HYPOKALAEMIA DURING EXTRACORPOREAL CIRCULATION

AN EXPERIMENTAL STUDY

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Temporary extracorporeal circulation has fulfilled its initial promise, making possible the surgical correction of many types of cardiovascular disease. The success of these major procedures does not only depend upon the skill of the surgeon, but also upon the ability of the operative team to maintain the stability of the patient's internal environment. Metabolic derangements, unless immediately recognized and corrected, significantly affect the morbidity and mortality in patients undergoing open heart procedures.

Availability of better laboratory equipment, the pursuit of numerous investigations in experimental surgery and the careful assessment of human results, all contribute to the improvement of the understanding of these problems. Consequently, many modifications have been adopted since the initial successful human application of extracorporeal circulation by Gibbon in 1951.[16]

We agree with others[6,13,22] that the use of haemodilution, with high flow rates at slightly reduced body temperatures, results in better total body perfusion. For the past two years the bubble oxygenator, primed with one-third 5% dextrose in water and two-thirds fresh, whole, heparinized blood, has been used at this centre. A flow rate of 2·3 litres/minute/sq.metre body surface area is maintained throughout cardiopulmonary bypass; 100% oxygen is used in the mixing chamber. However, the introduction of these techniques was associated with an increased incidence of post-bypass ventricular arrhythmias, especially in patients with acquired valvular disease.

A group of workers elsewhere[18] pointed out the relationship between ventricular irritability and low serum potassium levels, and emphasized that the resulting arrhythmias could be prevented by the administration of intravenous potassium chloride. Our subsequent clinical studies confirmed this observation. It was suspected that the hypokalaemia was not brought about by urinary loss and/or haemodilution alone. Before the introduction of haemodilution techniques, there had been occasional reports of the development of hypokalaemia after cardiopulmonary bypass.[5,14] However, several other groups using haemodilution techniques did not report decreases in potassium concentration of the same magnitude as those observed by us.[1,24]

This investigation was therefore designed to reproduce, in the experimental animal, cardiopulmonary bypass conditions similar to those used clinically. The changes in potassium concentration in both extra- and intracellular water were studied. As the relationship between extra- and intracellular shifts of potassium and hydrogen ions is well known, both extra- and intracellular pH were measured under the same experimental conditions.

EXPERIMENTAL METHODS

Operative Techniques

Adult mongrel dogs weighing between 15 and 25 kg. are used, anaesthetized with intravenous phenobarbitone sodium. A cuffed endotracheal tube is inserted and anaesthesia maintained by means of nitrous oxide and oxygen only. The cuff is inflated and intermittent positive-pressure respiration instituted.

Bilateral femoral cut-downs are made. The left femoral vein and artery are dissected free, cannulated with polythene tubing and connected to a Cardirex for continuous monitoring of pressures.

The thoracic cavity is entererd through a right thoracotomy by way of the 4th intercostal space, and the peri-

cardium is opened. The rectus muscle is exposed and carefully dissected free, removing all fibrous sheath and fat. The muscle fibres are not damaged.

The animal is heparinized (1·5 mg. heparin/kg. bodyweight). The left femoral artery is cannulated and connected to the arterial line of the bubble oxygenator. Venous drainage is via a catheter placed in the right atrium via the atrial appendage.

Before bypass commences, the following specimens are taken:

1. Blood for the estimation of plasma electrolytes.
2. Arterial blood for studies of acid-base disturbances.
3. Approximately 10 G of the rectus muscle is excised, carefully blotted free of blood, all fat and fibrous tissue removed and the muscle sample then placed in tinfoil on ice.
4. Approximately 5 G of cardiac muscle is taken from the right ventricle. At this stage the right ventricle is invariably opened, bypass being commenced immediately. Once the specimen has been removed, the ventriculotomy is repaired with a single layer of 'O' black silk. The cardiac muscle is carefully blotted free of blood and is placed in tinfoil on ice.

Bypass is continued for 2 hours, ensuring that the perfusion is at least 100 ml./kg./minute for the duration of the experiment. If hypothermia is used, rewarming is commenced and the experiment is completed when the oesophageal temperature reaches 37°C. At the end of bypass, the specimens of blood and muscle are taken again, in a similar manner.

Plasma sodium and potassium are measured with a Beckman flame photometer, and plasma chloride by the method of Schales and Schales.[20] Blood pH, pCO_2, base excess and standard bicarbonate are estimated by the micro-Astrup method.[3] The concentrations of these electrolytes and hydrogen ions in the extracellular water (Na^+e, K^+e, pHe) are calculated, allowing for the Donnan effect.

Each sample of muscle is treated in the same way:

1. Extracellular Fluid Space (ECF)

Immediately after the muscle biopsy is taken, the ECF is measured by a modification of the method of Rosenberg *et al.*[19] All estimations are done in duplicate. A piece of muscle weighing 0·4 - 0·6 G is trimmed neatly and, after weighing, cut ends are touched with a flamed loop to prevent leakage of ECF. This sample is incubated in 5 ml. Krebs-Ringer bicarbonate buffer in a shaking Dubnoff metabolic incubator. The incubations are carried out for one hour under 95% oxygen and 5% carbon dioxide. The incubating medium is made up fresh every day from a concentrated stock solution, which is kept at 4°C. All flasks are gassed continuously for 30 minutes before incubation. C^{14}-inulin (mol. weight of over 5000, specific activity 1 mC/m.mole) is present in the medium. At the end of one hour the sample of muscle is removed, washed 3 times in normal saline, and gently blotted dry. It is then re-incubated in a flask containing 5 ml. Krebs-Ringer bicarbonate buffer, but without added C^{14}-inulin. This incubation is carried out for 30 minutes in an atmosphere of 95% oxygen and 5% carbon dioxide. The tissues are then removed and their total water content estimated by drying in an oven at 110°F to constant weight.

One hundred µl. of the medium before and after incubation in the presence of C^{14}-inulin, and of the medium after re-incubation of the muscle sample without added inulin, are pipetted into glass vials. Each vial also contains 15 ml. of a counting solution, consisting of dioxane and ethanol as the solvents, with dephenyloxazolyl as the primary phosphor, and 1·4-bis-2-(5-phenyloxazolyl) benzene as the secondary phosphor. The counting solution also contains naphthalene. Radioactivity is assayed in a Packard Tri-Carb liquid scintillation spectrophotometer. All estimations are done in duplicate. The counting efficiency is 50 - 70% and the amount of quenching is constant.

The ECF is calculated from the following formula:

$$\text{ECF (ml.)} = \frac{\text{Total counts per minute in the medium after the second incubation}}{\text{Counts per minute per ml. of medium after the first incubation}}$$

This is then expressed as a percentage of total tissue water.

2. Electrolytes in Fat-free Dry Solid (FFDS)

Approximately 0·5 G of muscle is dried overnight in an electric oven at 110°F to constant weight. The loss of weight is taken as the weight of water contained in the sample, and the percentage of water is calculated on this basis.

The dried muscle is crushed and carefully transferred to a 10 ml. volumetric flask. Fat is extracted with ethyl ether and then with petroleum ether (BP 40 - 60°C). The ether is evaporated off and the process is repeated until the weight is constant. As a rule, 4 washings with ether are found to be sufficient.

Three ml. of concentrated nitric acid (70%) are added to the fat-free, dry muscle residue, and are slowly evaporated to incipient dryness, on an electric hotplate, in a hood. No charring should occur; if this does occur, 3 ml. of concentrated nitric acid are again added and the evaporation process is recommenced. The residue is allowed to cool, and is then made up to 10 ml. with a lithium nitrate solution (250 p.p.m.). The flask is warmed until all salts are in solution, and is cooled again. The solution is used for direct measurement of sodium and potassium, using a Beckman flame photometer.

3. Intracellular Electrolytes (Na^+i of K^+i)

The concentration of sodium and potassium in the intracellular water (ICF) is calculated from the data previously obtained. The ICF is determined by subtracting the ECF from the total tissue water. As the concentration of these electrolytes in the ECF is known, and as the total content of sodium and potassium in the ECF plus the ICF has been estimated, the concentration of these electrolytes in the ICF can be determined.

4. Intracellular Hydrogen Ion Concentration

This is measured by the method of Wadell and Butler.[23] The theoretical aspect of this technique has been fully discussed by Irvine *et al.*[12]

5·5-Dimethyl-2:4 oxazolidinedione (DMO), 70 mg./kg. bodyweight, is injected intravenously into the dog, and 1 hour is allowed for equilibration. DMO (200 mg./litre) is added to the priming fluid used for extracorporeal bypass.

To measure plasma DMO 0·5 ml. plasma, 4·5 ml. NaH_2PO_4 and 20 ml. ether are placed in a ground-glass, stoppered, Pyrex test tube (B.24) which is shaken for 15 minutes. Fifteen ml. of ether phase plus 5 ml. of borate buffer are added to a clean B.24 test tube, which is shaken for 10 minutes.

Muscle DMO is measured by grinding 0·5 G wet muscle thoroughly with 4·5 ml. NaH_2PO_4 and transferring it quantitatively to a B.24 test tube. Twenty ml. of ether are added. The tube is shaken for 15 minutes. To 15 ml. of the ether phase, 5 ml. borate buffer are added and shaken again for 10 minutes.

Absorbance in the final borate buffer phase is read at 215 and 220 micro m. on a Zeiss spectrophotometer PM Q11, the hydrogen lamp being used as the light source. Due regard is had for the muscle and plasma blank.

Intracellular pH (pH_i is calculated from the following equation:

$$pH_i = pKa + \text{Log}\left\{\frac{[Cr\,(1+Vr)-Vr]}{[1+10^{(pH_e-pKa)}]-1}\right\}$$

where pH_e = extracellular pH
pH_i = intracellular pH
pKa = negative logarithm of the dissociation constant of DMO and is equal to 6·13.
Cr = ratio of concentration of DMO in total muscle water and plasma water.
Ve = ratio between volumes of extracellular fluid and intracellular fluid in muscle sample.

RESULTS

The metabolic changes occurring during extracorporeal circulation in the dog were studied under 4 different experimental conditions.

Group A (4 dogs)

(*a*) Priming fluid: 1 litre fresh, heparinized blood, 1·5 litres 5% dextrose in water.
(*b*) Temperature: Moderate hypothermia (to 30°C).
(*c*) Anaesthesia: Normal ventilation using oxygen only for blood oxygenation in mixing chamber of pump.

The results are shown in Table I. It can be seen that under these experimental conditions there is only a slight fall in the potassium concentration of the plasma after bypass, and no significant change in potassium concentration in the intracellular water of cardiac or skeletal muscle, or of total muscle potassium expressed as mEq./100 G FFDS. Similarly, extracellular and intracellular pH are not materially altered. It is noteworthy that, while there is no significant change in total muscle water or in the ECF of cardiac or skeletal muscle before and after bypass, the plasma sodium and chloride are greatly diminished. There is no uniform change in intracellular sodium concentration in either cardiac or skeletal muscle. The fall in plasma sodium and chloride were interpreted as being due to haemodilution.

Group B (4 dogs)

(*a*) Priming fluid: 1 litre fresh heparinized blood, 1·5 litres 5% dextrose in water.
(*b*) Temperature: Normothermia (36 - 38°C).
(*c*) Anaesthesia: Normal ventilation, using oxygen only for blood oxygenation in the mixing chamber.

Group B differs from group A in only one respect: the bypass was carried out under normothermic conditions. The results are shown in Table II and it can be seen that the findings are essentially the same as those obtained in Group A (carried out under hypothermia).

Group C (4 dogs)

(*a*) Priming fluid: 1 litre fresh, heparinized blood, 1·5 litres Ringer's lactate solution.
(*b*) Temperature: Normothermia (36 - 38°C).
(*c*) Anaesthesia: Normal ventilation, using oxygen only for blood oxygenation in the mixing chamber.

Group C differs from the previous two groups in that Ringer's lactate solution was used instead of 5% dextrose water in the priming fluid. The results are shown in Table III.

It should be noted that in this experiment the plasma sodium and chloride did not fall, confirming the postulate that the fall in the concentration of these electrolytes in the plasma in the previous experiments was due to haemodilution.

Group D (3 dogs)

This experiment was designed to investigate primarily the effects of changes in extra- and intracellular pH on plasma and cellular potassium concentrations.

(*a*) Priming fluid: 1 litre fresh, heparinized blood, 1·5 litres 5% dextrose in water, 13·5 mEq. potassium chloride, 500 ml. sodium bicarbonate.
(*b*) Temperature: Normothermia.
(*c*) Anaesthesia: (*i*) 85% oxygen in 15% carbon dioxide is used for 1 hour in an attempt to produce respiratory acidosis. In addition, the animals are curarized and hypoventilated.
(*ii*) As soon as the specimens have been obtained, the anaesthetic mixture is changed to oxygen and nitrous oxide, and the animal is hyperventilated until bypass is commenced.

TABLE I. THE CHANGES IN PLASMA, INTRACELLULAR, TOTAL SKELETAL AND CARDIAC MUSCLE POTASSIUM AND SODIUM ARE SHOWN, TOGETHER WITH ALTERATIONS IN EXTRA- AND INTRACELLULAR pH AND PLASMA CHLORIDE BEFORE AND AFTER BYPASS, IN GROUP A

		Pre-bypass	*Post-bypass*
Plasma potassium (mEq./l.)		3·6 (3·1 — 3·9)*	3·4 (2·5 — 3·8)
Intracellular potassium (mEq./l.)	Cardiac muscle	99·4 (89·2 —121·3)	95·1 (85·2 —111·3)
	Skeletal muscle	109·3 (76·8 —127·5)	107·8 (99·3 —119·0)
Total muscle potassium (mEq./100 G FFDS)	Cardiac muscle	36·2 (34·2 — 40·1)	35·4 (34·4 — 37·3)
	Skeletal muscle	37·7 (35·1 — 40·1)	38·1 (36·5 — 39·1)
Extracellular pH (pH_e)		7·32 (7·25— 7·38)	7·30 (7·27— 7·33)
Intracellular pH (pH_i)	Cardiac muscle	6·88 (6·72— 6·99)	6·62 (5·75— 7·12)
	Skeletal muscle	6·94 (6·87— 7·07)	7·02 (6·91— 7·17)
Extracellular fluid volume (ECF)**	Cardiac muscle	20·5 (16 — 24)	18·0 (16 — 20·5)
	Skeletal muscle	22·4 (18 — 26·3)	20·0 (19 — 22·4)
Total muscle water***	Cardiac muscle	77·8 (76·0 — 79·1)	77·7 (76·4 — 78·3)
	Skeletal muscle	77·4 (74·8 — 79·6)	76·9 (73·9 — 79·6)
Plasma sodium (mEq./l.)		150 (146 —152)	122 (117 —129)
Intracellular sodium (mEq./l.)	Cardiac muscle	16·2 (2·1 — 31·8)	12·7 (1·9 — 22·11)
	Skeletal muscle	20·5 (9·8 — 32·8)	17·9 (6·3 — 26·4)
Total muscle sodium (mEq./100 G FFDS)	Cardiac muscle	12·0 (9·3 — 17·0)	11·3 (8·1 — 14·5)
	Skeletal muscle	14·2 (10·9 — 17·5)	13·0 (10·8 — 13·6)
Plasma chloride (mEq./l.)		113 (109 —115)	96 (91 —100)

* All figures are given as means of 4 experiments with the range in brackets.
** Expressed as % of total muscle water.
*** Expressed as % of net weight of muscle.

To counteract any haemodilution effect or urinary loss, 13·5 mEq. of potassium chloride are added to the priming fluid. The changes experimentally produced in pHe are always due to a combination of respiratory and metabolic factors.

The results for each of the 3 dogs are shown in Tables IV, V and VI, and in Fig. 1.

In contrast to the findings in all our previous experiments, these dogs showed consistent changes in plasma potassium. In the presence of an acidosis, the plasma potassium rose

TABLE II. THE CHANGES IN PLASMA, INTRACELLULAR AND TOTAL SKELETAL AND CARDIAC MUSCLE POTASSIUM AND SODIUM ARE SHOWN, TOGETHER WITH ALTERATIONS IN INTRACELLULAR AND EXTRACELLULAR pH AND PLASMA CHLORIDE BEFORE AND AFTER BYPASS, IN GROUP B

		Pre-bypass	*Post-bypass*
Plasma potassium (mEq./l.)		3·8 (3·3 — 4·0)*	3·4 (2·3 — 4·7)
Intracellular potassium (mEq./l.)	Cardiac muscle	94·0 (83·4 —112·6)	91·1 (90·9 —107·5)
	Skeletal muscle	116·6 (84·1 —129)	117·6 (98·6 —144)
Total muscle potassium (mEq./100 G FFDS)	Cardiac muscle	34·1 (27·9 — 43·8)	35·5 (29·9 — 45·7)
	Skeletal muscle	35·4 (28·1 — 40·9)	35·4 (30·6 — 39·4)
Extracellular pH (pH_e)		7·38 (7·31— 7·46)	7·24 (7·15— 7·30)
Intracellular pH (pH_i)	Cardiac muscle	6·77 (6·62— 6·99)	6·62 (6·37— 6·85)
	Skeletal muscle	7·01 (6·92— 7·06)	6·87 (6·64— 7·06)
Extracellular fluid volume (ECF)**	Cardiac muscle	19·0 (14 — 28)	16·0 (11 — 21)
	Skeletal muscle	21·0 (15 — 27)	20·0 (15 — 26)
Total muscle water***	Cardiac muscle	76·2 (75·0 — 77·5)	76·5 (76·0 — 76·9)
	Skeletal muscle	74·6 (71·0 — 77·5)	74·2 (71·1 — 75·1)
Plasma sodium (mEq./l.)		148 (140 —158)	119 (105 —129)
Intracellular sodium (mEq./l.)	Cardiac muscle	16·1 (4·1 — 40)	17·0 (6·3 — 32·9)
	Skeletal muscle	13·8 (6·4 — 27)	16·5 (5·1 — 32·5)
Total muscle sodium (mEq./100 G FFDS)	Cardiac muscle	15·2 (11·9 — 24·3)	16·8 (9·0 — 18·3)
	Skeletal muscle	12·4 (10·3 — 15·3)	12·6 (8·6 — 15·0)
Plasma chloride (mEq./l.)		113 (110 —117)	96 (89 — 99)

* All figures expressed as means of 4 experiments with the range in brackets.
** Expressed as % of total muscle water.
*** Expressed as % of net muscle weight.

TABLE III. THE CHANGES IN PLASMA, INTRACELLULAR AND TOTAL SKELETAL AND CARDIAC MUSCLE POTASSIUM AND SODIUM ARE SHOWN, TOGETHER WITH ALTERATIONS IN INTRA- AND EXTRACELLULAR pH AND PLASMA CHLORIDE BEFORE AND AFTER BYPASS IN GROUP C

		Pre-bypass	*Post-bypass*
Plasma potassium (mEq./l.)		3·7 (3·4 — 4·0)*	4·0 (3·1 — 4·8)
Intracellular potassium (mEq./l.)	Cardiac muscle	94·0 (83·4 —112·6)	91·1 (90·9 —107·5)
	Skeletal muscle	116·6 (84·1 —129)	117·6 (98·6 —124)
Total muscle potassium (mEq./100 G FFDS)	Cardiac muscle	30·3 (26·1 — 34·5)	32·4 (29·6 — 34·6)
	Skeletal muscle	30·4 (21·5 — 39·2)	36·6 (33·1 — 40·6)
Extracellular pH (pH_e)		7·36 (7·31— 7·4)	7·34 (7·21— 7·4)
Intracellular pH (pH_i)	Cardiac muscle	6·82 (6·62— 6·93)	6·96 (6·71— 7·01)
	Skeletal muscle	6·89 (6·87— 6·92)	6·81 (6·59— 7·03)
Extracellular fluid volume (ECF)**	Cardiac muscle	12·7 (8·0 — 17·6)	10·8 (8·0 — 14·0)
	Skeletal muscle	14·5 (10·5 — 22·6)	9·4 (10·5 — 22·6)
Total muscle water***	Cardiac muscle	77·1 (75 — 78·5)	79·3 (76·3 — 78·9)
	Skeletal muscle	75·2 (74·5 — 76·5)	75·4 (73·9 — 76·0)
Plasma sodium (mEq./l.)		151 (142 —158)	146 (138 —151)
Intracellular sodium (mEq./l.)	Cardiac muscle	13·6 (4·1 — 34·3)	12·9 (3·4 — 34·1)
	Skeletal muscle	12·6 (7·0 — 22·9)	17·5 (8·0 — 34·7)
Total muscle sodium (mEq./100 G FFDS)	Cardiac muscle	14·5 (10·5 — 22·6)	14·3 (9·4 — 20·5)
	Skeletal muscle	11·9 (8·9 — 17·3)	13·4 (12·1 — 15·3)
Plasma chloride (mEq./l.)		116·9 (112 —126)	121 (113 —135)

* All figures are given as means of 4 experiments with the range in brackets.
** Expressed as % of toal muscle water.
*** Expressed as % of net weight of muscle.

significantly and, when an alkalosis was induced, the plasma potassium fell considerably. The rise in the concentration of potassium in intracellular water, when the plasma potassium falls, is clearly demonstrated. It is also of interest that the changes in intracellular pH closely parallel those in extracellular pH. Of note is the inverse relationship which has been shown to exist between the concentration of K^+_i and intracellular hydrogen ions under these experimental conditions.

TABLE IV.* THE CHANGES IN PLASMA, INTRACELLULAR AND TOTAL SKELETAL MUSCLE POTASSIUM AND SODIUM ARE SHOWN, TOGETHER WITH ALTERATIONS IN EXTRA- AND INTRACELLULAR pH AND PLASMA CHLORIDE BEFORE AND AFTER BYPASS, IN GROUP D, DOG 1

	Pre-bypass	*Post-bypass*
Plasma potassium (mEq./l.)	6·2	2·5
Intracellular potassium (mEq./l.)	92	116·2
Total muscle potassium (mEq./100 G FFDS)	28·9	34·1
Extracellular pH (pH_e)	7·13	7·64
Intracellular pH (pH_i)	6·91	7·28
Extracellular fluid volume (ECF)**	14	13
Total muscle water***	72	71·9
Plasma sodium (mEq./l.)	116	114
Intracellular sodium (mEq./l.)	20·2	21·9
Total muscle sodium (mEq./100 G FFDS)	11·8	12·0
Plasma chloride (mEq./l.)	114	76

* All these observations were made on skeletal muscle.
** Expressed as % of total muscle water.
*** Expressed as % of net muscle weight.

TABLE V.* THE CHANGES IN PLASMA, INTRACELLULAR AND TOTAL SKELETAL MUSCLE POTASSIUM AND SODIUM ARE SHOWN, TOGETHER WITH ALTERATIONS IN EXTRA- AND INTRACELLULAR pH AND PLASMA CHLORIDE BEFORE AND AFTER BYPASS, IN GROUP D, DOG 2

	Pre-bypass	*Post-bypass*
Serum potassium (mEq./l.)	5·2	2·2
Intracellular potassium (mEq./l.)	122·5	140·5
Total muscle potassium (mEq./100 G FFDS)	38	40·9
Extracellular pH (pH_e)	7·31	7·73
Intracellular pH (pH_i)	6·41	7·05
Extracellular fluid volume (ECF)**	17	17
Total muscle water***	71	72·5
Plasma sodium (mEq./l.)	149	145
Intracellular sodium (mEq./l.)	7·3	16·2
Total muscle sodium (mEq./100 G FFDS)	10·9	13·9
Plasma chloride (mEq./l.)	108	90

* All these observations were made on skeletal muscle.
** Expressed as % of total muscle water.
*** Expressed as % of net muscle weight.

TABLE VI.* THE CHANGES IN PLASMA, INTRACELLULAR AND TOTAL SKELETAL MUSCLE POTASSIUM AND SODIUM ARE SHOWN, TOGETHER WITH ALTERATIONS IN EXTRA- AND INTRACELLULAR pH AND PLASMA CHLORIDE BEFORE AND AFTER BYPASS, IN GROUP D, DOG 3

	Pre-bypass	*Post-bypass*
Plasma potassium (mEq./l.)	5·4	2·0
Intracellular potassium (mEq./l.)	130·1	147·3
Total muscle potassium (mEq./100 G FFDS)	32·1	38·0
Extracellular pH (pH_e)	6·72	7·69
Intracellular pH (pH_i)	6·13	7·18
Extracellular fluid volume (ECF)**	18·3	19·4
Total muscle water***	71	74
Plasma sodium (mEq./l.)	141	148
Intracellular sodium (mEq./l.)	11·9	20·5
Total muscle sodium (mEq./100 G FFDS)	10·5	14·7
Plasma chloride (mEq./l.)	95	91

* All these observations were made on skeletal muscle.
** Expressed as % of total muscle water.
*** Expressed as % of net muscle weight.

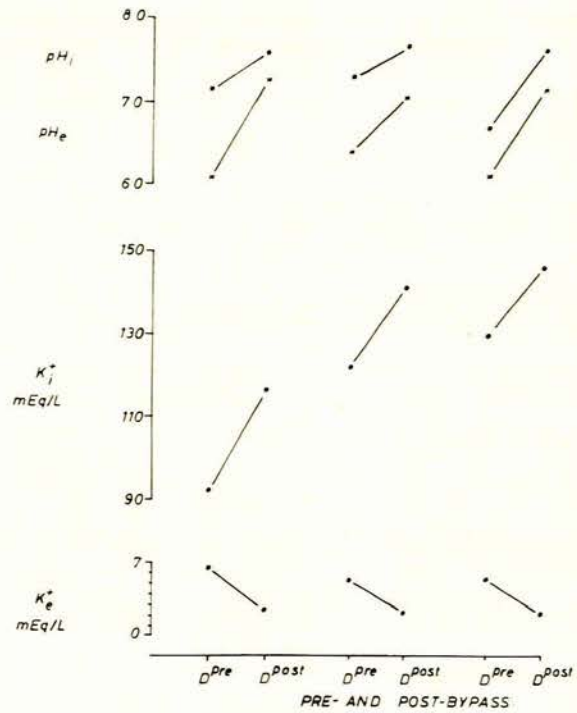
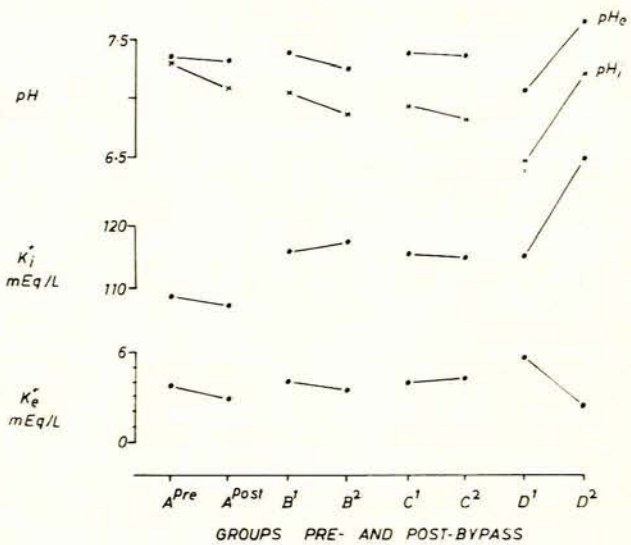


Fig. 1. The relationship between intracellular pH (pH_i), extracellular pH (pH_e), intracellular potassium (K^+_i) and extracellular potassium (K^+_e) with pre-bypass acidosis and post-bypass alkalosis (group D; 3 dogs).

Fig. 2 compares the results in the 4 experimental groups.



RELATIONSHIP BETWEEN INTRACELLULAR AND EXTRACELLULAR POTASSIUM AND pH.

Fig. 2. The relationship between pH_e, pH_i, K^+_i and K^+_e in the 4 experimental groups. The figures shown are the means of 3–4 observations.

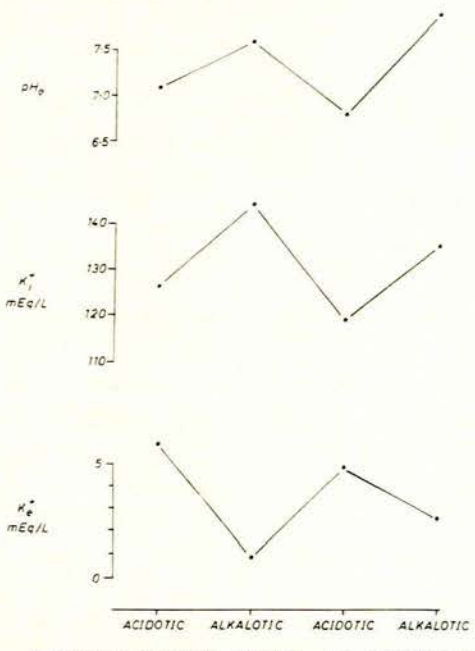
The results of a further experiment are shown in Table VII and Fig. 3. In this dog, acidosis and alkalosis were produced

TABLE VII.* THE CHANGES IN PLASMA, INTRACELLULAR AND TOTAL SKELETAL MUSCLE POTASSIUM AND SODIUM ARE SHOWN, TOGETHER WITH ALTERATIONS IN EXTRACELLULAR pH, CO_2 TENSION, STANDARD BICARBONATE AND PLASMA CHLORIDE DURING ACIDOSIS AND ALKALOSIS

	Acidosis	*Alkalosis*	*Acidosis*	*Alkalosis*
Plasma potassium (mEq./l.)	5·9	3·0	5·0	2·4
Intracellular potassium (mEq./l.)	125·9	142·2	119·1	136·3
Total muscle potassium (mEq./100 G FFDS)	32·8	35·2	27·9	34·4
Extracellular pH (pH_e)	7·12	7·61	6·85	7·89
pCO_2 (mm.Hg)	102	22	Over 150	14
Standard bicarbonate (mEq./l.)	14	30	10	32
Extracellular fluid volume (ECF)**	26	28	20	22
Total muscle water***	74·8	75·5	75·1	75·4
Plasma sodium (mEq./l.)	148	140	156	157
Intracellular sodium (mEq./l.)	9·6	11·2	13·6	12·8
Total muscle sodium (mEq./100 G FFDS)	11·5	12·4	13·6	17·4

* All these observations were made on skeletal muscle.
** Expressed as % of total muscle water.
*** Expressed as % of net muscle weight.

by alternating under- and overventilation. Intravenous sodium bicarbonate was also given at the appropriate time to induce alkalosis. Once again the fall in K^+_e was clearly shown to be associated with a rise in pH_e and in K^+_i concentration.



RELATIONSHIP BETWEEN ACIDOSIS AND ALKALOSIS OF K_e, K_i, & pH_e.

Fig. 3. The relationship between pH_e, K^+_i and K^+_e under conditions of alternating acidosis and alkalosis.

Total muscle potassium (expressed as mEq./100 G FFDS) rose in all instances when the K^+_e fell. When there was no fall in K^+_e no significant change was observed in total muscle potassium.

In only two of the dogs was there a rise in intracellular sodium but in none was there a fall in plasma sodium concentration. This change in Na^+_i in 2 dogs may have been related to the administration of sodium bicarbonate.

DISCUSSION

It has been postulated that the low plasma potassium levels which may be seen during and after bypass are due to a combination of hyperglycaemia and hyperventilation alkalosis.[7] Indeed, it has been established that plasma potassium is profoundly influenced by changes in extracellular pH.[4, 5, 21]

The early *in vitro* work of Fenn[9, 10] suggested that there might be a cause and effect relationship between K^+_e and pH_e. More recent *in vivo* studies[2, 15, 21, 22] suggest that changes in pH_e alter K^+_e levels independent of changes in total body potassium. Thus, acidosis increases and alkalosis decreases the plasma potassium without affecting total body potassium. These alterations are related to intracellular buffering and, therefore, are ultimately dependent upon intracellular pH changes. It is clear that variations in K^+_e are due to pH changes and do not depend on changes of pCO_2 or bicarbonate concentration.[4]

The fact that alkalosis lowers K^+_e independent of a change in total body potassium should not be confused with the fact that alkalosis also causes a loss of potassium from the body. Thus an increased renal excretion results in a further lowering of plasma potassium. However, the demonstration of a fall in plasma potassium in the presence of alkalosis occurs in the nephrectomized animal which excludes renal loss as the most important cause.[11]

We investigated the effect of large changes in extracellular pH on potassium shifts. All 4 dogs so studied showed a striking and significant relationship between pH_e and the K^+_e concentration. In each case, when the dog was acidotic, the K^+_e was high. In contrast the K^+_e was low in the presence of an alkalosis. This fall in K^+_e was consistently associated with a large increase in K^+_i demonstrating that shift of potassium had occurred across the cell membrane. This increase in the concentration of K^+_i was always associated with a rise in pH_i, i.e. a fall in the concentration of hydrogen ions within the cell. There was no consistent change in Na^+_i concentration. This inverse relationship between the concentration of intracellular potassium and hydrogen ions has also been demonstrated in potassium depletion of dietary origin, in which an intracellular acidosis occurs.[14] It is of great interest that under our experimental conditions intracellular alkalosis was associated with a shift of potassium into the cells.

The use of hyperventilation, excessive elimination of carbon dioxide in the heart-lung machine and the administration of sodium bicarbonate during cardiopulmonary bypass, can result in a dangerous degree of alkalosis. Our experiments show that these factors are at least partially responsible for the alterations in intra- and extracellular potassium levels. Many patients with acquired disease of the heart valves tend to be potassium-depleted before

surgery, as a result of years of diuretic therapy. Such patients are prone to uncontrollable ventricular arrhythmia when fully digitalized, and this hazard is greatly increased by any abrupt alteration in the potassium gradient across the myocardial cell membrane, such as we have shown to occur during alkalosis.

The clinical application of these studies, the more controlled use of hyperventilation and of the administration of sodium bicarbonate, and the use of 3% carbon dioxide in the heart-lung machine—prevented the alkalosis previously encountered. As a result, hypokalaemia after cardiopulmonary bypass has been eliminated and the incidence of postoperative ventricular arrhythmias has been reduced.

Hyponatraemia and hypochloraemia were noticed in the first two groups of experiments and were clearly the result of haemodilution. This has been the experience of other workers too.[7] We prevented these changes by the use of Ringer's lactate in the priming fluid.[37]

SUMMARY

Metabolic studies before and after cardiopulmonary bypass in the dog have shown that postoperative hypokalaemia under these conditions is due to alkalosis. The fall in plasma potassium is the result of a redistribution of this ion, with an increase in intracellular potassium concentration. An inverse relationship between intracellular hydrogen ion and intracellular potassium concentration has been demonstrated. The clinical importance of these observations is stressed.

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