide elimination can be accomplished by simply changing the ventilating gas flow rate. Increasing the flow of oxygen into a bubble oxygenator will increase the number of bubbles generated and the surface available for gas transfer, resulting in increased Po_2 in the blood. In lieu of adding more oxygen, attempts have been made (13) to add so-called "inert gases" to the ventilating gas in an attempt to control the oxygenation and carbon dioxide elimination independently. The perfusionist could then adjust the ratio of the oxygen and inert gas, i.e., nitrogen or helium, thus maintaining a constant flow of oxygen while varying the total ventilating flow. However, this is dangerous because the higher total ventilating flow increases the risk of gas emboli. Furthermore, inert gases in the bubbles would absorb more slowly than the oxygen, which avidly combines with hemoglobin. Inert gases are not generally used.

One vital aspect of using a bubble oxygenator is maintaining an adequate volume of blood in the reservoir. As mentioned above, this reservoir enhances debubbling of the blood by giving the bubbles the opportunity to rise to the top of the blood pool. This volume of blood also acts as a compliance chamber for the system, giving the perfusionist time to add volume, warn surgeons of decreased venous return, and/or temporarily decrease blood pump flow rate.

MEMBRANE OXYGENATORS

Standard Design—"True" versus Microporous Membranes

Membrane lungs attempt to achieve separation between blood and gas in a manner analogous to the natural lung. "True" membrane lungs provide a complete barrier between the gas and blood phases so that gas transfer depends totally on diffusion of gas through the membrane material. True membrane lungs are costly to manufacture and have a large priming volume, and as a result, most of the membrane lungs used for surgery today have micropores. The only true membrane oxygenator currently in production is the Sci-Med Spiral Coil Membrane Lung (Sci-Med Life Systems, Inc., Minneapolis, MN). This lung is utilized primarily in extracorporeal membrane oxygenation (ECMO) because of its ability to maintain stable CO_2 and O_2 for long periods of time (weeks) without the decrement in gas transfer that is commonly seen with microporous membrane lungs. As depicted in Figure 2.7, the Sci-Med membrane lung consists of a silicone membrane in the shape of an envelope that is coiled on itself. Blood flows through the integral heat exchanger and then past the membrane. This oxygenator is available in gas exchange surface area sizes from 0.5 m² to 4.5 m² to provide ECMO to patients ranging from neonates with congenital lung disease to adults with adult respiratory distress syndrome and conventional CPB.

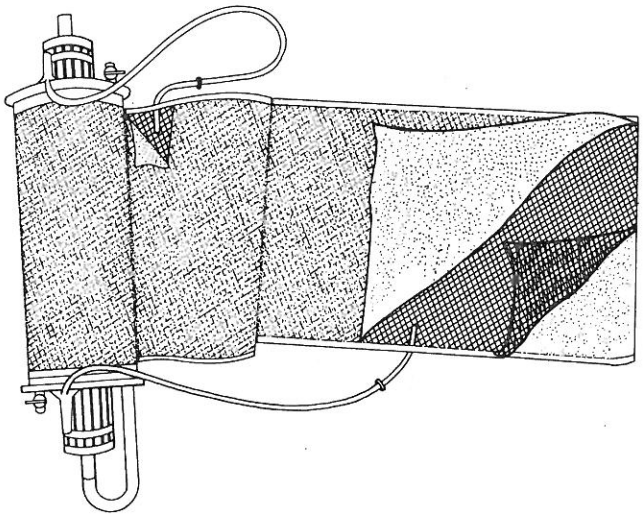

Figure 2.7. An unfolded view of a Sci-Med coiled membrane oxygenator showing the coiled silicone envelope with a mesh screen separating the membranes in the gas phase of the oxygenator. Fresh gas is supplied to the envelope by several silicone tubes (one is depicted in the figure) and removed in a similar manner. (Reproduced with permission from Snider MT, High KM, Campbell DB, Williams DR. Extracorporeal membrane oxygenation. In: Hensley FA, Martin DE, eds. The practice of cardiac anesthesia. Boston: Little, Brown & Co., 1990.)

Microporous membranes allow at least a transient direct blood-gas interfacing at the initiation of CPB. After a short time, protein coating of the membrane and gas interface takes place, and no further direct blood and gas contact exists. Typically, the surface tension of the blood prevents large amounts of fluid from traversing the small micropores during CPB. The micropores provide conduits through the polypropylene membrane that give sufficient diffusion capability to the membrane for both oxygen and CO_2 exchange.

However, over several hours of use, the functional capacity of micropore membrane oxygenators decreases because of evaporation and subsequent condensation of serum that leaks through the micropores (14–16). It has been suggested that this transfer may be reduced by heating the membrane lung and the gas entering it (15), the premise being that the condensation within the fibers can be minimized by maintaining the ventilating gas temperature above blood temperature to minimize condensation. Although currently unconfirmed, the initial results of this approach appear promising. Blood surface tension prevents gas leakage into the blood (provided excessive gas pressures do not occur).

Membrane Configuration and the Manifolding of Gas and Blood Flow

Two primary designs of microporous membrane structure are currently being used: the hollow fiber design originally described by Bodell et al. (17), and others of the folded envelope design. Hollow polypropylene fibers are extruded, annealed, and stretched to produce the micropores and then heated to stabilize the structure of the polymer (18). Pore size is less than 1 micron, although the size depends upon the manufacturing process used. Pores less than 1 micron are required to inhibit both gas and serum leakage across the membrane.

The widespread use of membrane lungs depended on the development of the microporous membrane. Prior to this innovation, available materials with the necessary structural integrity (Teflon, cellulose) were incapable of sufficient gas exchange without excess surface areas. The microporous membrane provides the necessary gas transfer capability via the micropores, where there is a direct blood-gas interface with minimal resistance to diffusion.

Two basic types of hollow fiber membrane lungs have been made: those with the blood phase on the inside or outside of the

fibers. Decreased oxygenator function from thrombosis within the fibers has occurred with the former design (19). However, satisfactory clinical performance continues to be achieved with both blood flow patterns. For oxygenators with blood flow outside the fiber, blood flows either perpendicular to the fiber bundle (cross-current) or in the direction of the fibers. In the latter case, blood usually flows in the opposite direction to the gas flow (counter-current). Cross-current blood flow offers the advantage of naturally induced secondary flow generation. The fibers tend to "trip" the flow, inducing eddies downstream of each fiber (Figs. 2.5 and 2.8). This flow alteration reduces the diffusion boundary layer of downstream fibers, thereby enhancing gas exchange.

Elimination of blood streamlining (direct flow through the oxygenator without gas exchange) through the oxygenator constitutes a key feature to ensuring optimal lung performance. Therefore, in hollow fiber designs where blood flows outside the fibers, adequate manifolding (the blood flow channel in and out of the oxygenator) of both the inlet and outlet blood flow is critical, as is the flow pattern within the oxygenator itself. In hollow fiber designs where blood flows inside the fibers, reducing fiber occlusions from thrombosis has been the key to successful design.

Operation and Control of Membrane Oxygenators

In contrast to bubble oxygenators, control of ventilation and oxygenation is relatively independent in membrane oxygenators. Increasing the total gas flow rate changes ventilation (CO_2 elimination) by reducing the gas phase CO_2 partial pressures and probably by decreasing the gas

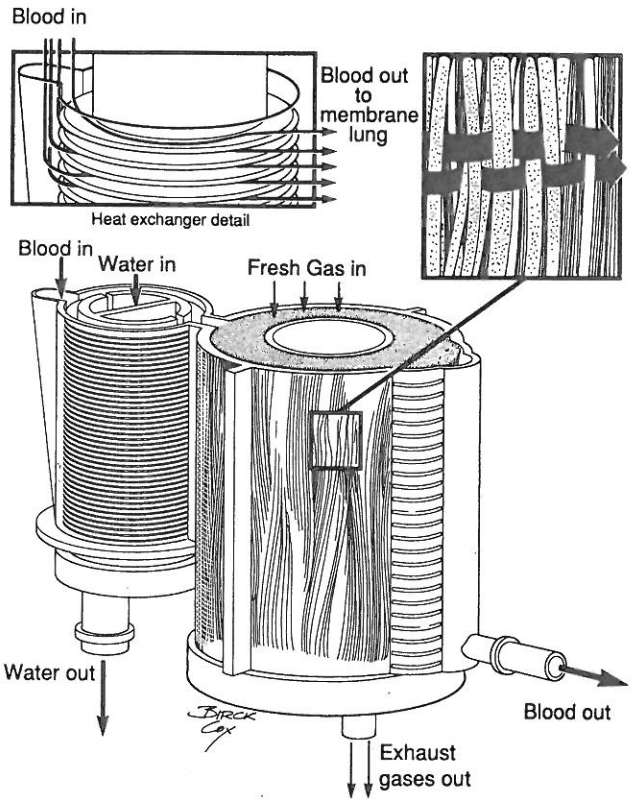

Figure 2.8. Schematic diagram of a typical membrane lung. In this case, the heat exchanger (shown in detail in the upper left of the figure) incorporates fins that act as channels through which the blood flows. The blood first passes through the heat exchanger and then through the gas exchange portion of the membrane lung. Both the heat exchanger and gas exchanger portions contain manifolding that distribute blood flow evenly to minimize shunting within the device.

phase boundary layers for CO_2 transfer. Gas flow is adjusted by a flow controller upstream of the oxygenator, such that some pressurization of the gas occurs (generally only a few centimeters of water pressure).

Blood oxygenation control is accomplished simply by increasing (or decreasing) the fraction of O_2 in the gas supplied to the oxygenator. Because the membrane oxygenator separates the blood and gas phases and does not introduce gas bubbles into the blood, the addition of nitrogen to the gas flows does not increase the risk of gas emboli to the patient (as it does with bubble oxygenators). Some experts have commended the ability of membrane oxygenators to function with a reduced supply of gas oxygen fraction as an indicator of efficiency, although this capability has limited clinical relevance, except in the rare instance of a hypermetabolic patient.

QUANTIFICATION OF OXYGENATOR PERFORMANCE

Measurement of Gas Transfer

It is not common practice at this time to measure the amount of O_2 and CO_2 that is transferred across the artificial lung. However, situations can arise (20) in which determination of oxygenator gas exchange is critical and perhaps lifesaving. In the case of oxygenator dysfunction, it is vital to distinguish between primary oxygenator dysfunction and hypermetabolic states of the patient. The gas exchange of the oxygenator can rapidly be determined using either blood or gas phase measurements.

In the blood phase, gas transfer can be calculated by application of conservation of mass (Fick's principle). This assumes that the transfer of O_2 across the membrane or bubble interface causes the difference between the oxygen content flowing into and emerging from the oxygenator. Thus, the oxygen content of the arterial and venous perfusion tubes is determined by continuous in-line monitors or blood gas determinations, and the difference is multiplied by the flow rate of blood (pump flow rate) as shown in equation 4:

$$\dot{V}O_2 = Q \cdot (C_a - C_v) \qquad (4)$$

where $\dot{V}O_2$ = the oxygen transport, Q = the blood flow rate, and C = the oxygen content, with a and v representing the arterial and venous values, respectively.

Gas transfer can also be determined in the gas phase, perhaps more accurately and rapidly in some cases than blood phase measurements. Using the operating room mass spectrometer, the gas concentrations of the gas flowing into and from the oxygenator can be sampled and gas fractions determined. The difference of O_2 in inlet and outlet gas concentrations can then be multiplied by the total gas flow rate to determine the O_2 transfer rate:

$$\dot{V}O_2 = Q \cdot (FiO_2 - FeO_2) \qquad (5)$$

In this case, Q = gas flow rate and FiO_2 and FeO_2 are in inlet and outlet gas oxygen fractions, respectively.

This method introduces what is usually a minor inaccuracy in the calculations. Because the rate of transfer of O_2 and CO_2 is not necessarily the same, the flow rate of the gas entering the oxygenator is slightly different than the exiting flow rate. If more accurate gas transfer rates are desired, then a dilutional gas can be added to the supply gas. Typically, a relatively inert and insoluble gas such as helium is added in a low concentration of 5–10%. Helium in the gas phase rapidly comes into equilibrium with blood-phase helium, so that after a short time the net transmembrane helium flux is zero. Again by continuity, the helium flow into the oxygenator equals the flow out of the oxygenator. This can be rearranged so that the outflow can be calculated by:

$$Q_e = (Fi_{He} / Fe_{He}) \cdot Q_i \qquad (6)$$

where Q_i and Q_e are the total gas flow rates in and out, respectively, and the subscripts Fi_{He} and Fe_{He} represent helium gas fractions in and out, respectively. The rate of oxygen transport can be calculated from conservation of mass by subtracting the amount of oxygen leaving the oxygenator from that entering:

$$\dot{V}O_2 = Q_i \cdot FiO_2 - Q_e \cdot FeO_2 \qquad (7)$$

or by substituting equation 6 in equation 7 and rearranging terms:

$$\dot{V}O_2 = Q_i \cdot [FiO_2 - (Fi_{He}/Fe_{He}) \cdot FeO_2] \quad (8)$$

Thus, oxygen transfer within the oxygenator can be calculated by measuring only one flow and inlet and outlet gas concentrations. Similar equations can be derived for CO_2, which are usually simplified because $FiCO_2 = O$.

Industrial Standardization of Gas Transfer and Blood Flows

The industrial method for describing oxygenator performance relates to standards outlined by American Association of Medical Instrumentation (Arlington, VA). Some of the more pertinent reference conditions are as follows:

Carbon Dioxide Reference Blood Flow. This is the flow rate of normothermic whole blood having a hemoglobin content of 12 g/100 ml, zero base excess, and oxygen saturation of 65%, that has its carbon dioxide content decreased by 38 ml carbon dioxide (standard pressure and temperature [STP]) per liter of blood flow by direct passage through the blood oxygenator.

Oxygen Reference Blood Flow. This is the flow rate of normothermic whole blood having a hemoglobin content of 12 g/100 ml, zero base excess and oxygen saturation of 65%, that has its oxygen content increased by 45 ml O_2 (STP) per liter of blood flow by passage through the blood oxygenator.

Reference Blood Flow. This is the lowest of the following: oxygen reference blood flow, carbon dioxide reference blood flow, the manufacturer's recommended blood flow, or a blood flow of 6 liters per minute.

Index of Hemolysis. Quantity (in milligrams) of plasma-hemoglobin generated in the in vitro cellular damage test per 100 liters of blood flow through the circuit containing the oxygenator less the quantity generated in the circuit without the oxygenator.

Initial Priming Volume. Static volume of blood (in milliliters) to fill the blood phase of the device to the manufacturer's recommended minimal running level. With bubble oxygenators, this is measured with the reference oxygen flow recommended by the manufacturer for the start of perfusion.

Maximum Operating Volume. Volume of blood contained in the device at the maximum reservoir level recommended by the manufacture at reference blood flow and reference oxygen flow.

Minimum Operating Volume. Volume contained in the device at the minimum reservoir level recommended by the manufacturer at the reference blood flow and reference oxygen flow.

BLOOD-ARTIFICIAL SURFACE INTERACTIONS: THE EFFECTS OF MEMBRANE AND BUBBLE OXYGENATORS ON PROTEINS AND FORMED ELEMENTS OF THE BLOOD

Although all of the chemical processes involved in blood-surface interactions are not clearly understood, it is relatively well-established (21, 22) that when blood comes into contact with a foreign surface, a predicted chain of events occur. Almost immediately at the onset of contact, protein deposition begins. Deposition of a thin protein covering (approximately 50 Å) occurs within a few seconds. The primary proteins

involved are albumin, fibrinogen, and globulin. This protein coat gradually thickens and changes its composition, which is somewhat dependent upon the polymer surface. This protein adhesion is followed by platelet deposition (as shown in Fig. 2.9) and white cell chemotaxis to the protein coat. Platelet adhesion would begin even without the protein coat by utilizing proteins on the surface of the platelet. This mass of protein and platelets is commonly referred to as a white clot. Red cells are entrapped as this mass extends into the blood flow, resulting in a red clot.

Baier (21) describes three basic modifiers of the interface surface: texture, surface charge, and surface chemistry. Surface irregularities less than 1 micron in size do not affect compatibility with blood (23), assuming that surfaces are prewetted to remove pockets of gas from the blood interface. Plasma protein adherence to the prosthetic surface tends to level these irregularities, thus reducing their effect. Some have suggested that surfaces having a net negative surface charge slowly erode during contact with blood (24, 25) and are antithrombogenic. Furthermore, Baier suggested that the chemical characteristics of the foreign surface affect the manner of protein deposition.

The interaction of gas bubbles in blood has been described by Butler (26). Gas bubbles in blood cause the formation of a "capsule" around the bubble consisting of platelets, a lipoidal material, and a protein layer containing clotting factors. Butler describes other blood-bubble interactions, which include red blood cell agglutination, leukocyte activation, denaturation of plasma proteins, release of vasoactive substances (serotonin, histamine, kinins, and prostaglandins), and changes in capillary permeability.

Hemolysis during cardiopulmonary bypass (27, 28) is most commonly associated with the roller or centrifugal pump, or suctioning into the cardiotomy reservoir. However, shear stresses induced by flow through the oxygenator will impart some damage to red cells. Nevaril et al. (27) utilized a concentric cylinder viscometer, which consists of an outer rotating cylinder and an inner stationary cylinder. They determined that for human blood a threshold shear stress of 3000 dyne·cm^{-2} existed (exposure period of 2 minutes). Hemolysis was relatively constant for long time periods. Leverett et al. (28) identified a threshold shear stress of 1500 dyne·cm^{-2} and a time dependency for hemolysis at higher stress rates.

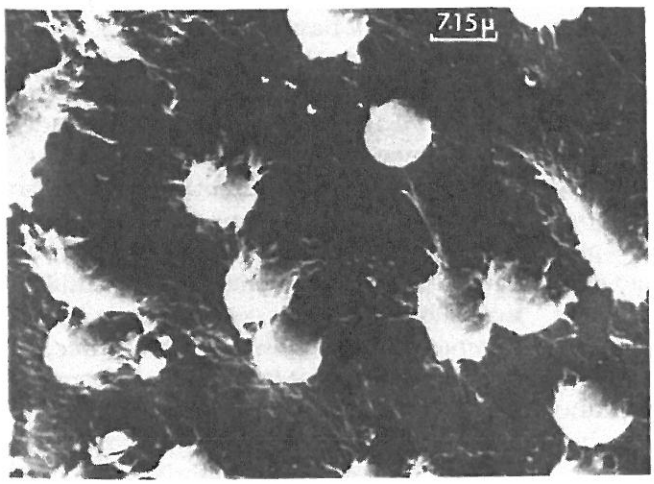

Figure 2.9. Scanning electron microscope view of platelet adhesion to polyurethane sac from a circulatory assist device. Note the aggregated platelets and incorporation of white cells into the growing thrombus. (×1880) (Photograph courtesy of Dr. William Pierce, Hershey Medical Center, Hershey, PA.)

Damage to platelets can occur either as a result of contact with the interface surfaces or from shear stresses within the blood (29–31). Platelet damage manifests either as alterations in platelet structure or aggregation. Brown et al. (29) utilized a rotational viscometer and demonstrated that when platelets were exposed to a threshold shear stress of 150 dyne·cm^{-2} for several minutes, significant loss of platelets and platelet function occurred. There was some return of platelet count and function when these measurements were made again 4 hours after platelet exposure, suggesting a reversible component to the platelet damage and to the platelet aggregation that contributed to the decreased platelet count. Colantuoni et al. (30) injected platelet-rich plasma through a capillary tube, thus exposing the platelets to high shear stresses for very short periods. For exposure times of approximately 1 msec, platelet exposure to shear stresses of 7,000 to 15,000 dyne·cm^{-2} were required to produce increases in plasma serotonin and decreases in platelet count and impaired aggregation to adenosine diphosphate.

Sorting out whether these changes are caused by shear stress directly or wall contact is difficult. Bernstein et al. (31) confirmed these earlier results by an injection of platelet-rich plasma into a stagnant pool, but suggested that differences in the shear stress required to induce abnormal platelets were caused by differences in the test systems and the exposure times. While it is difficult to delineate whether shear stress or wall contact is the primary irritant, increasing exposure time and shear stresses (increased turbulence in the boundary layer) increases platelet damage.

At blood-gas interfaces, globular proteins denature (32, 33), i.e., undergo conformational changes of secondary or tertiary structure without changes to the primary amino acid sequence. Dipolar molecules orient themselves with hydrophilic portions extending into the plasma, but coiled. However, folded proteins with polar groups on the external surface are physically altered to orient in such a fashion. Devices such as bubble oxygenators denature proteins, resulting in decreased protein solubility and increased exposure of the nonpolar protein and reactive side chains. This makes the protein available to the surface of erythrocytes, chylomicrons, and platelets. The resulting aggregates of blood cells and activated platelets can cause sludging in the microcirculation, and are postulated as an etiology of the postperfusion lung syndrome. The coagulopathy associated with prolonged perfusion may be, in part, related to the consumption of coagulation factors by this denaturation. Decreased immune mechanisms have been studied, and some evidence supports increased susceptibility to bacterial growth after clinical CPB (34) (see Chapter 10). All of these effects appear to depend on the length of the total exposure, i.e., the length of CPB and the amount of the exposure.

HEAT TRANSFER DURING CARDIOPULMONARY BYPASS

Heat Exchangers

The design of heat exchangers for cooling and rewarming blood in the oxygenator centers around making a biologically inert surface capable of achieving the desired rate of heat exchange, without producing any localized overheating of the blood. Generally, the energy transfer into and out of the heat exchanger is provided by nonsterile water that is circulated through a heater/cooler unit, which is part of the perfusion apparatus. When cooling is desired, the water is passed through an ice bath, and when warming is desired, it is heated by electric resistance heaters. Use of water as the heat transfer fluid is simple, reliable, and provides an even temperature distribution across the surface of the heat exchanger without localized hot spots, which might occur, for example, if the elec-

tric heating element were built into the oxygenator itself.

The heat transfer surface is usually made of stainless steel or aluminum. Both materials have good thermal conductivity and are readily coated with polymers to minimize blood interactions. To maximize heat efficiency of heat transfer, designers try to maximize the available surface area for heat exchange, either by making a larger heat exchanger (at the cost of increasing the priming volume) or by using fins extending into the blood. "Finning" also allows for a reduced number of water channels (Fig. 2.8), which in turn simplifies construction of the heat exchanger and decreases the potential number of sites at which fluid leaks might occur. Many presently used heat exchangers consist simply of a coiled tubing, wound so that the resulting cylinder acts as the blood conduit. This design has the advantages of simplicity and a low risk of leakage. Heat exchange is also enhanced in most devices by flowing the blood and water in opposite directions (Counter-current heat exchange).

Constraints on Rate of Heat Transfer

The temperature difference between the circulating water and the blood drives heat transfer. A thermal boundary layer exists in the blood flowing just beside the wall of the heat exchanger (i.e., the wall separating blood and water), an area where the temperature varies from the wall temperature to the free stream temperature (35). The exact temperature profile in the boundary layer depends on the nature of the velocity boundary layer, but a typical profile would appear similar to the curves shown earlier for gas concentrations during diffusion (Fig. 2.3). Rapid cooling is commonly employed at the onset of CPB, when the circulating water is cooled to temperatures approaching 0°C by an ice bath, thus rapidly cooling the blood. Typically, the rate of cooling at the onset of CPB is limited only by this thermal boundary layer and the temperature difference between the water and the blood.

On the other hand, at the conclusion of CPB the rate of rewarming is limited not by physical constraints, but by concerns regarding blood damage due to overheating and bubble formation because of the lower gas solubility of warmer blood. Blood damage, in the form of protein denaturation, limits the ***absolute*** maximum temperature (42°C) that can be safely achieved in the blood (36). In addition, the maximum ***difference*** in temperature between the water and the venous blood is limited in order to prevent bubble formation due to the rapidly decreasing gas solubility. It has been shown in vitro and in clinical CPB (37) that gaseous microemboli formation can be avoided by limiting the water/blood temperature difference to 10°C. Some manufacturers of membrane oxygenators have taken the additional precaution of placing the warmer upstream from the gas exchanger (where lower oxygen tensions are present). The actual advantage of this approach has not been demonstrated, and this configuration is not used by all manufacturers. Furthermore, it cannot be readily used in bubble oxygenators.

Determination of Rate of Heat Transfer

The amount of heat being transferred is readily quantifiable (38, 39) by simple energy balance as defined by the first law of thermodynamics. This relationship requires that the amount of heat transferred to the blood equals the thermal energy in the blood leaving the oxygenator less the thermal energy of the blood entering the heat exchanger. The thermal energy of blood can be determined by multiplication of the specific heat of blood, C, (0.90 $kcal \cdot kg^{-1} \cdot °C$) (40) by the absolute temperature. Thus, the heat transfer can be calculated by:

$$H = C \cdot F \cdot (T_i - T_o) \qquad (9)$$

ease of use. It is likely that, in the future, the use of *in vitro* techniques will be superseded by computational fluid-dynamic analyses (CFD).

Wear and durability can also be investigated in the laboratory. Valves are tested at accelerated rates of up to 20 Hz. In this way, the effects of 10 years' mechanical wear can be simulated in a period of 8 months. For mechanical valves, subsequent surface analysis enables the degree of wear to be quantified for individual valve components. Tissue valves are examined for evidence of tissue damage and tears.

22.3.2. *Cardiopulmonary bypass*

Concept of bypass

'Bypass' is a term employed by surgeons to indicate that fluid normally circulating through an organ is diverted around it, either to reduce the functional work-load and allow the organ to heal, or to isolate the organ for the duration of a surgical procedure.

During cardiopulmonary bypass (heart/lung bypass) the blood is diverted away from the heart and lungs. As this is incompatible with life beyond a few minutes, surgical procedures involving the heart and main blood vessels must be coupled with artificial maintenance of cardiorespiratory function by a heart–lung machine. This is a mechanical system capable of pumping blood around the body and oxygenating it by means of an appropriate gas exchange unit. Such a system is obviously a safety-critical system.

A heart–lung machine was first used for the treatment of pulmonary embolism in 1937 and cardiopulmonary bypass was first used for open-heart surgery in 1953.

Uses of cardiopulmonary bypass

- As a temporary substitute for heart and lung function during surgery.
- As an extracorporeal membrane oxygenation system to assist respiratory exchange.
- To maintain life after severe damage to heart or lung (myocardial infarction (MI), trauma, pulmonary embolism).
- For short-term assist during invasive therapy (lung lavage).
- For the treatment of respiratory imbalance (hypercapnia).

A typical circuit is shown schematically in figure 22.11. The blood is drained from the patient by cannulation of the inferior and superior vena cavae. The heart and lungs are isolated by cross-clamping the aorta downstream of the aortic valve and the venae cavae at the entrance to the right atrium. The venous blood enters the extracorporeal circuit and is transported to the oxygenator where it is oxygenated and carbon dioxide is removed. The example shown incorporates a specific type of oxygenator, a 'bubble' oxygenator. When using this type of device a defoamer and a bubble trap are required to remove gaseous emboli which, if allowed to enter the patient's circulation, may cause brain, lung and kidney damage. A heat exchanger enables the blood to be cooled in a controlled manner inducing systemic hypothermia. Before being returned to the patient the oxygenated blood is filtered. This arterial filter removes microaggregates and any residual gas micro-bubbles. Blood is then returned to the body by means of a cannula in the aorta.

Blood released into the chest during surgery is sucked through a second blood circuit from the surgical field and returned to the system.

Oxygenators

Two types of oxygenator are currently in clinical use. These are direct contact and membrane types.

Direct contact types are usually 'bubble' type oxygenators which allow direct contact between the blood and gas. Oxygen is bubbled through a series of compartments containing venous blood. This process

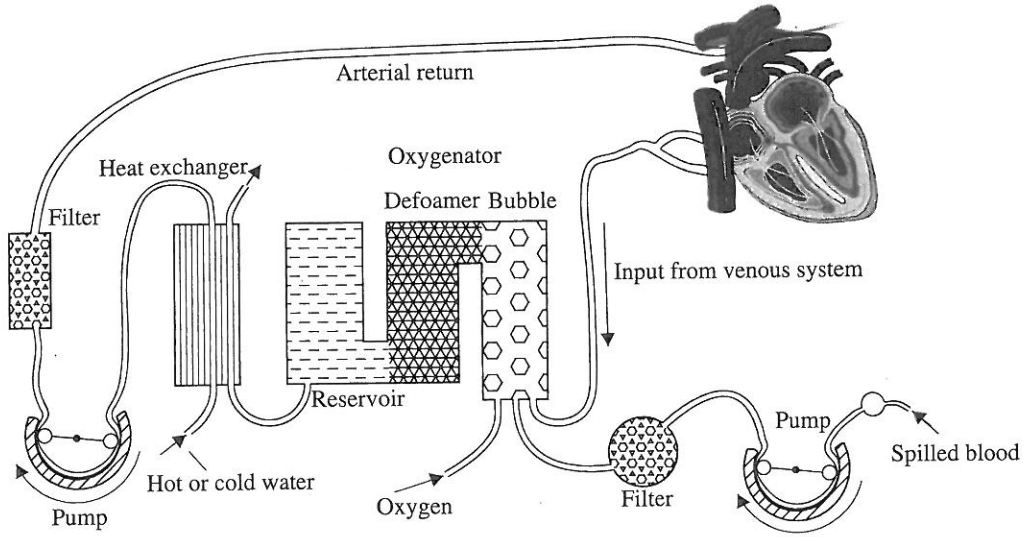

Figure 22.11. *A typical circuit for cardiopulmonary bypass.*

causes foaming of the blood. Defoaming is then carried out by passing oxygenated blood over silicone-coated screens. Contact between the blood and bubbles will result in damage to blood elements and protein denaturation due to the high interfacial energies involved. Foaming precipitates fibrin and increases platelet activation.

In membrane-type oxygenators blood is separated from the gas phase by a permeable polymeric sheet or tube.

Three types of membrane are currently used. Each has advantages and disadvantages.

- *Homogeneous*: the membrane takes the form of a continuous sheet of solution/diffusion membrane.
- *Microporous*: has a high void volume.
- *Composite*: thin film of solution/diffusion polymer on a microporous substrate.

Homogeneous. Gas diffuses into the membrane polymer at the interface and from the polymer into the blood. This process is slow, requiring long perfusion times and a large area for adequate exchange. (Materials used include PTFE, polyurethane and polysiloxane.)

Microporous. Pores are introduced during the manufacturing process (e.g. porous polypropylene).

Composite. A film of homogeneous polymer on a microporous substrate (e.g. 25 μm layer of polysulphone cast onto porous polypropylene.)

The choice of membrane will depend on the balance between gas permeability, strength and blood compatibility. There are two common geometries of membrane oxygenator design. These are multiple flat channels and multiple hollow fibre types. The area of membrane required to obtain the correct level of blood oxygenation will depend on the design and can be calculated if it is assumed that complete saturation of the haemoglobin is required.

Pumps

We can list the design requirements for a suitable pump:

- Be capable of flow rates up to 10 l min^{-1} and be able to achieve this against a pressure of 180 mmHg.
- Cause minimal clotting and thrombus formation.
- Not promote gas emboli.
- Have no hot spots which might damage the blood.
- Be easily sterilized.
- Be capable of being calibrated accurately.
- Be reliable.
- Cause low shear and turbulence.
- Give pulsatile flow.

The last design requirement listed is controversial. As pulsatile flow is more complex to achieve than steady flow, the use of a more sophisticated pump must be fully justified. The benefit of pulsatile flow remains a subject for debate. There is some suggestion that pulsatile flow is associated with an increase in O_2 consumption, reduced lactate accumulation and increased capillary blood flow to the brain.

Roller pumps are commonly employed. These have the advantages that the blood is only in contact with the tubing and little priming is required. However, there are disadvantages to the roller pump which does cause shear forces in the blood, will continue to appear to work against a blockage and causes stresses in the tube which may eventually crack.

The purpose of the heat exchanger is to control the blood temperature thus preventing progressive uncontrolled cooling. This is essential as abrupt temperature gradients result in cell damage and the release of gas from solution in the plasma. Filters are placed in the arterial return line and between the cannula used to clear the operative site and the oxygenator in order to remove particulate debris from the blood, thus preventing damage to the lungs, brain or kidney.

There is no ideal design of filter. If the pore size is too small the resistance of the circuit may rise as the filter blocks. In addition, the filter itself may cause blood damage. A typical design is made up of pleated polyester and has a pore size of about 40 μm.

22.3.3. Haemodialysis, blood purification systems

Our final example of a safety-critical system is that of haemodialysis. Dialysis is the removal of substances by means of diffusion through a membrane. Dialysis is used to replace the normal function of the kidneys in a patient with kidney failure. The loss of kidney function can be either acute or chronic. In acute renal failure, which can be caused by accident or disease, the kidneys will eventually recover their normal function. In the absence of dialysis the patient would die before the kidneys recovered. In chronic renal failure, the kidneys are permanently damaged and, in the absence of either a kidney transplant or regular dialysis, the patient will die.

Two types of dialysis are used. In peritoneal dialysis, the dialysing fluid is run into, and then out of, the patient's abdomen. This is a relatively simple technique that does not need either expensive equipment or access to the circulation, and it is used for certain patients with acute renal failure. Continuous ambulatory peritoneal dialysis (CAPD) has made peritoneal dialysis suitable for long-term use in chronic renal failure. In haemodialysis, blood is continuously removed from the patient, passed through an artificial kidney machine, and then returned to the patient.

Chronic renal failure patients who have not had a kidney transplant and who are selected as suitable for dialysis will be treated either by haemodialysis or peritoneal dialysis. Alternatively, a kidney can be removed from a live donor (usually a close relative) or from a person who has just died, and can be used to replace the kidneys in the chronic renal failure patient.