Review Article

Optimal Perfusion Flow Rates for Cardiopulmonary Bypass

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Abstract

In addressing the subject of optimal perfusion flow rates for cardiopulmonary bypass, we must be reminded of a remark made by a pioneer in the physiology of cardiac surgery, Dr. Frank Gollan, who said “We cannot command nature except by obeying her” (1). During extracorporeal circulation (ECC), we try to closely approximate the physiologic state, “but we never duplicate.” During my travels as a perfusionist, both in the United States and abroad, I have noted that flow rates during cardiopulmonary bypass vary widely from a low flow of 1.6 l/min in adults to a high flow of over 3.0 l/min in infants and children; flow rates were not written in stone and handed down to us. Flow rates are “optimal,” thus the variations we see are appropriate to the time, place and circumstances that prevail.

Historical Considerations

The subject of “optimal perfusion flow rates” for cardiopulmonary bypass must first be approached from a historical perspective and examined in the context of hypothermia, arterial pressure, hemodilution and pulsatility of flow.

Hypothermia has played a role in medicine over a long time. Hippocrates (2), wrote that cold produces a “moderate degree of numbness,” and “relieves pain,” to various practitioners of early medicine who(3, 4) used local hypothermia by applying snow to the body for various ailments and surgical procedures.

Currie (5), in 1798, reported the use of hypothermia in the treatment of a patient with a high fever by immersion in an icy cold bath. In some of the experiments he conducted, volunteers were placed in ice cold baths and cooled to an oral temperature of 32°C, the process was then reversed with warm baths. His work was the forerunner of the first method of hypothermia used in cardiac surgery.

In 1950, Bigelow, et al. (6, 7, 8) published their findings on the study of hypothermia in dogs as an aid to intracardiac surgery. He hypothesized that if the body’s metabolism, especially the cardiac and cerebral metabolism, could be reduced by lowering the entire body temperature, circulation could be arrested for a time without permanent damaging effects. It was discovered that if the metabolism is reduced by 10%, then the oxygen demands of the organs would be also reduced by the same proportion. Therefore, it will take more time than in the normothermic state to become hypoxic following circulatory arrest.

These classic experiments proved that the body temperature could be lowered and reversed without incurring an oxygen debt.

This work was followed by Boerema (9), who in 1951 added a new dimension to the fledgling art of intracardiac surgery. In 1952, Lewis and Tauffic (10) performed the first operation using hypothermia on a child with an atrial septal defect, employing circulatory arrest for a period of five minutes. This procedure was followed by Swan (11) who performed his first 35 cases without mortality.

Hypothermia

Hypothermia causes a variety of physiologic, hemodynamic, and rheologic changes in human beings. Changes in anesthetic requirements occur due to analgesic effects on the neuromuscular system, pain perception, consciousness and coordination (12, 13). Variations also occur in metabolic rates in patients undergoing cardiopulmonary bypass (CPB).

Hypothermia induces three basic changes in gas transport:

1. The solubility of gases in liquids is inversely related to temperature so substantially more oxygen and carbon dioxide will be carried in physical solution in the blood under hypothermic conditions.
2. As the blood temperature is lowered, the oxyhemoglobin dissociation curve shifts to the left so that for a given partial pressure of oxygen in the tissues, less of the gas is unloaded from the hemoglobin.
3. Decreasing temperatures increase the carrying power of blood for carbon dioxide through an increased activity of the blood buffers.

The animal cell depends upon the utilization of energy for its viability. This energy is supplied by a complex breakdown of several organic molecules that requires a constant supply of oxygen and results in the formation of carbon dioxide and water. Together with smaller metabolites of other end products, they are immediately excreted from the cell. This process depends upon a supply of oxygen to enhance the removal of waste products. The lack of oxygen does not stop the production of energy, however a transition to anaerobic metabolism takes

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place, which allows for an accumulation of metabolites in the breakdown process to occur.

Anaerobic conditions are limited because of an accumulation of these metabolites in the breakdown process, which are mainly acidic in origin and will result in a state of metabolic acidosis.

In brief, then: hypothermia retards the metabolic process in cells and protects them from anoxic death. The degree of retardation is dependent in large extent to the degree of hypothermia employed. The metabolic rates of organs vary and hence their anoxic survival time, which corresponds with the duration and depth of temperature.

Metabolism

The relationship between metabolic rate and temperature is neither linear nor exponential. There is an exponential relationship between temperature and the rate of a single chemical reaction. In the Arrhenius equation, the logarithm of the rate of a chemical reaction is inversely related to the reciprocal of the absolute temperature. Over a small range (37° to 30°C, 310° to 303° A), this relationship is almost equally well described by stating that the logarithm of the reaction is directly related to temperature. In this form, it conforms to Vant Hoff’s law, which states that a rise in temperature of 10°C increases the reaction rate two-to-threefold. The effect of this proportional increase or decrease in temperature is expressed by the symbol Q₁₄.

In biologic systems, the rate of a chemical reaction is directly related to temperature. The relationship between oxygen consumption and temperature is roughly exponential. In mammals, the decrease in oxygen consumption as the temperature is lowered can be transposed into a reduction of a metabolic rate of approximately 7% per degree. Oxygen consumption is considered a valid measurement of metabolic rate only if no oxygen debt has occurred.

Brewin (15) states that, “in practice, the metabolic rate for a given temperature is an empirical relationship determined experimentally once a steady state at the required temperature has been attained.” Various investigators have given approximations of temperature versus metabolic rate.

Gollan (16) states that oxygen consumption is reduced about 50% between 28°C to 30°C, 80% between 18°C to 20°C, and 90% between 8°C to 10°C. Brewin (15) observed that the metabolic rate is reduced to about 60% to 70% of normal at 30°C, 25% at 20°C, 15% at 15°C, and 5% at 5°C. Bjork (17) states that he found a greatly different range for oxygen consumption: 16 to 39% at 18°C to 20°C in three subjects, and one to 11% at 10°C to 13°C in 13 subjects. These approximations are from a few investigators and a small number of patients.

Oxygen (O₂) Transport

The effect of hypothermia on the transport of gases is of great significance because the solubility of gases in liquids is inversely related to temperature. Therefore, more oxygen and carbon dioxide are carried in the physical solution in blood during hypothermia.

The dissolved oxygen content in plasma increases as the temperature is decreased. The amount dissolved at 38°C is approximately 0.3 vols per cent; at 30°C, 1.6 vols per cent, 25°C, 2.0 vols per cent; at 10°C, 2.5 vols per cent; and at 0°C it is more than 4 vols per cent (18).

The oxyhemoglobin dissociation curve shifts to the left as the temperature is lowered (Figure 1).

In 1909, Barcroft and Hill (19) demonstrated how hypothermia shifted the oxygen dissociation to the left and upward, making less oxygen available at a given tension. This simply means that blood arriving at the tissue having an oxygen saturation of 100% and a tension of 40 mmHg at 38°C will unload approximately 25% of its oxygen, whereas at 10°C it will unload less than 10% because a greater quantity of oxygen molecules remain attached to the hemoglobin. Thus, as the temperature decreases, venous saturation becomes higher in spite of the tissue demand for oxygen.

The literature states that a shift to the left in the oxyhemoglobin dissociation curve is the probable cause of tissue anoxia in hypothermia. Therefore, for a given oxygen tension in the tissues, the unloading of oxygen may be much reduced. Once the tissues begin to use the oxygen at a faster rate than it is being delivered, the oxygen tension in the tissues will fall, and the amount of oxygen released from the hemoglobin will increase. This is a normal occurrence in active muscle, where tissue oxygen tension drops to an extremely low level because of the rapid uptake, allowing almost total unloading from the arterial blood. The tendency is for tissues to be supplied with oxygen even at a low partial pressure. This can be accomplished by the available oxygen that is carried in solution and by any change that occurs in the pH of the local tissue.

When hypothermia and hemodilution are used in conjunction with CPB at temperatures of 22-25°C, and if the flow rate is maintained at a sufficiently high level, no metabolic acidosis
will occur. This indicates that during hypothermia, hemodiluted CPB, blood and sufficient oxygen are available to meet the metabolic demands. During rewarming, once the tissues begin to use oxygen, if the oxygen tension is not increased commensurate with the oxygen consumption of the tissues, PO₂ falls and the amount of oxygen released by the hemoglobin will increase. Since the oxygen tension has not been increased, it is unable to meet this increased demand, resulting in a metabolic acidosis. Thus, arterial blood flow and gas flow must be increased to meet this increasing demand. This is one manifestation of alteration in flow rate, thus making flow rate “optimal.”

**Carbon Dioxide (CO₂)**

Carbon dioxide (CO₂) is the major end product of cellular metabolism. It is continuously produced by all cells in all tissues.

Carbon dioxide plays an important role in hypothermia. In 1904, Bohr (20) demonstrated how decreasing temperatures increased the carrying power of carbon dioxide in blood through an increased activity of blood buffers. Oxygen is released from the hemoglobin, shifting the oxyhemoglobin curve to the right. For example: if arterial blood at normal temperature (38°C) has a carbon dioxide tension of 40 mmHg, it will carry as dissolved gas 2.7 ml per 100 ml blood; but at 10°C, the amount of dissolved gas will be 5.4 ml per 100 ml blood. The carbon dioxide dissociation curve is linear, not like the oxyhemoglobin dissociation curve, which is sigmoid in shape. This linear relationship exists between carbon dioxide tension in blood and the carrying capacity of carbon dioxide by the red cell hemoglobin in the physiologic ranges (Hb=15 gm%) (Figure 2). Carbon dioxide has a reciprocal relationship with oxygen in that a decreased PO₂ aids in the loading of carbon dioxide and an increased PCO₂ aids in the unloading of oxygen at the tissues (Figure 3). More carbon dioxide is bound by deoxyhemoglobin than oxygen, which is physiologically advantageous. This enhancement of carbon dioxide transport by hemoglobin as it loses oxygen is known as the Haldane effect (Figure 1). When blood is cooled, it is subjected to: 1) increased solubility of carbon dioxide, which is 20 times more soluble in an aqueous medium than it is oxygen; 2) decreased dissociation and reduction of hydrogen ion activity, which results from the lowering of the temperature.

In a physical solution, based on its partial pressure, as carbon dioxide enters the following reaction takes place: the equilibrium of the reaction is in favor of the production of carbonic acid if the carbon dioxide tension is maintained during cooling. The reaction is hastened by the presence of carbonic anhydrase. The enzyme activity will lessen with a drop in temperature because the acid formed dissociates to a lesser degree at low temperatures. Proteins, being amphoteric, act as acids in an alkaline medium, and vice versa. They show a decrease in the base-binding capacity due to cooler blood temperatures. Decreased ionization produces a decrease in the amount of dissociated hydrogen ion and an increase in the amount of free base or hydrogen ion acceptor. This free base is readily available to combine with carbonic acid, thus resulting in carbon dioxide combining power of blood and, to a lesser extent plasma, being increased at low temperatures.

Figure 2 shows how, for a given tension of carbon dioxide, more of the gas is carried at the lower temperature.

![Figure 2](image1)

**Fig. 2**

Relationship of free and bound carbon dioxide to PO₂ (Haldane Effect). This curve is not sigmoid, as the oxyhemoglobin dissociation curve is. The relationship between carbon dioxide tension in the blood and carrying capacity of carbon dioxide by the red cell hemoglobin is relatively linear in the physiologic ranges. Hb = 13-15 gm%.

![Figure 3](image2)

**Fig. 3**

Carbon dioxide shift in the oxyhemoglobin dissociation curve. Higher carbon dioxide tensions shift the dissociation curve to a more physiologically advantageous position, facilitating the release of oxygen at the tissues.

**Hemoglobin**

Brewin, et al. (15) showed that blood with a high hemoglobin content gives rise to an alkalinity of the true plasma. Depending on its cellular content, the buffer system in various parts of the body behaves in like manner during hypothermia.

The red blood cell contains a high concentration of hemoglobin, which acts as a buffer since it ionizes as a weak acid under physiological conditions. As a buffer, the hemoglobin is capable of “absorbing” the hydrogen ions formed by the carbonic acid. In addition, the buffering power of hemoglobin is changed by certain physiological circumstances, such as the removal of oxygen from hemoglobin, which decreases its acidity. This increases the buffering power and enables venous blood to carry more carbon dioxide. The lowering of blood temperature also diminishes the ionization of acid groups of the hemoglobin molecule, thus increasing its buffering capacity and its carrying power. Blood pH is independent of temperature changes (Figure 3 illustrates that point). For a given carbon
dioxide tension, the plots of PCO\textsubscript{2} against the hydrogen ion concentration (both are expressed logarithmically) lie on the same line.

**Oxygen Requirements**

We know from various studies that oxygen is the most flow-limited molecular substance necessary for the sustenance of life.

It is believed that during CPB it is necessary that we mimic nature as closely as possible in terms of flow rates and oxygen consumption in order to avoid hypoxic death. Blood transports oxygen to tissues at a normal arterial partial pressure (PO\textsubscript{2}) of 95 mmHg. Arterial blood contains approximately 19.7 ml of oxygen per 100 ml blood, or 20 volumes per cent, 0.3 ml of which is in physical solution, and 19.4 ml is combined with hemoglobin. Mixed venous blood has a total oxygen content of approximately 16 ml/O\textsubscript{2}/100 ml blood. The whole body extracts approximately 4.1 ml/O\textsubscript{2}/100 ml blood (arteriovenous oxygen difference (A-VO\textsubscript{o}2)) with a cardiac output of approximately 5,000 ml/min.

Whole body oxygen consumption is the total sum of oxygen consumed by all the individual organs. It reflects the total metabolic requirements without specifying the needs of each organ. However, each organ’s metabolic need is based in some instances on its blood supply and in other instances on functions not related to its metabolism. For example, the kidney, with its blood flow of approximately 1200 ml. Only 1.7 ml/O\textsubscript{2}/100 ml is extracted for metabolism; the rest is available for filtration.

The skin, with the function of temperature regulation, also has a very large blood flow in relation to metabolic demands. Coronary blood flow is estimated at 300 ml/min at resting conditions, with an extraction rate of approximately 11.0 ml/O\textsubscript{2}/100 ml blood. The brain has a blood flow of approximately 750 ml/1/O\textsubscript{2}/min-1, and extracts between 3-10 ml/O\textsubscript{2}/min (See Table 1).

The oxygen requirements of the human body are based on weight, surface area, and age in both physiologic studies and clinical practice. However, from a biologic standpoint, surface area becomes more significant. In the early days of CPB, when calculating perfusion flow rates, either of these methods were used: ml/kg/min or l/m\textsuperscript{2}/min. In determining perfusion flow rates, however, the relationship of kilogram to oxygen consumption and increasing body mass is not linear.

Looking at Figure 4b, we see that oxygen requirements for infants and children per kilogram of body weight is twice that of an adult. For newborn infants between one and three weeks old, the minimum oxygen consumption is approximately 7.6 ml O\textsubscript{2}/kg/min rising to approximately 9 ml/kg/min by the age of two months. It has been suggested that their enormous consumption of oxygen per unit of body weight may be due in part to the metabolic requirements of the brain, which is disproportionately larger than the rest of the body, and developing at a faster rate (Average adult oxygen consumption is approximately 4 ml/kg/min) (See Figure 4b and Table 4b, 4c).
congenital anomalies corrected were of the most serious types, and his longest operating time was 40 minutes.

Up to 1955 it was still perceived that it was necessary to have a blood flow rate that approximates the cardiac output at a resting state to satisfy the basal oxygen needs of the whole body.

Swan (23) stated "that a low perfusion flow rate would compromise oxygen supply, reduce perfusion pressure, hinder factors which control resistance in vessels that differ in different parts of the body...the vascular system would probably deprive some organs of blood flow, while others would receive normal flow."

In referring to Table 1, it can be observed that various organs receive differing amounts of blood flow and oxygen uptake. It was necessary to formulate a system of perfusion flow rates that would, in all aspects, meet the needs of the various organs and the body as a whole.

In 1957 and 1958, Paneth (24), Levovitz (25) and others estimated that during perfusion, about one-third of the total blood flow in excess of 1.1 l/min goes to the upper extremities. Experimentally, he found that when the perfusion flow was increased substantially, the oxygen uptake in the upper extremities leveled off as soon as the flow reached 0.5-0.8 l/min; however, the oxygen uptake in the lower extremities were not met until the flow reached 1.2 l/min.

Bain and Mackey (27) stated that with an open chest in a lightly anesthetized patient, to achieve a flow rate approximate to the basal cardiac output, it would be necessary to increase the patient's circulating blood volume by at least 130%. Gianellli (28) felt that this volume expansion was indeed much lower, probably between 5-25%.

Several investigators such as Halley (29), Reemstma (30), Brown (31), Schwartz (32), and others began a systematic search for the ideal perfusion flow rates based on the blood flow and oxygen uptake of various organs. This prompted Bard (33), Brown (29), and Feruglio (34) — using data previously obtained on the A-V oxygen difference, basal oxygen uptake, resting cardiac output and body surface — to propose an arbitrary perfusion flow rate scale. High flow (2.4 l/min), medium flow (1.8 l/min), low flow (1.1 l/min), and aygys flow (0.5 l/min) were then considered the "optimal flow rates" for normothermic perfusion using whole blood as the prime.

Since it was firmly established that the estimated oxygen requirements of the body at resting conditions were based on weight, surface area and age, and are over 4 ml/kg/min, or 125 to 130 ml/min, Clark (33) formulated a perfusion flow rate chart from theoretical equations derived from the "Fick principle" by adding hemoglobin content, coronary sinus, and bronchial return blood flow, thus making it applicable to CPB.

The theory suggests that the perfusion flow rate should be indicated by the ratio of oxygen needed by the organism to the oxygen supply expected per unit of blood flow and that the oxygen need is determined by the basal requirement per unit of weight or surface area. The theory uses the following formula for calculating the "ideal" perfusion flow rate. Formula:

$$\text{H}_2\text{O} + \text{CO}_2 \rightarrow \text{H}_2\text{CO}_3$$

The above formula is an expression of the "Fick principle" where hemoglobin and percent of venous saturation is substituted for the usual denominator.

Thus:

- **Perfusion Flow Rate** = Oxygen needed divided by the oxygen supplied in a given volume of blood.

- Oxygen needed per minute = Requirement from basal metabolic requirement chart (Figure 4b) multiplied by the weight (kg).

- Oxygen supplied per minute = Hemoglobin content, as Gm. per 100 ml, multiplied by the oxygen content of a Gm. of hemoglobin (1.34 ml) multiplied by the A-V difference.

Therefore, **P** = W.R. divided by 1.34 H (A-V) or, moving the constant to the numerator,

- **P** = S.R. divided by 1.34 H (A-VO) or moving the constant to the numerator.

- **P** = 7.46 W.R. divided by H (A-V)

- **P** = 25.8 S.R. divided by H(A-V)

Clark chose a venous saturation of 50% as a compromise...
based on the normal basal venous saturation and the expected drop in oxygen requirement from anesthesia. His selection was based on the fact that oxygen needs vary from patient to patient and minute to minute during CPB.

Since hemoglobin is of such importance in the computation of flow rates and because it varies as a result of the prime and additions of solutions, it was assumed that the arterial blood from the oxygenator will be 100% saturated. The extra oxygen carried in the blood plasma at a PO₂ of 580 mmHg would be equivalent to one gram of hemoglobin (1.34 ml). Redmond (36) and Davies (31) demonstrated the importance of oxygenation to tissues from the venous side, thus making it vital to maintain normal venous pressures and adequate venous PO₂ and PCO₂.

Notice the relationship of hemoglobin to flow and body weight (Figure 5). The flow rate rises rapidly between 5 and 20 kg, then drops off and gradually decreases up to 80 kg. For example, a 10 kg child with a hemoglobin of 12 gm will receive a blood flow rate of 1.0 l/min or approximately one-third the flow rate of a 60 kg adult (2.9 l/min), while a 10 kg child with a hemoglobin of 14 gm will receive 0.8 l/min, compared to the 60 kg adult flow rate of (2.5 l/min) (See Figure 5). Knowledge of the hemoglobin is of great importance. Clark found it quite remarkable that some infants 9-10 kg (9-12 months of age) can meet their basal oxygen requirements and still more remarkable that some of them at this age have the reserve cardiac output to walk. At rest, they exchange their blood volume more than 1.5 times per minute.

Since Figure 4b shows us that the oxygen requirements for infants and children are twice that of an adult, it is obvious that their high oxygen consumption is based on their rapid growth and the disproportionate size of their brain to the rest of the body in development. For this reason, it has been advocated that the maintenance of a high hemoglobin content during the warming phase of CPB and post-operatively in patients should be between 5 and 20 kg of body weight.

Clark’s perfusion flow rates were, at that time, considered to be the “ideal perfusion flow rates.” Research was conducted to accurately adjust perfusion flow rate to the needs of individual patients during the course of long CPB. To make Clark’s complicated formula easily understandable and workable, it was transcribed into simple form (See Clark’s kg & BSA charts. Tables 3 & 3a). Take note of variations in flow rates in terms of (kg/min) with the patient size. The perfusion flow rate for a 9 kg infant is 105 ml/kg/min, for a 20 kg child it is 85 ml/kg/min, but is only 52 ml/kg/min for a 50 kg patient. Comparing these flow rates with those of a body surface area, there is a distinct difference that is not readily discernable. The perfusion rate should be equal to 2.4 l/m²/min. When the BSA is 0.5 m², the blood flow rate is 2.01 ml/min. When the BSA is 1.0 m², the blood flow rate is 1.8 l/m²/min in the average adult patient. On the average, flows generally fall in a narrow range (2.4 to 1.8 l/m²/min), regardless of the patient size or age. Some institutions use 2.0 l/m²/min as their optimal perfusion flow rate regardless of the patient size or age.

Nose (38) tabulated data from Clark’s formula into a simplified form (See Tables 4, 4a, 4b, 4c).

During that same period, Kirklin (39) recommended a flow rate of 2.2 l/m²/min for all patients regardless of age. Senning (40), in 1959, recommended a perfusion flow rate based on 80% of the patients’ cardiac output measured at catheterization, 14 gm percent hemoglobin, with arterial saturation of 95%, and a venous saturation of 65%. Subsequently, there were many reviews of the existing flow rates. Kirklin (41) in 1958; Andersen (42) in 1958; Margulis (43) in 1959. In 1960, McGoon (44) recommended flows in the order of 2.4 to 2.6 l/m²/min for children and 2.2 to 2.4 l/m²/min for adults. Pierce (45), in 1969, made another recommendation for change in the existing flow rates, suggesting that it should be based on the normal cardiac index of 3 l/min. He felt that the ideal perfusion flow rates needed to satisfy the basal oxygen requirements would require flow rates in ml/kg/min at normothermia, equivalent to 200 ml/kg/min for infants 5 kg, 170 ml/kg/min for 5 to 10 kg, 135 ml/kg/min for children 10-20 kg, 100 ml/kg/min for 20 to 30 kg, 85 ml/kg/min for 30 to 60 kg, and 60 to 70 ml/kg/min for those 60 kg and over (See Table 5). At this time in the development of perfusion it was almost impossible technically to maintain Pierce’s suggested flow rates, due to a combination of factors. Cannulae size, alterations in intravascular blood volume, distortions in venous return and whole blood prime rendered these flows impossible. Moreover, such high flows could cause considerable damage to the formed elements of blood, especially with the type of oxygenators then in existence. In retrospect, McGoon’s recommended flow rate of 2.2 to 2.4 l/m²/min allows oxygen uptake in the range of 130 ml/min/m² (Lewin 46). This is within the range of oxygen requirements at resting conditions in the intact anesthetized patient (Gump 47). However, the opinions were that flow rates based on the standard values in the textbooks for basal metabolism are about 7-10% too high (Fleisch 48). Since an open chest during CPB is conducive to a drop in the patient’s temperature, flow rates calculated on the basis of whole body oxygen requirements are probably about 20% too high (Engel 49). This overestimation allows for variations in the metabolic rate of patients.

Cerebral and Whole-body VO₂ vs. Flow Rates

Despite the experience gained in over 35 years of CPB in humans, we are still not fully knowledgeable of the precise relationship between oxygen consumption, oxygen availability and perfusion flow rates. This is due to our inability to accurately and continuously monitor these parameters during CPB. A number of studies indicate that modern methods of anesthesia tend to reduce whole-body oxygen consumption, especially when muscle relaxants are used. Moreover, information concerning patients undergoing CPB had been based on indirect calculations, using the product of perfusion flow rate and the arteriovenous oxygen difference. With the advent of in-line blood-gas monitoring electrodes, we will now be able to monitor oxygen consumption versus flow rates at
During hypothermic and hemodiluted perfusions, the relationship between oxygen consumption and flow rate is very important. The ultimate goals of CPB are the restoration of normal cardiac function and a cerebrally intact patient. Oxygen consumption of the brain is very important, because it is the organ most susceptible to hypoxia in the shortest time.

**Distribution of Blood Flow to Organs**

At basal conditions, blood flow to various organs differs due to their weight, function or metabolic activity. During CPB, when perfusion flow rate is increased or decreased, the variations in flow are not equal in all organs because of pressure-flow relationship. Each organ (heart, kidney, skin, skeletal, splanchnic organs and brain) reacts differently in its vasomotion to subtle changes in blood gases accompanying changes in flow rates.

For example: low flow to the kidney over a short time will cause a marked diminution in urine output, but its oxygen uptake would not be seriously impaired because of its enormous blood flow and minute A-V difference. When blood flow to the skin, skeletal, muscle and splanchnic organs is reduced—even over a long time—they are not seriously affected.

The brain and the heart are the best protected organs, by what is termed “protected redistribution.” When the brain is affected by hypoxemia, it reacts by vasodilating to any decrease in its cardiac output, and consumes 2% of the total body weight, but it receives 14% of the total body oxygen uptake because of its enormous metabolic demands (55), and if perfusion flow is allowed to fall below 1.5 l/m2/min for more than a short time, a progressive metabolic acidosis ensues despite fully saturated arterial blood. Venous oxygen tension falls because of the enormous tissue oxygen consumption. Hydrogen ions and organic acids increase, resulting in hypoxic acidosis.

Animal studies by Cheng (52), Starr (53), and Paneth (24), (Figure 3) show that at normothermia, a minimum flow rate of (2.4 l/m2/min) is required to achieve 85% of the estimated maximum oxygen uptake. The upper confidence limit of 70% in relationship of flow to whole body oxygen consumption overlaps the asymptote at a flow rate of 1.2 l/m2/min and above. This is interpreted to mean that during CPB, most of the microcirculation is being perfused. When the flow rate is reduced below this level, areas of microcirculation shut down and whole body oxygen uptake falls.

Hagerdal, et al. (58), in a study on animals, reported that for each degree fall in temperature, oxygen consumption is reduced by 10% and that metabolic rate decreases linearly in a temperature range between 22°C to 37°C, at which time cerebral blood flow (CBF) is not altered or reduced. But, when the temperature falls below 22°C, CBF is reduced to 15% of its level at normothermia. Even at a temperature of 20°C and a flow rate below 1.2 l/m2/min, CBF still remains approximately 15% of normal and cerebral oxygen uptake (CMRO2) is unchanged as a result of autoregulation. Normal autoregulation is a result of what is called flow-metabolism coupling.

It has been reported that at what is perceived be “ideal perfusion flow rates” for normothermic CPB (2.2 to 2.4 l/m2/min.) acid metabolites do accumulate (54). Even at 28 to 30°C, flow rates below 2.0 l/m2/min might not meet the tissue’s metabolic demands (55), and if perfusion flow is allowed to fall below 1.5 l/m2/min for more than a short time, a progressive metabolic acidosis ensues despite fully saturated arterial blood. Venous oxygen tension falls because of the enormous tissue oxygen consumption. Hydrogen ions and organic acids increase, resulting in hypoxic acidosis.
base management strategy which is employed. If the pH-stat strategy is employed, flow-metabolism coupling and auto-regulation are abolished. Normal CBF is about 45-50 ml/100 gm/min and CMRO₂ is about 3 ml/100gm/min. Changes in CBF that occur are directly related to temperature changes and cerebral metabolism. In regards to the effects of "optimal perfusion flow rates" during hypothermic CPB, Govier, et al. found a marginally significant (p=0.06) relationship between regional CBF and perfusion flow rates in a study of 67 patients. They also examined the influence of flow rates in 10 patients by randomly varying perfusion flow rates and keeping the mean arterial pressure, nasopharyngeal temperature and hypothermia (CPB 29.3 to 25.6°C) when flow rates were that there was no significant change in regional CBF during hypothermic non-pulsatile CPB using the alpha strategy; their pooled data showed no relationship between CBF and MAP over the range of 30-100 mmHg. Kubota, et al. (60) found that during CPB, regional cerebral blood flow and cerebral metabolism run parallel and that there is a 65% decrease in blood flow. Govier, et al. (50) had similar findings, but with a smaller decrease in flow (55%). The results of Henriksen, et al. (61) were markedly different, showing a high increase in flow (67%). They think that it was probably due to "reactive hyperemia." Lassen, et al. (62) suggested that cerebral emboli occurring during CPB may have caused an ischemic injury and concomitant hyperemia due to uncoupling of flow-metabolism. Kent and Pierce (63) calculated reduction rate in cerebral metabolism of oxygen to be 1 percent for a drop of 8°C in temperature for dogs; assuming that the Q10 for human brain to be 2.8 during CPB. Hickley, et al. (64) reported that during CPB at 25-28°C, with flows of 2.2-2.4 l/min, whole body oxygen uptake (VO₂) decreased as would be expected. However, by reducing the flow rate to 1.2 l/min, it did not alter the whole body (VO₂). Mixed venous saturation increased during hypothermia, but returned to normal control levels when flow was reduced, demonstrating the opposite and cancelling effects of two variables on oxygen extraction. They concluded in the report that flow rates as low as 1.2 l/min during CPB at 25-28°C provide whole body tissue perfusion. But this does not apply to flow-limiting arterial lesions in patients with stenosis of the carotid artery.

In 1982 Fox, et al. (65, 66) studied the relationship of whole body oxygen consumption to perfusion flow rates during hypothermic CPB. They reported that (VO₂) fell progressively as flow decreased, suggesting that areas of the microcirculation shut down. Mixed venous PO₂ and oxygen saturation fell in a linear fashion with decreasing flows below 1.2 l/min (Table 6), indicating decreased flows to perfused areas. Internal jugular venous PO₂ and saturation fell in the same linear manner with decreasing flows below 1.8 l/min, suggesting that the flow decreases to areas of the brain which act differently from the rest of the body. (Table 7).

Miyamato, et al. (67) conducted an experimental study on the relation between perfusion flow rate and cerebral oxygen consumption during hypothermic CPB at 20°C. The perfusion flow rates were reduced in steps from 100, 60, 30, and 15 ml/kg/min every 30 minutes. Although cerebral blood flow decreased as perfusion flow decreased, the ratio of cerebral blood flow to perfusion flow rate increased significantly (P=0.05) at 15 ml/kg/min, compared to flow rates of 100 or 60 ml/kg/min. In 50% of their experiments, the perfusion flow rate was reduced in one step from 100 to 15 ml/kg/min, and after 60 minutes at 15 ml/kg/min, the flow rate was returned to 100 ml/kg/min. Cerebral oxygen consumption decreased significantly during 60 minutes of perfusion at a flow rate of 15 ml/kg/min and did not return to its initial value after the flow rate was returned to 100 ml/kg/min. This data indicated that the "optimal perfusion flow rate" for the brain during CPB at 20°C, appears to be 30 ml/kg/min, with a possible oxygen debt in the brain resulting in anaerobic metabolism if the perfusion flow rate is kept at 15 ml/kg/min or less.

Okuda, et al. (68) also studied the relationship between perfusion flow rate and whole body oxygen consumption at 20°C during CPB. The study revealed that an oxygen debt and metabolic changes could possibly occur if CPB at 20°C was continued at a flow rate of 30 ml/kg/min; thus, the "optimal perfusion" flow rate at 20°C is considered to be 60 ml/kg/min. It was suggested that a relatively high flow rate is necessary to compensate for an increase in oxygen affinity for hemoglobin because of the shift to the left in the oxygen dissociation curve and to prevent shut down of the microcirculation, uneven distribution of the blood stream, and an increase of the arterio-venous shunt during CPB at 20°C.

Arterial Pressure

The question of arterial pressure and its relationship to optimal perfusion flow rates is of major importance, but the prevailing opinions are diverse and contradictory.

At one time it was the common belief that pressure was not as critical as long as the calculated flow rate was maintained during normothermic CPB. It cannot be ascertained that adequate perfusion flow is delivered to the brain by maintaining calculated flow without the use of either constant electroencephalographic (EEG) monitoring or monitoring of cerebral blood flow labelled with various gamma-emitting radioactive microspheres (51, 85, 85, 133, 95, or 125). These tests require scintillators and other equipment, and are time consuming. There are simpler tests that can be done, such as calculating cerebral oxygen consumption (CVO₂, the difference between arterial and internal jugular venous oxygen contents), and total brain blood flow by means of the Fick equation. Also, cerebral oxygen extraction, is calculated by obtaining the difference between arterial-internal jugular venous oxygen content difference, divided by arterial oxygen content (69).

Several investigators (60, 62, 69, 70, 71) have found that carbon dioxide directly affects cerebral blood flow during hypothermic CPB. By maintaining a relatively normal partial
arterial carbon dioxide (PaCO₂) during CPB, you can be reasonably sure that there is adequate cerebral blood flow, provided there are no pre-existing cerebrovascular disorder.

Several studies (72, 73, 74, 75) have reported a definite correlation between low mean arterial pressure (MAP) and numerous neurologic deficits. Javid, et al. (76) reported on neurologic damage when MAP was allowed to fall below 50 mmHg during CPB. Jueng, et al. (77) reported that even with moderate hypothermia (28-30°C), pressure below 50 mmHg for a protracted period will result in severe neurologic damage; especially if there are pre-existing cerebrovascular disorders. Kavan, et al. (79) and Van Bergen, et al. (79) reported that an arterial pressure below 50 mmHg is the critical level at which electrocortical depression occurs and that further decreases may lead to significant cerebral ischemia.

Stockard, et al. (74) developed a scoring system showing the correlation between the depth and the duration of hypotension, which indicates the degree and severity or performance of the post-operative cerebral dysfunction.

Units of hypotension are torr-minutes of perfusion pressure below 50 torr (tm50), tm50 is the value represented geometrically by the area between the 50 torr line on the blood pressure record and the mean arterial pressure tracing when it is below 50 torr. Alternatively, it is x[50 torr - MAP] dt.

Thus, the value of the ordinate reflects both the degree and the duration of the pressure drop below 50 torr and 100 tm.

For example: MAP for 10 minutes at 40 torr = tm50-40 (10 x 10) or 100 tm50.
MAP for 20 minutes at 45 torr = tm50-20 (20 x 5 ) or 100 tm50.
MAP for 25 minutes at 40 torr = tm50-25 (25 x 10) or 250 tm50 etc.

A value of 100 tm50 appears to be significant in terms of those patients who will have neurologic sequelae and those who will not. In their study, six of seven patients with a hypotensive index of greater than 100 tm50 manifested generalized neurologic deficits.

Stockard, et al. (80) adopted a policy that 50 torr was the minimum acceptable pressure. Subsequently, they raised that figure to 60 to 70 torr. This coincides with work by Schneider, et al. (81) who advocate 70 torr as the critical MAP level (1 torr = 1 mmHg at 0°C and 1 g acceleration). Stockard’s (74) report concluded that during CPB, perfusion pressures below 50 torr can result in ischemic brain damage and post-operative central nervous dysfunction. The risk of these complications is roughly proportional to the depth and duration of hypotension, but also varies with the extent of cerebral atherosclerosis, the age of the patient and the deliberate use of pressor agents to prevent MAP from falling below 50 torr. Higher minimum pressures are more desirable. Thus, optimal flow rates become an important factor during CPB. It is important to note that Ellis, et al. (82a) reported that a reduction in perfusion flow rates and arterial pressure do not result in cerebral dysfunction. Govier (59) reported that their study showed no evidence that a MAP lower than 50 mmHg is accompanied by a decrease in regional cerebral blood flow during CPB. However, if cerebral autoregulation is disordered during CPB, hypotension associated with decreased cerebral perfusion could produce central nervous ischemic injury.

The association between regional cerebral blood flow (CBF) and MAP is consistent with preserved autoregulation. During hypothermic CPB, the lower limit of autoregulation appears to be as low as 30 mmHg, according to Govier. This is in contrast to normotensive, normothermic human beings with normal cerebrovascular status in whom autoregulation maintains a constant CBF between 50 to 150 mmHg. The most likely reason for the lower limit (30 mmHg) of autoregulation is that less CBF is required during profound hypothermia (See Figure 8). But Henriksen, et al. (61) found that cerebral autoregulation was maintained down to a MAP of 55 mmHg. Below that pressure, there was a significant association between regional CBF and MAP during hypothermic CPB. Patients in that study received enflurane as an anesthetic before CPB and it is known that many anesthetic agents interfere with CBF (120, 121).

Fig. 8
Cerebral blood flow vs. mean arterial pressure during cardiopulmonary bypass.
The line represents an average regression line over all patients. There are 44 hidden observations (data points superimposed on each other). From Govier, et al.*

Govier concludes that the lower limit of cerebral autoregulation is extended during hypothermic CPB at a flow rate of 1.6 l/min/m², and that pharmacologic support is not necessary to maintain a constant CBF between a MAP of 30 to 110 mmHg. Furthermore, reducing perfusion flow rates to as low as 1.01/min/m² did not significantly reduce regional CBF, at least during the short intervals in which it was measured in their study. In examining the role of arterial blood pressure during CPB, a reference can be made to electronics: pressure can be defined as: I = E/R(ohm) where (I)= blood flow and is
equal to the quotient between the pressure head necessary for flow \((E)\); \((R)\) is the resistance of the vasculature. In other terms, perfusion pressure is directly related to the product of vascular resistance and blood flow. It is an approximate linear function of perfusion flow rate.

There are several factors which influence the arterial blood pressure:
1. Alteration in vascular response
2. Anesthetic agents
3. Operative trauma
4. Perfusion flow rate
5. Priming hemodilutional factor
6. Perfusate colloidal osmotic pressure (COP)
7. Temperature
8. An anatomic factor, such as an improperly managed patient ductus arteriosus or a large bronchial collateral return in patients with Tetralogy of Fallot.

For example: hemodilution mandates a much higher perfusion flow rate than the calculated rate, because the degree of hemodilution compromises oxygen content and delivery. The use of vasodilators require at least a 10% upward adjustment in flow rate to offset the hypotensive effect associated with its use. Abrupt reduction in flow rates should be avoided. If reduction is required, the ischemic period should be as short as possible, followed by a return to high normal flows and pressures.

In summary, it appears that moderate hypothermia (28 to 30°C) in conjunction with hemodilution (Hct 20 to 25%), regardless of the flow rate necessary to achieve a blood minimum MAP between 65-75 mmHg throughout CPB, will confer cerebral protection in most patients regardless of age or preexisting cerebrovascular conditions.

**Hemodilution-Hypothermia vs. Optimal Flow Rates**

Gollan, et al. (83), who established the physiologic principles for hemodilution in 1954, perfused dogs without hemoglobin at a temperature below 10°C with survivals. In 1959, Panico and Neptune (84) proposed a mechanism to eliminate donor blood from the pump-oxygenator.

Hemodilution has been a most important adjunct to CPB for many reasons. In most instances, it obviates the need for donor blood with its attendant risks. It decreases colloid osmotic pressure dependent on the degree of hemodilution. It enhances the clotting mechanism by decreasing antithromboplastins and it improves perfusion to the microcirculation by reducing perfusate viscosity.

The viscosity of blood during CPB is very important. There are two factors that control viscosity: hematocrit and temperature. Gollan (85) in 1965 reported that the viscosity of whole blood increases about 5% per degree drop in temperature.

The relationship between hematocrit and viscosity is proportional. A 50% decrease in hematocrit is approximately a 50% reduction in viscosity, which offsets the rheologic effects of hypothermia (86, 87). Reduced viscosity results in decreased resistance to blood flow through the capillaries, thus improving tissue perfusion to a degree that will compensate for the reduction in red cell concentration. Post-operative problems related to organ perfusion are somewhat lessened. It enhances renal perfusion, evidenced by an increase in glomerular filtration and an increase in diuresis. There is also evidence that suggests that there is a reduction in protein aggregates at the blood-gas interface in bubble oxygenators and less blood loss in the postoperative phase. This reduction in viscosity may also allow a calculated flow rate to be achieved with a lower perfusion pressure (88). These considerations are applicable to cerebral blood flow as well as the periphery. It is, therefore, necessary to reduce a normal hematocrit of 45% to approximately 25% to maintain a constant viscosity during CPB at 20°C. However, if the hemodiluted perfusate has a hematocrit greater than 25% of normal at 20°C, it leads to increased viscosity, decreased tissue blood flow at the same perfusion flow rate, arterial pressure and systemic vascular resistance.

The relationship between mean arterial pressure, systemic vascular resistance (SVR) and cardiac output (CO) can be expressed by the following formula if the viscosity remains constant:

\[
\text{MAP} = \text{Viscosity} \times \text{Systemic vascular resistance} \times \text{cardiac output}.
\]

During hemodilution CPB, there are several determinants that affect the calculated flow rate because of the constant rheologic changes that occur. When the perfusate’s temperature falls, viscosity rises, systemic vascular resistance rises as diuresis occurs and hematocrit rises; these determinants give rise to resistance of the calculated flow rate. Consequently, flow rates must be constantly adjusted to meet these variances.

During normothermic CPB, or at the initiation of CPB at which time the patient’s temperature is around 33-34°C, a constant calculated flow rate, will result in systemic vascular resistance and a drop in MAP that will vary with the degree of viscosity from the hemodiluted perfusate; most probably on the low side (30 to 40 mmHg). This phenomenon usually occurs for a short time before the prime mixes with the patient’s blood volume. Perfusion — at the calculated flow rate or beyond — would not solve this problem, and it is not deemed advisable to immediately resort to drugs to increase the arterial pressure. If the problem persists, even at much lower temperatures, it is advisable to cautiously begin a low-dose infusion of an alpha agonist.

Hemodilution is used universally, but the degree and composition of the priming solutions vary widely among institutions. Hematocrits also vary, ranging from 15-30%. Theoretically, hematocrits between 15-20% of normal can transport sufficient oxygen to meet metabolic demands but at severely reduced levels to maintain CNS function if fully saturated. Cerebral blood flow can be increased through higher flow rates and hypocarbia, which compensates for the reduced oxygen content. Studies have shown that hemodilution progressively increases cerebral blood flow (89).
Siejo, et al. (90) states that as long as cerebral perfusion pressure can be maintained, the brain can tolerate severe reduction in hemoglobin content. Siejo (90a) further adds that hypothermia reduces cerebral metabolic rate about 5% per degree.

Recent studies (91, 92) indicate the feasibility of total bloodless prime for pediatric patients under 10 kg, resulting in a mixed hematocrit of 13% to 20% (93), which ultimately rises to levels about 25 to 30% due to adequate diuresis by the termination of bypass. In the post-bypass phase, a hematocrit not less than 20% can be considered as acute normovolemic anemia. Keats (94) states that it increases cardiac output only about 50% without any increase in heart rate or AVO₂ difference and with no adrenergic stimulation and little increase in myocardial work or myocardial oxygen uptake. At this level of hematocrit, the relative distribution of blood flow to the major organs remains unchanged from normal.

Yes! There is a definite relationship between hemodilution and optimal perfusion flow rates. Since hemodilution reduces hemoglobin and its oxygen carrying capacity, it is essential to raise perfusion flow rate and concurrently the PO₂, especially during the warming phase of CPB, to increase gas transfer through the capillary walls into the tissue fluids and cells.

**Optimal Flow Rates in Profound Hypothermia and Circulatory Arrest**

Why, after more than three-and-one-half decades and over several million CPB procedures, are we still questioning optimal flow rates? The subject is still very controversial among practitioners of cardiac surgery, especially during profound hypothermia. Some surgeons insist that during adult perfusions, the flow rate should be the same as at normothermia (2.2-2.41/m²/min) even at reduced temperatures. Others request that the flow rate be reduced to 1.4-1.61/m²/min when a patient's esophageal temperature is between 20-25°C, and returned to 2.01/m²/min at a temperature of 30°C and above.

In infants and children with cyanotic heart disease, it is mandatory in many instances to reduce flow substantially for adequate surgical exposure. However, the controversy still exists as to the preferred flow rate during profound hypothermia and the safe limits of circulatory arrest. Do very low perfusion flow rates (0.51/m²/min) or lower (0.251/m²/min) provide more protection to the patient than total circulatory arrest? The answer lies somewhere among the divergence of opinions. Sixty minutes or less has been advocated (95, 96, 97, 98) by some as the safe limit. However, brain damage still occurs in a number of cases reported (99, 100, 101, 102). Kirklin (103), Miyamoto (104), and others recommend low flow during profound hypothermia instead of total circulatory arrest. Kirklin has advisably pointed out the need to avoid total circulatory arrest for any protracted period and suggests trying to maintain a low flow (0.05 l/m²/min) because of the possibility of introducing air into the arterial system. This approach seems prudent, because it provides some blood flow to the brain and other vital organs. Moreover, after circulatory arrest, air may enter the systemic circulation and embolize when perfusion is restarted.

Gordon, et al. (105) formulated a flow chart correlating temperature, oxygen consumption and circulatory arrest time. (See Chart, Table 11). Rittenhouse, et al. (106) indicate that the safe limits for any given species and age group is quite variable. However, they consider the safe limits to be 60 to 65 minutes at 22°C and 70 to 75 minutes at 17-20°C. Haneda, et al. (107) suggest a safe interval of 90 minutes if the level of hypothermia is reduced to 10°C. Several other authors have conducted studies to evaluate the safe levels of circulatory arrest.

The measurement of brain tissue pH, PO₂ and PCO₂ has been examined during profound hypothermia and circulatory arrest by Kawakami, et al. (108), and their results indicated that at a temperature of 20°C and that total circulatory arrest for a period of 30 minutes, brain tissue PO₂ decreased, whereas brain tissue PCO₂ increased. Another study by Katogi (109) showed that during 45 minutes of low-flow perfusion (25 ml/kg/min) at 20°C, the brain tissue PCO₂ increased without a decrease in brain tissue PO₂. The tissue values for pH, PO₂, and PCO₂ are thought to indicate their mean values in extracellular fluid in a limited tissue area.

Sako, et al. (110) and Meyer, et al. (111) indicate in their studies that ischemia decreases brain pH. However, during physiologic conditions, brain PCO₂ is lower than venous PCO₂ (112, 113), and high intracranial pressure increases the brain's PCO₂ due to tissue malperfusion and hypoxia (115). Recent experimental studies by Watanabe, et al. (114) reported the results on a comparative study of circulatory arrest, nonpulsatile low-flow perfusion and pulsatile low-flow perfusion (25 ml/kg/min). Using brain tissue pH, PO₂, and PCO₂, measurements as an indicator of brain damage resulting from 60 minutes of circulatory arrest, 120 minutes of nonpulsatile low perfusion and 120 minutes of pulsatile low-flow perfusion were compared. Their results showed that during circulatory arrest, pH kept decreasing. In contrast, pulsatile flow limited the decline in pH and a rapid recovery ensued. Brain tissue prior to CPB was within the normal physiologic range (112, 115). During circulatory arrest, PO₂ decreased, but not during low-flow perfusion. PCO₂ increased significantly during circulatory arrest without recovery. In contrast, pulsatile low-flow perfusion limited the increase, resulting in a plateauing of PCO₂ and a fast recovery. Nonpulsatile low-flow perfusion caused a continuous rise with a delayed recovery. They also found that in the arterial blood-gas analysis, the blood base excess decreased the least during pulsatile flow. A significantly high rate of whole blood oxygen consumption, 10 minutes after circulatory arrest, is considered as the result of an oxygen debt during the circulatory arrest period. It was concluded that a 60 minute period of circulatory arrest is the critical level and that low-flow perfusion (25 ml/kg/min) can prolong the safe period. Additionally, pulsatile blood flow reduces the risk of brain damage even during low-flow perfusion (See Figures 9, 9a, 9b). Studies by Orita, et al. (113) have shown that in man during fibrillation, myocardial tissue PCO₂ increased and remained high during
the period of fibrillation, and decreased immediately after defibrillation. This shows that a pulsating myocardium promotes flow to the microcirculation and, in effect, reduces the increase in PCO₂. The same physiologic effect takes place in a non-pulsating quiet brain with no-flow that has a high metabolic rate and is susceptible to hypoxia and hypercarbia. Moreover, a pulsating brain from a low-flow pulsatile perfusion will promote microcirculation and reduce hypoxia and hypercarbia during profound hypothermic CPB.

Another investigative team, Molina, et al. (117) concluded from their experimental study that brain changes during profound hypothermia with or without circulatory arrest at 18°C causes mild to moderate neuron degeneration throughout the CNS. There was no significant difference in preservation results between their experimental groups undergoing total circulatory arrest at 18°C for one hour versus two groups that sustained continuous nonpulsatile perfusion versus a group that sustained continuous pulsatile perfusion to the brain. Moreover, it has been assumed that pulsatile perfusion provides better preservation (118, 119, 120), but no such evidence was found in their experimental model.

Conclusion

The controversy of optimal flow rates for cardiopulmonary bypass, profound hypothermia and total circulatory arrest, or continuous low-flow, will continue for a long time. The evidence covered in this paper indicates that there is no significant objective evidence showing that one method is superior to another. Quite a number of infants survive profound hypothermia with circulatory arrest, but some degree of CNS dysfunction occurs which cannot be measured scientifically or objectively.

In regard to the overall picture of optimal perfusion flow rates during cardiopulmonary bypass, we have tried to answer the question by following its course from a historical and physiological perspective, its affect on whole body oxygen uptake, cerebral oxygen uptake and acid-base physiology and how it is affected by hemodilution and hypothermia, systemic arterial pressure and profound hypothermia with circulatory arrest.

The overwhelming evidence appears to indicate that there is no definite prescribed flow rate, but a range of physiologic parameters within which one can perfuse with a relative margin of safety, dependent on the prevailing circumstances.
Table 1

Distribution of Blood Flow to Various Organs

The approximate resting cardiac output is taken as 5800 ml/min⁻¹, the basal oxygen consumption as 240 ml/min, together with the arteriovenous oxygen difference. (From Wade, OL and Bishop, JM. Cardiac Output and Regional Blood Flow. Oxford; Blackwell, 1962.)

<table>
<thead>
<tr>
<th>Site</th>
<th>Blood Flow L/min⁻¹</th>
<th>A-VO₂ ml/100 ml⁻¹ difference</th>
<th>O₂ ml/min⁻¹ consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splanchnic bed</td>
<td>1500</td>
<td>4.1</td>
<td>60</td>
</tr>
<tr>
<td>including liver</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>1200</td>
<td>8.0</td>
<td>70</td>
</tr>
<tr>
<td>Skin</td>
<td>500</td>
<td>1.0</td>
<td>5</td>
</tr>
<tr>
<td>Kidneys</td>
<td>1100</td>
<td>1.3</td>
<td>34</td>
</tr>
<tr>
<td>Heart</td>
<td>250</td>
<td>11.5</td>
<td>25</td>
</tr>
<tr>
<td>Brain</td>
<td>750</td>
<td>6.3</td>
<td>48</td>
</tr>
<tr>
<td>(range 3-10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other organs</td>
<td>600</td>
<td>3.0</td>
<td>12</td>
</tr>
<tr>
<td>Whole body</td>
<td>5800</td>
<td>4.0</td>
<td>240</td>
</tr>
</tbody>
</table>

Table 1a

The Patient Under Anesthesia

Cardiac Output 3 L/m²/min
Oxygen Uptake 125-130 ml/m²/min
Mixed Venous 14.8 ml/100 ml blood saturation 70-75%
VO₂ 4.2 ml/O₂/100 ml blood

Table 2

Normal Cardiac Index

Normal cardiac index is the total body perfusion whether it is supplied by the left ventricle or an extracorporeal pump or both, assuming that the PaO₂ is greater than 65% and the hemoglobin is fully saturated.

Normal value: Flow - 3.2 l/m²/min
Oxygen uptake (VO₂): 100-130 ml/m²/min
Hemoglobin value: 15 gm%
Hematocrit value: 45%
Normal systemic oxygen transport (SOT): 20 Vol. % x 3.2 l/m²/min, or 640 ml/O₂/min

Table 3

Perfusion Flow Chart Based on Weight (Clark, 1958) (35)

<table>
<thead>
<tr>
<th>Kg</th>
<th>Flow (ml/kg/min)</th>
</tr>
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<tbody>
<tr>
<td>9</td>
<td>105</td>
</tr>
<tr>
<td>20</td>
<td>85</td>
</tr>
<tr>
<td>50</td>
<td>52</td>
</tr>
</tbody>
</table>

Table 3a

Perfusion Flow Based on Body Surface Area

<table>
<thead>
<tr>
<th>M²</th>
<th>(L/M²/Min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>2.4</td>
</tr>
<tr>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>1.1</td>
<td>1.8</td>
</tr>
</tbody>
</table>
### Table 4

**Perfusion Flow Rate Based on Body Weight (kg). (Clark, 1958.)**

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Blood Flow in (L/min)</th>
<th>10 gm hemoglobin</th>
<th>12 gm hemoglobin</th>
<th>14 gm hemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>1.2</td>
<td>1.0</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>2.0</td>
<td>1.7</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>2.4</td>
<td>2.0</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>2.7</td>
<td>2.2</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>3.1</td>
<td>2.5</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>3.5</td>
<td>2.9</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>4.0</td>
<td>3.3</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>4.5</td>
<td>3.8</td>
<td>3.2</td>
<td></td>
</tr>
</tbody>
</table>

Tabulated from data by Clark by Nose'. Reproduced with permission.

### Table 4a

**Perfusion Flow Rate Based on Body Surface Area (BSA) (Clark, 1958.)**

<table>
<thead>
<tr>
<th>Body Surface Area (m²)</th>
<th>Blood Flow in (L/min)</th>
<th>10 gm hemoglobin</th>
<th>12 gm hemoglobin</th>
<th>14 gm hemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4</td>
<td>1.1</td>
<td>0.8</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>0.6</td>
<td>1.7</td>
<td>1.4</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>0.8</td>
<td>2.0</td>
<td>1.7</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>2.4</td>
<td>2.0</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>1.2</td>
<td>2.7</td>
<td>2.2</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>1.4</td>
<td>3.0</td>
<td>2.4</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>1.6</td>
<td>3.4</td>
<td>2.8</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>1.8</td>
<td>3.9</td>
<td>3.2</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>4.3</td>
<td>3.6</td>
<td>3.1</td>
<td></td>
</tr>
</tbody>
</table>

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### Table 4b

**Basal Oxygen Requirement (Clark, 1958)**

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Oxygen (ml/kg/min)</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>8.7</td>
<td>7.0</td>
<td>5.4</td>
<td>4.7</td>
<td>4.1</td>
<td>4.0</td>
<td>3.9</td>
</tr>
</tbody>
</table>

### Table 4c

<table>
<thead>
<tr>
<th>Body Surface Area (m²)</th>
<th>Oxygen (ml/m²/min)</th>
<th>0.4</th>
<th>0.6</th>
<th>0.8</th>
<th>1.0</th>
<th>1.2</th>
<th>1.4</th>
<th>1.6</th>
<th>1.8</th>
<th>2.0</th>
<th>2.2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>180</td>
<td>178</td>
<td>172</td>
<td>163</td>
<td>152</td>
<td>146</td>
<td>145</td>
<td>142</td>
<td>141</td>
<td>140</td>
</tr>
</tbody>
</table>

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Table 5

Ideal Perfusion Flow Rate (mg/kg/min) Normothermia (whole blood). Pierce, 1969 (45)

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Flow (ml/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>200</td>
</tr>
<tr>
<td>5-10</td>
<td>170</td>
</tr>
<tr>
<td>10-20</td>
<td>135</td>
</tr>
<tr>
<td>20-30</td>
<td>100</td>
</tr>
<tr>
<td>30-60</td>
<td>85</td>
</tr>
<tr>
<td>60 and over</td>
<td>60-70</td>
</tr>
</tbody>
</table>

Table 6

Relationship of Perfusion Flow Rate to Oxygen Consumption, Oxygen Extraction and the Arteriovenous (AV) Oxygen Content Difference at 20°C.

<table>
<thead>
<tr>
<th>Perfusion Flow Rate (L/min)</th>
<th>(O_2) Consumption (ml/min)</th>
<th>Percent (O_2) Extraction</th>
<th>AV (O_2) Content Difference (Vol %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25±0.084</td>
<td>14±5.4</td>
<td>45±9.6</td>
<td>5.6±1.30</td>
</tr>
<tr>
<td>0.54±0.101</td>
<td>20±4.1</td>
<td>27±5.3</td>
<td>3.7±0.87</td>
</tr>
<tr>
<td>1.02±0.107</td>
<td>25±5.7</td>
<td>17±3.4</td>
<td>2.5±0.53</td>
</tr>
<tr>
<td>1.56±0.129</td>
<td>28±5.8</td>
<td>13±3.5</td>
<td>1.8±0.38</td>
</tr>
<tr>
<td>2.08±0.180</td>
<td>33±8.2</td>
<td>11±3.3</td>
<td>1.6±0.41</td>
</tr>
</tbody>
</table>

During cardiopulmonary bypass at a temperature of 20°C, the lower the flow, the lower the \(VO_2\). From Fox, et al. (65). Reproduced with permission.

Table 7

Relationship of Perfusion Flow Rate to Mixed and Internal Jugular Venous Oxygen Tensions and Saturations at 20°C.

<table>
<thead>
<tr>
<th>Perfusion Flow Rate (L/min/m²)</th>
<th>Mixed Venous Blood</th>
<th>Jugular Venous Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>(PO_2) (mm HG)</td>
<td>(O_2) sat. (%)</td>
<td>(PO_2) (mm HG)</td>
</tr>
<tr>
<td>0.25±0.084</td>
<td>6±0.8</td>
<td>29±7.9</td>
</tr>
<tr>
<td>0.54±0.101</td>
<td>10±1.9</td>
<td>54±10.8</td>
</tr>
<tr>
<td>1.02±0.107</td>
<td>15±5.3</td>
<td>78±10.7</td>
</tr>
<tr>
<td>1.56±0.129</td>
<td>47±27.6</td>
<td>94±9.2</td>
</tr>
<tr>
<td>2.08±0.180</td>
<td>61±18.0</td>
<td>99±0.6</td>
</tr>
</tbody>
</table>

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The internal jugular venous \(PO_2\) and oxygen saturation are strongly correlated with flow below 1.8 l/min/m². There was no correlation of internal jugular venous \(PO_2\) or saturation to flow above 1.8 l/min/m². From Fox, et al. (65).
Table 8

Organ Blood Flow Rates During Profoundly Hypothermic (20°C) Nonpulsatile, Hemodiluted Cardiopulmonary Bypass

<table>
<thead>
<tr>
<th>Organ</th>
<th>Organ Blood Flow Rate (ml/min-1/100 gm -1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.5*</td>
</tr>
<tr>
<td>Whole Body</td>
<td>10.29+0.080</td>
</tr>
<tr>
<td>Brain</td>
<td>45+6.3</td>
</tr>
<tr>
<td>(5.4%)</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>280+84</td>
</tr>
<tr>
<td>Lung</td>
<td>3.8+0.96</td>
</tr>
<tr>
<td>Liver</td>
<td>70+36</td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
</tr>
<tr>
<td>Medulla</td>
<td>55+14.2</td>
</tr>
<tr>
<td>Cortex</td>
<td>590+112</td>
</tr>
</tbody>
</table>

Figures in parentheses indicate the brain blood flow as a percent of total body blood flow.
*Perfusion flow rate (L/min-1/m2). From Fox, et. al. (66).

Reproduced with permission. From Fox, et al. (66)

Table 9

Brain and Body Minus the Brain Blood Flow Resistance at Various Perfusion Flow Rates

<table>
<thead>
<tr>
<th>Organ</th>
<th>Resistance (Units/100 gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.75*</td>
</tr>
<tr>
<td>Brain</td>
<td>1.2+0.51</td>
</tr>
<tr>
<td>Whole body</td>
<td>2.8+0.157</td>
</tr>
<tr>
<td>minus brain</td>
<td>3.3+0.22</td>
</tr>
<tr>
<td></td>
<td>1.5*</td>
</tr>
<tr>
<td>Brain</td>
<td>0.80+0.080</td>
</tr>
<tr>
<td>Whole body</td>
<td>3.3+0.22</td>
</tr>
<tr>
<td>minus brain</td>
<td>3.3+1.21</td>
</tr>
<tr>
<td></td>
<td>1.25*</td>
</tr>
<tr>
<td>Brain</td>
<td>0.8+0.22</td>
</tr>
<tr>
<td>Whole body</td>
<td>3.9+0.24</td>
</tr>
<tr>
<td>minus brain</td>
<td>3.9+0.24</td>
</tr>
<tr>
<td></td>
<td>1.0*</td>
</tr>
<tr>
<td>Brain</td>
<td>0.78+0.126</td>
</tr>
<tr>
<td>Whole body</td>
<td>4.6+0.077</td>
</tr>
<tr>
<td>minus brain</td>
<td>4.6+0.077</td>
</tr>
<tr>
<td></td>
<td>0.75*</td>
</tr>
<tr>
<td>Brain</td>
<td>1.05+0.165</td>
</tr>
<tr>
<td>Whole body</td>
<td>5.1+0.49</td>
</tr>
<tr>
<td>minus brain</td>
<td>5.1+0.49</td>
</tr>
<tr>
<td></td>
<td>0.5*</td>
</tr>
<tr>
<td>Brain</td>
<td>0.80+0.117</td>
</tr>
<tr>
<td>Whole body</td>
<td>9.5+0.70</td>
</tr>
<tr>
<td>minus brain</td>
<td>9.5+0.70</td>
</tr>
<tr>
<td></td>
<td>0.25*</td>
</tr>
<tr>
<td>Brain</td>
<td>1.02+0.173</td>
</tr>
<tr>
<td>Whole body</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>minus brain</td>
<td>&lt;0.000</td>
</tr>
</tbody>
</table>

*Perfusion flow rate (l/min-1/m-2). From Fox, et al. (66).

Table 10

Oxygen Consumption During Profoundly Hypothermic, Nonpulsatile Hemodiluted Cardiopulmonary Bypass

<table>
<thead>
<tr>
<th>Organ</th>
<th>Oxygen Consumption (ml/min-1/100 gm-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.5*</td>
</tr>
<tr>
<td>Whole body</td>
<td>0.119+0.0077</td>
</tr>
<tr>
<td>(17.3+1.16)</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>0.51+0.095</td>
</tr>
<tr>
<td>Whole body</td>
<td>0.114+0.0074</td>
</tr>
<tr>
<td>minus brain</td>
<td>0.081+0.0085</td>
</tr>
<tr>
<td></td>
<td>1.0*</td>
</tr>
<tr>
<td>Whole body</td>
<td>0.086+0.0045</td>
</tr>
<tr>
<td>(12.5+0.65)</td>
<td></td>
</tr>
<tr>
<td>minus brain</td>
<td>0.086+0.0045</td>
</tr>
<tr>
<td></td>
<td>0.5*</td>
</tr>
<tr>
<td>Brain</td>
<td>0.057+0.0029</td>
</tr>
<tr>
<td>(8.3+0.44)</td>
<td></td>
</tr>
<tr>
<td>minus brain</td>
<td>0.057+0.0029</td>
</tr>
</tbody>
</table>

Legend: The numbers in parentheses are the whole body oxygen consumption expressed as ml/min-1/m-2. Perfusion flow rate (l/min-1/m-2). Reproduced with permission. From Fox, et al. (66).

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Table 11

<table>
<thead>
<tr>
<th>Temp. C°</th>
<th>Oxygen Consumption</th>
<th>Circulatory Arrest (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>100%</td>
<td>4-5</td>
</tr>
<tr>
<td>29</td>
<td>50</td>
<td>8-10</td>
</tr>
<tr>
<td>22</td>
<td>25</td>
<td>16-20</td>
</tr>
<tr>
<td>16</td>
<td>12</td>
<td>32-40</td>
</tr>
<tr>
<td>10</td>
<td>6</td>
<td>64-80</td>
</tr>
</tbody>
</table>


Table 12

<table>
<thead>
<tr>
<th>Temperature (Nasopharyngeal)</th>
<th>Duration (Minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28°C</td>
<td>20</td>
</tr>
<tr>
<td>26°C</td>
<td>30</td>
</tr>
<tr>
<td>22°C</td>
<td>45</td>
</tr>
</tbody>
</table>


References


3. Bartholin T: De Nivis Sydenhamiae (i.e. Copenhagen), 1661.


43. Margulis MS: On optimal artificial blood now in extracorporeal circulation. Eskp Khr (Russian) 1959; 4:58-60.

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