

## Potassium Levels, Acid-Base Balance and Massive Blood Replacement

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THE cardiotoxic effects of an elevated concentration of extracellular potassium have been recognized for a long time. The fact that bank blood preserved in acid-citrate-dextrose solution contains from 10 to 25 mEq. of potassium per liter of plasma<sup>1</sup> has led to the assumption that hyperkalemia is a major factor in the production of the cardiovascular problems associated with the administration of large volumes of bank blood. The investigations of LeVein and co-workers<sup>2</sup> on dogs lent support to this hypothesis. They found markedly increased serum concentrations of potassium in animals rendered hypovolemic by bleeding and retransfused with bank blood. In the same type of investigation on dogs, Nahas<sup>3</sup> failed to observe elevation of serum potassium. Howland and co-workers<sup>4</sup> confirmed Nahas' observations in man. They found that serum potassium levels remained within normal limits at rates of blood administration as high as 7,500 ml. an hour. Scribner<sup>5</sup> and other investigators have noted the relationship between respiratory or metabolic acidosis and hyperkalemia. Since the majority of patients requiring massive blood replacement are in a state of metabolic acidosis secondary to inadequate tissue perfusion, it is conceivable that elevation of the serum potassium can be attributed to depression of the pH level rather than to the administration of excessive potas-

sium in bank blood. The present study was conducted to clarify the relation between serum potassium concentration, acid-base balance of the blood, and massive blood replacement.

### Method

Thirty-five patients were studied who received acid-citrate-dextrose preserved blood in volumes ranging from none to 21 pints. The maximum rate of transfusion in the majority of cases was 60-70 ml./minute with a range of 27 to 120 ml./minute. All blood was warmed after 3-5 pints were given by means of a blood warmer described previously.<sup>6</sup>

Arterial blood samples were obtained from the brachial or femoral artery immediately before operation, at intervals during operation, and at the conclusion of the procedure. The blood was drawn into a heparinized syringe which was stoppered and transferred immediately to the Anesthesiology Laboratory for determination of the pH, CO<sub>2</sub> content, and potassium level. The pH of the whole blood and of the equilibrated separated plasma was measured by the Astrup technique.<sup>7,8</sup> By the use of conversion factors the carbon dioxide content and carbon dioxide tension were calculated from this data by a method described in a previous report.<sup>9</sup> The nomogram of Singer and Hastings was employed for determination of the buffer base and interpretation of the acid-base status of the patient. Potassium determinations were made by the Department of Biochemistry employing a flame

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TABLE 1. Comparison of Acid-Base Status and Potassium Levels

Acid-Base Status	No. of Cases	K <sup>+</sup> Change from Preoperative Level*				Range of K <sup>+</sup> Change from Preoperative Level	
		Point of Lowest BB <sup>†</sup>		End of Operation		Point of Lowest BB <sup>†</sup>	End of Operation
		Up	Down	Up	Down		
Normal:							
1. Blood: 0-2,500 ml.	7	3	4	3	4	-.30 to +.70	-.30 to +.70
2. Blood: 3,000 ml. and over	6	3	3	3	3	-.65 to +.75	-.65 to +.75
Compensated metabolic acidosis:							
1. Blood: 0-2,500 ml.	3	0	3	0	3	-.05 to -1.10	-.05 to -.70
2. Blood: 3,000 ml. and over	4	2	2	1	3	-.05 to +1.80	-.20 to +.65
Uncompensated metabolic acidosis:							
1. Blood: 0-2,500 ml.	8	2	5	2	5	-1.25 to +.40	-1.25 to +.40
2. Blood: 3,000 ml. and over	7	7	0	6	1	+.40 to +2.80	-.50 to +2.80

\* K<sup>+</sup> values within normal limits except in two patients (6.0 mEq./liter and 7.6 mEq./liter).

photometer. The normal range of values for serum potassium at Memorial Hospital is 3.8 to 5.2 mEq./liter.

### Results

Thirteen of the 35 patients maintained a normal acid-base status during the entire course of operation. The blood replaced in these 13 patients varied from none to 19½ pints, with seven patients receiving 3,000 ml. or more of blood.

The remaining 22 patients developed metabolic acidosis due to hypovolemia with re-

sultant inadequate tissue perfusion. In the majority of the 22 patients, the pH values were considerably below normal. Respiratory compensation restored the pH to normal in seven patients in spite of a low carbon dioxide content and buffer base. The range of blood replacement varied from none to 21 pints. Eleven of the 22 cases received 2,500 ml. or less of blood and a similar number were transfused with more than 2,500 ml. before the end of operation.

Table 1 compares the preoperative level of potassium with the changes that occurred at (1) the point of the lowest buffer-base value during operation and (2) at the conclusion of the procedure. In the 13 patients with normal acid-base balance during operation, the pH values ranged from 7.36 to 7.52 with the majority between 7.38 and 7.43. The number of patients showing an increase in potassium level approximately equal the number showing a decrease in potassium levels during operation, compared with the preoperative values (table 1). Irrespective of the volume of blood replacement (as high as 19 pints), there was no evidence of hyperkalemia in any patient. The highest potassium value was 5.35 mEq. in a patient who had received only three pints of blood.

A similar situation existed in all but one of the seven patients with normal pH values (7.36-7.43) resulting from respiratory com-

TABLE 2. Comparison of Degree of pH Change and K<sup>+</sup> Change in Patients with Uncompensated Metabolic Acidosis

Patient	Blood: 0-2,500 ml.			
	Point of Lowest BB <sup>†</sup>		End of Operation	
	pH Change from Pre-operative Value	K <sup>+</sup> Change from Pre-operative Value	pH Change from Pre-operative Value	K <sup>+</sup> Change from Pre-operative Value
1	-.04	+.20	+.05	+.20
2	-.09	-.20	-.09	-.20
3	-.09	-.35	-.09	-.35
4	-.10	.00	-.10	.00
5	-.13	-1.25	-.13	-1.25
6	-.15	-.10	-.15	-.10
7	-.16	-.15	-.16	-.15
8	-.18	+.40	-.18	+.40

compensation of a metabolic acidosis. The exception was a patient subjected to a bilateral radical neck dissection and resection of the mandible who developed a potassium level of 6.00 mEq./liter after receiving 10 pints of blood. Following the administration of an additional 10 pints, the potassium level fell to 4.00 mEq./liter at the conclusion of the operation. The pH of the blood at the time of the elevated potassium level was 7.41.

In the 15 patients with uncompensated metabolic acidosis subsequent to hypovolemia, the blood pH ranged from 7.19 to 7.35 in the eight patients transfused with less than 3,000 ml. of blood and from 7.18 to 7.34 in the seven cases who received 3,000 ml. (or more) of blood. Table 1 indicates that the changes in potassium level in the eight patients who received less than 6 units of blood were very similar to those in the group with normal pH values during operation. Five cases showed decreased levels of potassium at the time of maximal depression of the buffer-base value, the potassium level was increased in two patients and unchanged in another. In contrast, all seven patients who received 3,000 ml. (or more) of blood during the course of operation developed an increase in potassium level beyond the preoperative value at the time of metabolic acidosis. At this point the volume of blood replacement varied from 2,000 to 5,000 ml.

All but three of the 15 patients with uncompensated metabolic acidosis still had hypovolemia with a decreased blood pH at the conclusion of the operation. One of the three

TABLE 3. Comparison of Degree of pH Change and K<sup>+</sup> Change in Patients with Uncompensated Metabolic Acidosis

Patient	Blood: 3,000 ml. and over			
	Point of Lowest BB <sup>+</sup>		End of Operation	
	pH Change from Pre-operative Value	K <sup>+</sup> Change from Pre-operative Value	pH Change from Pre-operative Value	K <sup>+</sup> Change from Pre-operative Value
1	-.08	+.60	-.08	+.60
2	-.10	+.45	-.10	+.45
3	-.10	+.40	+.03	-.50
4	-.10	+2.80	-.11	+2.80
5	-.14	+.90	-.14	+.90
6	-.17	+.60	+.04	+.60
7	-.19	+1.10	-.19	+1.10

patients with a normal postoperative acid-base balance developed a marked drop in potassium level after restoration of the pH to higher levels. The respective values in this case were as follows: preoperative: pH 7.39, K<sup>+</sup> 4.15; point of lowest buffer base: blood administered 3,000 ml., pH 7.29, K<sup>+</sup> 4.55; end of operation: blood administered 10,500 ml., pH 7.42, K<sup>+</sup> 3.65. In the other two patients there was no change in potassium level associated with the increased level of pH.

In spite of an elevation in operative potassium level beyond the preoperative value in many of the patients with uncompensated metabolic acidosis, there was only one instance of a serum potassium value (7.60 mEq.) in the definite hyperkalemic range. This occurred during a period of severe hemorrhagic

TABLE 4. Acid-Base Status and K<sup>+</sup> Levels in Patients Receiving 5,000 ml. or more Blood

Patient	Units of Blood Replacement		pH and K <sup>+</sup> Levels						Change in K <sup>+</sup> from Preoperative Level	
	Units at Point of Lowest BB <sup>+</sup>	Units at End of Operation	Preoperative		Point of Lowest BB <sup>+</sup>		End of Operation		Point of Lowest BB <sup>+</sup>	End of Operation
			pH	K <sup>+</sup>	pH	K <sup>+</sup>	pH	K <sup>+</sup>		
1	6½	21	7.39	4.15	7.29	4.55	7.42	3.65	+.40	-.50
2	7	10	7.37	4.45	7.43	4.60	7.36	4.00	+.15	-.45
3	10	20	7.45	4.20	7.41	6.00	7.41	4.00	+1.80	-.20
4	18	19½	7.41	4.20	7.44	3.90	7.43	4.00	-.30	-.20
5	12	12	7.42	4.50	7.41	4.10	7.41	4.10	-.10	-.40
6	10	18	7.35	4.35	7.18	4.95	7.39	4.95	+.60	+.60
7	5	21	7.46	4.05	7.41	4.00	7.55	4.70	-.05	+.65

shock in a patient subjected to bilateral radical neck dissection and was associated with a blood pH of 7.33.

In tables 2 and 3 the extent of the change in pH and potassium level are compared at the point of maximum depression of buffer base and at the end of operation in the 15 patients with uncompensated metabolic acidosis. Although in many cases the potassium level rose in association with a fall in pH (especially in the group with blood replacement of 3,000 ml. and over) there was no consistent mathematical ratio between the two sets of values.

Table 4 shows the pH values, potassium levels and blood replacement in the seven patients in the series who received 5,000 ml. or more of blood during operation. The potassium levels at the conclusion of operation showed no consistent change in comparison with the preoperative values in spite of blood replacement as high as 10,500 ml. A decrease in postoperative potassium level occurred in five cases. Although the potassium value was increased in two patients at the end of operation, the levels were still within normal limits. There were no deaths in the series.

### Discussion

A discussion of the clinical implications of hyperkalemia or hypokalemia must be based on the interrelation between the concentration of potassium in the extracellular space and the potassium content of the rest of the body. At normal serum concentration the potassium in the extracellular space represents only about 1.4 per cent of the total body content of the cation. The major stores of intracellular potassium are found in association with muscle and tissue protein, red blood cells, liver and muscle glycogen stores, and to a small extent in bone and other areas. In an effort to define accurately the terms "potassium depletion" and "potassium excess" Scribner and Burnell<sup>10</sup> relate these disturbances in potassium metabolism to the ratio between the potassium content and the potassium capacity of the body. The latter term is defined as "the ability or capacity of the body to hold or bind potassium ions." On this basis, potassium depletion represents a greater capacity than content,

whereas the reverse situation exists in the case of potassium excess.

In the majority of clinical conditions concentration of potassium in the serum is an accurate index of the content and capacity of the cation in the rest of the body. With serum potassium values above 3 mEq./liter, Scribner found that changes in total body potassium of 100–200 mEq./liter produced corresponding 1.0 mEq./liter changes in serum potassium. When the initial potassium level was below 3.0 mEq./liter, changes of 200–400 mEq./liter in total body potassium were required to effect the same 1.0 mEq./liter change in serum concentration.

The only major factor influencing the level of serum potassium concentration apart from the total body content is the acid-base balance of the blood. Several investigators have proved that acidosis increases and alkalosis decreases the potassium concentration of the serum. The relationship, as described by Burnell and Scribner,<sup>11</sup> is an inverse change of approximately 0.4 to 1.2 mEq./liter in serum potassium concentration for every 0.1 unit variation in the pH of the blood. Simmons<sup>12</sup> found that the potassium level corresponded to the pH of the blood rather than to the causative factor, metabolic or respiratory, responsible for the deviation of the pH from normal. In addition to changes in the acid-base status of the blood, independent lowering of serum potassium levels may result from the administration of glucose and insulin. Other factors, such as diminution of renal function, dehydration, variations in extracellular fluid volume and steroid depletion and excess, have failed to affect alterations in serum potassium concentration which were at variance with changes in the total body content of potassium.

LeVeen and co-workers<sup>1</sup> believe that the major cause of cardiac arrest in hypovolemic patients receiving large volumes of bank blood preserved in acid-citrate-dextrose solution is hyperkalemia due to (1) the elevated potassium content of the bank blood and (2) the glycogenolytic effect of epinephrine on the liver with concomitant release of potassium into the hepatic veins. The results of the present series do not support this contention. In the group of 17 patients who received 3,000 ml. or more of bank blood, 10 patients had

normal operative and postoperative blood pH values. Only two of these 10 patients showed any significant elevation of the serum potassium level above the preoperative value. A level of 6.0 mEq./liter during operation in one of the two patients returned to normal at the end of the procedure after the administration of an additional 5,000 ml. of bank blood. The potassium level in the second patient did not exceed 5.15 mEq./liter. There was a fall in the concentration of potassium in six patients and no significant change in the other two. In contrast, the other seven patients who developed markedly decreased blood pH values as the result of uncompensated metabolic acidosis all showed an increase in serum potassium level above the preoperative value at the time of the metabolic acidosis. The potassium concentration was sufficiently elevated (7.60 mEq./liter) to warrant a diagnosis of hyperkalemia in only one of the seven cases. Although the 18 patients in the series who received less than 3,000 ml. of blood showed a considerable variation in potassium level during operation, there was no evidence of any marked increase at any time.

The absence of dangerous hyperkalemia in the human subject during massive blood replacement can be attributed to several factors. As Howland<sup>4</sup> has shown, the administration of a unit of bank blood in five minutes results in a total dosage of 0.6 to 1.6 mEq. of potassium per minute. The danger level of sustained potassium infusion in a 70 kg.-man is 1.8 mEq./minute.<sup>13</sup> In the present series the maximum rate of transfusion was 120 ml. per minute and the average 60–70 ml./minute. The blood was also warmed after 3–5 pints were given. Since refrigeration causes potassium to leave the erythrocytes and an increase in temperature has the reverse effect, this could be a contributory factor in reducing the amount of administered potassium.

In addition to the increased potassium content of bank blood, LeVein attributed the hyperkalemia of his hypovolemic dogs to elevated levels of catechol amines resulting from the stimulation of hemorrhagic hypotension. He also referred to high levels of carbon dioxide as a possible contributing factor. Legon and Nahas<sup>14</sup> have shown in dogs infused with lactic acid that elevated catechol-

amine levels do not occur until the pH has fallen to 7.0 or lower. In the present series, the minimum pH value was 7.18 and the carbon dioxide tension was either low or within normal limits.

The most consistent increase in potassium levels during operation occurred in the seven patients who developed metabolic acidosis during the course of procedures involving replacement of more than 2,500 ml. of blood. The elevated potassium levels, which appeared at the time of maximum depression of the buffer base, did not increase further after the administration of additional quantities of blood varying from 2 to 13 units. This is contributory evidence that bank blood *per se* is not the major factor responsible for increase in potassium concentration during massive blood replacement.

In view of the evidence that the transfusion of large quantities of bank blood does not result in marked elevation of the serum potassium level, other factors must be present in the patients in whom the operative potassium value rose significantly above the preoperative value. Scribner<sup>9</sup> and other investigators have demonstrated the marked sensitivity of serum potassium levels to changes in the pH of the blood. In addition, Howard<sup>15</sup> and Moore<sup>16</sup> have noted the role of extensive tissue trauma in the production of increased serum potassium values. Both factors were present in the seven patients with uncompensated metabolic acidosis and blood replacement of 6 or more units. Although a significant increase in potassium level did not occur in the eight patients with uncompensated metabolic acidosis who received less than 6 units of blood, this result was not necessarily the effect of decreased volume of transfusion, since tissue trauma was also minimal in all the patients in this group. The maximal elevation of potassium level above the preoperative value (+.40) in these eight patients was associated with the minimal blood pH value of 7.19. The two patients with normal pH values who developed elevated operative potassium levels in the presence of massive blood replacement were both subjected to operations involving extensive tissue dissection. In one of the patients the potassium level returned to normal after

the administration of an additional 10 units of bank blood.

Although a large number of patients showed an elevation of serum potassium level in association with a decrease in blood pH, there was no consistent mathematical relationship between the two sets of values. A similar finding was attributed by Burnell and associates<sup>17</sup> to the variety of factors which influence the total potassium content of the body and are reflected in the level of potassium in the extracellular space.

### Summary and Conclusions

The administration of large volumes of bank blood preserved in acid-citrate-dextrose solution does not play a significant role in the development of increased levels of serum potassium concentration during operation.

The major factor responsible for elevation of the serum potassium level during operation is a decrease in pH of the blood. Massive tissue trauma may be a contributory factor.

In the presence of both extensive tissue trauma and uncompensated metabolic acidosis there is a consistent increase in the level of potassium during operation in comparison with the preoperative value. Less consistent results occur when only one of the two factors is present.

Only two of the 35 patients in the series showed potassium levels during operation high enough to warrant the diagnosis of hyperkalemia.

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