

Controlled Acid-Base Status with Cardiopulmonary Bypass and Hypothermia

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EDMARK,* in trying to maintain a blood pH of 7.40 during hypothermia, discovered that adverse effects were produced. He therefore, deliberately lowered the pH and noted improvement. Osborn *et al.*¹ using Edmark's technique² confirmed the desirability of lowering pH during extracorporeal circulation and hypothermia. Both Edmark and the Osborn group have observed that with control of pH with hydrochloric acid there is less cardiac irritability than otherwise is associated with hypothermia in that there is a lower incidence of ventricular fibrillation. If fibrillation should occur with this technique, there may be spontaneous reversion to normal rhythm on rewarming or, if not, then the heart is easily defibrillated electrically. In addition, they express the clinical impression that patients controlled in this way have a decreased morbidity and a smoother postoperative course.

Niazi and Lewis³ demonstrated that it was possible to surface cool dogs to body temperature levels of below 10° C. with survival provided carbon dioxide was added to the respiratory mixture during cooling. When oxygen alone was used, pH of the blood increased and plasma CO₂ decreased with a concomitant increased incidence of ventricular fibrillation as cooling progressed. With sufficient carbon dioxide in the respiratory mixture, the pH tended to decrease rather than increase and the plasma CO₂ increased somewhat. They also demonstrated that the animals receiving oxygen alone had an increasing serum potassium with cooling, whereas those receiving a mixture of oxygen and carbon dioxide had a much smaller increase. Osborn *et al.* also reported a series of cases in which carbon dioxide was added to the pump oxygenator in a

concentration of 5 per cent or more rather than adding acid. They found that during rapid cooling carbon dioxide was absorbed in large quantities by the patient. When a constant temperature was maintained for 30 minutes or more, this uptake ceased and most patients began to eliminate carbon dioxide again at a reduced rate in proportion to their temperature at that time. On rewarming, all patients rapidly increased their carbon dioxide output to high rates. It was necessary to continue extra-corporeal circulation not only until a temperature near normal was reached but also until the rapid rise in venous P_{CO₂} had ceased. Otherwise a large amount of carbon dioxide would have to be eliminated through the patients lungs and this would be an added load on the circulation at this time.

This paper presents studies made on dogs and patients in an effort to find the best acid-base conditions for the patient on cardiopulmonary bypass with hypothermia.

The Relationship of Metabolic Acidosis to Cardiac Output

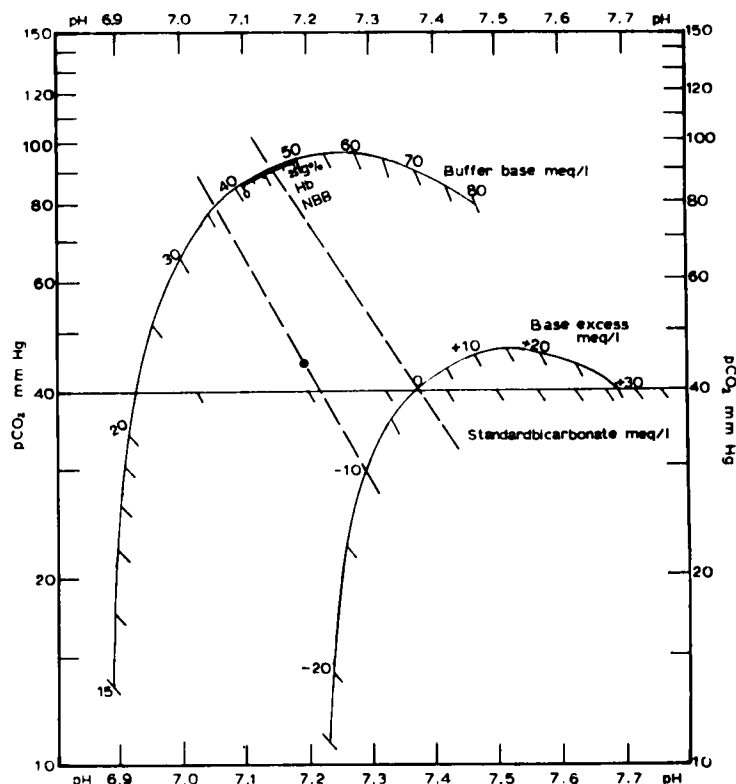
METHODS

Cardiac output was measured in dogs using both an electromagnetic flowmeter with the probe around the ascending aorta and also with the indocyanine (Cardiogreen) dye-dilution method using a Gilford densitometer. The electromagnetic flowmeter, which gave a continuous dynamic recording of cardiac output, was calibrated and checked periodically by the dye method using indocyanine.⁴ The dye was injected through a catheter placed through the femoral vein into the inferior vena cava and blood was withdrawn through the densitometer from a catheter placed into the aorta through the femoral artery. Cardiac output was converted to cardiac index by dividing by the body surface area which was taken as $0.112 \times (\text{wt. in kg.})^{2/3}$. Five dogs were stud-

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FIG. 1. Simplified diagram of the Astrup nomogram. In this example with a hemoglobin of 15 Gm./100 ml., pH of 7.20 and P_{CO_2} of 44.0 mm. of mercury, there was a base deficit of 10 mEq./liter as bicarbonate.



ied at normothermia and one was cooled using a veno-venous shunt from the femoral vein to the external jugular vein passing the blood through a coil in an ice bath. Temperature was taken by a thermistor probe placed in the esophagus. The shunting was stopped while the dye curves were being recorded. Arterial blood pressure was recorded and blood samples withdrawn from the femoral artery catheter into heparinized syringes were measured for pH, P_{CO_2} and P_{O_2} , care being taken to exclude air from the samples. An Astrup pH electrode, Severinghaus P_{CO_2} electrode, and modified Clark P_{O_2} electrode were employed, all being read on a Beckman Model 160 Physiological Gas Analyzer and all temperature controlled at 37° C. Serial amounts of each sample were introduced into the P_{CO_2} and P_{O_2} cuvettes until repeatability of the reading was obtained, the electrodes having been calibrated with gases of known P_{CO_2} and P_{O_2} as analyzed by the Scholander apparatus. The pH electrode was calibrated with Radiometer certified buffers. The hemoglobin concentration was

estimated using a Spencer hemoglobinometer. The endogenous P_{CO_2} was varied by altering ventilation using a Harvard animal respirator and the pH was varied by infusing 0.3 M HCl or 0.3 M NaOH intravenously. All these dogs were anesthetized with sodium pentobarbital and ventilated with 100 per cent oxygen.

The P_{CO_2} and pH readings from each blood sample were applied to an Astrup nomogram⁵ to obtain a measure of base deficit or base excess. This nomogram was designed to find P_{CO_2} and base excess indirectly from pH values after equilibrating blood with known gas tensions of carbon dioxide. When the Severinghaus electrode is used, the P_{CO_2} is found directly. The nomogram is still useful, however, to derive base excess or deficit. A line is drawn through zero on the base excess curve and through the hemoglobin in Gm./100 ml. on the upper curve. If another line is now drawn through the point given by the pH and P_{CO_2} not parallel but in such a position as to be the same number of mEq./liter away from the first line on both curves, then the reading

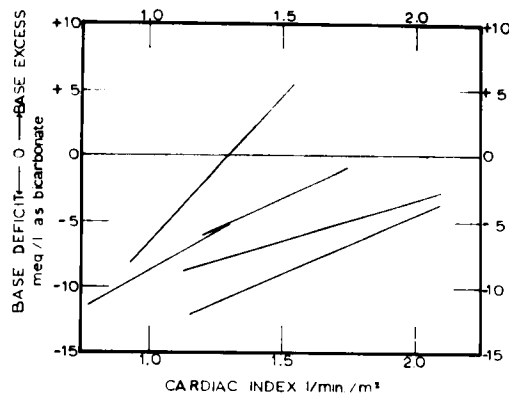


FIG. 2. The relationship of cardiac index to base deficit at normothermia.

on the base excess curve will give an estimation of the degree of metabolic acidosis or alkalosis (fig. 1).

Since the nomogram is designed for blood at 37°–38° C. values for pH and P_{CO_2} as measured at 37° C. and uncorrected for temperature are used to find the base excess or

deficit. It is thought that this value should be valid for blood from hypothermic subjects since base excess or deficit does not change with anerobic change in temperature. Hence from each blood sample values are obtained for pH , P_{CO_2} , P_{O_2} , hemoglobin and base excess or deficit estimate as bicarbonate in mEq./liter.

RESULTS OF ANIMAL EXPERIMENTS

In experiments with five normothermic dogs cardiac output was measured during various conditions of arterial blood pH and P_{CO_2} . It was found that the cardiac output varied inversely with metabolic acidosis, *i.e.*, cardiac index decreased as base deficit became more severe. This relationship is demonstrated in figure 2.

Under conditions of hypothermia there was a decrease in cardiac output below that observed at normothermia, but in addition, increasing metabolic acidosis further depressed cardiac output (fig. 3).

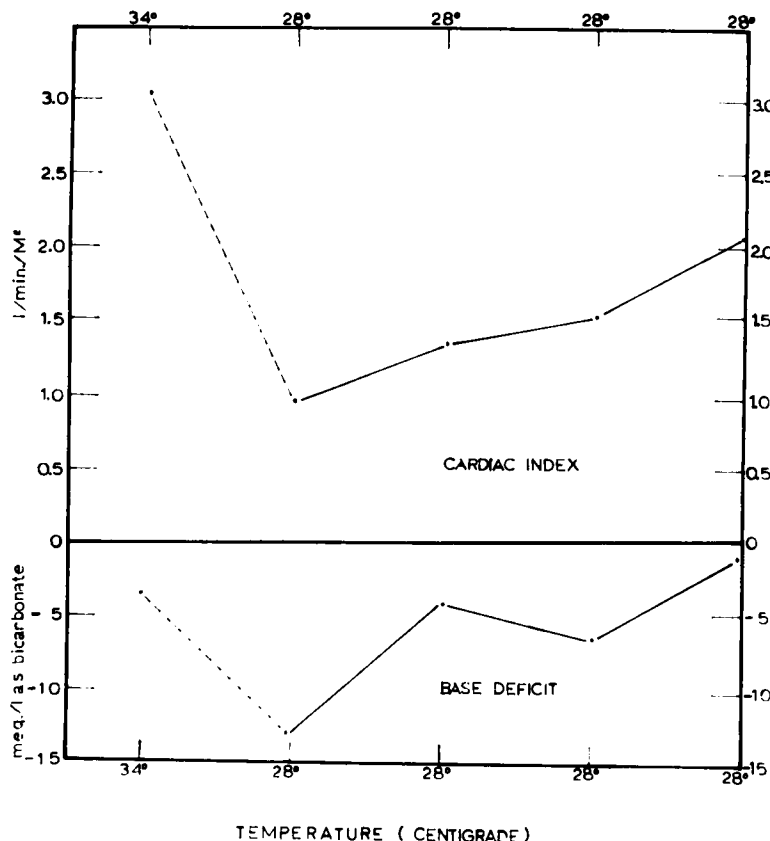


FIG. 3. The relationship of cardiac index to base deficit under conditions of hypothermia.

Edmark⁶ has suggested that there is a difference between exogenous addition of acid and spontaneously occurring metabolic acidosis, the latter probably being more intracellular in nature. From the experiments reported above it is seen that there is a depression of cardiac output with addition of acid and, if cardiac output can be taken as an indication of myocardial effort, then it would not appear to be desirable to use the technique of adding hydrochloric acid to lower the pH. However, from the aspect of myocardial irritability a controlled lowering of pH during hypothermia is apparently desirable. It is possible to accomplish this without inducing metabolic acidosis by adding CO₂ in quantities sufficient to produce what appears to be a marked respiratory acidosis when thought of in terms of the normothermic patient.

Controlled pH with Cardiopulmonary Bypass and Hypothermia

METHODS

The Edmark technique accomplishes control of pH by the introduction of 0.3 M hydrochloric acid into the blood during cooling and maintenance of hypothermia followed by addition of sodium bicarbonate or sodium hydroxide in approximately equivalent amount while rewarming. By this means the pH is maintained within narrow limits on a predetermined scale of 0.0147 pH unit drop per degree centigrade fall in temperature. This scale may be viewed as a reciprocal of the correction factor for shift in the blood pH with *in vitro* change in temperature as described by Rosenthal.⁶ At a temperature of 25° C., for example, the desired pH would be $7.38 - [(37 - 25) \times 0.0147] = 7.20$ (fig. 4). It must be remembered, however, that if blood taken at a temperature of 25° C. is measured with a pH electrode at 37° C., the correction factor must also be applied. Otherwise the reading will be 0.0147 pH unit low for each degree centigrade difference between that of the blood when the sample was taken and that at which the pH was measured. Hence with blood taken at 25° C. and measured with a pH electrode at 37° C., an instrument reading of 7.03 would give a temperature corrected pH of $7.03 + [(37 - 25) \times 0.0147] = 7.20$ corrected for 25° C.

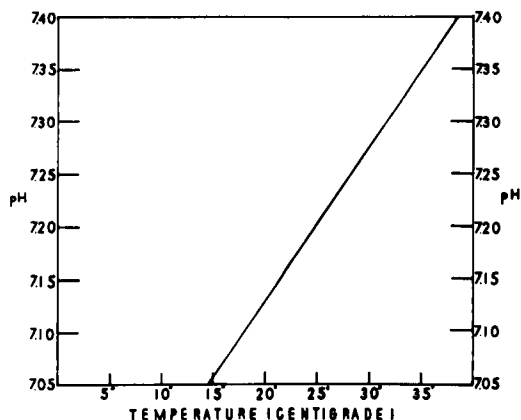


FIG. 4. The relationship of desired pH to temperature during controlled pH with cardiopulmonary bypass and hypothermia as suggested by Edmark.

An anesthesia machine was specially constructed with two independent circuits. One of these provides a regular clinical apparatus with circle absorber and a 'copper kettle' vaporizer⁷ with which nitrous oxide, oxygen and halothane can be administered to the patient. The other circuit delivers oxygen, halothane from another 'copper kettle' vaporizer and carbon dioxide to the pump oxygenator (fig. 5, top.)

On a rack behind the flowmeters at the back of the machine is mounted a Physio-Control Model 808 continuous flow pH meter † (fig. 5, bottom).

An Edmark thermo-stable pH reference electrode ‡ is inserted with a special glass electrode in a cuvette on the arterial side of the pump oxygenator. Samples of blood are also taken from this site for pH, P_{CO₂}, P_{O₂}, and hemoglobin estimations on the equipment already described. From the spot samples the continuous flow pH meter is calibrated and later checked from time to time. Without the continuous flow electrode a great many more samples would have to be taken throughout the bypass procedure to minimize deviation of pH from the desired level.

RESULTS OF HUMAN INVESTIGATIONS

Without Control of pH. In a series of five cases in which no attempt was made to control pH, but 2 per cent carbon dioxide was

† Obtained from Physio-Control Company, Inc., Seattle, Washington.

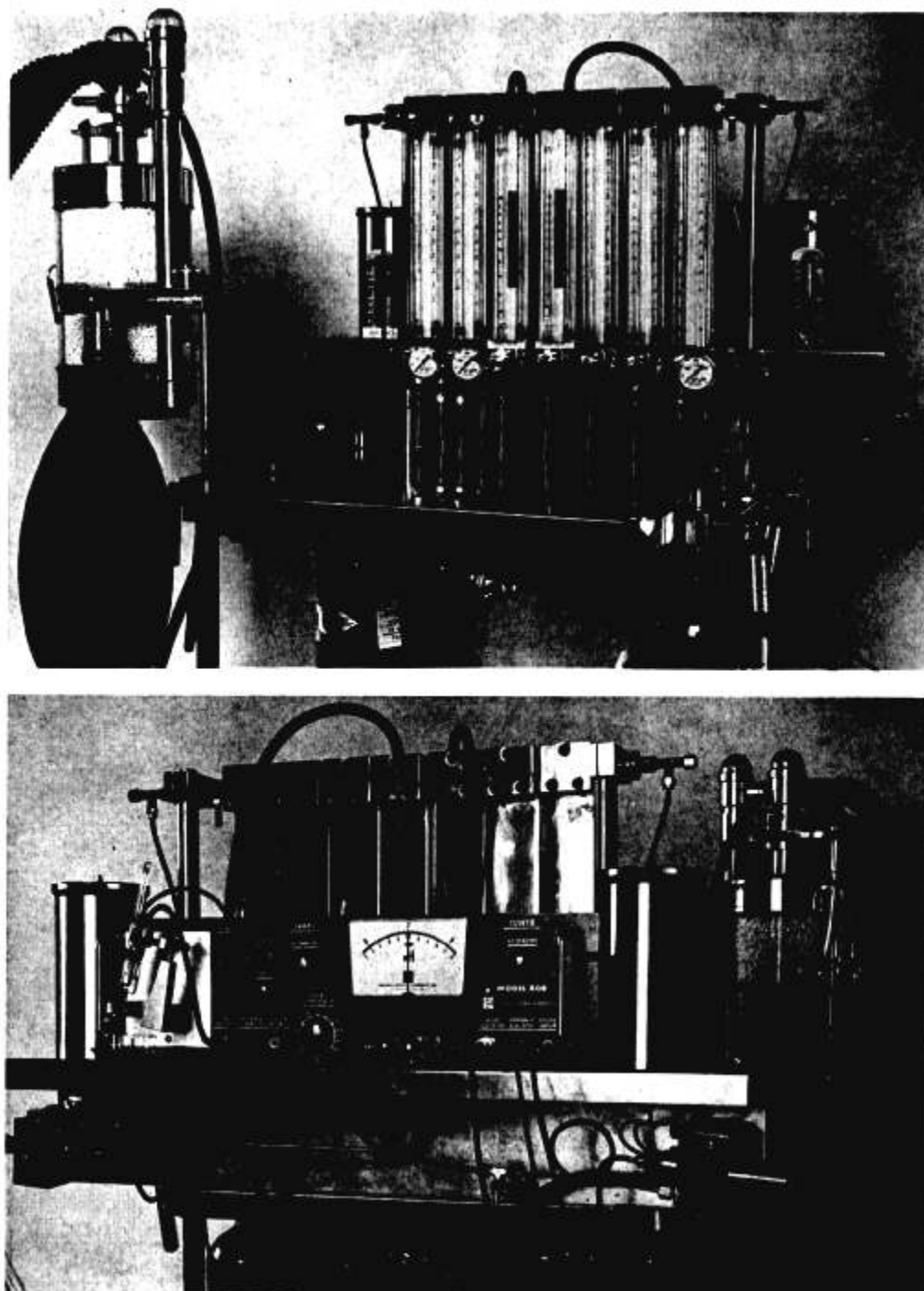


FIG. 5. *Top:* Front view of special anesthesia machine. *Bottom:* Rear view of special anesthesia machine showing the continuous flow pH meter.

used in the respiratory mixture to the pump oxygenator, there was an increasing metabolic acidosis during bypass (table 1). One of these cases is illustrated in figure 6.

Almost all these hearts fibrillated and defibrillation after rewarming was often difficult. In addition, cardiac action was often poor following bypass. The metabolic acidosis generally decreased over several hours following operation provided the surgical correction was successful.

Controlled pH with Hydrochloric Acid. Using the Edmark technique of controlling pH during hypothermia by infusing 0.3 M hydrochloric acid into the oxygenator blood and later neutralizing this on rewarming with an equal amount of 0.3 M sodium bicarbonate, there was a decrease in the incidence of ventricular fibrillation or, if this occurred, defibrillation on rewarming was rarely a problem. With this method there was a marked base deficit during hypothermia and sometimes this did not return to normal for several hours postoperatively in spite of addition of sodium bicarbonate. Since base deficit figures on the clinical cases con-

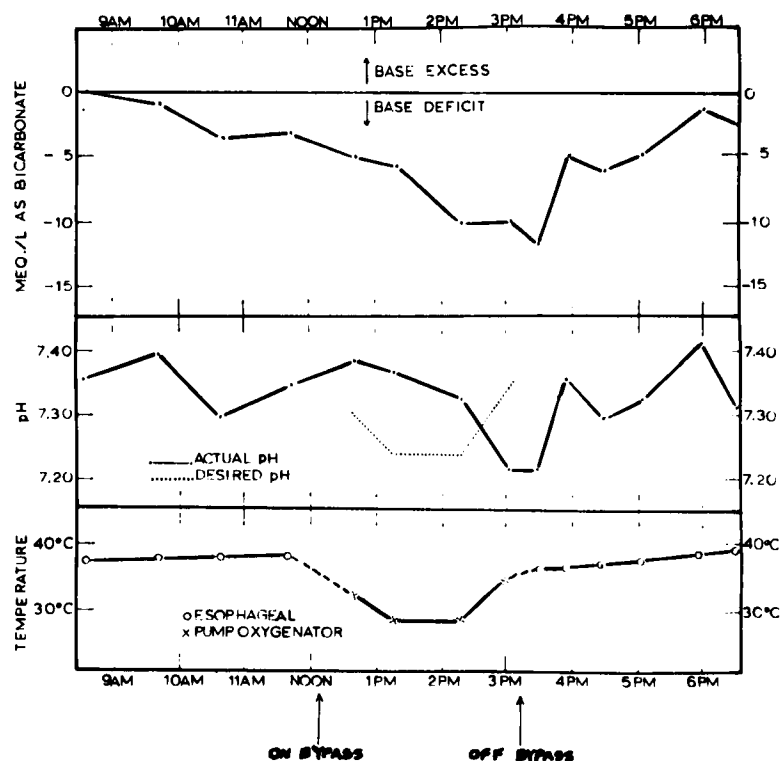
TABLE 1. Base Deficit as Related to Time on Bypass with Hypothermia in Patients Without Control of pH

Patient No.	Operation	Oxygenator Blood Temperature (°C.)	Elapsed Time on Bypass (Hours-Minutes)	Base Deficit (mEq./liter as Bicarbonate)
1	I.V.S.D. repair	31.0	9	-6.5
		28.0	45	-8.5
		36.0	1, 47	-8.0
2	I.V.S.D. repair and modif. pul. stenosis	25.0	21	-8.7
		23.0	31	-10.0
		22.5	52	-10.0
		32.0	1, 18	-10.0
3	Atrial septal construction	31.5	9	-5.0
		27.5	45	-6.0
		27.5	1, 47	-10.3
		34.5	2, 31	-10.0
4	Pul. valvulotomy	28.6	18	-2.0
		28.6	48	-11.0
		35.7	1, 3	-10.0
5	Aortic valve commissurotomy	28.0	9	-5.0
		33.0	1, 15	-9.5
		35.0	1, 50	-9.0

trolled in this way are unavailable, results from a dog are illustrated in figure 7.

These subjects appeared to fare better postoperatively and appeared to be in better con-

FIG. 6. A typical case without control of pH showing the relationship of temperature, base excess or deficit, actual and desired pH.



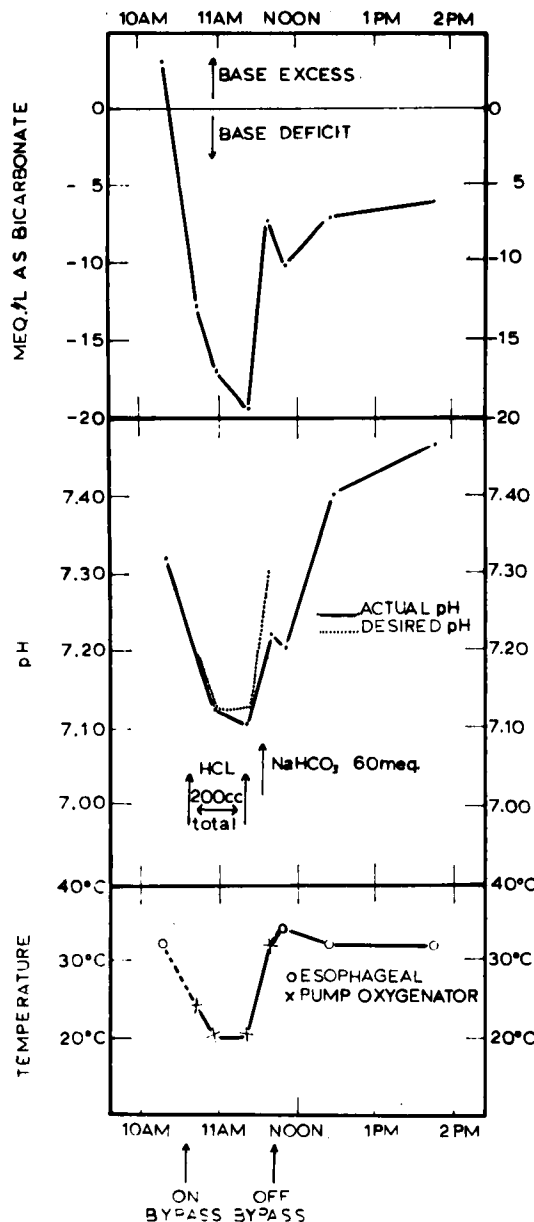


FIG. 7. Typical results from a dog on bypass with hydrochloric acid control of pH showing the relationship of temperature, base excess or deficit, actual and desired pH.

dition in the immediate postanesthetic period than those without pH control. In the example illustrated, this dog was easily defibrillated and had an uneventful postoperative course.

Controlled pH With Carbon Dioxide. When carbon dioxide is used in the oxygenator re-

spiratory mixture to control the pH at the same level with hypothermia as in the Edmark technique a different picture is seen. The base excess or deficit rarely varies more than a few mEq./liter from zero even after several hours on bypass as is shown in table 2. A typical case is also shown graphically in figure 8.

With these hearts it is usual to find a relatively normal electrocardiogram even at temperatures as low as 25° C. and fibrillation has occurred only when there has been a period of interference with coronary blood flow. These patients have done well in the immediate postoperative period provided the surgical correction is satisfactory. In unsuccessful cases a falling pH has been observed after coming off bypass in spite of a normal P_{CO_2} . In these instances this increasing metabolic acidosis was postulated as due to a low cardiac output from mechanical difficulty in the heart which probability was confirmed at autopsy.

Discussion

Osborn *et al.* have discussed the possible causes for the reduced myocardial irritability observed when pH is lowered during hypothermia. They point out that since the hemoglobin-oxygen dissociation curve shifts to the left with both cooling and alkalosis the oxygen available to the tissues from hemoglobin under these conditions is limited. Dropping the pH during hypothermia will tend to shift the curve back to the right and the ratio of available oxygen to oxygen need is maintained.^{1,8} If sufficient oxygen is not available to the tissues an anoxic metabolic acidosis will result. Furthermore, this would be an intracellular metabolic acidosis which is slow to correct on rewarming. Hence the action of the heart may be inhibited when coming off bypass which is a critical time.

We have also found both with experimental animals and with patients that if they are hyperventilated before bypass and cooling and therefore have a high pH and low P_{CO_2} at this time, they develop a more marked base deficit on cooling than subjects who are maintained at a more normal minute ventilation prior to bypass. Also if cooled rapidly they fibrillate sooner than optimally ventilated subjects. Furthermore, if the pH is to be controlled during cooling of these previously hy-

perventilated subjects, they will require much more hydrochloric acid or carbon dioxide initially than optimally ventilated subjects.

It is interesting to note that when the *pH* is accurately controlled with carbon dioxide there is during hypothermia continuous respiratory effort which ceases if the *pH* is allowed to rise above the desired level and becomes very vigorous if the *pH* falls too low due to too high a concentration of carbon dioxide in the mixture. This suggests that Edmark's choice of 0.0147 *pH* drop per degree centigrade fall in temperature is an admirable one. It is also found that with this method it is necessary to administer halothane in amounts which are similar to those used on normothermic perfusion as with less of this drug the patient appears to be awakening. This is in contrast to the more usual finding with hypothermia in the absence of carbon dioxide controlled *pH* when the anesthetic may be reduced or omitted as the temperature falls. This confirms and extends the prior observations of Niazi and Lewis³ that animals receiving carbon dioxide required more anesthesia than those receiving oxygen alone.

TABLE 2. Base Deficit as Related to Time on Bypass with Hypothermia in Patients with *pH* Control Using Carbon Dioxide

Patient	Operation	Oxygenator Blood Temperature (°C.)	Elapsed Time on Bypass (Hours-Minutes)	Base Deficit (mEq./liter as Bicarbonate)
A	Part. repl. mitral valve	34.5	6	-2.5
		28.0	34	-5.2
		27.8	1, 4	-5.0
		27.7	1, 34	-5.7
		33.5	2, 17	-5.7
B	Part. repl. aortic valve	36.0	3, 18	-6.8
		32.8	10	0
		25.0	28	-5.0
		33.2	56	-5.7
C	Total repl. aortic valve	35.0	1, 40	-6.7
		28.5	19	0
		25.5	1, 6	-3.0
		26.7	1, 58	-4.8
		31.0	2, 38	-2.5
D	Total repl. aortic valve	35.2	3, 20	-2.5
		31.0	12	0
		28.8	1, 10	-4.5
		28.6	1, 40	-4.5
		28.5	2, 26	-3.0
E	Mitral commissurotomy	30.0	3, 13	-3.0
		33.0	3, 54	-5.3
		34.5	7	-4.5
		31.0	35	-0.5
		27.0	51	-2.5
		30.0	1, 5	-3.0
		34.8	1, 35	-3.5
		35.2	1, 51	-2.5

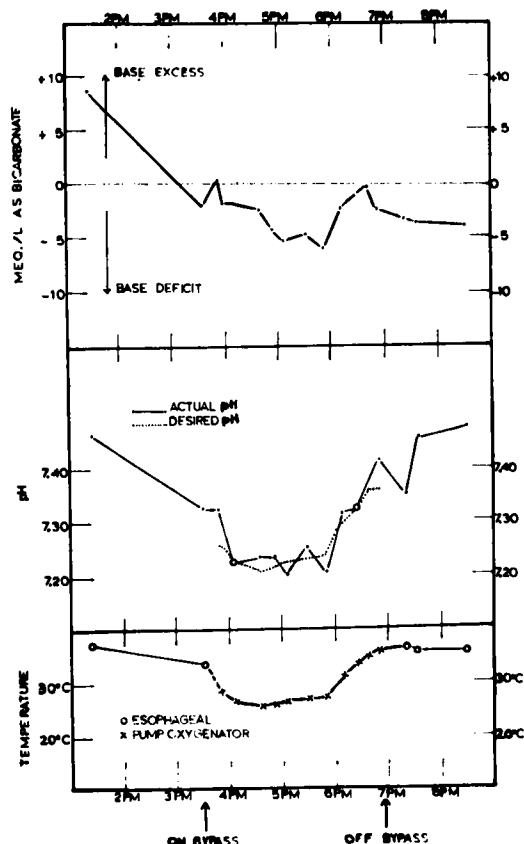


FIG. 8. A typical case with carbon dioxide control of *pH* showing the relationship of temperature, base excess or deficit, actual and desired *pH*.

It is not possible to give a fixed percentage of carbon dioxide in the pump respiratory mixture to control *pH* during hypothermia, as the *pH* must be controlled within narrow limits if this technique is to work to best advantage and prevent the occurrence of metabolic acidosis. The amount of carbon dioxide varies from patient to patient and with rate of change of temperature, perfusion rate and disc rotation speed. Also, if 100 per cent carbon dioxide is introduced into the mediastinum to exclude air from the open heart, some of this is drawn through the coronary sinus suction into the oxygenator and the concentration of carbon dioxide from the anesthesia machine must be reduced accordingly. Hence the necessity for continuous monitoring of *pH* and careful adjustment of the carbon dioxide concentration. On an average 8 to 10 per cent carbon dioxide is administered during fairly rapid

cooling, reducing to about 4 per cent at a steady temperature of 25° C. Osborn *et al.* have pointed out that when high concentrations of carbon dioxide are used in the pump respiratory mixture, patients had to stay on bypass until the high P_{CO_2} was reduced to normal on rewarming. So far, we have found that with gradual rewarming towards the end of the bypass procedure it is not necessary to maintain perfusion longer than the time required by the surgeon. The concentration of carbon dioxide in the mixture of gases through the oxygenator is reduced during rewarming, thereby keeping the pH at the desired level for the changing temperature of the blood. With fairly rapid rewarming the carbon dioxide often has to be discontinued altogether. However, if necessary, it is possible to discontinue perfusion before the P_{CO_2} is reduced to normal levels at normothermia provided THAM (tris-hydroxymethyl-amino-methane) is titrated intravenously to maintain the pH and the patient hyperventilated until the P_{CO_2} is normal. Careful control of pH and prevention of metabolic acidosis is just as important during the rewarming phase as at any other time.

It would appear that to control pH through additions of carbon dioxide a marked respiratory acidosis is employed. However, it may be that at hypothermic levels the concept of what is "normal" acid-base status must alter. Concentrations of carbon dioxide which result in what appears to be a respiratory acidosis when thought of in terms of 37° C. may indeed be "normal" and desirable during hypothermia.

Summary

A method of controlling acid-base balance during hypothermia on cardiopulmonary by-

pass is presented. This is achieved through the use of carbon dioxide in the pump respiratory gas mixture by means of which the pH is controlled on a predetermined scale. It is suggested that this technique largely prevents the occurrence of metabolic acidosis and its consequent ill effect on cardiac action and greatly reduces the myocardial irritability usually associated with hypothermia. Possible reasons for the advantages of reduced pH with hypothermia are considered. Clinical observations with the use of this technique are also reported.

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