
Myocardial Preservation during Hypothermic Cardiopulmonary Bypass: A Team Endeavor

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Abstract

Myocardial failure is the primary cause of death following operation using hypothermic cardiopulmonary bypass. The mean mortality rate for coronary bypass in Medicare patients in the United States for 1984 was 5.5%. Injury to the heart is caused by aortic cross-clamping or total circulatory arrest. The lesion of hypoxia is characterized by progressive acidosis. The severity of acidosis correlates with the degree of post-operative myocardial dysfunction. In decision making concerning the management of perfusion or of operative technique, prevention and/or treatment of myocardial acidosis takes precedence over other considerations. Recent advances in understanding the effect of temperature on acid-base equilibria, and the recent introduction of on-line blood gas monitoring devices have given the perfusionist the necessary means to achieve perfusion which keeps the patient on the alkaline side of biological neutrality. Similarly, the surgeon should utilize the protective value of frequent coronary infusions with a cold, oxygenated, alkaline, buffered, anti-oxidant blood cardiopreservation solution. Figures and tables are presented which enable the perfusionist to understand hypothermic acid-base management, and to use appropriately hyperventilation and high flow perfusion, avoiding any use of CO₂ gas, while monitoring the patient's course using venous blood samples which are uncorrected for temperature. With this team approach, improvement in operative mortality can be expected.

Heart surgery is major surgery and causes a significant mortality rate. In the only large scale national study available, the Department of Health and Human Resources released late in 1985 an analysis of the death rate in all 57,804 patients whose coronary bypass procedures in 1984 were paid for by Medicare. The analysis was by hospital in every state of the country. The average death rate following surgery in these patients was 5.5%. This paper explores in depth the major component of that risk and discusses the means available to diminish it.

What are the operative sequelae which are the cause of mortality and morbidity? In the opinion of every cardiac surgeon with whom I have discussed this problem, myocardial failure is No. 1. Difficulty in weaning the patient from the pump and the necessity for post-operative circulatory support is a dreaded scenario for all. Slow and progressive myocardial insufficiency may also prove eventually to be terminal. True, other sequelae also occur. Technical failure is the one to which the surgeon is most sensitive, and strives to perfect his skills and judgment so these will not occur. Embolic episodes, clotting disturbances, pulmonary or renal complications are important too, but myocardial failure apparently is a more frequent cause of death than all these put together. To lower the risk of heart surgery, attention should be concentrated on protection and preservation of the myocardium, which must not be allowed to develop acidosis. The myocardium was adequately supporting the life of the patient when he or she was on the way to the operating room in all but a very few instances. If it fails to achieve this capability after surgery, one must face up to the fact that *injury inflicted during the operation* is the chief cause of its failure.

Procedures in the interior of the heart involving valve excision and replacement, insertion of baffles, suture closure of defects, or myomectomy inflict significant myocardial surgical trauma. Mechanical muscular injury is intrinsic to these procedures and cannot be avoided, only minimized. In today's cardiac surgery scenario,

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however, the great majority of operations are performed with the intact heart immobilized and cold. Bypass procedures do not require cardiac incision beyond cannulation; they only require aortic cross clamping. The damage is inflicted by circulatory abuse. Ischemic myocardial acidosis can and is being surgically inflicted in large and potentially lethal doses throughout the world. However, with careful management this type of myocardial impairment can and should be largely prevented and successfully treated.

It has been known for years that acidosis reduces myocardial contractility (1). If the acidosis becomes severe enough, it will lead to structural damage and eventual cell necrosis. At some point in this progression, the damage is irreversible, and the heart is doomed. At normothermia, this occurs between 15 and 30 minutes of ischemia. And even deep hypothermia will not prevent these changes but will only delay them for about two hours. The degree of post operative myocardial disability correlates exactly with the level of maximum depression in myocardial pH irrespective of myocardial temperature or duration of ischemia. In a careful study by Takash et al. (2) using micro-myocardial pH and temperature probes in ischemic left ventricles in sheep, any terminal intramyocardial pH less than 7.0 resulted in marked decrease in left ventricular function whether that pH level was reached rapidly during normothermic ischemic or more slowly during hypothermic (25°C) ischemia. In both instances, a pH of 6.8 resulted in only about 50% return of left ventricular function, and of 6.6 in about 30% return of function at one hour. Below 6.5 no animal could be weaned from the pump without circulatory assist. It is clear that intramyocardial acidosis is damaging to the functional integrity of the heart.

Before irreversibility sets in, the myocardium will still look essentially normal under the microscope; but if reperfusion with an oxygenated acidotic fluid is instituted there is an explosive change in the micropathologic characteristics. Hypoxically distorted enzyme systems fail to suppress the violent formation of oxygen free radicals. Superoxides and hydrogen peroxides flood the cell structures causing damage everywhere. Edema forms in the matrix; calcium floods the mitochondria and precipitates as phosphate conglomerates. This is the cataclysm of the so-called "reperfusion injury." But it can be successfully prevented by the avoidance of hypoxic acidosis and it can be essentially ablated by reperfusion which is strongly alkaline.

Myocardial protection is truly a team endeavor involving particularly the perfusionist and the surgeon. These two control the modalities which are primarily concerned with preservation of the heart. When perfusion cooling begins, the perfusionist is in control of maintaining the patient's general well-being and adapting the perfusion to preserve the heart before the aorta is cross-clamped

and again at the critical moment when reperfusion is begun. All of the body except the heart is well perfused throughout and suffers no risk of hypoxia or acidosis if perfusion is adequate. The cerebral circulation, although a potential victim of microemboli is not threatened by perfusion hypoxia. Only the heart is ischemic and during this period its fate is in the hands of the surgeon. It is his total responsibility, not only to carefully achieve the manipulative goals of the procedure, but also, with a strong feel for the patho-physiology of hypoxic acidosis, to protect the myocardium with local hypothermia and the frequent use of cardio-preservation solutions. The acid-base management of perfusion by the perfusionist and hypothermic coronary cardiopreservation infusions by the surgeon are the two keys. This discussion will take them up in that order.

The concept of *biological neutrality*, which one should keep clearly in mind, is the guide to rational interpretation of acid-base data when temperature is changing. Biological neutrality is defined as the intracellular acid-base status at any viable temperature; neutrality is achieved when hydrogen ion concentration and hydroxyl ion concentration are equal, so that their ratio is 1. This is the case with every vertebrate cell ever measured; they all lie on such a line between 37° and 10°C with almost no variability (3). Biological neutrality follows exactly the neutrality line of water as it changes with temperature.

As water cools, its dissociation decreases so that there are fewer hydrogen ions; therefore, their *negative log* (the pH) rises. In the world's waters and in all vertebrate animals including man, this is the way it is: the hydroxyl-hydrogen ion ratio of water and of the cells is maintained at one. (See Figure 1). This is achieved by keeping the total CO₂ in the body constant. These temperature rela-

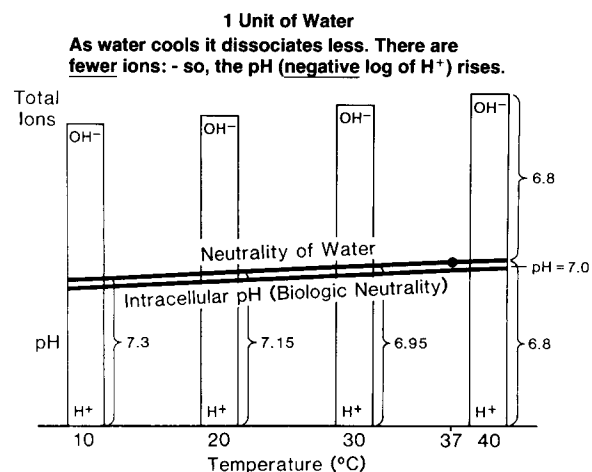


Figure 1. The graph illustrates how intracellular biological neutrality ($H^+ = OH^-$) as measured in a multitude of different animals follows exactly the neutrality pH of water (pN) as temperature falls from 37° to 10°.

tionships are controlled absolutely by fundamental physico-chemical laws, such as the change in the pK of water, the changing solubility of CO₂ and the effect of rising pH on the pK of bicarbonate as temperature falls.

However, the blood and other fluids circulating in the body maintain a pH higher than pN, (that is, the pH of neutrality). Thus the pH of blood is pN + k, a figure governed by the characteristics of the cell membranes. We see this concept diagrammed in Figure 2, a classic cartoon by Hermann Rahn (4). In man, the cell membranes have established that k equals .6 pH units.

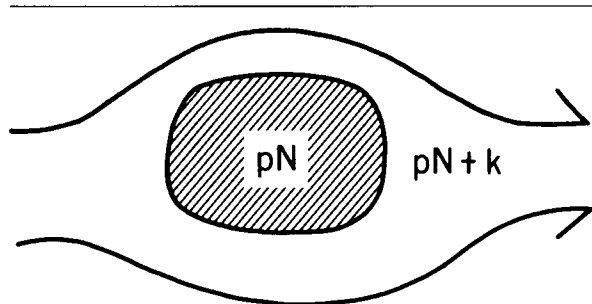


Figure 2. How the cell membrane separates the intracellular pH of neutrality from the extra-cellular pH, 0.6pH units higher, is seen in this diagram by Rahn et al. (10), reprinted with permission of the American Review of Respiratory Disease, New York.

Thus the relationships of body cells and body fluids to pN is illustrated in Figure 3 as temperature varies from 0° to 40° centigrade. In arterial blood, these pH plus .6 values are 7.4 at 37°, 7.57 at 27°, and 7.74 at 17°. Thus Figure 3 displays biological neutrality for all mammalian cells and for their extracellular pN + k fluid environment at all temperatures between 0°C and 40°C.

As pH rises during cooling PCO₂ falls in accordance with these laws. A naturally occurring illustration is the change in arterial pH in man as blood courses through our arteries from our core to our skin. As it does so it is cooled from 37° to about 25°. Since it is running through a closed system, the arteries, its total CO₂ is unchanged; it behaves as it would in a sealed test tube. Figure 4 is a graph of what the pH and PCO₂ of our arterial blood are doing as it continuously flows from warm interior to cool exterior. This is a chart of the biological neutrality of arterial blood (5). We don't have a single normal pH of 7.4; in our dorsalis pedis artery the normal pH is 7.6; it all depends on the temperature.

In an attempt to develop a graph which might serve as a nomogram for respiratory acid-base changes during current hypothermic cardiopulmonary bypass (H-CPBP) procedures, Kindig et al. presented an analysis (6) which showed that when human blood undergoes erythrocyte dilution by 50% to an hematocrit of 20, associated with similar plasma dilution, the buffer strength falls about 33%. Thus, whole blood with a buffer strength of 28,

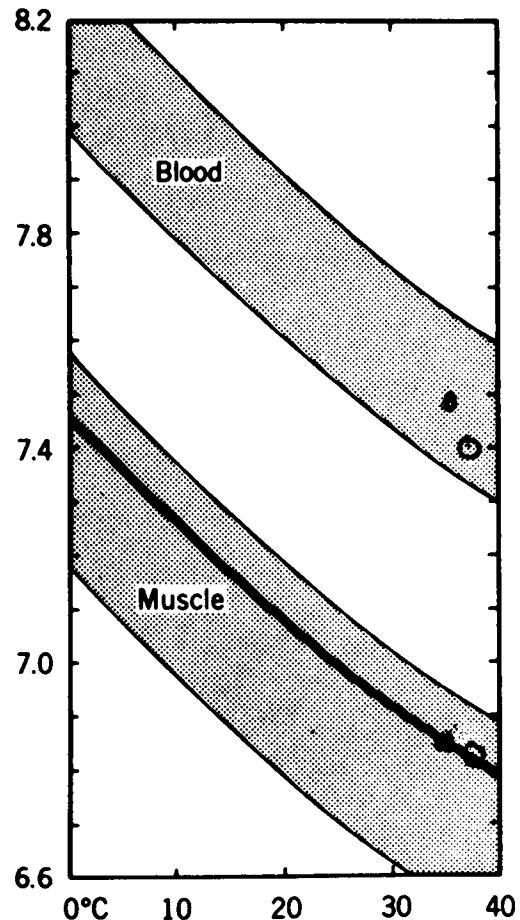


Figure 3. The relationship of the pH of blood and the pH of muscle in a variety of vertebrates as related to temperature is shown. The constant relative alkalinity of blood to muscle cells is apparent. Modified from Rahn et al. (10) and reprinted with permission of the American Review of Respiratory Disease, New York.

diluted to an hematocrit of 20, now has a buffer strength of 20 slykes.

This dilution affects the pH temperature coefficient so that it averages .016. This coefficient places the pH isopleths in a precisely horizontal position on a log PCO₂ concentration versus temperature chart throughout the temperature range of 17° to 37° C. Thus it is a remarkable coincidence that current practice for H-CPBP calls for dilution of the blood to an hematocrit level of about 20, which results in a buffer strength of 20 slykes, a value at which pH and log PCO₂ lines charted versus temperature remain perfectly horizontal. With a ΔpH/°C of .016 such a graph describes the acid-base parameters of any point when TCO₂ remains constant or is altered by respiration, for the temperature range 17° to 37° C, a range commonly experienced by man undergoing H-CPBP in 1988. PCO₂ decreases 5% per degree Celsius under these conditions. It should be used by perfusionists as a nomogram for the management of H-CPBP.

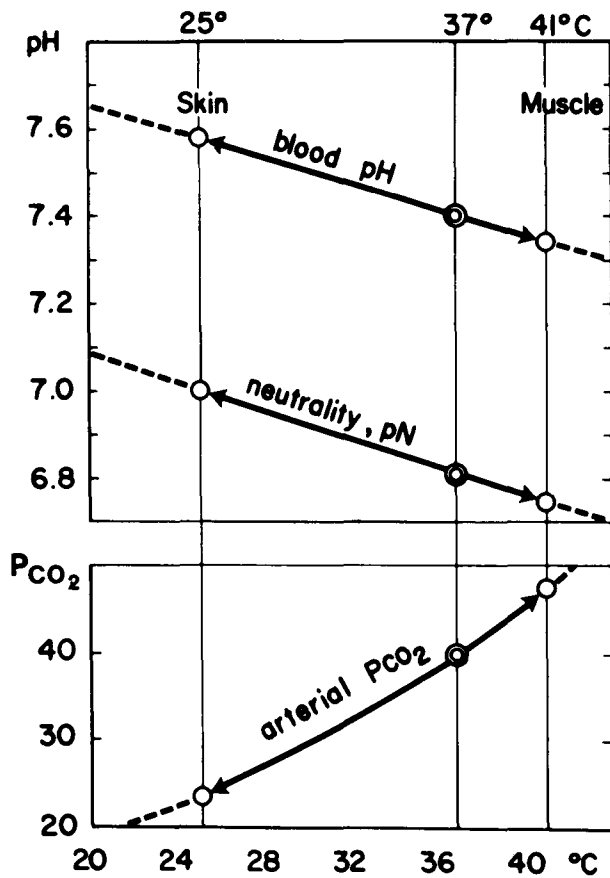


Figure 4. The typical changes in blood pH and PCO_2 as arterial blood flows from working muscle to skin capillary in normal man with a core temperature of 37° . Reprinted by permission of Springer-Verlag, New York.

The author has previously published (1,7) a similar graph using arterial blood values for pH and PCO_2 . But Figure 5 displays values more pertinent to the acid base management of perfusion, namely venous values as sampled at the inflow port of the oxygenator. For years, arterial samples were monitored in patients undergoing heart surgery, primarily because in the intact human no obtainable venous sample was considered to represent truly mixed whole body venous blood. When Swan-Ganz catheters began to be inserted early in the procedure, a reasonably mixed venous site became available. But it was seldom used and after perfusion is initiated, the site is no longer available. The habit of using arterial values continued. However, these values are only indirectly related to the metabolic condition of the patient. They only show that the pump-oxygenator has succeeded in correcting the abnormalities existing in the blood returning to it from the patient. Arterial samples monitor the pump-oxygenator. On the other hand, blood sampled at the venous inflow port is truly mixed venous blood and reflects the state of the mean whole body metabolism of the patient. When monitoring for control of acid-base

Respiratory Acid-Base Status as Effected by Temperature; Human Blood, Diluted to Hct = 20

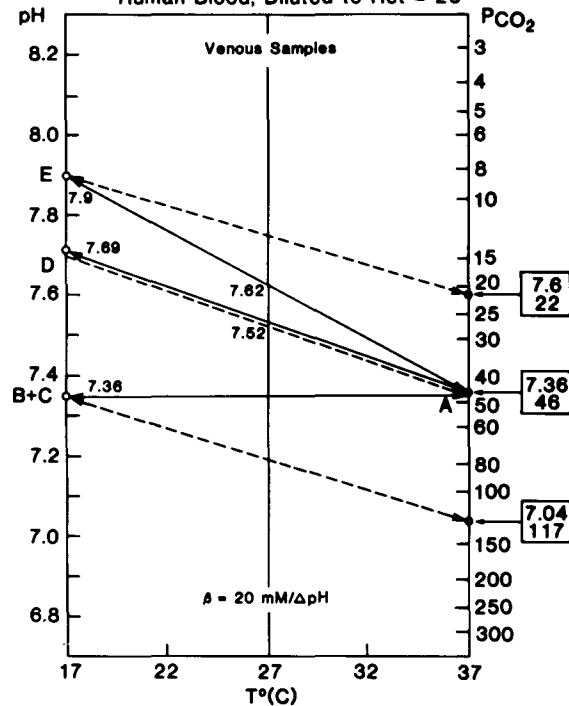


Figure 5. A log PCO_2 concentration versus temperature graph illustrating the three possible acid-base strategies during H-CPB when the perfusing fluid is 20-Hct blood. All pH and PCO_2 values defining these strategies are based on venous blood sampling. This diagram should be used as a nomogram for the control of acid-base status during perfusion.

management and the adequacy of oxygenation of the patient's tissues, only venous samples should be used (8,9). Arterial samples reflect the functional integrity of the pump oxygenator; venous samples reflect the state of the patient and thus the adequacy of the perfusion.

In the interpretation of this diagram the reader must recognize that as a patient cools, his acid-base status will follow some course from right to left starting on the ventricular 37° C line or near it, then proceeding left towards the 17° C line. A point with commonly accepted normal venous values for pH (7.36) and PCO_2 (46) was selected as the point of beginning. All patients, therefore, are illustrated as entering the graph at point A. The solid lines pointing left illustrate the locus of the venous pH and PCO_2 values which will be found when three specific acid-base management strategies are successfully achieved.

Consider line AD first; this is the line of *biological neutrality* largely determined by the near identity of the change due to falling temperatures in the dissociation constant of water (pK_w) and the dissociation constant of imidazole (pK_{Im}) (10). Because of these pK changes, as the body cools the pH will steadily rise while the PCO_2 steadily falls, provided that TCO_2 remains constant. Note

that pH, the negative log of the hydrogen ion concentration, marked on the left-hand ordinate scale, is largest at the top of the scale whereas log PCO₂ indicated on the right-hand ordinate scale, is smallest at the top of the scale. The two functions are inversely related on a logarithmic scale and can simultaneously follow the same line on the graph. Thus, if the \dot{V}_g/\dot{V}_b ratio* of the perfusion is properly adjusted to achieve this strategy, the *in vivo* values of venous pH and PCO₂ will fall on line AD. The actual pH at 27° is 7.52 and at 17° is 7.69, and corresponding values for PCO₂ are 27.3 and 16.5 respectively. The “uncorrected” 37° values are pH 7.36 and PCO₂ 46 at every point on the line.

Line AD represents specifically the acid-base status versus temperature when TCO₂ remains constant. It represents the strategy which Reeves called ‘alphastat (11).’ This is the biologically neutral condition which maintains a stable OH⁻/H⁺ ratio, a constant alpha-imidazole, and a constant protein charge state, thus preserving protein functions which depend on charge state (especially enzyme function). The dashed lines leading left to right which are shown parallel to line AD represent the pH and PCO₂ values which would occur in a blood sample in a syringe or in the chamber of a blood gas analyzer as it is being warmed from the temperature at which it was drawn to 37°C, the temperature at which the analyzer reads and reports the sample values. Thus the reader should understand that all the dashed lines running from left to right represent the changes which occur in pH and PCO₂ when a sample of blood is warmed to be analyzed. These changes, because they occur in a sealed environment, must parallel the biological neutrality line AD where TCO₂ remains absolutely constant. Thus, all the meter readings illustrated in the graph lie on the 37° vertical line, and are represented by solid circles.

Line AD has the characteristics of a biologic absolute. All points on the graph below this line at any temperature represent a state of acidosis. Any point above the line depicts an acid-base state of alkalosis. The further above or below AD the greater the variance from biological neutrality. This management strategy has the added value that internal temperature gradients do not effect the acid-base status of different organs or tissues. Since TCO₂ is held constant, every tissue in the body is in a state of neutrality no matter what its temperature may be. Moreover, the practice of “correcting” the meter values for temperature is shown to be ridiculous. It makes no difference what the pH and PCO₂ values are at various temperatures, the 37° meter reading will be 7.36 and 46 torr at every temperature. Any deviation above or below these values can be interpreted in exactly the same man-

ner as they would be were the patient normothermic. Moreover, the so called “correction for temperature” invariably introduces an error of considerable and variable magnitude. The thermodynamic lifestyle of turtles, frogs, snakes, and fish is based on passive acceptance of equilibration with environmental temperature. Usually changes in the thermal environment occur slowly. Body temperature control is almost entirely locomotor; the animal seeks more acceptable surroundings by moving to a new location. Internal body thermal gradients are minimal or absent. Thus we may excuse physiologists who study turtles when they use the term “body temperature.”

But to transfer this concept to the world of homeotherms introduces grave misconceptions. If perfusionists made their living perfusing turtles or bull frogs, the body temperature would indeed be meaningful and could be used to “correct” gas analysis readings. But man is a homeotherm. He does not have a “body temperature” which can be measured *in situ*. In homeotherms the peripheal tissues anatomically provide a temperature buffer zone for the inner tissues and contain adjustable heat exchange mechanisms to preserve the stability of the inner temperature.

Thus, even in a very stable environment, quite different temperatures exist throughout the “shell” as compared to the “core.” When the body temperatures are changing rapidly, as during the induction of hypothermia by either surface or perfusion cooling, large thermal gradients occur between different organs of the core. These differences are greater with rapid perfusion cooling than with surface cooling; nonetheless, they are always present. The blood flow to the various organs varies under these conditions, so that warm tissues with high metabolic rates may be relatively poorly perfused with cold blood. Hypoxic metabolism in these areas may contribute to a general acidosis.

This is why there has been a total lack of agreement among clinicians as to which site in the body, i.e. rectal, nasopharyngeal, esophageal, tympanic, or bladder, is the best for the measurement of “body temperature.” And this is why “correcting” a blood sample using a temperature obtained from some irrelevant site is frivolous. The practice should be abandoned.

Admitting that there is no single temperature taken in the body itself which represents “body temperature,” the best site for both temperature and gas analysis measurement is the venous blood at entrance to pump oxygenator. This site most closely represents the mean temperature of all the tissues of the patient, since it is essentially unchanged in transit. It is also the best sampling site from which to obtain the important PO₂ reading as it reflects tissue levels. Thus, in every way the best sampling site during perfusion is the venous port of the oxygenator.

*Physiologic notation relating the volume of gas flowing through the oxygenator with the volume of blood flow during a unit of time.

These facts emphasize the tremendous practicality of strategy AD. With this acid-base management, internal gradients make no difference since every tissue in the body, no matter what its temperature, will be at biological neutrality.

For these reasons, it seems useful to portray the entire locus of biological neutrality versus temperature by defining its arterial and venous limits. Figure 6 is such a chart, illustrating the area of normal blood gas samples which are compatible with neutrality.

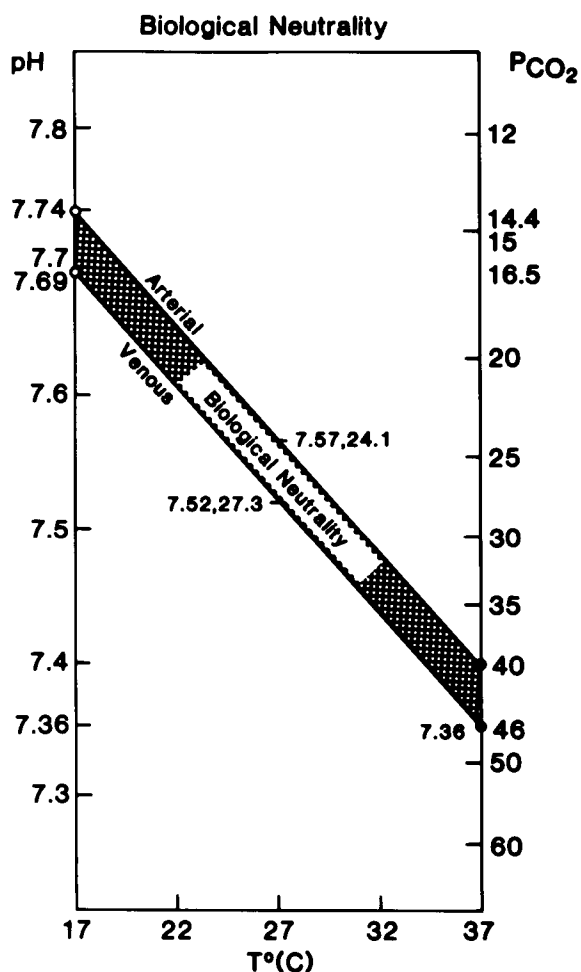


Figure 6. A graph of pH and PCO₂ values defining the arterial and venous borders of biological neutrality in the thermal range between 17° and 37° C when the individual's hematocrit is diluted to 20.

Strategy A-BC (Figure 6) depicts one of the most common currently sought acid-base management strategies. It is achieved by adding CO₂ to the respiratory gas mixture. To maintain a constant *in vivo* 37° venous pH of 7.36 and PCO₂ of 46 torr is to explore the depths of respiratory acidosis. There is no question that this is harmful, especially to the patient's heart (vide infra). At 17° the 'uncorrected' meter readings will be pH 7.04 and

PCO₂ 117. This is a degree of respiratory acidosis severe enough to threaten the successful outcome of the operation if it is prolonged.

Adding CO₂ to the respiratory gas mixture became a widespread habit in the earlier years of CPBP. The practice admitted that the induced respiratory acidosis was injurious to the heart, but was adopted in the wide spread belief that, since CO₂ dilates the cerebral vessels its presence in excess would protect the brain during the prolonged ischemia of circulatory arrest in infants and children. That it does so has not to date been proven in either adult or child.

In the adult, aortic cross-clamping excludes only the heart, the rest of the body is totally perfused, especially the brain. As mentioned earlier the cerebral circulation, although a potential victim of micro-emboli, is not threatened by perfusion hypoxia when perfusion as a whole is adequate. In the adult, therefore, the need for CO₂ "to protect the brain" is non-existent. This is not to say that the brain does not commonly suffer injury during prolonged bypass. Attention might better be applied to micro-filtration devices.

The evidence for the value of added CO₂ in pediatric perfusion-cooling has been completely reviewed by the author (3). He concluded this review with the opinion that the widespread practice of accepting the known myocardial toxicity of mild and severe acidosis in the belief that the brain would be better protected from ischemia has received no support from the results of experimental studies or from existing post-operative intelligence evaluations. In short, although CO₂ does dilate cerebral blood vessels, it has not been shown to help cerebral preservation during ischemia; the only thing that is currently proven about adding CO₂ is that the practice is deleterious to the heart. The addition of CO₂ to the perfusion gas mixture is always undesirable.

Returning to Figure 5, strategy AE illustrates an attempt at significant respiratory alkalosis achieved by hyperventilation. The open circle at E represents successful achievement of this strategy at 17°C. At this point the *in vivo* venous pH is 7.9 and PCO₂ 8.0 torr. The warming blood sample following the dashed line to the right will lead to a 37° meter reading of pH 7.6 and PCO₂ (22). This is genuine alkalosis and is highly desirable (see below).

In terms of the management strategies of acid-base during hypothermia outlined above, it is to be emphasized that these are based entirely on respiratory changes in TCO₂ in relationship to temperature. It would be well for the anesthesiologist to start with a pulmonary ventilatory program appropriate to the strategy which the perfusionist will later adopt when hypothermia is being induced. The rate of CO₂ elimination must be adjusted in the steady state to the rate of metabolic CO₂ production in a purposeful fashion to achieve each of the strategies. Then, if tissue oxygenation by perfusion is ade-

quate, metabolic acidosis due to hypoxia is unlikely to be superimposed.

Figures 5 and 6, it must be noted, represent only patients who have had their blood diluted with a non-protein priming solution. Since the buffer strength of the perfusion fluid has been reduced by a third of that contained in whole blood, it should not be concluded, just because this is common practice, that the technique is ideal. It surely should be possible to retain the full buffering strength of whole blood in spite of dilution if the diluting fluid were to contain significant non-bicarbonate buffer strength. If a priming fluid could be produced at reasonable economic cost which contained sufficient imidazole or similar buffer to achieve a resultant perfusion solution with a buffer strength of at least 28 (equivalent to whole blood) it would appear desirable to do so. Thus one could enjoy the undoubted advantages of dilution perfusion, but also maintain the full buffering capacity of whole blood to support good acid-base balance during the hypothermia. If such a priming fluid were to be developed, a new diagrammatic nomogram would need to be derived.

In selecting an acid-base management strategy most favorable to the patient one should be guided by the objective of preservation of the myocardium during the period of circulatory arrest. The evidence is overwhelming that deliberate hyperventilation alkalosis is best for this purpose.

In the early application of hypothermia to open heart surgery, extensive experience in the experimental laboratory with dogs led Swan et al. (12) to adapt and to recommend the use of vigorous hyperventilation throughout the course of clinical hypothermia. A rectal temperature of 28°–30° was sought. At this level of hypothermia pH 37° was 7.56 ± .9.

This recommendation was made because this degree of respiratory alkalosis apparently stabilized the rhythm of the cold heart. Ventricular fibrillation, the early *bête noire* of canine hypothermia, was almost entirely eliminated, and electric shock defibrillation, when needed, became effective and reliable. This respiratory strategy was widely adopted for surface cooling without perfusion in the middle and late 1950s (13). The Japanese used this technique (14,15) to explore surface-induced deep hypothermia with prolonged circulatory arrest. Respiratory alkalosis was later fully endorsed by Mohri and his group at Seattle in an extensive experience with surface-induced deep hypothermia for the correction of congenital cardiac defects in infants (16,17).

Strong experimental evidence has documented a favorable effect of both respiratory and metabolic alkalosis on cardiac contractility and more importantly on the recovery of contractility after a period of prolonged ischemia at normothermia. Ebert et al. (18) showed that during hypothermia in dogs to 12° C associated with 30

minutes of aortic occlusion, if the perfusate were made alkaline (pH 7.6) by the addition of NaHCO₃, post-occlusion myocardial contractility was markedly improved compared to controls or ones given dilute HCl. Follette et al. (19) clearly showed that the pH of the blood used to reperfuse after one hour of hypothermic aortic occlusion had a critical effect on the return of myocardial contractility toward control values as measured at 30 minutes. The optimal pH level for reperfusion was 7.8. This striking phenomenon is illustrated in Figure 7.

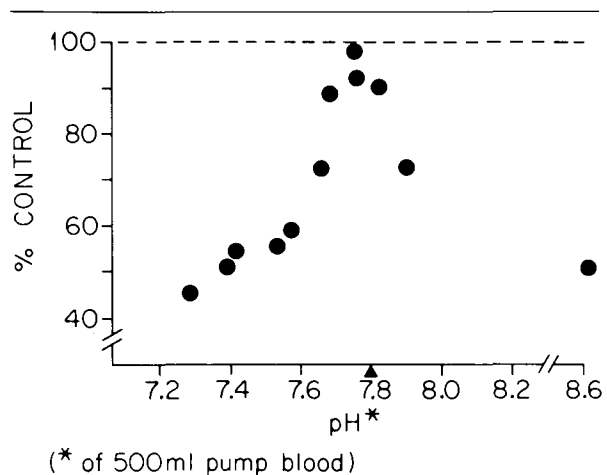


Figure 7. Left ventricular performance (intraventricular balloon *dp/dt* values) thirty minutes after one hour of ischemic arrest at 16°C compared with pre-arrest values when the pH of the initial reperfusate was modified from 7.3 to 8.6. The clear cut superiority of reperfusion at pH 7.8 is evident. Modified from Follette et al. (19), and reproduced with permission of CV Moseby Co, St. Louis.

McConnell et al. in 1975 (20) manipulated blood pH by hyperventilation and injecting NaHCO₃. Their dogs were cooled to 28° C with CPBP. When the pH (corrected for temperature) was elevated to 7.72 and compared to those maintained at 7.4, a definite increase in total left ventricular coronary blood flow, particularly in the sub-endocardial region was seen. This was accompanied by an increase in left ventricular performance.

In an important (but frequently confusing) report Becker et al. (21) presented convincing data that with surface cooling of puppies subendocardial blood flow and cardiac index fell less with marked respiratory alkalosis (pH 8.1) than with maintenance of 37° pH of 7.4, and moreover, lactacidemia was avoided, and excess base remained normal during post-arrest perfusion rewarming. Most striking of all, however, was the rapid return of left ventricular function toward normal with hyperventilation in contrast to the lingering suppression of left ventricular function where 37° pH was maintained at 7.4. In their hands, alkalosis was superior to alaphstat.

Thus, in summarizing the studies on alkalosis, the strength of myocardial contraction is enhanced at a pH

of 7.7 to 8.1 at temperatures below 30°. Moreover, the negative inotropic effects of the acidosis of ischemia are partially prevented by alkalization before circulatory occlusion, and significantly benefited by initial alkaline reperfusion at a pH of 7.8 at 30°C.

So there can be little doubt that although biological neutrality (alphastat) is the best strategy for the body as a whole, the clear cut benefit to the hypoxic heart of alkalosis makes this latter strategy the one of choice. The desirable acid-base status of the patient as temperature falls, as illustrated in Figure 8, is to induce a 37° pH of 7.6 by using a high gas flow immediately after cooling is begun. Thus the heart will approach the moment of aortic cross-clamping in optimal condition. During the occlusion period, the perfusion parameters may be modified to achieve biological neutrality. However, for several minutes before aortic unclamping is to occur, high gas flow should be resumed to assure that the reperfusion fluid will be highly alkaline. In this fashion the perfusionist can best deliver his contribution toward preservation of the myocardium. The other organs and tissues will tolerate this period of alkalosis extremely well.

As recently as two years ago, no accurate on-line blood-gas monitor was available which would allow one to make a timely evaluation of how the patient was doing. Practices, then current, made it essentially impossible for the perfusionist to have any opinion as to how well the perfusion was achieving the intended management. Arterial samples sent to a laboratory bearing inappro-

priate and irrelevant temperature tags, to obtain erroneously "corrected" values received 20 minutes later is a picture of futility. Now, at last the scene has changed. There are three different monitoring systems available* which will, in the long run, result in significant savings to the patient and to the institution, to say nothing of the sure improvement in the welfare of every patient undergoing perfusion. I think the three systems are competitive economically. The patient will definitely benefit because his course will be better monitored — more samples at less cost than at present. As of now, to conduct safe, rational cardiopulmonary bypass, use of one or the other of these blood-gas monitors to track *venous* blood samples throughout the operation should be standard operating procedure in all hospitals.

Alkaline perfusion, then, is one crucial step to protect the heart; the other is the frequent coronary infusion during the period of aortic cross-clamping of an effective cardio-preservation solution. This is the surgeon's tool for myocardial protection. Over the years there has been extensive debate over the merits of one group's cardioplegic solution as compared to that of another. But this begs the issue. The term cardioplegia itself should be abandoned; it doesn't cover what we are talking about. Myocardial paralysis is only part of our objective. We should be talking and thinking in terms of *cardiopreservation*.

Since hypoxic acidosis is what kills the heart, any infusion which does not employ every available proven means to forestall or combat this danger is inadequate and unacceptable. These weapons are: cold suppression of metabolism and paralysis, oxygenation, alkalization, buffering, and biochemical control. Table 1 presents a suggested cardiopreservation solution embodying these principles. It is recommended that at least 500 ml of this solution be perfused through the coronary system no less frequently than every 20 minutes, and

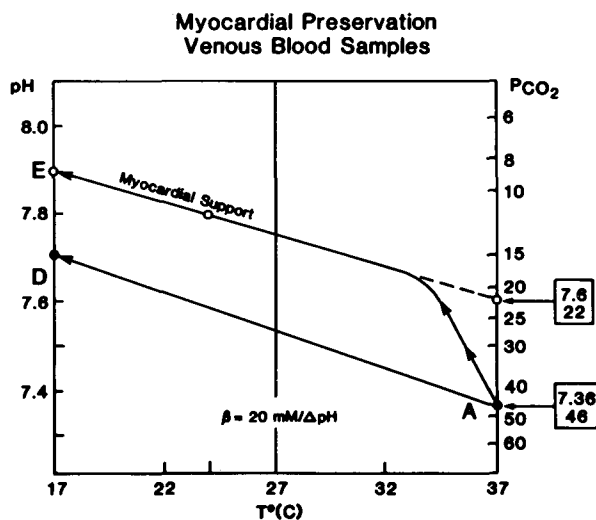


Figure 8. A graph of the recommended acid-base strategy for all patients who will undergo myocardial hypoxia during H-CPB. A level of alkalosis, wherein a venous blood 37° pH of 7.6 is rapidly sought with high gas-flow perfusion, which is then adjusted to maintain this level until several minutes after myocardial circulatory occlusion is released, is the optimal management for myocardial preservation.

Table 1

Composition of a recommended (1988) coronary perfusion cardiopreservation solution (500 ml every 20 minutes)

1. Temperature 4°C
2. Balanced salt solution plus blood, Hct = 20%
3. Oxygenated
4. Alkaline 37° pH = 7.6
5. Plegic ions: K + 12, Mg + + 6, Ca + + 2
6. Free radical antagonists
 - a. Mannitol 5%/volume
 - b. Allopurinol 1mM/ml

*1) Cardiovascular Devices Incorporated CDI-300 2) Diamond Sensor Company Gem-6 3) Biomedical Systems Cardiomet-4000

that a final perfusion should be made just before the aortic clamp is removed.

Thus, the solution should be cooled to 4° C, and oxygenated in some sort of oxygenating device (22). Some teams modify the pump-oxygenator system for this purpose. Even die-hard "crystalloid only" protagonists, such as the St. Thomas Hospital group, have recently admitted that oxygenation improves its cardioplegic solution (23). The solution should contain autologous blood to an hematocrit level of 20%. Hemoglobin serves here both as an aid to oxygen transport and, even more importantly at these temperatures, as a powerful buffer, helping to combat acidosis as cross-clamping continues. Crystalloid solutions give no help to this important aspect of cardiopreservation. A recent study using micro-myocardial pH probes (24) strongly documents this opinion, and a careful clinical trial of blood versus crystalloid cardioplegias seems to confirm it (25).

As the solution is being prepared before cooling and oxygenation, it can be alkalized using a strong base. Sodium and/or potassium hydroxide, or perhaps THAM (pH = 10.1), could be added until the 37° pH is 7.6. In fact, THAM might enhance slightly the buffer strength.

At the present time I think it must be accepted that the explosive release of superoxide radicals upon reoxygenation with return of perfusion is the major cause of disruptive structural damage to the myocardium. The period of hypoxia has created two symbiotic forces which cause this event. According to McCord (26), a progressive failure of ATP generation during hypoxia arrests the conversion of hypoxanthine to uric acid and the level of AMP and hypoxanthine builds up excessively. In addition the enzyme xanthine dehydrogenase is steadily converted to xanthine oxidase when oxygen is reintroduced. The oxidase converts the hypoxanthine to superoxides, which through conversion to peroxide secondarily yields the powerfully active hydroxyl free radical (27).

The alkaline pH of the cardiopreservation solution is

the first weapon to combat this reaction. The surgeon will be sure to make an infusion just before unclamping the aorta. We have seen in the work of Follette (19) just how effective this modality alone can be.

Moreover in the recent past many experimental studies (28–38) have shown that a direct enzymatic attack on the free radicals using superoxide dismutase (SOD) and catalase (CAT) is very effective in blunting the damaging onslaught of these marauders. All these studies were in complete agreement on this point. But at the present time, the use of SOD and CAT has not yet been approved by the Federal Drug Administration. However, allopurinol, a superoxide antagonist, and mannitol, which is thought to be a hydroxyl free-radical scavenger, are approved for human use. Allopurinol is being given preoperatively in a few centers already (39–41). But surely, until SOD and CAT and/or dimethylthiourea can be used, our solution should contain the free radical scavengers currently available, namely, allopurinol and mannitol.

Finally, although regional cooling of the heart together with ice cold coronary perfusion will almost surely arrest the heart, very rapid paralysis can be assured by the use of the plebic ions K^+ and Mg^{++} . Some Ca^{++} should always be included when these ions are given. After the initial cold arrest, however, those ions are no longer pertinent to cardiopreservation and should be added only to the first infusion and omitted thereafter.

In final summary, the proven effectiveness of an alkaline perfusion by the perfusionist especially and specifically at two specific periods during open heart procedure—namely, the few minutes before aortic cross-clamping or circulatory arrest, and again for a few minutes at the time of coronary reperfusion—if supplemented with multi-modality coronary perfusions by the surgeon during cardiac hypoxia, lead us to the hope and expectation that the mortality and morbidity of open heart and coronary bypass surgery would be markedly reduced if this team strategy were to be widely adopted.

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