

Causes of metabolic acidosis in extracorporeal circulation at normothermia

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The development of a mild metabolic acidosis during general anaesthesia has been reported by many workers (Bunker, Brewster, Smith, and Beecher, 1952; Pontius, Watkins, Manheim, Allen, Sauvage, and Gross, 1958; Robertson and Frazer, 1958). Likewise the early onset of a slight but definite metabolic acidosis has been observed in dogs during cyclopropane anaesthesia and the degree of acidosis was increased by thoracotomy (unpublished observations). Metabolic acidosis has also been described as a serious complication of open heart surgery (Kolff, Effler, and Groves, 1960). During operation with the aid of an extracorporeal circulation there is a relatively long anaesthetic phase before the start of the bypass procedure. Hyperventilation and the consequent respiratory alkalosis have been advocated as a compensation for the metabolic acidosis produced by low flow perfusion (Keats, Kurosu, Telford, and Cooley, 1958). Subsequently it has become the custom in many clinics for the anaesthetist to hyperventilate the patient before the start of the bypass procedure (Ito, Faulkner, and Kolff, 1957; Norlander, Pitzele, Edling, Norberg, Crafoord, and Senning, 1958; McGoon, Moffitt, Theye, and Kirklin, 1960; Sloan, Harris, MacKenzie, and Stern, 1962). Although superficially this may be considered a logical approach, the substitution of a state of respiratory alkalosis cannot be expected to correct that of a metabolic acidosis and in fact it will aggravate such a state. We therefore decided to study this problem further in a controlled investigation during experimental bypass procedures in dogs.

Part I of this report concerns a comparison of the acid-base ratio before the onset of cardio-pulmonary bypass in dogs which had been subjected to hyperventilation during pre-bypass anaesthesia and that in dogs which had not been subjected to such pre-bypass hyperventilation.

Part II of the report presents the results of studies of the acid-base physiology in the course of six consecutive normothermic bypass operations with-

out hyperventilation during the correction of ventricular septal defects in children.

MATERIALS AND METHODS

PART I Measurements of the acid-base equilibrium of arterial blood were carried out on dogs in the thoracotomy phase before the onset of total cardio-pulmonary bypass.

Mongrel dogs of both sexes, weighing from 12 to 36 kg., were anaesthetized with intravenous sodium thiopentone (20 to 25 mg./kg. body weight) and anaesthesia was maintained thereafter on a cyclopropane-oxygen mixture given through a closed circuit by endotracheal intubation and hand ventilation. Nylon catheters were inserted into the left femoral artery, through the femoral vein into the inferior vena cava, and through the cephalic vein into the superior vena cava. Pressures were transduced by inductance manometers and recorded on a multi-channel ultraviolet light recorder (N.E.P.). Mean pressures were determined by electrical integration and zero reference point was measured from the surface of the operating table. The electrocardiogram was monitored continuously. A standard sternal splitting thoracotomy was performed. Cannulae for gravity drainage to the heart-lung machine were placed in the superior and inferior venae cavae through the right atrium. The right femoral artery was cannulated for pump inflow. All dogs were given heparin, 3 mg./kg. body weight, before insertion of the atrial cannulae. After these initial procedures cardio-pulmonary bypass was begun at normothermia.

The dogs were divided into two groups according to the degree of ventilation to which they were subjected. A significant level of hyperventilation was arbitrarily defined as that giving a partial pressure of carbon dioxide (P_{CO_2}) of less than 30 mm. Hg in the arterial blood. Group A comprised six dogs which had been hyperventilated and group B comprised five dogs which had not been significantly hyperventilated (arterial P_{CO_2} 30 mm. Hg or more).

In each group arterial blood samples from the left femoral artery were taken before the onset of cardio-pulmonary bypass.

PART II Measurements of the acid-base equilibrium of arterial blood were carried out before, during, and in

the first three post-operative hours after cardio-pulmonary bypass at normothermia for the correction of a ventricular septal defect in each of six children.

The surface area of these six children ranged from 0.7 to 1.4 m.² The anaesthetic and thoracotomy procedures were as described in Part I. The cannulation procedure was modified. Nylon catheters were inserted into the right radial artery, the inferior vena cava via the saphenous vein at the groin, and the superior vena cava via a forearm vein. Pressures were recorded as previously described. The electrocardiogram was monitored continuously. The patients were given heparin, 3 mg./kg. body weight, before insertion of the atrial cannulae. After these initial procedures cardio-pulmonary bypass was started at normothermia for the repair of the ventricular septal defect. A Melrose N.E.P. heart-lung machine was used and primed with heparinized, cross-matched and inter-matched donor blood collected into siliconed glass bottles on the day of operation. Fifty millilitres of a 5% solution of sodium bicarbonate was added to the blood in the machine. When the machine was primed 5% carbon dioxide was added to the oxygen in the oxygenator and at the onset of perfusion the CO₂ content was reduced to 2½% and maintained at that level throughout the operation. (It is important to measure accurately the quantity of CO₂ used, otherwise unpredictable and wide variations in the arterial PCO₂ may be obtained. It has been found that the concentration of carbon dioxide in commercial cylinders of mixed 5% carbon dioxide and oxygen may vary between 2 and 9% on gas analysis. We therefore now deliver each gas separately through rotameters to the machine.)

A perfusion rate of 2.4 l./m.² surface area/min. was used without alteration during each of the six perfusions. Frequent arterial blood samples were taken from the right radial artery or the arterial line of the machine. Venous blood from the gravity drainage line was also sampled every 15 minutes during the bypass procedure. No patient was cyanosed, anaemic or polycythaemic before operation and all had serum electrolytes, liver function tests, and blood urea nitrogen within the normal range.

Acid-base equilibrium of arterial blood Arterial blood samples were collected into sterile syringes, the dead space of which had been occluded by undiluted heparin solution (1,000 I.U./ml.), and analysed immediately. Arterial blood pH was determined according to the method of Wynn and Ludbrook (1957). Total plasma CO₂ content was measured according to the method of Van Slyke and Neill (1924). Packed cell volume (P.C.V.) was determined by the Hawksley micro-centrifuge method. Arterial and venous blood oxygen saturation was determined by a Brinkman haemoreflexor. From these values and using the nomogram of Singer and Hastings (1948) the remaining variables, PCO₂ and whole blood buffer base, were derived.

RESULTS

As shown in Table I, in the six dogs deliberately hyperventilated, all with an arterial PCO₂ of less

than 30 mm. Hg, the average whole blood buffer base before bypass was 43 mEq/l. (range 40 to 45 mEq/l.). In the five dogs which were not subjected to significant hyperventilation, *i.e.*, their arterial PCO₂ was 30 mm. Hg or more, the average whole blood buffer base before bypass was 46.8 mEq/l. (range 46 to 48 mEq/l.) (Table II). The arterial blood oxygen saturation during each of these 11 experiments was always above 95% and the systemic arterial pressure was always above a mean of 60 mm. Hg.

TABLE I

ACID-BASE EQUILIBRIUM OF ARTERIAL BLOOD OF DOGS IMMEDIATELY BEFORE BYPASS WITH HYPERVENTILATION (PCO₂ < 30 mm. Hg)

Dog No.	Weight (kg.)	pH	Whole Blood Buffer Base (mEq/l.)	PCO ₂ (mm. Hg)	P.C.V. (%)	After Induction (min.)
1	26.5	7.595	44	15	50	70
2	36	7.424	44	27	52	119
3	16	7.540	40	12.5	52	105
4	13	7.614	45	15	52	104
5	12	7.439	40	23	42	110
6	17	7.464	45	23.5	56	103

TABLE II

ACID-BASE EQUILIBRIUM OF ARTERIAL BLOOD OF DOGS IMMEDIATELY BEFORE BYPASS WITHOUT SIGNIFICANT HYPERVENTILATION (PCO₂ > 30 mm. Hg)

Dog No.	Weight (kg.)	pH	Whole Blood Buffer Base (mEq/l.)	PCO ₂ (mm. Hg)	P.C.V. (%)	After Induction (min.)
7	20.2	7.456	48	30	67	141
8	18.1	7.384	46	34	54	122
9	29	7.410	48	34.5	55	130
10	12.8	7.411	46	32.5	49	65
11	17.4	7.339	46	42	49	65

The normal whole blood buffer base value for dogs in our laboratory is 48 to 50 mEq/l. Although pre-anaesthetic buffer base values are not available for the 11 dogs used in this study, there is no reason to believe that these healthy dogs differed in any way from normal animals.

Acid-base studies of arterial blood during the course of six consecutive human perfusions using a Melrose N.E.P. pump oxygenator at normothermia are presented in Table III. They show no significant change in whole blood buffer base values during or at the end of perfusion nor up to three hours after completion of the bypass procedure. The mean systemic arterial pressure was never below 60 mm. Hg at any stage during the six operations. The arterial blood oxygen saturation was always above 90% before, during, and after perfusion except in case 1, in whom there was some arterial blood oxygen unsaturation in the post-operative phase, the arterial blood being 81% saturated.

TABLE III

ACID-BASE EQUILIBRIUM STUDIES IN CHILDREN DURING NORMOTHERMIC PERFUSIONS FOR CORRECTION OF VENTRICULAR SEPTAL DEFECTS

pH	Whole Blood Buffer Base (mEq/l.)	PCO ₂ (mm. Hg)	P.C.V. (%)	Arterial Blood Oxygen Saturation (%)	
<i>Case 1, male, 12 years. Surface area 1.2 m.² Duration of perfusion 28 min.</i>					
After induction of anaesthesia	7.369	46	41	40	98
Immediately pre-bypass	7.387	46	39	41	98
Immediately post-bypass	7.393	44	37	40	94.5
Late post-bypass	7.355	44	41	39	81
<i>Case 2, male, 15 years. Surface area 1.4 m.² Duration of perfusion 52 min.</i>					
After induction of anaesthesia	7.436	48	37	38	96
Immediately pre-bypass	7.390	46	40	38	96
Immediately post-bypass	7.406	45	34.5	38	98
Late post-bypass	7.346	46	44	38	95
<i>Case 3, male, 7 years. Surface area 0.8 m.² Duration of perfusion 39 min.</i>					
After induction of anaesthesia	7.324	39	43.5	39	97
Immediately pre-bypass	7.254	41.5	48.5	42	95.5
Immediately post-bypass	7.278	42	46	41	91
Late post-bypass	7.260	40	43	41	91
<i>Case 4, female, 7 years. Surface area 0.8 m.² Duration of perfusion 32 min.</i>					
After induction of anaesthesia	7.247	42	59	38	97.5
Immediately pre-bypass	7.382	42.5	35	39	97.5
Immediately post-bypass	7.493	46	32	36	97.5
Late post-bypass	7.308	43	46	38	94.5
<i>Case 5, male, 14 years. Surface area 1.4 m.² Duration of perfusion 54 min.</i>					
After induction of anaesthesia	7.348	45	43	40	98
Immediately pre-bypass	7.356	45	42	39	98
Immediately post-bypass	7.434	45.5	33	39	98
Late post-bypass	7.345	44	40.5	37	94.5
<i>Case 6, female, 4 years. Surface area 0.7 m.² Duration of perfusion 41 min.</i>					
After induction of anaesthesia	7.418	45	36	36	94
Immediately pre-bypass	7.458	44	34	39	99
Immediately post-bypass	7.477	43	28	38	99
Late post-bypass	7.438	44	32	37	97

During the actual period of bypass the venous blood returning to the machine was between 65% and 75% saturated in each case.

DISCUSSION

Davies, Haldane, and Kennaway (1920) were probably the first to demonstrate that hyperventilation resulted in a depression of the plasma bicarbonate level and a simultaneous increase in the rate of bicarbonate excretion by the kidney. Stanbury and

Thomson (1952) showed that the increased excretion of bicarbonate in response to hyperventilation was accompanied by an equivalent increase in the urinary excretion of sodium and potassium. Barker, Singer, Elkinton, and Clark (1957) voluntarily hyperventilated six normal subjects and found the characteristic renal response to respiratory alkalosis to be a decrease in urinary hydrogen ion output, which was measured principally by an increase in the excretion of bicarbonate and potassium ions in an alkaline urine. Associated with these changes there was a decrease in the output of ammonia and titratable acidity. The resultant effect on total body fluids was a loss of buffer base. It has been known for some time that hyperventilation results in an accumulation of lactic acid (Nims, Gibbs, and Lennox, 1942), and Huckabee (1958) has demonstrated that the increase in lactate under these conditions is accompanied by a simultaneous increase in pyruvate and that in fact no excess lactate over pyruvate is produced. Huckabee concludes that this increase in lactate during hyperventilation is not due to tissue hypoxia and this is supported by the recent work of Eichenholtz, Mulhausen, Anderson, and MacDonald (1962). Giebisch, Berger, and Pitts (1955) as well as Elkinton, Singer, Barker, and Clark (1955) have shown that there is an immediate tissue as well as a renal compensation to respiratory alkalosis. These workers have shown that the electrolyte shifts and lactic acid accumulation which occur during hyperventilation disappear rapidly on return to normal breathing. However, the renal compensation which involves the excretion of large amounts of bicarbonate with sodium and potassium is much less rapidly reversible on return to normal breathing.

A comparison of the results for the two groups of dogs studied shows the development of a greater degree of metabolic acidosis (as measured by a decrease in whole blood buffer base values) in the dogs which had been deliberately hyperventilated in the pre-bypass phase.

There were no arterial hypoxic or hypotensive factors which could have explained the development of this metabolic acidosis in the hyperventilated dogs. The anaesthetic conditions were similar in both groups of animals and the very mild metabolic acidosis which was observed in the non-hyperventilated dogs is wholly compatible with the effects of the cyclopropane anaesthesia and thoracotomy as reported by other workers (Bunker *et al.*, 1952).

Hyperventilation has been used by Geddes and Gray (1959) as a supplementary anaesthetic agent and it has the advantage that it abolishes the need for more potent and less controllable anaesthetic

substances and also that, since carbon dioxide is a normal metabolite, recovery from hyperventilation is rapid. With the particular anaesthetic technique used by Gray and Rees (1952), namely nitrous oxide, oxygen, and muscle relaxants, hyperventilation is necessary to prevent movement by the patient. The analgesic effects of hyperventilation have been thought to be due to cerebral hypoxia consequent upon reduced cerebral blood flow (Clutton-Brock, 1957). Robinson and Gray (1961), however, consider that the changes in arterial PCO_2 and pH usually observed are sufficient to account for the depression of cerebral function.

Papadopoulos and Keats (1959) and Robinson (1961) considered the metabolic acidosis induced by hyperventilation to be of little clinical significance. Although this may be acceptable for the patients studied by these authors, who were undergoing a variety of minor operative procedures, the problem in patients undergoing cardio-pulmonary bypass is entirely different. Anaesthesia and surgery are more prolonged in these patients and perfusion itself is liable to lead to the development of a metabolic acidosis either because of its length or because of other complicating factors. It appears to be both unnecessary and indeed undesirable for the patient to have a metabolic acidosis consequent upon hyperventilation, no matter how mild, before the stage of bypass with its risk of increasing acidosis has been reached.

The causes of metabolic acidosis related to cardio-pulmonary bypass itself have been extensively studied and may be considered under the following headings.

HYPOXIC ACIDOSIS Inadequate tissue oxygenation will lead to anaerobic metabolism and an accumulation of acid metabolites. This state of affairs is liable to develop during an inadequate blood perfusion rate (DeWall, Warden, Gott, Read, Varco, and Lillehei, 1956; Pontius *et al.*, 1958; Clowes, Neville, Sabga, and Shibota, 1958; Clark, 1958). Arterial oxygen unsaturation, even in the presence of adequate perfusion, will produce the same metabolic changes (Pontius *et al.*, 1958). Systemic arterial hypotension either before, during or after bypass will produce the same effect. Ito *et al.* (1957) have correlated the degree of metabolic acidosis developing during 35 consecutive perfusions with the presence of hypotension before, during or after perfusion and found a significant positive relationship.

It is now widely accepted that in humans a perfusion flow rate of 2.4 l./m.² surface area/min. is adequate (Starr, 1959) and this flow rate was

unaltered during all our perfusions. Ito *et al.* (1957) considered hypotension to be significant if the mean systemic arterial pressure was less than 50 mm. Hg for more than two minutes during perfusion. During the six human perfusions reported, the mean systemic arterial pressure was never below 60 mm. Hg at any time. In addition the arterial blood oxygen saturation was maintained above 90% and venous blood returning to the machine was always above 65% saturation.

COMPENSATION FOR HYPOCAPNIA If no carbon dioxide is added to the gas mixture in the oxygenator subnormal levels of arterial PCO_2 will be obtained with the consequent metabolic compensations as previously discussed. This problem has been investigated by Pontius *et al.* (1958). It is our custom to add carbon dioxide to the oxygenator as previously described in the section on methods.

ACIDOTIC PRIMING BLOOD Stored blood becomes increasingly acidotic due to anaerobic metabolism of dextrose for the maintenance of the red cell membrane electrolyte 'pump' (Loutit, Mollison, and Young, 1943). However, it is agreed that this acidosis is unavoidable if the electrolyte shifts, in particular that of potassium moving out of the cells, are to be minimized by the addition of the dextrose. In addition acid citrate dextrose has a pH of 5.5 (Loutit, 1945). During normal transfusion procedures neither of these factors is detrimental to the patient but in the sudden massive exchange transfusion of the extracorporeal circulation both are important. It is our practice, therefore, to mitigate the acidosis of storage by using blood freshly collected into siliconed glass bottles immediately before operation and by using heparin saline (30 mg. heparin with 15 ml. physiological saline and 400 ml. blood) instead of acid citrate dextrose as the anticoagulant diluent. The pooled blood is buffered in the machine before bypass by adding 50 ml. of a 5% solution of sodium bicarbonate.

It is therefore suggested that by using an adequate perfusion rate and adequate blood oxygenation, and by avoiding systemic arterial hypotension, acidotic priming blood, and hyperventilation at any stage, metabolic acidosis need never be a problem during normothermic perfusion of up to one hour's duration. The results here reported show that hyperventilation, which is commonly and fallaciously held to be a satisfactory compensating mechanism against the development of metabolic acidosis, is in fact not so and is neither desirable nor necessary. Applying these principles to human perfusions, we have not observed metabolic acidosis

in any patient at any stage. It should be stressed that it can be misleading to rely purely on pH estimations which can be within the normal range in the presence of a marked compensated metabolic acidosis secondary to hyperventilation. It is essential to measure in addition to pH at least one other parameter, such as whole blood buffer base, as previously outlined, or alternatively the PCO_2 .

SUMMARY

The acid-base ratios of two groups of dogs immediately before bypass are compared. In the first group the dogs had been subjected to pre-bypass hyperventilation and in the second group the dogs had not been hyperventilated. It has been shown that the dogs subjected to hyperventilation suffered a greater reduction in whole blood buffer base than those not hyperventilated and that this is due to the development of a metabolic acidosis secondary to the respiratory alkalosis.

The causes of metabolic acidosis during extracorporeal bypass are discussed.

Studies of acid-base equilibrium were undertaken during the course of six consecutive normothermic open heart operations.

The principles used in the avoidance of a metabolic acidosis in these patients are outlined.

The danger of accepting pH as the sole estimation of the blood buffering capacity is stressed, and the fallacy of hyperventilation as a compensation of metabolic acidosis is discussed.

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