
Metabolic Rate, Temperature, and Acid-Base Control: The Best Strategy and Our Needs to Achieve It

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Abstract

Important recent knowledge concerning acid-base status during hypothermia is briefly summarized. A basic diagram of pH-CO₂ relationships during cooling with diluted blood is presented to illustrate the three possible acid-base management strategies during hypothermic perfusion. On the basis of an extensive review of pertinent literature on the effect of excess CO₂ and acidosis on the hypothermic brain and heart during hypothermic cardiopulmonary bypass (H-CPB), it is recommended that no CO₂ be added to any ventilatory gas and that respiratory alkalosis is the optimal acid-base strategy during perfusion cooling with circulatory arrest. The great need for on-line blood gas monitoring instrumentation, so that perfusionists may actually identify and control the acid-base status of the patient during hypothermia, is emphasized.

Discussion

The effects of cold tissue temperatures on acid-base balance have long been poorly understood by physiologists and clinicians alike. In the last decade, giant strides in the basic understanding of the effect of temperature on biologic acid-base equilibria have been made. Recently, I have reviewed and evaluated this newer knowledge and its implications in *Surgery, Gynecology, and Obstetrics*.^{1,2} Evidence is now available that common current management of patients during perfusion either ignores or improperly manages the acid-base relationships of hypothermic patients, because of several erroneous assumptions regarding the measurement of temperature, and the effect of blood gases on the blood pH

at various temperatures. Thus, for years, deliberate respiratory acidosis induced by adding CO₂ to the respiratory gas mixture has been the accepted custom for the conduct of hypothermic cardiopulmonary bypass (H-CPB) in spite of recent evidence that such a patient management strategy is harmful to the heart of the patient. There is strong evidence that an acid-base management strategy that uses no added CO₂ and emphasizes the achievement of hyperventilation alkalosis is more appropriate during perfusion hypothermia.

Moreover, perfusionists do not currently have proper tools for acid-base control. Prompt adequate blood gas information is lacking. For example, blood samples must be sent from the operating room to a laboratory, often at a remote location, which can introduce considerably delay in receiving the information in the operating room. Occasionally, errors are made in the reports delivered to the operating room. Current instrumentation for gas analysis makes the measurement on blood samples which have been warmed to 37° C. This measurement is commonly "corrected" mathematically to the so-called "body temperature" of the patient, and is reported as a "corrected" measurement. Although the analyzers can be quite precise, a blood sample submitted with a temperature reading taken from some remote site which is called "body temperature" will not produce realistic "corrected" blood gas values.

We often speak of "the body temperature." What does this term mean? Probably in poikilotherms the term has meaning, since physiologic mechanisms to increase, preserve, or lose body heat are poorly developed. Superficial fat layers that provide a thermal buffer zone are absent. The thermodynamic lifestyle of turtles, frogs, snakes, and fish is based on passive acceptance of equilibration with environment 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

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minimal or absent. Thus we may excuse physiologists who study turtles when they use the term "body temperature."

But when they try to transfer this concept to the world of homeotherms, they introduce grave misconceptions. If perfusionists made their living perfusing turtles, 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 peripheral 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 differences 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. Minimizing internal thermal gradients is an important reason for combining surface cooling (and rewarming) with perfusion as a better modality for controlling hypothermia.

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." In addition, blood samples are sometimes drawn from various sites in the patient-pump-oxygenator system during perfusion. If pump-oxygenator arterial samples are taken, the blood gases read are those already altered by the machine and therefore do not provide an indication of the condition of the patient's blood as it exits the body before oxygenation. Such arterial samples test the oxygenator rather than the patient.

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 pO_2 reading as it reflects tissue levels. This is without question

the best sampling site, because during the procedure it is truly a mixed venous sample. The usual objections of physiologists to venous sampling are not pertinent here. I will repeat that statement. Perfusion blood from the venous line is truly a mixed venous sample representing the whole body, both its mean temperature and its mean tissue partial pressures of CO_2 and O_2 .

Typically, in practice, the cost of each blood-gas analysis is individually charged to the patient. Sometimes, in an effort to reduce the overall cost of the procedure, a less than adequate number of samples is analyzed. Each surgical team will select a limited number of specific times to take samples. These samples are not necessarily selected for the benefit of the perfusionists, and may be taken at such a time that, when the results eventually are known to the perfusionist, they are no longer pertinent to the present circumstances. Corrective action always lags well behind biological information.

For the foregoing reasons, it is not currently practical for there to be realistic control of acid-base status during H-CPB surgery. When samples are taken from inappropriate sites, without pertinent temperature values, significant patient management errors result. The practice of correcting analyzer readings for temperature superimposes an inaccurate and unreliable dimension on an otherwise fairly reliable measurement. Delays in obtaining results presently render these results inadequate as a guide to effective perfusion management. Fortunately, the relative brevity of most procedures allows the physiology of most patients during perfusion to compensate for, and tolerate, the variety of conditions present in the poorly documented acid-base status which is occurring. However, mortality and morbidity both increase significantly during longer procedures. It is in this 25 to 30 percent of patients where pump times exceed 90 minutes, and where mortality rates are climbing rapidly, that better control of acid-base status will make a significant improvement in the surgical results.

What we need are measurements of the temperature and the blood gases of the venous blood just before it enters the oxygenator, taken at least as frequently as every two to three minutes, with immediate digital readout. I will discuss this further a little later in the paper. Meanwhile, let us look at a diagram which will explain to us our options for the management of acid-base status (as if we could actually achieve what we elect to do).

In an attempt to clarify these possible options in the clinical management of hypothermia, Kindig, Filley, and Swan³ have shown by graphic analysis the effect of various strategies on pH and pCO_2 between 17° and

37° when total carbon dioxide content of the body TCO₂ is the variable. TCO₂ can be held constant, increased by adding CO₂ to the system, or decreased by hyperventilation. In essence, four acid-base strategies emerge; namely, respiratory neutrality, two levels of acidosis, and alkalosis. Figure 1 illustrates these strategies.

This diagram charts the available strategies for patient maintenance during perfusion. According to this binary model containing only the buffers bicarbonate and imidazole, line AD (along which total CO₂ remains constant) represents biologic neutrality as temperature falls from 37° to 17°. Remember that pH and pCO₂ change as temperature falls, even when TCO₂ is con-

stant. Any point on line AD will give you the neutral values for pH and pCO₂ at that temperature.

Since $\Delta\text{pH}/\Delta\text{T}$ depends almost entirely on the change with temperature of the dissociation constant of imidazole pK_{IM}—and not on bicarbonate levels or buffer strength—this curve is invariant with buffer strength. In a sense, it represents a biologic constant, applicable to graphs of respiratory changes in relation to temperature when varying concentrations of imidazole are in solution with bicarbonate. Any point on the chart below the neutral line AD represents acidosis; the further below AD, the more severe the acidosis. Similarly, progressive alkalosis is demonstrated above AD.

The binary buffer model described here has a non-

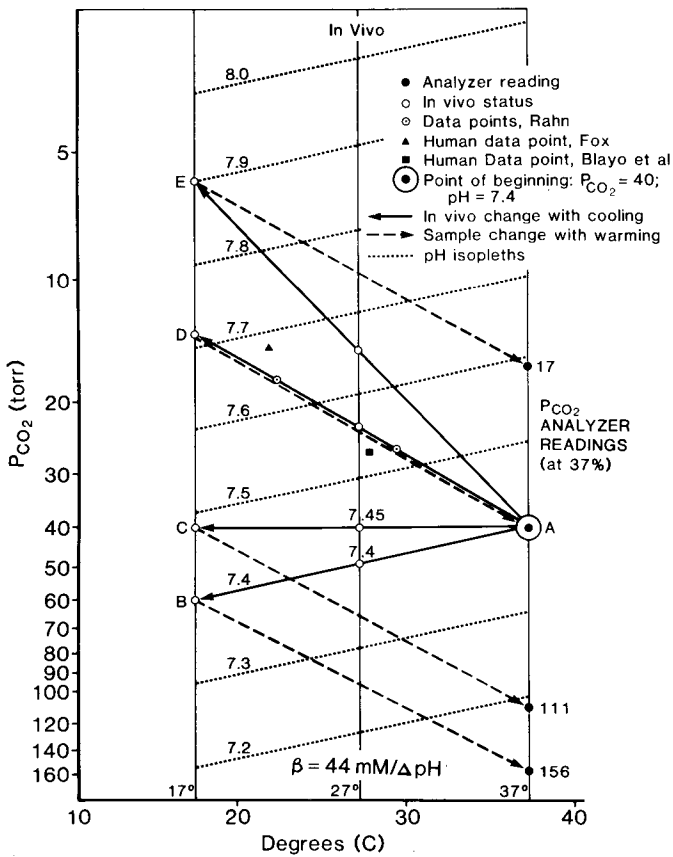


Figure 1

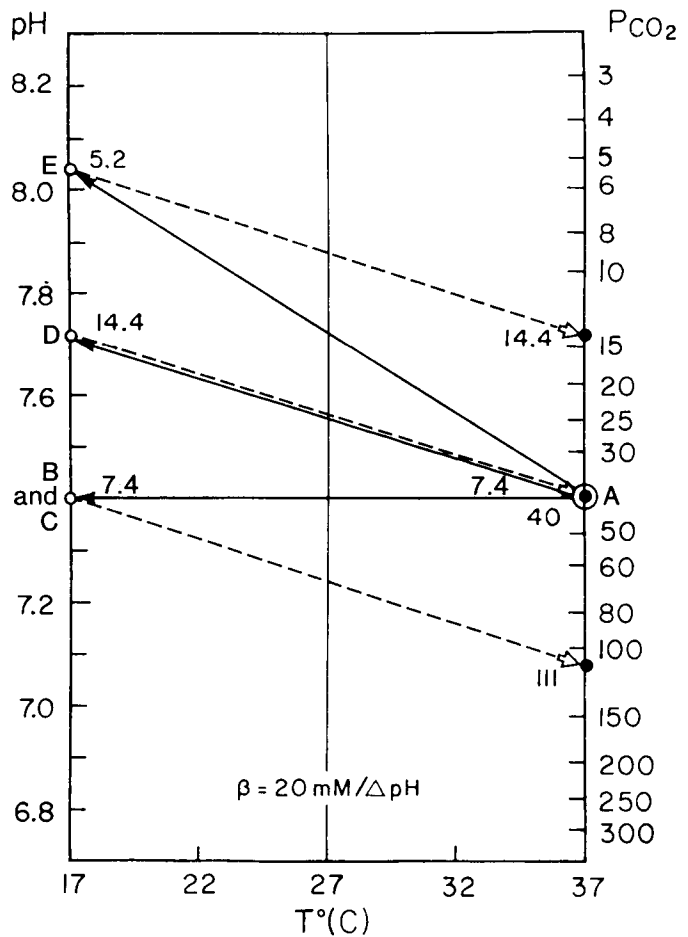


Figure 2

Figure 1: Diagram of pH, log pCO₂, and temperature relationships in a binary buffer system containing NaHCO₃ and imidazole (modified from Reeves⁴). Imidazole concentration is 30mM/L and the non-bicarbonate buffer strength is 44 slykes. The pH isopleths are shown as dotted lines; $\Delta\text{pH}/^\circ\text{C}$ is .0147. Reproduced by permission of Surgery, Gynecology, and Obstetrics, Chicago, Illinois.

Figure 2: Diagram of pH, pCO₂, and temperature relationships when the patient's blood has been diluted to an hematocrit of 20 percent (based on calculations made by Kindig and Filley)¹⁸. Buffer strength is now 20 slykes; $\Delta\text{pH}/^\circ\text{C}$ with this dilution is .016. Since the pH isopleths are horizontal, they are not dotted. The variable is change in TCO₂ due to ventilation. This chart approximates common current experience in the operating room. Reproduced by permission of Surgery, Gynecology, and Obstetrics, Chicago, IL.

bicarbonate buffer strength of 44 slykes* and compares more or less exactly to the measured responses in pH and pCO₂ of frog blood and plasma subjected to cooling when the model's imidazole concentration was in the range of 20-30mM/L. Human blood of normal plasma protein and hematocrit is thought to contain approximately 30mM/L of imidazole. In other words, undiluted human blood apparently behaves as if it had a buffer strength of about 44 slykes.

Reeves⁴ has pointed out, however, that any manipulation that alters plasma protein concentration has a direct effect on the measured pH-temperature co-efficient. When human blood for H-CPB is diluted with a non-protein-containing salt solution, the non-bicarbonate buffer strength is significantly decreased. Red blood cell (Rbc) dilution by 50 percent using saline, associated with similar plasma dilution, results in a decrease in buffer strength. Thus, when the hematocrit (Hct) is 20, a buffer strength of about 20 slykes (rather than 44) can be expected at this Rbc concentration.

The slope of the pH isopleths (which illustrate the effect of temperature on pH) varies with the buffer strength of the solution. The greater the buffer strength, the steeper the slope. Thus, as blood of 44 slykes is diluted, the pH isopleths become flatter, until at 20 slykes they are essentially horizontal between 17° and 37°C. In a temperature-log concentration diagram of typical perfusion blood with an hematocrit of 20, a change in the log of pCO₂ will effect a similar change in the log of the hydrogen ion (pH = negative log of [H⁺]). These relationships are diagrammed in Figure 2, which shows the relationship of pH, pCO₂ and temperature when total CO₂ is varied or kept constant during perfusion hypothermia.

This chart could well be used as a nomogram for acid-base control of a patient undergoing modern heart surgery.

Let us see what these charts tell us about the possible management strategies based on plans for controlling either pH or pCO₂ as the patient cools. The pH isopleths in Figure 2 are not shown since they are horizontal. The solid arrows leading left, representing these strategies, show what is occurring to pH and pCO₂ in the open system with changing total carbon dioxide in a ventilated patient. The dashed lines represent the changes in pCO₂ and pH in the closed system of a blood sample in a syringe where TCO₂ stays constant as it is warmed in the

analyzer to 37°. Thus the samples parallel the constant TCO₂ strategy, AD, as they are warmed. All patients are considered to enter this system at point A, representing normal 37° pH 7.4 and pCO₂ 40 torr. Let us specifically consider Figure 2.

Strategy AB illustrates an attempt to maintain the *in vivo* pH at 7.4 by hypoventilation and by the addition of CO₂ to the respiratory or oxygenator gas mixture. If successful, the strategy exactly follows the pH 7.4 isopleth. As the patient cools, the *in vivo* pH is always 7.4. At 17°C the pCO₂ is 40 *in vivo*. When the blood gas sample is warmed in the analyzer, the 37° readings are pH 7.08; pCO₂ 110. Total CO₂ is increased. This strategy mimics the pH-stat regulating mechanisms of homeotherms and hibernators.** It represents a state of progressively severe acidosis as temperatures falls. I repeat, if you maintain a "corrected" pH of 7.4, you impose severe acidosis on the patient.

Strategy AC proposes to keep the *in vivo* pCO₂ constant also by adding CO₂ to the ventilating gas mixture. If achieved, one observes the horizontal arrow at the level of pCO₂ equals 40, it indicates that the *in vivo* pCO₂ remains unchanged as the patient cools (right to left). At 17° the corresponding pH is 7.4. This procedure produces a progressive acidosis as temperature falls which is identical to that seen with line AB. In fact, these two slightly different strategies seen when the blood is undiluted (Figure 1) merge into a single strategy. This maintenance of the "corrected" pH of 7.4 or pCO₂ of 40 is called the strategy of acidosis. It requires added CO₂. It is hoped that you will agree that it should never be used.

Strategy AD attempts to maintain TCO₂ constant by maintaining constant the volume of ventilation using a gas mixture without added CO₂. At 17° pH is 7.72 and pCO₂ is 14.4. Since CO₂ remains constant, the blood in the sample as it warms will go back on the same line over which it came; the meter always reads 7.4 and 40 torr. This strategy is called alpha-stat.*** It will maintain an intra-cellular OH⁻/H⁺ ratio of 1, and a stable alpha-imidazole and protein charge state. It is biological intracellular neutrality. Moreover, I wish to emphasize that the strategy is independent of body temperature or of internal temperature gradients, and thus has the great

**Homeotherms and hibernators attempt to keep blood pH at 7.4 when body temperature changes. This is referred to as pH-stat.

*** Poikilotherms attempt to keep total CO₂ constant when body temperature changes. This is referred to as alpha-stat⁴.

* Buffer strength is expressed in slykes, the amount of acid or base in millimoles needed to effect a change of one unit of pH.

advantage of avoiding the errors caused by inaccurate or inappropriate temperature measurements to correct meter readings. Keeping the *uncorrected* meter values at 7.4 and 40 torr will result in biological neutrality at any temperature. It is the poikilotherm strategy seen in turtles.

Strategy AE, a deliberate severe respiratory alkalosis is achieved by vigorous hyperventilation. Indeed, the alveolar gas flow must increase almost four-fold to achieve a pH of 8.3 and a $p\text{CO}_2$ of 5.2 at 17°. The blood gas sample at 37° reads pH 7.72 and $p\text{CO}_2$ 14.4. Early clinical and more recent experimental and clinical evidence strongly suggest that alkalosis is beneficial in preventing myocardial deterioration and in aiding return of cardiac function after a period of myocardial ischemia. Any endpoint on the 17° line between E and D might be chosen to achieve a lesser degree of alkalosis. Any such endpoint would be satisfactory for all the tissues of the body within the temporal limits of current H-CPB.

Any perfusionist, if he had on-line, real-time monitoring capabilities, could by careful respiratory management send the patient's acid-base balance on a journey more-or-less along one of these solid lines during perfusion hypothermia. The questions I wish to address with you here are: Which one is the best, and why?

Figure 2, it must be noted, represents only patients who have had their blood diluted about 50 percent with non-protein containing saline prime. Common priming solutions combine a commercial extracellular salt solution buffered to pH 7.4 (2 liters), 25mM NaHCO_3 , with or without some mannitol or dextrose (200ml). Other clinics add concentrated human albumin, plasma, or some other protein substance, a practice quite different than dilution with saline alone and one which would decrease the effects of dilution on buffering capacity. Since the buffer strength of the illustrated perfusion fluid with an Hct of 20 is reduced when compared to whole blood, it should not be concluded that this system is ideal. Economic considerations are currently overriding the theoretical optimum. A dilutant solution containing non-bicarbonate protein buffer with a strength above 28, even perhaps to 38 or 40 slykes, (if it could be produced at practical economic cost) would appear to be much more desirable, as it would decrease the pH changes resulting from a given load of acid or base.

The determination of the proper rate of ventilation by the anesthetist, if the patient were being surface cooled, to achieve alpha-stat (AD) would be highly pragmatic. The important variables are the probable decreased capability of the lung to extrude CO_2 and the variability of the change in the production of CO_2 as temperature

falls. This latter change is subject to so many variables that a precise graph of $\dot{V}(\text{CO}_2)$ expressed as a percent of normal vis-a-vis temperature cannot be drawn with present data. Indeed, it seems unlikely that such a relationship actually exists, except in a general sense. The different components of resting metabolic rate change differently with cooling under various endocrine states. Different organs have different Q^{10} s and are at different temperatures during cooling. Oxygen consumption will change with pump flow rates, hypothermic temperatures, and with oxyhemoglobin dissociation curves under the influence of pH and CO_2 . For more detailed analysis of this problem, see the discussion by Swan⁵.

However, as soon as perfusion starts and the perfusionist is in charge, a mechanical lung not subject to the effects of cold, as is the living lung, is in use. One can rely on his or her experience with gas-blood flow rates constrained by the parameters of age and weight of patient, volume of return flow to the pump oxygenator (P-O), the specific gas exchange characteristics of the oxygenator (screen, disc, bubble, or membrane), the venous $p\text{O}_2$, etc. Monitoring is then the key. As soon as you have continuous on-line monitoring capability, you will be able to achieve precise control.

However, under current circumstances, it is important for the perfusionist to know the acid-base state at the onset of perfusion. Therefore, a blood sample 15 minutes before H-CPB begins is a crucial sign post, since the results will be posted almost exactly the moment perfusion begins.

In evaluating the question of which management strategy is preferable, it is important to identify precisely which organs or systems are specifically in jeopardy as hypothermia deepens, pump times become more and more prolonged, and the period of aortic cross clamping or total circulatory arrest stretches to unexpected lengths. The neuromuscular system is surprisingly tolerant. The kidneys and liver also appear to tolerate current perfusion methodology remarkably well, as do the endocrine and gastrointestinal systems. The blood, the vascular systems, and the lungs each have specific toxic reactions. That hemorrhagic and thrombotic phenomena are not uncommon is recognized by current techniques, which include clotting mechanism depressants, reactivators, and specific replacement components. Pulmonary congestion, atelectasis, and inflammatory complications have become progressively infrequent as perfusion apparatus has improved. Under present circumstances, therefore, it can be agreed that the two organs at most risk are the heart and the brain.

Since the addition of CO₂ to the respiratory and perfusion gas mixture has been customarily adopted during the past 15 to 20 years, the problem will be approached by analysis of the effect of higher-than-normal CO₂ on the heart and on the brain. Since this analysis is exhaustively described in an article by Swan², I will only summarize the evidence and conclusions here.

In regard to the heart, extensive experimental and clinical experience has documented almost beyond doubt that both respiratory and metabolic alkalosis enhances the myocardial function of a hypothermic heart, and stabilizes its rhythm. McConnell et al⁶ showed experimentally that 28° subendocardial blood flow was definitely increased at pH 7.7 as compared with 7.4 ("corrected" value).

That systematic acidosis reduces myocardial contractility has been known for over a hundred years. Respiratory or high-CO₂ acidosis have the most rapid and profound effect. Apparently, extracellular acidosis leads to intra-myocardial acidosis, and reduces contractility by the inhibition of the slow transmembrane current of calcium.

The progressive lesion of prolonged myocardial ischemia is specifically characterized by acidosis. It is not prevented even by deep hypothermia. In an experiment

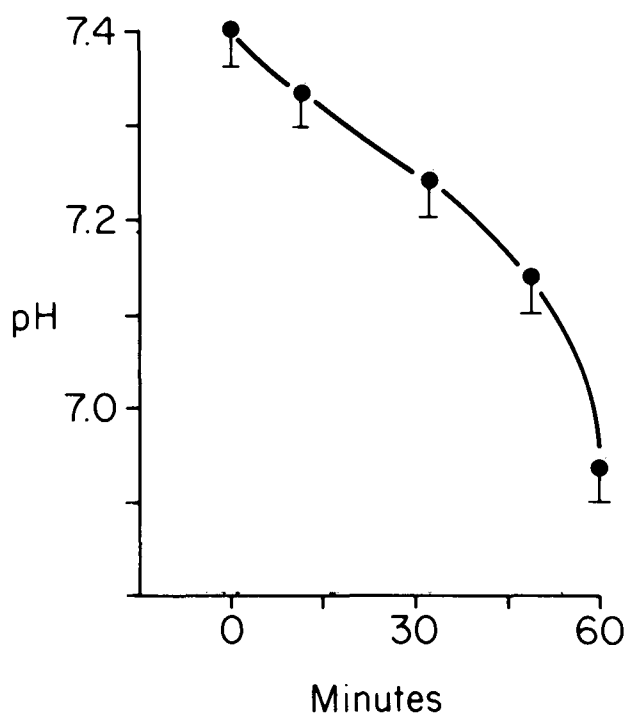


Figure 3: Coronary sinus blood pH during one hour of myocardial ischemia at 16°. Reproduced as modified with permission of C. V. Mosby, St. Louis, Mo.

by Follette et al⁷ the coronary sinus blood pH from a non-beating canine heart at 16° during aortic cross-clamping falls to 6.8 after 60 minutes. The non-coronary collateral flow amounted to 4ml/100 gm/min. A graph of this data is shown in Figure 3. If extracellular acidosis at a level of 6.8 or below persists, intracellular acidosis soon equilibrates at the same level. If myocardial ischemia persists long enough, intracellular acidosis of a similar degree will ensue.

Thus, as mild intracellular acidosis progresses towards severe acidosis the molecular steps leading toward irreversibility are these: aerobic glycolysis fails; anaerobic glycolysis causes increased levels of lactic acid, which in turn accentuates the acidosis. Energy deficiency from progressive adenosine triphosphate exhaustion contributes to loss of contractility directly and also by resultant failure of membrane water and electrolyte pumps. There is increased sarcolemma permeability and loss of capacity for volume regulation. At some point in these reactions, irreversibility dooms the heart. At normothermia, irreversibility occurs between 25 and 40 minutes of ischemia. This period is stretched to about two hours with deep hypothermia. Even when irreversibility occurs, the myocardium will still look essentially normal under the microscope, but if reperfusion with normal blood is instituted there is an explosive change in the micropathology. Edema forms in the matrix. Ca⁺⁺ floods the mitochondria and precipitates as phosphate conglomerates. Lysosomes are activated and frank cellular necrosis begins.

One should note that the damage to the cell infrastructures occurs during the ischemia. The term "reperfusion injury" has unfortunately crept into the literature. In fact, the reperfusion does not cause the injury; rather it, provides the water, ions, and other ingredients which the injured acidotic cell cannot handle, and allows the damage to become visible.

However, the myocardial lesion of the acidosis of ischemia can be partially prevented by alkaline perfusion before the onset of circulatory arrest or aortic cross-clamping. Austen⁸ and later Ebert et al⁹ showed that pre-occlusion administration of bicarbonate or THAM provided significant protection.

Moreover, even after prolonged periods of ischemia, the return of myocardial function can be greatly enhanced by the use of strongly alkalotic solution at the onset of reperfusion.

Figure 4, reproduced from Follette et al⁵, compares left ventricular performance (intraventricular balloon dp/dt values) 30 minutes after one hour of ischemic arrest at 16° compared to pre-arrest values when the ini-

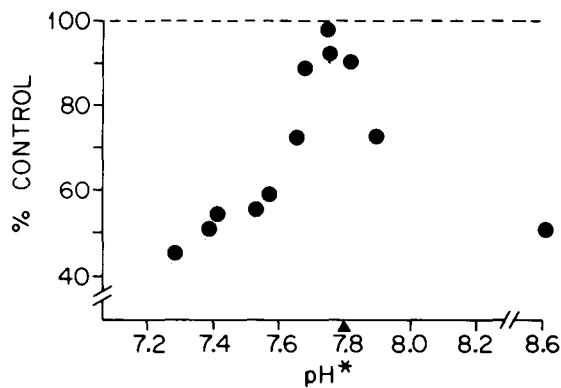


Figure 4: Left ventricular performance (intro-ventricular balloon dp/dt values) 30 minutes after one hour of ischemic arrest at 16°C compared to pre-arrest values when initial reperfusion at 30°C was modified from pH 7.3 to pH 8.6. The clearcut superiority of reperfusion at pH 7.8 is evident. Reproduced as modified with permission of C. V. Mosby, St. Louis, MO.

tial perfusate at 30° was modified from pH 7.3 to pH 8.6. The clearcut superiority of reperfusion at 7.8 is evident. Exactly comparable return of left ventricular function was seen by Becker et al¹⁰ in deeply hypothermic puppies when reperfused by alkaline solutions and hyperventilated after one hour of circulatory arrest.

Thus, in summary concerning CO₂ and the cold heart, high-CO₂ respiratory acidosis significantly depresses myocardial function, whereas both metabolic and respiratory alkalosis enhance it. Moreover, the negative inotropic effects of the acidosis of ischemia are partially prevented by alkalization before circulatory occlusion, and significantly improved by initial alkaline reperfusion at a pH of 7.8 at 30°C.

As regards CO₂ and the brain, there is no doubt that CO₂ dilates cerebral blood vessels at normothermia. The question is, does it do so in the hypothermic brain and if so, does it significantly protect the cold brain during prolonged circulatory arrest?

Experimentally, Perna et al¹¹ showed in 1973 that cerebral oxygen tension was depleted in about 20 minutes of ischemia and thereafter anaerobic metabolism caused increasing acidosis. Their cold dogs were all hyperventilated. Blood flow decreased 47 percent at 20°C. However, all the animals tolerated 45 minutes of circulatory arrest without neurological sequelae. In short, in these animals at 20°, blood flow did decrease during alkalosis—but flow was still appropriate to metabolism, and tolerance to ischemia was apparently not diminished. Other studies in rats gave similar results^{12,13}.

Moreover, pump flow rate has a significant effect on cerebral circulation. Fox et al^{14,15} showed that circula-

tion to the brain was selectively protected as flow rates were decreased experimentally until other areas of the body were underperfused. They used ventilatory rates adequate to maintain neutrality as body temperature fell. Thus, during H-CPB at 20° conducted using the alpha-stat strategy A-D, any flow rate adequate for whole body perfusion is adequate for the brain. They conclude that attempts to increase cerebral blood flow are unnecessary.

In addition, Becker et al¹⁰ found that in puppies cooled to 17° with both surface and perfusion cooling the cerebral blood flow did not decrease as much during cooling with hyperventilation as it did when CO₂ was added. He suggested that the overall depression of cardiovascular dynamics caused by CO₂ acidosis more than offsets any merits CO₂ vascular dilation may have. If the pump fails, big pipes do not maintain flow.

It would be very useful to have a large, carefully performed clinical study with late follow-up observations on cerebral function and intelligence quotients both with and without the added CO₂. Unfortunately, no such study—large, careful or otherwise—can be found in the literature. Many small follow-up series have been reported, but shed no significant light on the CO₂ question. They do, however, suggest that a significant number of infants who have undergone deep hypothermic circulatory arrest show immediate post-operative signs of brain damage and prolonged evidence of deterioration of intelligence quotients.

The two most recent studies also equate the degree of cerebral damage with the duration of the ischemia. Both Clarkson¹⁶ and Lincoln¹⁷ have come to the conclusion that one hour of circulatory arrest at 20°C, long considered quite safe, does indeed inflict a penalty in loss of residual brain function; and that 45 minutes should be considered the limit. If the surgeon realizes that he will not be finished by that time, alkaline perfusion can be resumed for 10 minutes by returning intro-thoracic blood loss to the P-O system, and then circulatory arrest could be resumed safely for another half hour. Such a maneuver would definitely benefit the myocardium as well as protect the cerebrum, and the perfusionist should insist on it.

Thus, the widespread practice of accepting the known myocardial toxicity of mild to severe acidosis in the belief that the brain would be better protected from ischemia has received no support from experimental studies, nor from post-operative intelligence evaluations.

In short, although CO₂ does dilate cerebral blood vessels, it has not been shown to help cerebral preservation during hypothermic ischemia. The only thing that is

currently proven about adding CO₂ to the respirator gas mixture is that the practice is deleterious to the heart.

What, therefore, seems to be the current optimal management of the acid-base aspects of hypothermic total body perfusion for operations on the heart?

In regard to infants during profound hypothermia with total circulatory arrest, based on the considerations developed above; namely, that CO₂ acidosis does not in fact "protect the brain" and that respiratory alkalosis does in fact preserve myocardial function during circulatory arrest, it is strongly recommended that the anesthesiologist and perfusionist should coordinate their efforts to achieve significant respiratory alkalosis. Strategy AE or a close approximation would appear to be optimal, achieved by respiratory hyperventilation followed by perfusion using a high gas-blood flow ratio. The oxygen/compressed air ratio should keep uncorrected arterial pO₂ at a level between 250 and 350 torr, and venous pO₂ above 50 torr. At the time of reperfusion the perfusate should be as alkaline as possible.

For the adult, the strategy, which otherwise would be alpha-stat (AD), must also be AE because of the overriding need for preservation of the ischemic heart. Uncorrected venous pHs of 7.7 and 7.8 and pCO₂s of 15 to 20 torr should be sought as the patient cools below 27°. The period in the operation when a highly alkaline perfusion is especially needed is at the moment of unclamping the aorta thereby reperfusing the coronaries. The surgeon should have just finished delivering a cardiopreservative coronary infusion with a buffered solution at pH 7.8. The pump perfusion should continue to combat myocardial acidosis as the patient warms. The perfusionist might anticipate this need by accelerating his gas flow or even adding THAM. At no time should CO₂ be added to any gas mixture.

If deep hypothermia and CPB are performed for other purposes, for example, operation on the brain or liver, strategy AD would appear to be optimal, since it represents neutrality.

These strategies can both be managed with great ease *without* using any temperature corrections for the analyzer. Since AD represents neutrality at any temperature, internal temperature gradients are not important. Because the remarkable buffering mechanisms result in the fact that $\Delta\text{pH}/^\circ\text{C} = .0147$ to $.017$ and because the solubility and ΔpH effects on the Henderson-Hasselbach formulation result in a ΔpCO_2 of 5 percent/ $^\circ\text{C}$, the internal environment will be at neutrality no matter what the temperature when TCO₂ remains constant and the 37 degree readings are 7.4 and 40 torr. Any deviation from these numbers can be interpreted in

the usual and customary way. If, as now seems to be most desirable, significant internal alkalosis is sought, the perfusionist can think (in round numbers) of pH rising steadily to 7.7 at 27° and to 8.0 at 17°, while pCO₂ falls steadily to 27 at 27° and 17 at 17°. Think of that, 27 at 27°, 17 at 17°. What could be simpler?

For these reasons, therefore, it is strongly recommended that no temperature "corrections" of the 37° analyzer readings be made.

Finally, to help one's ability actually to achieve the strategy desired, and to confirm the fact that it is being achieved on a minute-to-minute basis, I am currently negotiating with various instrument companies to determine if they can produce an on-line gas analysis* meter with frequent intermittent digital read-out. With this you may be able to react instantaneously to the patient's responses by adjusting the gas flow to the oxygenator. Automation of gas flow control based on continuous on-line monitoring would make your acid-base control both precise and simple. I hope, therefore, that positive control of the hypothermic patient during perfusion may soon become a realistic capability of all the members of this society.

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*Since this paper was presented, an entirely new technology allowing an immediate on-line readout of pH, pCO₂ and venous temperature values has been marketed. The author considers this technology an important addition to the armamentarium of cardiopulmonary perfusion.

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