Extracorporeal circulation; Practical considerations for the anesthetist

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The author provides a comprehensive overview of the basic principles and practical considerations involved with extracorporeal circulation, otherwise known as cardiopulmonary bypass. The intent of the article is to afford the anesthetist a basic understanding of not only the procedure itself, but its effects on the blood elements, oxygen transport, and tissue perfusion.

Extracorporeal circulation (ECC) or cardiopulmonary bypass (CPB) evolved over the years and has contributed to great advances and a rapid growth in cardiac surgery. Keeping abreast of the rapid advances in management and therapy of patients with cardiac disease has necessitated a team concept. And, the anesthetist is a vital part of that team which provides a complex array of services of a pharmacologic, surgical, biochemical, anesthetic, and physical nature. A considerable amount of knowledge and judgment is expected of the anesthetist, ranging from an understanding of the physiology of the particular lesion, the surgical procedure, the physiology of CPB, to the normal and pathologic circulatory, respiratory and renal physiology.

This article is designed to give a brief, yet specific, overview of the basic elements involved with ECC so that the anesthetist will have a better understanding of ECC. Not only is it essential for the anesthetist to understand these particular mechanisms, but a knowledge of the effects ECC places on blood elements, oxygen transport, and tissue perfusion is of the utmost importance in providing safe and optimal care to the patient.

History

The earliest ideas and investigations into artificial oxygenation of the blood, both intra- and extra-corporeal, probably dates back to 1812 when Legallois wrote, “If one could substitute for the heart a kind of injection of artificial blood, either naturally or artificially made, one would succeed in maintaining alive indefinitely any part of the body whatsoever.” Nearly 50 years later in 1858, this became a near reality when the physiologist Brown-Seguard attempted, with moderate success, to perfuse the decapitated head of a dog. He was one of the first researchers to emphasize the importance of cerebral blood flow and showed that a five-minute period of ischemia to the brain was sufficient to cause death. Nevertheless, these futile attempts were only the beginning of a long line of intensive investigations to oxygenate blood artificially.

It was not until the 1930's that other breakthroughs occurred. Gibbon in 1937 gave an initial report on experimental total cardiopulmonary bypass using a mechanical heart and lung. This method, however, was not perfected until the 1950's. In 1951, Dennis and associates were the first to attempt the repair of an intracardiac defect.
in a human patient with the aid of a totally mechanical heart-lung apparatus. Though their efforts failed, the knowledge that resulted led Gibbon in 1953 to a successful repair of an atrial septal defect using ECC for total CPB. Further investigations have enabled ECC to become a procedure which has achieved both a high degree of perfection and which has given hope to many patients requiring open heart surgery.

**Pump**

Once serious research began into ways of producing CPB, it became evident that some type of mechanical pump would have to be utilized for tissue perfusion purposes. Early thoughts and research were directed toward imitating nature, that is, producing a pump with pulsatile flow which would give reasonably physiological pulse contours. Research has demonstrated that flow should be pulsatile for optimal organ function and certainly for perfusion periods lasting six hours or longer.

In 1911, Hooker designed a pump that would produce just such a flow. However, the small size of the arterial inflow connectors found in the conventional heart-lung machine compared to the larger size of the aorta with which it connected, dampened these physiological contours, rendering them less physiological. Also, this pump was very complex in design, employing reciprocating positive displacement effected by a plastic diaphragm and ball valves to control inflow and outflow. Due to the mechanical action of such a pump, considerable damage to the blood and plasma proteins occurred. Developmental efforts in this area later led to the adoption of the double roller pump, as there was no convincing evidence that serious disruption of organ function occurs from continuous flow non-pulsatile pumps lasting less than six hours.

Roller pumps belong to the class of positive displacement pumps, that is, the roller progresses along a resilient tube in order to "milk" blood out of it. Such pumps should have the capacity to provide the equivalent of a basal cardiac output under the circumstances of perfusion, working against a moderate pressure gradient. They should be easily calibrated, controlled, and operable manually or by a self-contained power source if necessary. They should also provide a flow with minimal development of turbulence and shear forces as well as minimal risk to blood integrity.

The double roller pump, which is most common, has rollers at either end of an arm which is pierced in the center by a power drive shaft. This pump utilizes a horseshoe-shaped casing and two rollers revolving at the same axis, 180° out of phase. In this way when one roller finishes its stroke, the other has already started and provides the valving action. Backflow is impossible because the tube is always occluded by the roller at one point or another. These rollers can be adjusted to produce significant negative pressure to aspirate blood from the surgical field and heart chambers. The average heart lung machine will have one pump for arterial inflow, one for venting the heart, and one or two for aspiration of free blood from the surgical field.

There is evidence that hemolysis is quantitatively related to the number of passages of the roller over the blood. The application of positive pressure to the cells being driven forward is generally low and well tolerated, therefore, the amount of trauma to the blood cells is relatively small. When the rollers are used to create a negative pressure for suctioning, this force may have the magnitude of several hundred millimeters. Forces this great will be associated with frothing, violent turbulence, acceleration and shear forces that most cells will be unable to withstand. Therefore, the risk of hemolysis will depend more upon the amount and duration of suction used during a procedure than on the rollers.

The tubing and interlinking connectors used for ECC by the roller pump should have low thrombo-resistance and minimal effects on flow. Kaplan gives a good outline of the characteristics that tubing should have. Normally, the arterial line diameter of the tubing used in a patient weighing above 40 kg is $\frac{1}{2}$ inch. However, resistance to flow and priming volumes will govern the diameter of the tubing used.

The structural integrity of pump tubing is threatened to some degree by continuous use of a roller pump, and some fragmentation of the inner surface can occur. When this happens, platelets and other blood components will be destroyed giving rise to an increased chance of microemboli. The connectors linking the components of the system should be designed and finished so as to maintain smooth laminar rather than turbulent flow. These connectors should also minimize the development of eddy currents, or cavitation caused by abrupt interior contour changes due to stenosis or ridges at tubing junctions. One problem of this type is seen with the arterial connection.

An aortic arch cannula has a smooth, curved right-angle bend leading to a narrowed segment that is inserted into the aorta. High pressures may be required to deliver the pump output through such stenoses. This will cause marked flow ac-
celeration of the stream of red cells and the consequent development of shear forces, convection and eddy currents, along with a fall in pressure. This has the potential for microbubble generation, red cell and platelet disruption, and may be a factor leading to the de-stabilization of the blood.9

Since it is evident that microemboli are present, filtration in the CPB circuit is essential. Very high levels of red cells, platelet and leukocyte aggregates have been demonstrated by Doppler counting and filtration studies.10 Also air, fat, silicone, and plastic particles have been found. In one study the incidence of cerebral non-fat emboli was reduced from 31.0 to 4.1% by filters.11 Presently, the Pall Ultipor™ filter is the most commonly used. It has resulted in less hematologic disturbances and is associated with a continuing reduction in the risk of microemboli to all organs, though particularly the brain and lungs.

**Oxygenators**

Three types of oxygenators are currently available for clinical use, and may be categorized in terms of their interface with blood. In bubble and disc oxygenators, oxygen and blood are in direct contact with each other. With membrane oxygenators, blood and oxygen are physically separated.

The rotating disc oxygenator was first developed by Craford, Andersen and Bjork12 in 1948, and later modified by Kay and Cross.13 This oxygenator consists of a horizontal glass cylinder containing a row of flat steel discs mounted vertically on a horizontal steel rod and fitted between two steel end plates which rotate about a central shaft at a rate of 120 rpm. Venous blood enters through one endplate and fills the cylinder to about one-third of its diameter. This then causes a thin film of blood to be forcefully spread over the rotating disc. Oxygen, in ample supply, transfers to the blood in an amount dependent on the number of discs used, the area of the blood films, the rate of disc rotation, the O₂ saturation of venous blood, and the hemoglobin content of the red cells. With these conditions optimal, a siliconized flat disc of 12.02 cm diameter effects a transfer of 1.1 ml of O₂ per minute.

In the early days of CPB, this oxygenator was widely used and was the most popular oxygenator. However, this oxygenator was cumbersome to clean, prepare, and resterilize. Eventually, overcoming these disadvantages led to the development by DeWall14 of an efficient bubble oxygenator.

The modern bubble oxygenator consists of two incompletely fused plastic sheets separated to form a channel for the inflow of un oxygenated blood and the ventilating gas mixture. The ventilating gases are passed through multiple perforations in a diffusing plate giving rise to bubbles which exit into the venous blood at the bottom of a columnal reservoir. This produces frothing and turbulence which assist in driving the now partly arterialized blood forward into a debubbling chamber. Once here, coalescence of the foam and elimination of the last remaining bubbles are achieved by the action of antifoam surface active substances and by simple physical means such as settling, trapping, filtration, or vacuum.

Oxygenation in the bubbler is not membrane limited as in the normal lung, but depends upon the gas-blood surface contact area, the thickness of the blood film, the mean red cell transit time, and the partial pressure of O₂ used. Normally, the gas-blood surface contact area is in the range of 15 m², and is governed by total gas flow and bubble size. It is well known that the smallest bubbles produce the greatest surface area, however, these small bubbles are more stable and thus more difficult to remove. Therefore, bubbles 2-7 mm in diameter are used which result in an effectively thicker blood film. Since the time required for oxygenation is a function of the square of the film thickness, a red cell mean transit time of 1-2 sec is required. The result for most bubblelizers in current use is a flow of gas through the oxygenator column that must be at least equal to the flow of blood to maintain both reasonable flow and gas exchange.

Since it is evident that current bubble oxygenators are not perfect, researchers have developed an oxygenator that more closely resembles the natural lung—the membrane oxygenator.

As mentioned earlier, the membrane oxygenator operates with the blood and oxygen physically separated. Its membranes are either solid or microporous. The membranes are arranged in flat, stacked, or coiled sheets, or in a tubular array. These membranes are constructed so that numerous small capillary tubes in the device are compressed by external pressure, causing the blood in the tubes to form a thin blood film layer over the membrane. Oxygen then flows between these layers of the membrane and diffuses into the blood. The type of material that composes the membrane is of utmost importance and usually consist of teflon, silastic or silicone. Silicone membranes have a CO₂/O₂ transfer capacity of 5:1 or 6:1, and thus more closely resemble the situation in the lung.

Though there are advantages and disadvantages to each type of oxygenator, the membrane oxygenator is superior when used for prolonged CPD support. However, since most procedures in-
volving ECC have an average pump time of 60-90 min, little benefits is derived from using the membrane oxygenator over the bubble oxygenator.

The fact that CO₂ is about 20 times more diffusible in body fluids than is O₂ is well known. This same principle also applies to disc and bubble oxygenators. In fact, with O₂ flows sufficient to produce acceptable arterial O₂ tensions, the addition of CO₂ is required to avoid hypocarbia and maintain normal arterial tensions. In many centers, 3% CO₂ and 97% O₂ mixtures are used to maintain the blood gases at more nearly normal levels. However, this approach may vary as CO₂ solubility varies inversely and CO₂ output varies directly with the temperature. As a consequence with cooling, more CO₂ will be needed for addition to the mixture to maintain a normal PaCO₂; with rewarming, less CO₂ will be needed.

The importance of precision in the control of the PaCO₂ lies for the most part in its effects on the metabolic state, the autonomic nervous system, catecholamine secretion, and thus on organ system blood flow and function. Furthermore, alkalosis and hypothermia can cause a double leftward shift in the oxyhemoglobin dissociation curve. This shift would then reduce the available O₂ to extremely low levels, thus making very little available for respiratory activity in tissue.

As for the membrane oxygenator, it is interesting to see that diffusion of CO₂ through membranes follows Graham's law, which is: "The relative rapidities of diffusion of two gases vary inversely as the square roots of the densities." Therefore, most membrane oxygenators are unable to handle an increased CO₂ load, but are able to handle CO₂ exchange without any problem when PaCO₂ is normal.

The heat exchanger is an essential component of each bypass circuit. For many years, the Brown-Harrison and Sarns models were popular. As these devices are made of stainless steel, they are thus reusable; however, they do increase the priming volume and may present problems related to the cleaning. They have sufficient resistance to flow to necessitate their placement on the arterial side and, with rewarming, pose the risk of bubble generation caused by the reduction of gas solubility in the blood being rewarmed.

Today, most modern oxygenators have incorporated the heat exchanger into one of the chambers. This has the dual value of simplifying and reducing the internal volume of the circuit and reducing its priming volume. The risk of bubble formation is still present and so a distal bubble trap is essential. To enhance efficiency, the flows of blood and water are usually arranged in a counter-current fashion. The temperature control and source of the water are the ordinary hot and cold water system, which can be augmented by active water cooling if necessary.

In describing the oxygenators that are presently used, we see that each involves man-made mechanical parts that are essential to the function of the oxygenators. Undoubtedly, when blood comes into contact with these components, some trauma to the blood and its constituents is bound to occur.

In actual use, oxygenators lead to a number of undesirable and limiting functional problems such as the destruction of erythrocytes, leukocytes, and platelets, formation of microemboli, denaturation of plasma proteins, coagulation defects, hyperoxia, hypoxia, hypocapnia, the need for large-volume pump primes, sterilizing difficulties and, lastly, the inability to maintain the bypass safely for long surgical procedures.

When blood comes in contact with the plastic and the gas interface, it gives rise to protein denaturation and the adhesion and agglutination of platelets. The denatured protein layer then attracts platelets, which also become adherent. Eventually, this becomes self-limiting. Once the plastic becomes coated, further extension of the process is largely halted. In contrast, the reactions at the air-blood interface, which also alter the coagulation proteins and consume platelets, continue as long as the oxygenator is in use. Also, the disc and bubble oxygenators tend to form large amounts of free hemoglobin in the plasma due to red cell hemolysis, especially after more than two hours of bypass.

As stated earlier, the membrane of the membrane oxygenator contains a multitude of small pores which, on initial contact with blood, induces a mild degree of protein denaturation and platelet agglutination. This appears to combine with the protein lying immediately above it to give a relatively fixed and non-moving layer that is essentially cell free. The protein layer, once formed, stabilizes the membrane reducing its subsequent reactivity with respect to blood. Therefore, less trauma to the blood is seen with the membrane oxygenator than with a disc or bubble oxygenator.

Currently, research is being conducted into the use of anti-platelet drugs that can be added to oxygenators to decrease the loss of platelets in these systems. Addonizio and associates have been studying the effects of Prostaglandin E₁ on platelets in various oxygenator systems. Their research has shown that the addition of this hormone to
membrane oxygenators will decrease platelet loss. With bubble oxygenators, Prostaglandin E, 1 has again been shown to decrease platelet loss, however, it must be used in a four-fold concentration and at this strength Prostaglandin E, 1 becomes a potent vasodilator.

**Bypass**

In total bypass, ties are simultaneously placed tightly around the superior and inferior venae cava and the caval catheters previously inserted. The arterial pulsatile pressure tracing will disappear and become a mean perfusion pressure tracing, changes in the level which reflect the pressure fluctuations of the pump heads.

Although 5% of the total cardiac output supplies the coronary arteries, the majority of coronary blood flow returns to the right ventricle via the coronary sinus. A small amount of blood from the bronchial vessels and thebesian veins contribute to the left ventricular venous return. Therefore, a sump drain is needed to empty the left ventricle and prevent over-distention during bypass.8

When total bypass is started, many modalities must be observed. One is the arterial blood pressure, usually monitored intraarterially by a pressure transducer. If venous return is inadvertently started before arterial infusion, loss of blood from the patient can cause severe hypotension. If the arterial side is allowed to pump too long, severe hypertension, circulatory overload, and even cardiac failure will occur. Most perfusionists usually give the patient 100-200 cc of blood through the arterial side before starting venous outflow. If the blood pressure should fall precipitously while the patient is going on bypass and does not respond to increased flow, the possibility of arterial dissection must be considered.

Adequate venous return must also be watched. If a catheter is placed too far into the superior vena cava, either the internal jugular vein or the subclavian vein could be occluded. When this occurs, a precipitous increase in the central venous pressure may occur and immediate corrective action is needed. Obstruction of vena caval catheters will result in a marked decrease in venous return and a sharp drop in the reservoir level. Obstruction of the jugular vein may produce a severe decrease in the effective cerebral perfusion pressure. Since venous return is usually determined by gravity, the operating table may need to be raised to increase gravity flow if the return is inadequate.

As for partial bypass, the name is indicative of the procedure, because some of the blood is still pumped by the heart. More specifically, some blood is pumped by both right and left ventricles creating pulsatile flow. This blood flows through the lungs, back into the left heart, and out through the aorta. The rest of the circulating blood is collected from the vena cava, sent through the pump and then back into the patient. Partial bypass may be used to provide partial support in the immediate pre- and post-operative period in which low cardiac output states may develop.

Femoral-femoral bypass is the conventional form of partial bypass, though recently left atrial-to-femoral arterial bypass has become popular. These methods are most commonly used for repair of aneurysms of the descending thoracic aorta and are seldom seen with procedures involving open heart or coronary artery bypass grafts.

**Hemodilution**

Now that we have described the pump and the various oxygenators used in ECC, we must look closely at the circulatory changes brought about by hemodilution and the pump primes. It is essential that the anesthetist understand these concepts and the effects they have on the patient.

Rheology of blood refers to the flow properties of blood. For most clinical purposes, only two rheological parameters of blood need to be considered: (1) the viscosity function and (2) the yield stress. The viscosity function is a measure of the resistance of blood to flow and is defined as the ratio of shear stress, or force per area that causes flow, to the velocity gradient, or shear rate. Practically speaking, the viscosity of blood is proportional to the pressure gradient divided by the speed of flow. For simple liquids such as water, the pressure gradient is a constant. This theory is known as Newtonian behavior. With blood, the relationship between pressure and flow is nonlinear and the viscosity depends on shear rate; this is known as non-Newtonian behavior.

The yield stress of blood is a measure of the minimal force required to cause blood to flow. Below a certain force, or pressure, the attraction between adjacent red cells is too strong to be overcome, hence, the blood does not "yield." As soon as the yield stress is exceeded, flow begins; but the large aggregates of red blood cells at this low level of stress highly resist flow and thus have a high viscosity. As the pressure gradient and the speed increase, the aggregates disperse and blood viscosity decreases. At high shear rates, the deformability of the cells becomes important. Factors which increase the tendency of red blood cells to aggregate affect the yield stress and the low shear rate properties, while factors which increase the
rigidity of red blood cells affect flow at high shear rates.

A variety of factors increases viscosity and yield stress, but the more important ones are hematocrit, the concentration of plasma proteins, and temperature.

The viscosity of blood highly depends on hematocrit (Hct) for two reasons: (1) the yield stress or the tendency of blood to aggregate increases substantially with Hct and (2) the viscosity increases rapidly when Hct is above 40%. If one looks at the clinical application of these theories, we also see that other parameters come into view. The mean arterial pressure (MAP) is determined by the product of cardiac output and total peripheral resistance (TPR).

Total peripheral resistance in turn, depends on two factors: (1) the local caliber of the arterioles, venules, and capillaries making up the bulk of the resistance to flow and (2) the viscosity of blood. Studies have shown that the TPR is directly proportional to the high shear rate blood viscosity. This implies that marked changes in hematocrit during ECC at a constant flow may substantially decrease MAP secondary to decreased viscosity and TPR. Also, acute isovolemic hemodilution during anesthesia can occur with a decrement in the total transport of O2. This is because at a constant MAP, cardiac output is inversely proportional to the viscosity of blood. Studies by Crowell, Gordon, LaVeen, and Malberg18,21 show that an Hct of 25-30% leads to the optimal combination of flow and O2 carrying capacity of blood.

If we further investigate viscosity, we see that it is also affected by changes in the concentration of plasma proteins. Of all the plasma proteins, only fibrinogen and the gamma globulins significantly influence viscosity (1) because the yield stress of blood depends on fibrinogen concentration, and (2) because both fibrinogen and the gamma globulins have the greatest effect on plasma viscosity.22

With hemodilution, the level of concentration of serum proteins falls, thus reducing viscosity. This fall, however, is not without other effects. Unless there is some substitute for its oncotic pressure, the transcapillary shift of water to tissue will be increased in all organ systems.28 Part or all of this extracellular fluid (ECF) increase may be nonfunctional and represents a third space. Excess fluid shifts to the tissue will be made evident by the need to continuously add fluids to the CPB circuit in order to maintain the same blood level in the oxygenator.

The final factor affecting viscosity is temperature. Temperature affects the viscosity of blood primarily by influencing plasma viscosity. Generally as a rule, viscosity increases 5% for each 1° C drop in temperature. However, with hemodilution and a decrease in TPR, this change in viscosity is usually insignificant.

Many solutions have been used to prime the oxygenator, which normally has a volume ranging below 1.5 and 2.2 l. In the early days of ECC, blood was thought to be the most physiological fluid to prime the oxygenator, but the poor results and difficulties with all blood primes soon became apparent.24 Later, Zudhi25 did extensive work with pump primes and was a strong advocate of D3W.

The basic principle governing the management of the connection of a patient to the CPB circuit is to do so in a fashion requiring minimal metabolic adaptation by the patient. This means that the pump prime should be as close as possible to the composition of the patient's extracellular fluid. For most purposes, this has been interpreted to mean the use of a balanced salt solution with or without supplemental Ca++ and Mg++. Calcium has been omitted by many groups in hope of reducing O2 demand in the myocardium and the O2 debt associated with ischemia.

We have already stated that a shift of fluid to a 'third' space occurs when we hemodilute the blood volume and lower oncotic pressure. It must be assumed that due to the stress of anesthesia and surgery, increased levels of glucocorticoids and mineralocorticoids will be seen. Despite isotonic expansion of the blood and total ECF at the end of bypass and the maintenance of adequate urinary output, the net effect of the development of a third space and the activation of these mechanisms is to produce moderate degrees of sodium and water retention.

The changes, primarily involving aldosterone, also tend to significantly increase the perioperative rate of potassium loss and may contribute to low serum K+ levels. Other factors that may contribute to this situation are the use of diuretics, hyperventilation, and ECF expansion with fluids isotonic with respect to sodium at a time in which sodium retaining mechanisms are active. This latter mechanism might be expected to lead to increased rates of intrarenal Na+ for K+ exchange and thus increased K+ loss. Therefore, careful monitoring of K+ levels is essential.

Body compositional changes entailing reductions in Ca++, Mg++, PO4=, and Zn may also be seen. In the absence of Ca++ and Mg++ in the prime, total values will decrease with hemodilution,
paralleled the decrease in serum proteins. Hypocalcemia is usually seen during bypass but seems relatively insignificant. Nevertheless, occasional administration of Ca++ may be a useful adjunct in the management of the hypotension often seen at the end of bypass.

The role of Mg++ is not clear. In the clinical setting, reductions in the total Mg++ and the ionized fraction occur with hemodilution. This deficiency may make the heart more prone to arrhythmias, especially those associated with the use of digitalis.

**Metabolic oxygen demand**

We have now looked at many components of ECC, but none are more important than the ability to provide adequate tissue perfusion and oxygenation. The blood flow requirements for patients during CPB that any oxygenator should be able to satisfy may be described in terms of milliliters per kilogram of body weight or milliliters per square meter of body surface area. If one examines the O₂ delivery equation⁸, it indicates that O₂ delivery is a function of cardiac output and O₂ carrying capacity and that there is a certain basal requirement of O₂ that must be satisfied. Normally this is in the range of 300 cc of O₂ per min. With red blood cell dilution and hematocrit reduction, lower O₂ carrying and delivery capacity results. Therefore, cardiac output must be increased or the O₂ demand reduced by hypothermia.

At the onset of bypass, with the patient normothermic, O₂ carrying capacity will be low, but may be compensated for by a rightward shift in the oxyhemoglobin dissociation curve resulting in increased peripheral O₂ extraction. In addition, the metabolic acidosis resulting from the O₂ debt will lead to a reduction in red cell O₂ affinity. However, reduction in O₂ demand by hypothermia is the essential factor used to deal with this problem. Once hypothermia is induced and the patient hemodiluted, the decreased capacity of blood to carry O₂ will be more than offset by the increased flow resulting from a reduced TPR.

In the early days of ECC, oxygenators were inadequate and a low flow of blood was used. Today's modern oxygenators are capable of adding 300 cc and greater, of O₂ per min to the blood flow, thus diminishing the need for lower flows. As we pointed out earlier, certain basal metabolic demands are required, which means certain flow rates must be met. In the average adult, flow rate ranges from 3.2-3.6 L/m²/M. Once hypothermia and hemodilution have been initiated, the metabolic O₂ demands can be met with flows in the range of 2.2-2.5 L/m²/M or 50-80 ml/kg/min. If flows greater than this occur in the oxygenator, the chances of increased red blood cell destruction invariably rises.

Originally, hypothermia was induced by surface cooling. It was soon learned that this tedious process cooled the vital organs less effectively than fat or muscle. Today internal cooling using the heat exchanger is much more effective both cooling and rewarming vital organs more readily than fat and muscle.

The cooling-rewarming process is not a steady state and is non-uniform in terms of its temperature distribution from one organ system to the other in the body. Therefore, supplemental surface heating and cooling using a K-thermia blanket is often used. Because of the difference in time course, organ blood flow, and resulting organ temperatures, core or average temperatures can only be estimated.

The fall in O₂ consumption with reduction in temperature is not a linear process and is difficult to assess. Oxygen consumption normally will be reduced to 50% at 30°C, to 25% at 25°C, to 15% at 20°C, and to 10% at 15°C. It is also important to realize that as temperature decreases, the dissolved O₂ content of plasma increases. The amount of dissolved O₂ is approximately 0.3 volume % at 38°C, 1.5 volume % at 30°C, 2 volume % at 25°C, 2.5 volume % at 20°C, and over 4 volume % at O°C. As stated earlier, the normothermic, hemodiluted patient will have a low O₂ carrying capacity. After rewarming, if a low cardiac output state develops, this induced O₂ capacity could be critical. Therefore, alkalosis and decreases in the Hgb concentration should be avoided. If necessary, packed red cells can be infused.

Hypothermia, in addition to reducing O₂ consumption, may have other effects. Like hemodilution, it enhances the stability of blood and serum lipids, and reduces the risk of subsequent hemato logical disruption after bypass. By constriction of the body's capacitance vessels, hypothermia also leads to complex changes in the size and distribution of the blood volume. The blood volume is usually reduced in a non-uniform fashion that is undoubtedly related to the temperature and the reduced O₂ demand of each particular organ system.

When rewarming the patient, care must be taken that the temperature of the infused blood does not exceed 40°C, because gross hemolysis with subsequent development of a bleeding diathesis may occur. Care should also be given to the patient shivering in the postoperative period. The
increase in total body O₂ consumption that may result varies between 100 and 400% of normal. This is significant in that it must be matched by corresponding increases in cardiac output in order to maintain O₂ delivery at the normal rate. In the presence of significant hemodilution, the increased peripheral O₂ extraction may result in marked venous desaturation which may contribute to systemic arterial hypoxemia. Also, with cardiac output (CO) increased, the possibility of a shortened pulmonary red blood cell mean transit time exists. Together, these two defects could easily lead to a marked reduction in arterial O₂ tension.

Myocardial preservation

Protection of the myocardium during ECC depends upon the extent to which it is possible to control surgical trauma and the effects of ischemia. This is of the utmost importance to the anesthetist because it is our responsibility to see that the heart functions as well, if not better, at the end of bypass.

Cardiac surgical procedures often require a bloodless, relaxed and motionless field during the operation, which is easily accomplished by ischemic arrest induced by aortic cross-clamping. Any period of ischemia is accomplished by metabolic and structural changes which determine the functional recovery of the heart in the postoperative period.

The safe period of ischemia is not well defined, but 20-30 min is generally considered the upper limit. If this time period is extended, substantial subendocardial necrosis may occur with low output syndrome in the postoperative period. The need for protection of the myocardium during ischemic arrest has been well recognized and a number of methods have been employed. Of these, hypothermia and pharmacological arrest with cold cardioplegia solutions have now gained wide acceptance in clinical practice.

Hypothermia and surface cooling of the heart was first used by Shamway. It provides a bloodless, arrested heart, and lower energy requirements; delays the depletion of high-energy phosphate reserves, and lactic acid accumulation; and retards the morphological and functional deterioration associated with ischemic arrest. Moderate hypothermia and surface cooling have been sufficient for 20 min, but profound cooling of the myocardium is known to cause myocardial damage due to crystallization of the membrane lipids and poor ventricular performance on perfusion.

The concept of pharmacological arrest was initially introduced by Hooker in 1929, with extensive research by Melrose in 1955. These initial solutions contained high concentrations of K+ and were normothermic. Since that time, a number of other constituents have been added and the solutions cooled. Cold cardioplegia solutions are definitely advantageous and protect the myocardium by virtue of their cooling effect and added components. When injected into the aortic root after cross-clamping, the cold cardioplegic solutions are distributed throughout the myocardium by natural pathways, thus producing homogenous cooling of the myocardium. The myocardial energy requirements, O₂ debt, and accumulation of metabolites which inhibit the anaerobioses are prevented. The subendocardium is well protected and the hemodynamic instability as a result of poor myocardial contractility and reduced compliance associated with ischemic arrest is considerably reduced.

In recent years, a number of constituents have been added in various concentrations to different cardioplegia solutions, and an understanding of their mechanisms of action is essential.

Potassium has been known to arrest the heart in diastole for many years. Potassium causes ionic paralysis of the cellular membrane transport system by blocking the initial fast phase of myocardial cellular depolarization and thus preserves the energy reserves for the maintenance of integrity of cell membranes and active transport of Na-K pump. Initially, the Melrose solution contained over 200 mEq of K+/L with a toxicity greater than 400 mOsm/L that produced many side effects and proved to be unfavorable. Today, K+ in a concentration of 10-30 mEq/L has been considered optimal for good postoperative recovery.

Magnesium and procaine are also effective cardioplegic agents and augment the arrest induced by K+. Magnesium blocks the initial depolarization by its effect on transmembrane ion movements and also has the benefit of blocking intracellular metabolism. Magnesium aspartate has been considered more advantageous as it accelerates the regeneration of adenosine triphosphate (ATP) from inosine phosphate. Procaine hydrochloride, a local anesthetic, binds to the proteins in the membrane itself and reduces transmembrane ion movement.

The cellular metabolic process (such as the membrane pump) are pH dependent, therefore, slight alkalosis would appear beneficial. Bicarbonate, inorganic phosphates, and tromethamine (THAM) have been used as buffering agents to minimize the ischemic injury and to raise the pH between 7.4 and 7.8. Energy substrate support may be conferred by the inclusion of glucose and insulin. Similarly, a slight increase in osmolarity appears to be useful in minimizing intracellular
water accumulation and has led to the use of sorbitol, mannitol or plasma proteins to reduce edema.

Now that we have identified some of the constituents of cold cardioplegic solutions and understand how they work, we see that multidose administration of cold cardioplegia with moderate hypothermia and surface cooling has been found most satisfactory for prolonged aortic cross clamping and has undoubtedly improved the prognosis of a number of patients undergoing surgical correction of complex cardiac lesions.

**Heparin and protamine**

An inability to prevent clotting of the blood was one of the principal causes of failure in the early experiments with ECC. Defibrinogenated blood was later used, but also proved to be a failure. In 1916, a young medical student named Jay McClean discovered a mucopolysaccharide extracted from the liver of a dog that prevented coagulation. Heparin was investigated over the next several decades and was introduced clinically in the 1940’s.

Heparin is the strongest organic acid found in the body; it is most commonly prepared from bovine lung and porcine or bovine intestinal mucosa. Heparin, in the presence of its co-factors, leads to the almost instantaneous production of a thrombin-antithrombin complex deactivating the thrombin. This heparin-antithrombin co-factor complex also appears to inactivate factors IX, X, XI, and XII.¹

Once administered, heparin becomes protein bound and is distributed in the plasma. It has a half-life of 60-100 min in normothermic man but may be extended with increasing dosage and decreasing temperature. Its elimination pattern is unclear, but may involve biodegradation in the reticuloendothelial system.

After entering the circulation, the anticoagulant response will vary depending upon such factors as temperature, age, body composition, and most particularly the lean body mass. For total heparinization, the usual dose is 2-3 mg/kg or 200-500 units/kg. To assess precisely the initial effect and rate of decline in each patient, a number of tests have been suggested.² One method that is easy and convenient to use in the operating room is the Celite® activated clotting time (ACT) described by Hattersley.³

A baseline value is determined prior to heparinization and repeated just after giving heparin and at 30-min intervals. With the dose of heparin in mg/kg on the vertical axis, a dose response curve can be constructed. Bull and associates⁴ have advocated that heparin be given initially in a dose of 2 mg/kg, an ACT determined, and the line extrapolated to give a value between 400-480 sec. They suggest using the line drawn from this point through the original value to calculate the remaining dose of heparin required. The remaining doses should maintain values of at least twice control and not less than 350 sec.

The use of protamine as a heparin antagonist was suggested in 1937. It has been found that protamine binds almost mg/kg with heparin. In the absence of heparin, protamine has anticoagulation properties of its own. Probably this is a result of its capacity to activate the coagulation mechanism and produce a consumption coagulopathy involving platelets.

To calculate the dosage of protamine required, residual heparin activity should be measured. The ACT test, as noted, can be used to estimate the biological half-life of heparin and the amount remaining. It can then serve as a guide for the amount of protamine required for heparin reversal. Normally, this is about 2.3 mg/kg of protamine. When protamine is administered, care should be taken to inject the dose slowly and over several minutes. Protamine given as a bolus has been associated with direct myocardial depression followed by hypotensive episodes. The exact etiologic mechanisms for its hypotensive effects are not entirely clear, but it is thought that protamine will act directly on the smooth muscle of the vessels and cause vasodilatation.

**Monitoring**

As with all major procedures, adequate monitoring is essential. It is the responsibility of the anesthetist to understand and precisely interpret the results attained from all measurements and act accordingly—in the least amount of time.

During bypass, blood gases are frequently measured using an intra-arterial catheter, to check \( \text{PaO}_2, \text{PaCO}_2, \text{pH}, \text{O}_2 \text{ saturation}, \text{CO}_2, \) and base excess. These parameters are monitored usually every 30 min, unless circumstances suggest the need for more frequent determinations. Increasing metabolic acidosis usually suggests inadequate tissue perfusion, and must be defined and corrected immediately. Central venous \( \text{PO}_2 \)'s are also measured and should be kept in the range of 40 torr. If metabolic acidosis persists, sodium bicarbonate can be administered using the Astrup equation. This is calculated by the following: taking body weight in kilograms \( \times \) base deficit \( \times \) 0.3 to equal milliequivalents of bicarbonate to be administered.
Hematocrit and electrolytes should also be measured with each blood gas sample taken. Normally, while on bypass, the hematocrit should be kept between 25-30%, while the K+ level should be kept around 4.5 mEq/L.

In recent years, pulmonary artery pressure (PAP) and pulmonary artery wedge pressure (PAWP) have been monitored by the use of a Swan-Ganz™ catheter. The PAP and PAWP should all be low or zero while on bypass. If these indices become elevated, it means the left ventricle is becoming distended as a result of inadequate venting.

The arterial pressure needs to be watched very closely to maintain a mean pressure of 50-100 torr. If the mean pressure falls below 50 torr, blood volume is increased either by adding fluid to the pump or directly to the patient. If a reasonable volume of fluid is given with no response, then an alpha agonist such as phenylephrine may be indicated. If the mean blood pressure increases to 100 torr or greater, a vasodilator such as sodium nitroprusside or one of the inhalational agents may be administered.

During ECC, a urinary output of 1 cc/kg/hr is desirable. When urinary output is inadequate, renal hypoperfusion may be the cause. Since the renal threshold for hemoglobin is approximately 100-150 mg/100 ml, red urine is a sign of massive hemolysis. Metabolic acidosis and a low urinary output combined create an ideal condition for the development of acute tubular necrosis. Therefore, urine output should be increased with a diuretic and alkalization of the urine.

As with all surgical procedures, the ECG should be monitored continuously. Specific attention should be placed on the S-T segment for the development of ischemia or conduction disturbances. It is generally accepted that a modified V-5 lead will show changes of this type best. Once asystole has occurred by the use of a cold cardioplegic solution, the anesthetist must watch for the return of ventricular fibrillation. Once this is noticed, the surgeon should be notified so that more cardioplegic solution can be used.

Pulmonary complications

Theoretically, during total bypass the only blood entering the lungs is 0.5-1.0% of the pump output that enters the bronchial arteries. At high flow rates, bronchial arterial flow may be normal or even increased. Consequently, pulmonary venous congestion may develop. While the patient is on total bypass, the lungs are often held in their deflated state, which predisposes to a progressive loss of surfactant and decreased distensibility. These tend to return toward normal when normal circulation is restored.

Hypoxia of lung tissue itself, due to the absence of ventilation, may also contribute to alveolar damage. To avoid these complications, some groups recommend maintaining the lungs in a constant state of inflation with O$_2$, CO$_2$, or helium. Others have shown that pulmonary complications are decreased when the lungs are intermittently ventilated throughout the course of bypass, or when positive end-expiratory pressure is used.

Several additional factors related to ECC can contribute to pulmonary dysfunction. Fluid overload, unrecognized during bypass, may become evident almost immediately after the patient comes off the pump. Left ventricular failure with low cardiac output secondary to poor myocardial function is a classic cause of lung impairment. High O$_2$ concentrations for prolonged periods in an already functionally or anatomically compromised lung will accelerate the onset of pulmonary damage characteristic of O$_2$ toxicity. Vasactive substances released by various tissues or damaged cells during bypass may induce pulmonary vasoconstriction sufficient to produce ischemic damage.

Methylprednisolone sodium succinate has been recommended for both therapeutic and prophylactic use for pulmonary changes following ECC. However, the still unsettled questions of effectiveness and high cost make its routine use debatable.

Renal effects of ECC

As stated earlier, a pulsatile flow to the kidneys is of great benefit since perfusion is better and the renin-angiotension activity and aldosterone secretion are reduced. However, long-term pulsatile flow appears to be clearly superior for the preservation of organ function.

Acute renal failure is a complication of operations for the correction of cardiac abnormalities, especially when such correction involves the use of ECC. The mortality due to this acute disease process in postoperative cardiac patients approaches 75%. Acute tubular necrosis may occur as a direct clinical entity in a patient who is otherwise enjoying a satisfactory postoperative course or it may occur as part of a generalized organ failure in a patient who is approaching a terminal state. In either case, acute tubular necrosis is a disease process of which the anesthetist must be aware, with particular attention given to its prevention.

Patients undergoing cardiac surgery are subjected to a period during which decreased renal
perfusion is likely to occur. Many of these patients have low cardiac outputs which will result in low renal perfusion. In addition, if the cardiac disease is the result of a generalized vascular disorder such as atherosclerosis, then the same disease process which produced the cardiac abnormality is likely to also involve the kidneys. Whether the onset of renal ischemia is triggered by the pre-existing low flow state or whether it results from a further decrease in perfusion in association with ECC, the net effect appears to be intense vasoconstriction in the superficial cortex with a reduction in glomerular filtration.39

A second factor which is associated with acute tubular necrosis is the presence of free hemoglobin in the urine. Earlier pumps and oxygenators were associated with a high degree of red cell hemolysis that resulted in the release of free hemoglobin into the circulation. Initially this hemoglobin will be protein bound, largely due to haptoglobin, and will subsequently be removed by the reticuloendothelial system. As the binding sites become occupied, more hemoglobin will remain free in the circulation. Above a threshold of 100-150 mg/100 ml, hemoglobin will be excreted by the kidney with little trouble. However, with low rates of renal tubular flow and aciduria, significant amounts of hemoglobin may be converted into acid hematin crystals resulting in acute tubular necrosis.

Summary
The anesthetist involved with cardiac procedures which require ECC must have a vast array of knowledge to be properly prepared to deal with any complications that may arise in the care of the patient. This article has focused only on the basic principles and practical considerations involving ECC. For the anesthetist who will make cardiac anesthesia his or her specialty, a more in-depth understanding that is beyond the scope of this article would be required.

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ADDITIONAL READING

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