THE CONTROL OF THE ACID-BASE BALANCE DURING OPEN-HEART SURGERY*

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THE MAINTENANCE of the acid-base balance during extracorporeal circulation is of increasing importance as the scope of cardiac surgery is extended requiring prolonged periods of bypass. A metabolic acidosis occurs frequently during bypass and commonly during hypothermia. Various methods have been described to deal with this problem. It is the purpose of this paper to describe studies carried out in the years 1961-62 leading to a method which is now employed in all cases of extracorporeal circulation including those of several hours' duration. At the beginning the effects of hypothermia were studied both clinically and experimentally. The principles evolved in this study were later applied to extracorporeal circulation with and without hypothermia.

Many of the physiological disturbances caused by induced hypothermia have not been investigated adequately, although cooling procedures have been accepted as valuable adjuncts to cardiovascular surgery and to neurosurgery. General hypothermia affects every organ and many of the biochemical components of the milieu interieur. The significance of these alterations is largely unknown, and often it is even unknown whether a certain change is beneficial or detrimental to the organism under induced hypothermia. Observations made in the laboratory are slowly improving our understanding, but the persons who are responsible for the clinical use of induced hypothermia still frequently find themselves in a dilemma. In the planning of an operation and during the procedure they have to make certain decisions which are based on previous observations and experience but which are not based on a thorough understanding or on sound scientific knowledge.

This situation pertains to the acid-base balance. Changes in temperature influence the buffer systems in various ways and sometimes in opposite directions. In the absence of hard and fast rules it was decided to set up a working hypothesis based on theoretical considerations and on certain experimental observations. The hypothesis consists of three parts:

- 1 Extracorporeal circulation, especially during hypothermia, is not as effective as the normal circulation. Therefore, it is desirable to induce vasodilatation, particularly in the brain since this organ is most likely to suffer damage by hypoxia associated with insufficient perfusion.

- 2 Under hypothermia and after anoxic cardiac arrest, ventricular fibrillation may occur. Therefore, towards the end of the cardiopulmonary bypass,

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conditions must be created which are favourable for defibrillation. A temporary lowering of the pH is thought to be indicated at this time.

3 The normal acid-base balance is maintained within a narrow range and deviations are not well tolerated. Therefore, during cardiopulmonary bypass fluctuations of the pH should be avoided except the temporary lowering mentioned above.

The practical application includes the following components:

1 Routine anaesthesia, but before bypass, excessive hyperventilation is avoided. Anaesthetic agents having a vasodilating effect, such as halothane, are preferred during bypass.

2 The $p\text{CO}_2$ is kept within the normal range during bypass and it is raised slightly towards the end of bypass if ventricular fibrillation occurs.

3 After bypass the $p\text{CO}_2$ is reduced by controlled hyperventilation.

4 Interference with the metabolic side of the acid-base balance is avoided. Ammonium chloride, which is said to facilitate defibrillation, is never given. Sodium bicarbonate is administered only if indicated.

MATERIAL AND METHODS

Seventy-two consecutive patients undergoing open-heart surgery were studied, 23 of these under hypothermia (25°C).

In adults and older children an arterial needle was placed in the left radial artery and in these patients the acid-base balance was followed from the beginning of the anaesthesia through the operation and during the first few hours in the recovery room. During the extracorporeal bypass samples of blood were taken from the oxygenator. In the smaller children, the arterial needle was not inserted. Thus, only the samples taken from the oxygenator were available, supplemented by one or two blood samples taken by the surgeon from the aorta, shortly before and after bypass. Heparinized syringes were used throughout and suitable precautions were observed to avoid admission of air into the syringe.

The specimens were then analysed without delay on Astrup's apparatus¹ with the microelectrode at a temperature of 37°C . The pH was corrected for temperature using Rosenthal's factor² and the $p\text{CO}_2$ was corrected for temperature using Severinghaus' nomogram.³

All operations were done by means of a Kay-Cross rotating disk oxygenator and roller pumps.* The size of the oxygenator was chosen according to the weight of the patient. A perfusion rate of 2.3–2.4 L/m²/min was achieved in most patients. In some the venous return was not adequate and the flow had to be decreased accordingly. The roller pumps were calibrated and the actual flow was checked by measuring the venous return at intervals during the procedure. At a blood temperature of 25°C the perfusion rate was decreased to approximately 75 per cent of the predetermined flow. Since at that temperature the total oxygen requirements are less than 50 per cent of normal,⁴ the high flow principle was maintained during hypothermia. The temperatures of the patient and of the blood in the oxygenator and in the heat exchanger were recorded by means of 401 thermistors and telethermometers.†

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RESULTS

The presentation of biochemical data in a form which is accurate, simple, and clinically acceptable is not easy⁵ In this presentation the pH/ $p\text{CO}_2$ diagram⁶ and the diagram introduced by Siggaard Anderson⁷ were used It is to be noted that in the latter diagram the pH is plotted on a linear scale and the $p\text{CO}_2$ on an inversed logarithmic scale in mm Hg Excesses of base are expressed as positive

TABLE I
CLINICAL DATA

Diagnosis	Number	Age	Mortality
Atrial septal defect	21	4-53 yr	0
Pulmonary stenosis	6	5-44 yr	1
Ventricular septal defect	20	2-38 yr	3
Congenital aortic stenosis	11	3-16 yr	0
Tetralogy of Fallot	7	11-28 yr	2
Acquired heart disease	6	23-60 yr	5
Pulmonary atresia	1	8 mo	1
Total	72		12

FIGURE 1 Acid-base balance of a patient undergoing open-heart surgery for correction of a tetralogy with extracorporeal circulation and hypothermia After cooling to 25° oesophageal temperature there was a 9-minute period of circulatory arrest, followed by hypothermic bypass with cardiac arrest During a second period of normothermic bypass the right pulmonary outflow tract was enlarged The corrected pH and $p\text{CO}_2$ values obtained during the hypothermia are included

values and deficits as negative values in mEq/L on a logarithmic scale with a serum bicarbonate of 22.9 mEq/L as zero. The normal range is indicated by the two horizontal lines

The diagnosis and age of the patients are given in Table I

The biochemical data obtained in a patient undergoing open-heart surgery for complete correction of a tetralogy of Fallot are summarized in Figure 1. The patient, a girl, was born with a tetralogy of Fallot and had a Potts' procedure at the age of five years. At age 12 definitive repair of the lesions was performed. During anaesthesia and before bypass, the changes associated with hyperventilation were found. As soon as the partial bypass and the hypothermia commenced there was an increase in $p\text{CO}_2$, a drop in pH, and an increase in the base deficit.

At a temperature of 25° complete circulatory arrest was instituted for a period of nine minutes, while the Potts' anastomosis was closed. Then with the patient on complete cardiopulmonary bypass, the pulmonary stenosis and the ventricular septal defect were repaired, the latter under cardiac arrest produced by clamping the aorta at an oesophageal temperature of 25° . At point A (Fig 1) the flow of gas into the oxygenator was decreased to less than one litre per minute because the $p\text{CO}_2$ was found to be levelling off at too low a level. Following the circulatory arrest a metabolic acidosis became evident and when a base deficit of 10 mEq/L had been reached 10 mEq of sodium bicarbonate was given intravenously. The patient was then rewarmed. After 20 minutes the temperature had returned to normal, the heart resumed a rhythmical action spontaneously, and

FIGURE 2 Same patient as in Figure 1 Uncorrected values plotted in pH/pCO₂ diagram

FIGURE 3 Acid-base balance of a patient undergoing neurosurgery with extracorporeal circulation and hypothermia. The lowest oesophageal temperature was 21°. There were three periods of circulatory arrest totalling 36 minutes.

the bypass was discontinued. Pressures taken at that time revealed an excessive gradient between right ventricular and pulmonary artery pressures and it was decided to enlarge the right ventricular outflow tract by inserting a patch of pericardium. Accordingly, cardiopulmonary bypass was again instituted but without hypothermia. The $p\text{CO}_2$ increased again and since a further drop in base was anticipated, another 10 mEq of sodium bicarbonate was given. After termination of the bypass the anaesthetist hyperventilated the patient and at the completion of the operation the pH and base were within the normal range, whereas the $p\text{CO}_2$ was slightly lower than normal. The pH/ $p\text{CO}_2$ diagram is reproduced in Figure 2. The straight-line relationship is not as clear as in less-complicated cases, indicating some disturbance of the acid-base balance.

The second case was operated upon shortly after the termination of the series and is presented as another example of a complicated procedure. The patient, a 41-year-old white male, had undergone several previous operations attempting to improve an intracranial arteriovenous fistula. Finally it was decided to approach the lesion again under circulatory arrest and hypothermia, using the routine

procedures of cardiopulmonary bypass. The circulation was arrested three times, the total period of arrest being 36 minutes. The intra-operative acid-base status is presented in Figures 3 and 4. Several similarities with the last patient are apparent: evidence of hyperventilation before bypass, then fall of pH and increase of $p\text{CO}_2$ at the beginning of bypass and hypothermia. At the time when the $p\text{CO}_2$ levelled off, the flow of the gas mixture to the oxygenator was decreased to 1½ litres per minute and, following this, the $p\text{CO}_2$ and the pH reached the desired levels. The base deficit was not excessive, even after complete circulatory arrest, and no bicarbonate was given. The straight-line relationship is maintained in the pH/ $p\text{CO}_2$ diagram, confirming the absence of a marked metabolic acidosis.

These two patients were chosen for detailed presentation because they illustrate the changes produced in the acid-base balance. In other patients the period of cardiopulmonary bypass was shorter and the increase in $p\text{CO}_2$ and the fall in pH were less pronounced.

Figure 5 is a composite graph of all the uncorrected data obtained. The dots

FIGURE 4 Same patient as in Figure 3. Uncorrected values plotted in pH/ $p\text{CO}_2$ diagram.

FIGURE 5 Composite pH/pCO₂ diagram incorporating all data obtained in the course of the study

are results obtained in survivors, the circles are data obtained in patients who died on the day of the operation. It can be seen that the circles are scattered throughout the whole range but are relatively more frequent on the left side of the centre. This illustrates the well-known fact that death following cardiopulmonary bypass is often associated with a metabolic acidosis. In these patients 12 or more biochemical determinations were performed, whereas in many short and successful cases only 3 or 4 were made. This explains the large number of circles in the diagram. The circles in the left upper corner were obtained in a patient with acquired heart disease affecting both mitral and aortic valves. The heart

TABLE II
MEANS AND STANDARD DEVIATIONS OF pH, $p\text{CO}_2$, AND BASE DEFICIT
IN DONOR BLOOD AND DURING CARDIOPULMONARY BYPASS
 (Figures in parentheses indicate the number of observations)

	pH	$p\text{CO}_2$ (mm Hg)	Base deficit (mEq /L)
Donor blood	7.29 $\pm$ 0.05 (63)	40.6 $\pm$ 7.3 (59)	6.1 $\pm$ 2.3 (57)
Before anaesthesia	7.41 $\pm$ 0.03 (7)	34.6 $\pm$ 4.1 (7)	0.7 $\pm$ 2.7 (7)
One hour of anaesthesia	7.48 $\pm$ 0.07 (35)	27.3 $\pm$ 7.9 (35)	1.4 $\pm$ 1.4 (35)
Before bypass	7.45 $\pm$ 0.09 (39)	28.0 $\pm$ 7.1 (38)	3.0 $\pm$ 3.1 (38)
End of bypass			
Normothermia	7.28 $\pm$ 0.08 (46)	38.7 $\pm$ 13.8 (44)	6.3 $\pm$ 2.7 (42)
Corrected	7.32 $\pm$ 0.08 (27)	37.9 $\pm$ 10.0 (27)	
Hypothermia	7.20 $\pm$ 0.07 (24)	51.2 $\pm$ 15.4 (23)	7.52 $\pm$ 2.6 (23)
Corrected	7.33 $\pm$ 0.08 (24)	35.8 $\pm$ 11.3 (23)	
End of operation	7.36 $\pm$ 0.11 (35)	31.0 $\pm$ 13.6 (36)	5.0 $\pm$ 3.2* (33)

*Hypothermia cases 5.8 $\pm$ 3.2 (11) Normothermia cases 4.2 $\pm$ 3.2 (22)

resumed a regular rhythm after defibrillation but the patient died later, from haemorrhage. In Figure 5, as well as in the Table II, all the data obtained during the course of this study are incorporated.

Since the period of bypass was different in each patient it was difficult to obtain mean values of comparable states. In Table II this was attempted by presenting the mean obtained at different stages: (1) the donor blood, exposed to air, after it had been circulated through the pump oxygenator, (2) arterial blood before anaesthesia, (3) arterial blood after induction of anaesthesia; (4) arterial blood immediately before bypass, (5) blood taken from the arterial end of the oxygenator towards the end of the bypass when the pH had reached its lowest value, divided into a hypothermic and a normothermic group (in many patients in the latter group the temperature had dropped 2–3°, in these and in all hypothermia cases the corrected values are also given), (6) arterial blood at the end of the operation. Values for 2, 3, and 6 could only be obtained in patients who had an indwelling arterial needle.

The donor blood was one day old and slightly acidotic. Immediately before bypass the effects of hyperventilation were evident, as shown by a high pH, a low $p\text{CO}_2$ and a small base deficit. At the end of the operation there was evidence of a metabolic acidosis, more pronounced in the hypothermia cases than in those operated upon at normal body temperature. The same data are represented graphically in Figure 6.

DISCUSSION

Before discussing the working hypothesis and the results obtained, a short description of the method used for the intra-operative monitoring of the acid-base balance and an outline of the direct effect of hypothermia on the acid-base balance is presented.

1 *The Intra-operative Monitoring of the Acid-Base Balance*

Additional interference with the acid-base balance demands additional safeguards. The extent of the changes should be known at all times. Continuously

FIGURE 6 Means and standard deviations of the pH, $p\text{CO}_2$, and base excess in donor blood, in arterial blood before anaesthesia, after induction of anaesthesia, immediately before bypass, at the end of bypass, and at the end of the anaesthesia. The time relationships are approximations.

recording instruments present a number of inherent difficulties and are not really required. On the other hand, routine laboratory methods are too time-consuming and do not lend themselves to rapid serial determinations. Nomograms are of limited value, since the conditions for which these are calculated may not prevail during open-heart surgery.

The ideal method, which is yet to be found, should be completely uninfluenced by changes other than those occurring in the acid-base status, and should also be rapid, easy to perform, and dependable. The method and the apparatus recently described by Astrup and co-workers in Copenhagen fulfills many of these requirements.⁸ It has been shown by Brewin *et al.*⁶ that if the same blood sample is equilibrated at varying CO_2 tensions, and then the pH values and the corresponding $p\text{CO}_2$ values are plotted on semilogarithmic paper, the dots fall on a straight line. The line is shifted to the left in acidosis and to the right in alkalosis. Based on three pH determinations (the actual pH and two done after the blood sample has been equilibrated with known CO_2 tensions), the actual pH, the $p\text{CO}_2$, and the base excess or deficit⁹ can be obtained. Since a separate pH/ $p\text{CO}_2$ line is drawn for each sample, the results are independent of changes

in the concentration of haemoglobin and plasma proteins. The pH/ $p\text{CO}_2$ line is also said to be independent of temperature⁶

Astrup's method has been designed for use at normothermia, and at the present time it is impossible to evaluate the method when the blood samples are taken at a lower temperature and warmed in the apparatus. It is highly probable that the results obtained are not accurate even if correction factors are used. However, experience has shown that, if a base deficit is found during hypothermia, it is still present after the patient is rewarmed, and vice versa. The same observation has been made in regard to the $p\text{CO}_2$ changes and it is thought that the values obtained, although perhaps inaccurate, are still helpful in the assessment of the patients.

2 *The Changes in the Acid-Base Balance Produced by Hypothermia*

It is not easy to give a résumé of the present state of knowledge, one of the main difficulties being the terminology. The term pH was introduced in 1909 by Sorensen and defined as the negative logarithm of the hydrogen ion concentration. The hydrogen ion concentration itself is an unwieldy figure with several decimal points and Sorensen's concept simplified matters greatly. The pH units are small figures and have been accepted uniformly, but it is conceivable that, in the light of newer knowledge, other units might be introduced.¹⁰ Today according to both U.S. and British standards, the pH values are purely arbitrary units, a certain value being assigned to a certain test solution. Strictly speaking, then, it is not admissible to define the blood pH by means of the Henderson-Hasselbalch equation. However, everybody is familiar with this equation, it is used in every treatise on the subject, and it serves well to explain some of the changes in the acid-base balance occurring when the temperature of the blood is changed. With these limitations in mind the equation is used in the following discussion.

(a) *Physicochemical Considerations*

In discussing the Henderson-Hasselbalch equation, E. Neil¹¹ stated that "other people (non-experts) are rushing in where angels fear to tread." Nevertheless, before attempting to describe the effect of temperature changes on the acid-base balance, a partial review of the theoretical background appears mandatory. Only a cursory description of the concepts which are needed to explain the temperature effects will be given.

The situation is not as clear-cut as one might wish and it seems advisable to begin with a definition of the terms. What do we mean by "acid" and "base"?

According to Clark¹² the word "base" has at least five different meanings. For Lavoisier a base was the principal ingredient of a compound. The definitions of G. N. Lewis are difficult to understand for those untrained in advanced chemistry. In between, are the ionization theory and Bronsted's theory, which are thought to be most useful in the present context. According to the former, a base is a substance that ionizes in water to give hydroxyl ions (an acid gives hydrogen ions) and the interactions between base and acid are associated with a combination of the hydroxyl and the hydrogen ion. J. N. Bronsted's concept is more general. An acid is a proton donor, a base is a proton acceptor. In the formula

$HR \rightleftharpoons R^- + H^+$, HR is the acid and R^- its conjugate base. Both the acid and the base may be a cation, an anion, or an uncharged molecule, but R^- must always be more negative (or less positive) than HR .¹³

In this paper, the term "base" will be used in this sense. This is in contrast to Henderson's usage, which is often employed clinically (fixed bases, buffer base), meaning cations. Thus protein is a base, since it combines with H^+ to form the conjugate acid HP , and the bicarbonate ion HCO_3^- is a base conjugate to carbonic acid H_2CO_3 .¹³

For the quantitative assessment of the acid-base balance (or of the degree of acidity or alkalinity) pH units are employed. The exact measurement of the pH is difficult, requiring a hydrogen electrode. Most laboratory pH meters make use of a glass electrode.¹⁴ In these, the test solution is separated from a reference solution by a glass membrane. An electrode is in contact with the reference solution, another electrode is in contact with the test solution by means of a liquid junction. The interstices in the special glass used for the membrane permit the exchange of protons (H^+) and accordingly a certain electromotive force is produced across the glass, which after suitable amplification can be read off a meter. The pH meter is first calibrated with a solution of known pH and then the test solution is introduced.

The value obtained with a pH meter does not conform strictly to Sorensen's definition of the pH. The activity rather than the concentration of the hydrogen ions is measured¹⁵ and, when defined thermodynamically, the pH is an expression of the availability of protons, rather than of the hydrogen ion concentration.¹² In modern biochemistry pH units are arbitrary and the pH of a test solution is related to the pH of a standard solution. In the definition, the difference between the pH of the test solution and the pH of the standard solution is proportional to the difference in electromotive force produced across the glass electrode by the two solutions.¹⁶

If this difference in E M F is known, the pH value can be calculated theoretically using a certain mathematical formula which includes the absolute temperature. It follows that the pH values measured by the pH meter change with temperature. The pH of the buffer solutions used for the standardization also is temperature-dependent.¹⁷ Thus when reporting pH values obtained during hypothermia it is essential to state at which temperature the pH was measured.

In the following paragraph the discussion will be restricted to an outline of acid base changes occurring in patients under general anaesthesia with artificial respiration, cooled by blood stream cooling.¹⁸ As a further simplification only two buffer systems (bicarbonate-carbonic acid and proteins) will be considered. The pH can therefore be defined according to Henderson and Hasselbalch as follows

$$pH = pK_1' + \log[(HCO_3^-)/(H_2CO_3)] = pK_2' + \log(prot^-/Hprot)$$

If two (or more) buffer pairs coexist in the same solution, they must be in equilibrium with the same hydrogen ion concentration (pH) (isohydric principle). pK' is the symbol for the negative logarithm of K' , the apparent dissociation constant of the acid. Each buffer system has its own pK' , which under ordinary circumstances remains constant. It must be remembered, however, that the

K' is temperature-dependent and changes under hypothermia. These changes have been studied by a number of investigators, and Severinghaus³ produced a nomogram for the calculation of the carbonic acid pK' at varying temperatures.

Rosenthal² studied the effect of temperature on the blood pH. He determined the pH of the same blood sample at varying temperatures and found a linear rise in pH during cooling. The mean change was -0.0147 units/ $^{\circ}\text{C}$ for blood, and this figure is widely quoted as "Rosenthal's correction factor." Many components of the acid-base balance are temperature-dependent, e.g. the dissociation constants, and the fact that according to physical laws more CO_2 is dissolved in the plasma at a lower temperature than at normothermia. The ionization of all buffer anions is reduced at the lower temperature.¹⁸ This leads to a decrease in the number of available hydrogen ions and thus to an increase in pH. Evidently different processes influence the pH during temperature changes and the net change in pH would be the sum of the different forces that may act synergistically or antagonistically.

(b) Physiological Considerations

The results obtained by *in vitro* studies cannot be applied directly to the living organism under hypothermia. Correction factors which have been determined by measuring a certain variable anaerobically at different temperatures are applicable only under these conditions. They are indispensable in the laboratory. The blood sample is taken anaerobically at a low temperature and then warmed in the apparatus to body temperature before the measurement is made.¹⁹

In a living animal under hypothermia the blood re-equilibrates. Under anaerobic conditions the total CO_2 content does not change, therefore cooling is associated with a decrease in $p\text{CO}_2$. In the lungs (or in the oxygenator) the blood re-equilibrates with a similar alveolar carbon dioxide tension and accordingly, during the cooling, the CO_2 content increases because of the increased solubility of CO_2 . It was first stressed by Brewin *et al.*⁶ that conclusions based on *in vitro* experiments cannot be applied to the hypothermic animal.

Conversely under hypothermia the same blood CO_2 content is in equilibrium with a lower alveolar tension and consequently less CO_2 will be excreted through the lungs. However, in the tissues, less CO_2 is being produced under these circumstances. Other changes in the respiratory system, such as the increase in dead space at a lower temperature,⁷ also may influence the acid-base balance.

The reasons for the acidosis which is commonly associated with hypothermia are not entirely clear. Evidence has been presented that the hypothermic kidney cannot increase the excretion of hydrogen ions in the presence of acidosis.²¹

In conclusion it can be stated that the effect of hypothermia on the acid-base balance is rather complex. The ionization of all the buffer systems is decreased when the temperature is lowered and the effect of these changes is an increase in available bicarbonate. Thus pH rises when the temperature falls. On the other hand, more carbon dioxide is dissolved at the lower temperature and the increase in carbonic acid tends to counteract the pH shift to the alkalotic side.²²

The decreased ionization of the other buffer pairs, together with an increase in the concentrations of bicarbonate and of carbonic acid under hypothermia, results

in a relative preponderance of the latter buffer pair. The total buffer capacity of the blood is thus reduced, the bicarbonate-carbonic acid system being comparatively inefficient in the physiological pH range with a pK' of approximately 6.1. Accordingly, under hypothermia alterations in the pCO_2 are relatively more effective in changing the pH, and the small changes in pCO_2 produce considerable pH shifts.¹⁸

All the variables of the Henderson-Hasselbalch equation are temperature-dependent. The determination of the acid-base balance in the laboratory at 37°C thus presents a number of difficulties since correction factors and nomograms must be used which may not give precise results in a given patient. The situation is further complicated by the observation that during the cooling process, there are temperature gradients between various parts of the body and even between various areas of the same organ.^{18,23-26} Finally even if an exact assessment of the acid-base balance under hypothermia were possible its meaning would be doubtful since the optimal values for pH and blood gases at any given temperature are unknown.²⁰

3 Discussion of the Working Hypothesis

During extracorporeal circulation and hypothermia, an adequate blood supply to the vital organs usually can be maintained. However, the artificial heart is not as efficient as the normal heart and maintenance of the cerebral circulation is a primary concern while the bypass is in progress. Towards the end of the bypass the state of the myocardium assumes an importance equal to that of the brain since conditions must be created which are favourable for defibrillation and for the subsequent function of the heart. These two aspects will now be discussed.

In adult men, the brain, the weight of which is approximately 2 per cent of the body weight, receives 15 per cent of the cardiac output and consumes almost 20 per cent of the total oxygen requirement.²⁷ It is well known that the cerebral circulation is not governed by the same factors as the systemic and the pulmonary circulation.²⁸ Provided the systemic blood pressure does not drop below a critical level of 60–70 mm Hg,²⁹ the cerebral circulation is independent of the usual vasoconstricting and vasodilating effects.³⁰ The main factors influencing the cerebral circulation are the blood gas concentrations with a high pCO_2 and a low pO_2 producing cerebral vasodilatation and a low pCO_2 and a high pO_2 producing cerebral vasoconstriction.³¹ It is not clear whether the high pCO_2 causes the vasodilatation directly or whether the lowering of the pH is the responsible factor. Some investigators have presented evidence for the former,^{31,32} whereas others favor the latter theory.³³ Since this question is unsettled, it would appear to be preferable to induce both a high pCO_2 and a low pH instead of a low pH only if a high cerebral blood flow is desired. A similar vasodilating effect caused by carbon dioxide and said to be independent of pH has been described in the systemic circulation³⁴ and in the coronary circulation.³⁵

Under the conditions of extracorporeal circulation and bypass, a high oxygen tension is desirable. It has been shown that this alone will not lead to an excessive decrease of cerebral blood flow.^{36,37} To raise the pCO_2 under these conditions may appear contrary to common practice since hyperventilation has been

recommended during anaesthesia³⁸ and especially during hypothermia³⁹. The earlier discussions centred mainly around the prevention of ventricular fibrillation, which is one of the limiting factors of surface hypothermia. It has been shown experimentally that a rapid fall from a high $p\text{CO}_2$ level may produce ventricular fibrillation⁴⁰. Others attributed the increased myocardial irritability to the acidosis produced by the high $p\text{CO}_2$ ^{39,41,42}. Depression of the myocardial contractility was found to be associated with a low pH⁴³. Accordingly, it has been recommended that increases in $p\text{CO}_2$ be avoided altogether by hyperventilation during the period of hypothermia^{44,45}. This concept, however, has not been universally accepted⁴⁶⁻⁴⁹. Under conditions of hypothermia and hypocapnia the dissociation of oxygen from haemoglobin in the tissues may be impaired⁵⁰. Hyperventilation also produces several changes in the blood chemistry in addition to a respiratory alkalosis⁵¹. In a discussion on the maintenance of the acid-base balance the increased excretion of sodium and potassium bicarbonate is of particular importance⁵². It has been well documented that acute respiratory alkalosis leads to a decrease in blood bicarbonate and to an increased bicarbonate excretion in the urine^{53,59}. An increase in blood lactic acid has also been observed⁵⁴.

Conversely, in respiratory acidosis the renal tubular reabsorption of bicarbonate is increased, thus decreasing the bicarbonate excretion in the urine. A high $p\text{CO}_2$ has been shown to be the main stimulus affecting the tubular reabsorption⁵⁵. Conservation of base is of importance during any surgical operation, but especially under conditions of hypothermia since the hypothermic kidney is unable to produce an acid urine^{21,56}. It would seem, therefore, that excessive hyperventilation before bypass should be avoided and that a moderate increase in $p\text{CO}_2$ and a moderate decrease in pH during bypass are of benefit since these changes cause a vasodilatation in the cerebral circulation.

If hypothermia is produced by means of an extracorporeal circulation with an oxygenator in the circuit, the occurrence of ventricular fibrillation is of no significance. At the low temperatures commonly used with this system and after cardiac arrest, the incidence of ventricular fibrillation is increased unless certain drugs are given⁵⁷. The important thing, therefore, is not to prevent fibrillation but to create conditions which are favourable for defibrillation at the end of bypass. It has been suggested that defibrillation is accomplished most easily in the presence of an acidosis⁵⁸, although the evidence presented is rather meagre. Based on this same evidence, it has been the practice in certain centres to produce an acidosis by the intravenous administration of ammonium chloride, which later is neutralized with sodium bicarbonate. Since the occurrence of a metabolic acidosis is one of the major complications following hypothermia^{6,59}, this routine may not be without danger. A respiratory acidosis can easily be corrected by subsequent hyperventilation and, while present, it actually preserves base⁶⁰.

The vasodilating effect of carbon dioxide has already been mentioned. It appears to be particularly important under hypothermia when the viscosity of the blood is increased⁶¹. Further, the circulating blood volume has been reported to be increased during hypothermia^{62,63}. This may be due to pooling as a result of a loss in vasomotor tone⁶⁴, although the total peripheral resistance has been reported to be increased under hypothermia⁶⁵. A high blood flow and the pre-

vention of a fall in blood pressure appear to be of special importance under hypothermia, since it has been reported that at lower temperatures the critical closing pressure in certain areas of the circulation may be higher than normal because of the increased viscosity⁶⁶ If the blood pressure drops below the critical closing pressure this particular area would not be perfused at all The importance of maintaining a state of vasodilatation not only in the cerebral circulation but also in the systemic circulation by preventing hypocapnia under these circumstances is evident

At this point, reference may be made to the experimental work on cooling to lower temperatures than those employed in this study, on freezing and supercooling Under these circumstances, as first shown by Giaja, the survival rate is increased if the animals are in a state of hypoxia and hypercapnia This work has been reviewed recently⁶⁷ It appears that the effects of hypercapnia are maintained at low temperatures Experimental evidence that circulatory reactions to a high CO_2 are not abolished at 20°C has been presented⁶⁸

During extracorporeal circulation when the gas exchange takes place in the oxygenator, the $p\text{CO}_2$ can, within limits, be altered by the composition and the flow rate of the gas to which the blood is exposed in the oxygenator The commonly used high flow rates of several litres of the gas mixture (approximately 97.5 per cent O_2 and 2.5 per cent CO_2) per minute provide an excess of oxygen It was found in preliminary studies that flow rates of one litre per minute and less provide adequate oxygenation of the arterial blood, this quantity of oxygen fully covering the oxygen requirements of the patient At these flow rates, the blood does not get rid of the CO_2 and the $p\text{CO}_2$ rises A high flow of the gas leads to a lowering of the $p\text{CO}_2$ (a situation described by others⁶⁹) but this type of "hyperventilation" is by no means as effective as the gas exchange in the lungs

Before the plan was finally adopted in patients, the literature was searched for evidence of possible side-effects of a temporary respiratory acidosis Although the problem is touched upon by several authors, no definite evidence of deleterious effects could be found High CO_2 tensions were well tolerated by experimental animals^{32 60 68} and by patients⁷⁰ Following hyperventilation with oxygen in normal subjects it was found that during breath holding the $p\text{CO}_2$ may reach 90 mm Hg⁷¹ After the Astrup apparatus was set up, the acid-base balance of several patients was determined during open-heart surgery, using the perfusion methods which were in routine use at that time It was found that a change towards a higher $p\text{CO}_2$ and a lower pH took place during normothermic and hypothermic bypass and that a comparatively small further increase in the $p\text{CO}_2$ would lower the pH to the levels desired at the end of the cardiopulmonary bypass

The acid-base balance may be different in the various compartments of the body The measurement of the intracellular pH may produce new data which will help in the understanding of these problems Determination of the acid-base balance of the cerebrospinal fluid may be of considerable importance since it may reflect certain metabolic aspects of the functions of the central nervous system Only few data are available⁷² It has recently been shown that little bicarbonate penetrates into the cerebrospinal fluid and that the pH is mainly determined by the $p\text{CO}_2$ ⁷² These findings indicate that changes in the pH of the blood may not

reflect pH changes in the cerebrospinal fluid and that the administration of bicarbonate into the blood stream may not correct an acidosis in the cerebrospinal fluid. The significance of this discrepancy, however, is unknown.

Hence it was postulated that during extracorporeal bypass, a $p\text{CO}_2$ in the high normal range would be desirable. It was further postulated that towards the end of a hypothermic bypass procedure a small further increase in $p\text{CO}_2$ would provide a fall in pH which would facilitate defibrillation. An adequate monitoring technique for the control of the acid-base balance was available. Whereas the value of the addition of CO_2 to the gas mixture had been recognized before, it is only since the introduction of a satisfactory monitoring technique that a deliberate attempt at increasing the carbon dioxide tension of the patient has been undertaken. Carbon dioxide has also been used to lower the pH to the desired level by a group using the Edmark technique, i.e. deliberately lowering the pH as the temperature falls.⁷⁴

Although primarily designed for use in patients under hypothermia, the concept was thought also to be of value for bypass procedures done at normal temperature. General and cerebral vasodilatation again is important but the additional acidosis at the end of the bypass is not necessary since ventricular fibrillation ordinarily does not occur. Accordingly, an attempt was made to raise the $p\text{CO}_2$ to the normal range during bypass but not higher. The other phases of the operation were handled as described for the hypothermic cases.

4 Discussion of Results

In this clinical study the temperature of the Astrup apparatus could not be altered since the equipment had to be available at the same time for the routine laboratory work of the hospital. Further, under conditions of fairly rapidly induced hypothermia there are considerable temperature gradients between various parts of the body and the body temperature as such cannot be defined. For these reasons all the determinations were done at a temperature of 37°C and correction factors were applied. The values were corrected to the temperature of the blood in the oxygenator. This temperature is close to the temperature of the mixed venous blood of the patient since the heat exchanger was incorporated in the arterial line.

The correction factor $-0.0147/^\circ\text{C}$ described by Rosenthal² is similar to the ones reported by others.⁷⁵⁻⁷⁷ Considering the old definition of the pH as an expression of the hydrogen ion concentration, a similar factor can be calculated taking into account the increase in the dissociation constant of water with an increase in temperature and disregarding all other changes. At 25°C a pH of 7 signifies neutral reactions, according to the old formula

$$(\text{H}^+) = (\text{OH}^-) = 10^{-7}$$

With increasing temperature the dissociation constant of water increases and at 37°C a neutral reaction is indicated by a pH of 6.81. Accordingly, the pH drops $0.19/12 = 0.0158$ per degree temperature rise.⁷⁸

When the patient's blood was warmed to 37°C , before the $p\text{CO}_2$ was determined, erroneously high results were obtained and these were corrected using the nomogram of Severinghaus.³

With regard to base excess or to deficit, data on temperature changes have not been found in the literature. Small changes may take place and this problem needs further investigation. In this work the uncorrected values obtained with Astrup's method were reported.

There are two major difficulties in assessing the possible benefits of the method. In this series all the hearts which fibrillated (except one) could be defibrillated with one electrical shock. But it is a clinical series without controls and it is impossible to state definitely that the low pH really did facilitate the defibrillation. It is equally difficult to assess the cerebral circulation quantitatively with the evidence available. Unfortunately the electroencephalogram was recorded on an oscilloscope, and no permanent records have been kept in the majority of cases. It is our impression that at 25° C body temperature, the E E G shows more fast wave activity and a higher amplitude when the $p\text{CO}_2$ is deliberately increased.

The other difficulty of assessment stems from the fact that the method was introduced gradually. As outlined previously, a mixture of O_2 and CO_2 was used in all our pump cases. After the introduction of an adequate monitoring system, it was found that a certain degree of CO_2 retention took place during extracorporeal bypass with and without hypothermia. Based on the theoretical considerations mentioned above, the CO_2 retention was then deliberately increased. This was done gradually, trying to obtain higher and higher $p\text{CO}_2$'s as time went on. Consequently there is no sharp dividing line between two groups which could be compared by means of the conventional statistical methods.

The mean values obtained in the patients' arterial blood before bypass, towards the end of the bypass, and at the end of the operation are given in Table II. In seven adult patients the first arterial blood sample could be taken before anaesthesia. The samples labelled "after anaesthesia" were taken 30–60 minutes after the start of the anaesthesia. The samples labelled "before bypass" were taken from the patient either through an arterial needle in the radial artery or from the aorta. By that time the patient had been under anaesthesia for two hours or longer. The effects of moderate hyperventilation are readily apparent. The progressive base deficit has been observed by others under similar circumstances^{79,80}. In order to assess the base deficit, the same figure obtained in an arterial blood sample taken before the patient is given the preanaesthetic medication should be available for comparison. However, in the patient's interest it was decided not to take this sample, which would have necessitated an arterial puncture at 6.30 a.m. on the day of surgery. The zero value used by Astrup⁸ corresponds to a standard bicarbonate concentration of 22.9 mEq/L in the serum. It cannot be assumed that all our patients started out with this concentration, although the means and standard deviations indicate that some were in the zero range at the beginning of anaesthesia and also after one to two hours of anaesthesia.

During bypass blood samples were taken every 10–20 minutes at the arterial end of the oxygenator. For the purpose of comparison the data obtained in the sample with the lowest pH for each run were analysed further and the means are reported in the table. Since a progressive acidosis developed while the bypass was in progress, this usually was the last sample taken during bypass. In the patients whose temperature dropped at least two degrees, correction factors were applied,

and the means of both corrected and uncorrected values are reported. The mean corrected pH values were 7.32 in the normothermia group and 7.33 in the hypothermia group values which are considered to be slightly acidotic. The $p\text{CO}_2$ values (corrected for temperature when necessary) were found to be near the normal range during the bypass, but the means do not give the correct picture. A gradual increase of $p\text{CO}_2$ values to the normal range and slightly higher than normal occurred during bypass. During short runs, the normal range was not reached, hence the values obtained towards the end of bypass in the short cases as a rule were below the mean, whereas those obtained in longer cases were above the mean.

Occasionally a rapid increase of the $p\text{CO}_2$ was observed as soon as the cardiopulmonary bypass was started. This may be due to the fact that the $p\text{CO}_2$ of the blood increased as its temperature increased. If blood is warmed from 25°C to body temperature the $p\text{CO}_2$ almost doubles and CO_2 may be given off to the body under these circumstances.⁸¹ In accordance with this theory the practice was adopted in hypothermia cases of exposing the blood in the oxygenator to air instead of the $\text{O}_2\text{--CO}_2$ mixture. Another reason for this practice is the possibility of oxygen bubble formation if the cold blood is exposed to a high oxygen concentration.⁸²

The increase in base deficit during bypass was not unexpected. Large quantities of bank blood had been added to the patients' blood. Although a large transfusion is well tolerated by a patient in the absence of shock,⁸⁰ during bypass this may account for part of the acidosis. Furthermore, in the course of prolonged procedures, a base deficit develops even when high perfusion flows are used⁸³ and in the two cases with circulatory arrest it was anticipated that a deficit would occur⁸⁴ although other investigators have not confirmed this finding.⁶⁹ Under no circumstances was the base deficit allowed to drop below 10 mEq/L. When that arbitrary limit was reached, sodium bicarbonate was given intravenously (3 patients).

At the end of the operation the pH had risen to low normal values. The $p\text{CO}_2$ had fallen slightly and there was still a base deficit although less than at the end of the bypass. The deficit was slightly less pronounced in patients who were operated upon under normothermia than in those who were cooled. The small difference may be accounted for by the fact that the hypothermia group comprises the more difficult cases with longer bypass periods. On the other hand, the possibility that a metabolic acidosis always occurs following hypothermia cannot be discounted.^{18, 59} The causes of this tendency towards acidosis are not readily apparent. It was conceivable that under hypothermia the availability of oxygen to the cells decreases more than the oxygen requirements of the cells, resulting in a relative hypoxia. There is some experimental evidence that this may be the case.⁸⁵

The increase in base deficit during the first period of the procedure, before the bypass was started, was found to be similar in magnitude to the further increase which occurred during and following bypass. This second period was considerably longer than the first one and furthermore, during the second period, large amounts of the more acidotic blood were given as priming volume of the pump oxygenator and as transfusion. The further increase in acidosis may indicate, however, that the perfusion was not as efficient as the normal blood circulation,

resulting in inadequate tissue perfusion which in time may cause anaerobic metabolism and acidosis⁸⁰ Following bypass, the compensatory mechanisms decreased the base deficit again and no patients received additional base during this period.

In order to produce an acidosis at the end of the cardiopulmonary bypass, as postulated in the working hypothesis, it was not necessary to give intravenous ammonium chloride. A base deficit (or excess acid) was already present. If the $p\text{CO}_2$ was increased from the low levels found before bypass to the normal range or somewhat higher, the pH dropped to the desired level. Following bypass the $p\text{CO}_2$ was lowered again by controlled respiration and the base deficit was partly corrected by the body's regulatory mechanisms. Thus at the end of the operation the acid-base balance was close to the normal range. By paying meticulous attention to the acid-base balance throughout the whole procedure this was usually achieved without additional infusion of sodium bicarbonate.

Over-breathing may occur with controlled respiration under anaesthesia and a progressive loss of base may follow. Indeed, it has been shown that the acidosis associated with thoracic operations for a variety of reasons is similar to that observed following open-heart surgery^{79,86}. The results obtained in this study confirm this finding since they suggest that a part of the acid shift occurred before the bypass was started. The production of a respiratory alkalosis is common anaesthetic practice³⁸. In this series vigorous hyperventilation was avoided and the results show that the respiratory alkalosis was of a mild degree. After completion of the extracorporeal circulation hyperventilation was employed in order to increase the carbon dioxide excretion but no attempt was made to induce a respiratory alkalosis. Again vigorous hyperventilation was avoided as before bypass.

The pH thus underwent a cyclical change. After an initial rise during bypass there was a progressive fall in pH associated with a return of the $p\text{CO}_2$ to normal levels or slightly higher. After termination of the bypass the $p\text{CO}_2$ was reduced by controlled respiration. At the end of the operation the pH returned to a normal level in the majority of the patients. In some cases a slight metabolic acidosis persisted at that time, which always was corrected spontaneously without further treatment. This would appear to be a physiological way to handle the acid-base balance during extracorporeal circulation and hypothermia avoiding the addition of acidifying substances and avoiding the administration of base unless it is specifically required.

At every stage of the procedure large shifts of the pH in either direction were avoided. The importance of preventing extensive changes in pH has been outlined by several investigators^{87,88}. It is interesting to note that the prevention of an excessively low pH during extracorporeal circulation and hypothermia was one of the main arguments of those who recommend hyperventilation and/or the use of pure oxygen in the oxygenator⁸⁹. It is questionable, however, whether all authors included the necessary correction factors in the calculation of the actual pH of the patients. Furthermore, according to the working hypothesis, a temporary lowering of the pH at the end of the bypass was thought to be desirable and no attempt was made to prevent the fall, in fact, it was deliberately induced. In addition to facilitating ventricular defibrillation and the other effects outlined in the discussion, the high CO_2 conserves base by diminishing the renal excretion

of bicarbonate and in so doing it may help prevent a metabolic acidosis in the recovery period. By carefully monitoring both the respiratory and the metabolic acid-base balance⁹⁰ and by adopting the management described, the patients can have the benefits of a high CO_2 during long perfusions and those combined with hypothermia, without being exposed to the risks of excessive changes in the blood pH. The principles of the method, therefore, are close to those outlined recently by Theye *et al*,⁹¹ e.g. "minimal interference with and maximal preservation of" the various body functions.

It should be remembered, however, that the whole concept is based on a number of assumptions, some of which may not be found acceptable in the future. The problems associated with the measurement of pH, $p\text{CO}_2$, and bicarbonate at low temperatures are being actively investigated in many centres and it is quite possible that some of our ideas will change.

SUMMARY AND CONCLUSIONS

Many aspects of the acid-base balance during extracorporeal circulation and during hypothermia are still problematic. In this paper the theoretical background is reviewed which led to the adoption of the following working hypothesis:

The acid-base balance has a direct influence on two important aspects of cardiopulmonary bypass. During bypass a high carbon dioxide tension will ensure an adequate cerebral blood flow and at the end of the bypass a low pH is said to facilitate defibrillation. Both these conditions can be created by avoiding excessive hyperventilation of the patient before bypass and by increasing the $p\text{CO}_2$ during bypass. The arterial $p\text{CO}_2$ was controlled by varying the volume of the O_2/CO_2 gas mixture delivered to the oxygenator.

The method has been employed in 72 consecutive patients. The acid-base balance was monitored using Astrup's apparatus. Large pH shifts were avoided and clinically the patients appeared to do well under this type of management.

The rationale of the concept is discussed and it is concluded that it has been of benefit for the patients upon whom it was used.

RÉSUMÉ

Plusieurs aspects de l'équilibre acide-base au cours de la circulation extracorporelle et de l'hypothermie demeurent encore problématiques. Dans cet article, nous revoyons la théorie de base qui conduit à l'adoption de l'hypothèse suivante:

L'équilibre acide-base exerce une influence directe sur deux aspects importants de la circulation cardio-pulmonaire extracorporelle. Au cours de la circulation extracorporelle, un taux élevé de gaz carbonique va assurer un débit sanguin cérébral adéquat et, à la fin de la circulation, un pH bas est supposé faciliter la défibrillation. Ces deux états peuvent être réalisés en évitant une hyperventilation excessive du malade avant la circulation extracorporelle et en augmentant la pression de CO_2 au cours de cette circulation. La $p\text{CO}_2$ artérielle a été maintenue en variant le volume du mélange gazeux O_2/CO_2 introduit dans l'oxygénateur.

Nous avons utilisé cette méthode chez 72 malades consécutifs. La courbe de l'équilibre acide-base a été visualisée grâce à l'appareil Astrup. Nous avons évité des changements marqués du pH et, cliniquement, cette façon de procéder a semblé avantageuse à nos malades. Nous avons exposé la logique de ce point de vue, et nous en venons à la conclusion que, chez les malades où nous l'avons utilisée, cette méthode a rendu service.

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