Hyperkalaemia during massive blood transfusion in paediatric craniofacial surgery

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Children undergoing major craniofacial surgery (MCFS) often require transfusion in excess of one blood volume. Therefore they were the subject of a retrospective review which looked at the longitudinal trend of plasma potassium concentration [K^+] during surgery. Ten of eleven children had a statistically significant increase in plasma potassium concentration during their intraoperative course and in five the potassium concentration exceeded 5.5 mmol · L^{-1}. This was in contrast to the stable intraoperative plasma [K^+] observed in a control group which did not receive blood transfusion. All MCFS children received a blood transfusion with red blood cell concentrates (RBCconc). The age of the units of RBCconc which had been transfused was 16.1 ± 8.4 days. The amount of extracellular potassium in 28 units of RBCconc was determined in order to estimate the amount of free potassium (K_{dose}) which the MCFS group received. The plasma [K^+] in units of RBCconc < 1 week of age was < 20 mmol · L^{-1}, whereas in units aged > 2 weeks it was > 40 mmol · L^{-1}. The estimated K_{dose} was 0.2–1.6 mmol · kg^{-1}. We concluded that the amount of extracellular potassium in units of RBCconc was clinically important and may give rise to hyperkalaemia during massive blood transfusion.

Il faut souvent transfuser massivement les enfants subissant une reconstruction crâniofaciale majeure. Nous avons revu le profil kaliémique intra-opératoire de onze d'entre eux. Chez dix, la kaliémie augmentait de façon statistiquement significative pendant l'intervention et chez cinq, elle dépassait 5,5 mmol · L^{-1} alors que la kaliémie intra-opératoire demeurait stable chez les enfants non transfusés d'un groupe contrôle. Lors des reconstructions, tous les enfants avaient été transfusés avec des culots globulaires récoltés en moyenne 16,1 ± 8,4 jours auparavant. Nous avons mesuré la concentration plasmatique de potassium de 28 culots globulaires et avons trouvé qu'elle était inférieure à 20 mmol · L^{-1} dans les culots récoltés moins d'une semaine plus tôt et de plus de 40 mmol · L^{-1} dans ceux de deux semaines et plus. Nous avons ainsi pu estimer que les enfants avaient reçu entre 0,2 et 1,6 mmol · kg^{-1} de potassium. Les culots globulaires contiennent donc une quantité appréciable de potassium, susceptible d'amener de l'hyperkaliémie lors de transfusions massives.

Key words
ANAESTHESIA: paediatric;
COMPLICATIONS: hyperkalaemia;
TRANSFUSION: complications, massive blood, stored blood.

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Hyperkalaemia is a recognized complication of massive blood transfusion with whole blood. Both the *quantity* of blood transfused and the *rate* of blood transfusion have been identified as risk factors.[1–4]

Since the introduction of blood component therapy in the 1970's, all whole blood donations are separated into specific cellular and plasma components for storage. Therefore blood loss during surgery requires transfusion of each blood component. Massive transfusion with red blood cell concentrates (RBCconc) is not believed to carry the same risk of hyperkalaemia as does transfusion with whole blood because the amount of extracellular potassium per unit of RBCconc is believed to be small.[3,5] However, the plasma [K^+] in units of RBCconc has been measured to be in excess of 30 mmol · L^{-1}, and thus the extracellular mass of potassium in a unit of RBCconc may be of clinical importance even though the plasma volume in the unit is small.[6–8]

Our hypothesis was that massive blood transfusion with RBCconc presented a clinically important potassium load. Children undergoing major craniofacial surgery may require blood transfusion in excess of one blood volume. In addition some of these children have been observed to have high intraoperative plasma [K^+]. Therefore children undergoing major craniofacial surgery (MCFS) were the focus of our investigation. The study is presented in two parts. The first is a retrospective chart

review. The second is an analysis of the amount of potassium contained in units of RBCconc.

Methods

The following study was undertaken with Institutional Approval.

Criteria for patient selection

CONTROL GROUP

In order to document the normal variability in plasma $[K^+]$ during surgery the charts of ten patients who had undergone surgical procedures which did not require blood transfusion were reviewed retrospectively. Each patient had had at least four arterial blood samples drawn for plasma $[K^+]$ at hourly intervals.

MAJOR CRANIOFACIAL SURGERY GROUP (MCFS)

Records of 30 children undergoing MCFS between January 1987 and March 1988 were reviewed. Inclusion criteria were: (1) an intraoperative sampling frequency of once per hour, (2) a minimum of five recorded samples and (3) intraoperative blood transfusion of at least one blood volume. Cardiac arrest was considered an exclusion criterion.

The plasma $[K^+]$, Hct, urine output and the hourly rate of blood transfusion were recorded from the chart. The age in days of the transfused blood was traced through the blood bank records. The free potassium load was assumed to reside only in the plasma volume of the unit of RBCconc (plasma $Kmass_{RBCconc}$) such that:

$$\text{plasma } Kmass_{rWB} = \text{plasma } Kmass_{RBCconc}$$

where rWB refers to the unit of reconstituted whole blood and plasma $Kmass_{rWB}$ was the amount of extracellular potassium in the unit of rWB. The age-matched units of RBCconc, described in detail below, were grouped according to age by week and the mean plasma $Kmass_{RBCconc}$ calculated as the product of the plasma volume and the plasma $[K^+]$. The dose of potassium (K_{dose}), expressed as $mmol \cdot kg^{-1}\ hr^{-1}$, was estimated as the product of $Kmass_{rWB}$ and the transfusion rate of rWB (TR_{rWB}):

$$K_{dose} = \frac{\text{plasma } Kmass_{RBCconc}}{V_{rWB}} \times TR_{rWB}$$

where V_{rWB} is the total volume of the unit of rWB.

Twenty-eight units of RBCconc of similar ages to those which had been transfused in the chart review were analyzed. The total volume per unit ($V_{RBCconc}$) was determined by weight (Electronic Toploader Scale, L2200P, Sartorius Laboratory). The haematocrit ($Hct_{RBCconc}$) was determined from a well mixed 2 ml sample (Coulter Counter Model S-Plus IV, Coulter Electronics). The plasma $[K^+]$ ($K_{RBCconc}$) of a 1 ml sample was measured by flame photometry (Instrumentation Laboratory, 943 Automatic Flame Photometer). Calculated variables were derived as follows:

1 Plasma Volume ($PV_{RBCconc}$) = $(1 - Hct_{RBCconc}) \times V_{RBCconc}$

2 Plasma $Kmass_{RBCconc} = PV_{RBCconc} \times K_{RBCconc}$

where $K_{RBCconc}$ was the plasma [K] in the unit of RBCconc.

Patient arterial blood samples had been analyzed for plasma $[K^+]$ and Hct (Nova Biomedical Stat Profile 4 Analyzer). The Nova Biomedical Stat Profile 4 Analyzer measured $[K^+]$ with an ion selective electrode. Within the analytical range, the assay performance had a coefficient of variation of two per cent. Hct was measured by an impedance electrode. The plasma $[K^+]$ in the units of RBCconc was analyzed by flame photometry (Instrumentation Laboratory, 943 Automatic Flame Photometer). The assay was accurate to within two per cent of the expected values using recovery experiments up to a plasma $[K^+]$ of 80 $mmol \cdot L^{-1}$. Longitudinal plots of plasma $[K^+]$ and Hct were constructed for each patient. Intrapatient variability in plasma $[K^+]$ was expressed as a mean, range ($\Delta\ [K^+]$) and a coefficient of variation for each patient.

Group means ($\pm$ SD) for the control and MCFS groups were calculated for: (1) the mean $[K^+]$, (2) the range ($\Delta\ [K^+]$) and (3) the coefficient of variation. Differences between the control and MCFS groups were assessed with an unpaired t test. A level of statistical significance of $P < 0.05$ was accepted. In the MCFS group, within group differences in plasma $[K^+]$ over time were assessed by analysis of variance for repeated measures.[9]

Results

Control group

Table I shows demographic data for patients in the control group, whose ages ranged from 2–11 yr (12–37 kg). The mean intraoperative plasma $[K^+]$ for this group was 3.9 ± 0.5 $mmol \cdot L^{-1}$. The mean $\Delta[K^+]$ was 0.6 ± 0.3 $mmol \cdot L^{-1}$. The mean coefficient of variation was 5.3 ± 1.5 per cent.

MCFS group

Of the 30 MCFS charts reviewed, 11 met the inclusion criteria. These data appear in Table II. The MCFS group mean intraoperative plasma $[K^+]$ was 4.3 ± 0.5 $mmol \cdot L^{-1}$, a value which was not statistically different from that of the control group. The mean $\Delta[K^+]$ was 1.8 ± 0.6 $mmol \cdot L^{-1}$. Five patients had a plasma $[K^+]$ which

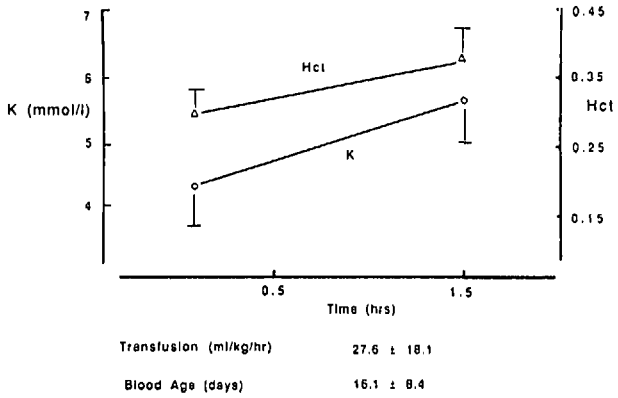

FIGURE 1 Figure 1 summarizes the mean increment in plasma [K^+] and Hct for the ten patients, excluding patient #11, in whom an acute increase in plasma [K^+] was observed. Data were expressed as mean (±SD).

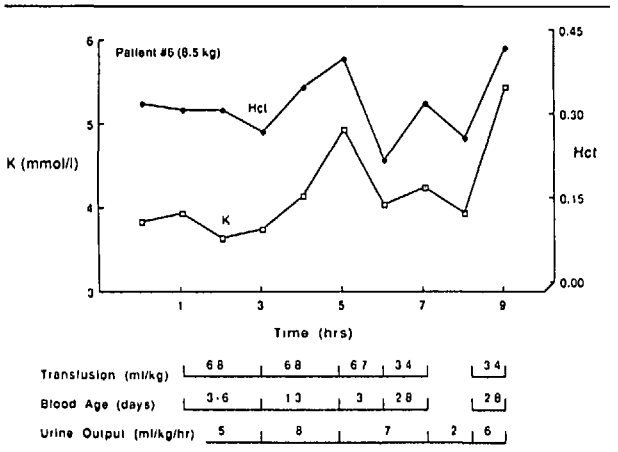

FIGURE 2 Representative patient showing the longitudinal trend of plasma [K^+] and Hct. The volume of rWB and the age of the units of RBCconc which were transfused were also presented.

shown in Figure 2. This patient experienced two increases in plasma [K^+]. The first increase in plasma [K^+] occurred during the fourth hour of blood transfusion. The second occurred during the ninth hour. At the time of the first increase the age of the unit RBCconc being transfused was 13 days. The K_{dose} at the time of the first increase in plasma [K^+] was 1.34 mmol · kg^{-1} delivered in 137 ml · kg^{-1} of rWB over four hours. The second peak followed the transfusion of 34 mg · kg^{-1} blood over one hour. The unit of RBCconc was 28 days old representing a K_{dose} of 0.63 mmol · kg^{-1} · hr^{-1}.

Stored blood

Twenty-eight units of RBCconc were analyzed. The V_{RBC} ranged from 140–325 ml. The mean volume of

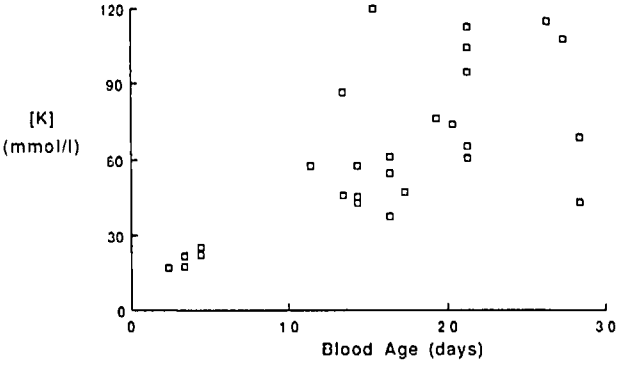

FIGURE 3 The relationship between storage time in days and the plasma [K^+] of units of RBCconc.

RBCconc was 228 ± 63 ml. The mean haematocrit was 0.73 ± 0.10. The mean plasma volume was 60.5 ± 30.7 ml. The relationship between plasma [K^+] and age of the blood is shown in Figure 3. Despite the small plasma volume, the units of RBCconc contained an extracellular potassium load of 1.4 mmol at one week of age and > 3.7 mmol at three weeks of age.

Discussion

Our results showed that during MCFS, children undergoing massive blood transfusion with units of RBCconc experienced a greater variability in plasma [K^+] than the control group and a biochemically important increase in plasma [K^+]. The mean age of children in the MCFS group was 3.1 ± 3.2 yr which is younger than the children in the control group. This supports the clinical impression that it was unusual for infants to undergo long surgical procedures which required invasive monitoring but did not require blood transfusion. There were no adverse biological sequelae of the acute increases in plasma [K^+], in particular no electrocardiographic changes were recorded. However, it should be pointed out that cardiac arrest was considered to be an exclusion criterion.

The longitudinal variability in intraoperative plasma [K^+] in the ten MCFS patients was more than twice that of the control patients. There was a relationship between the acute increase in plasma [K^+] and the trend in Hct. Since the major factor increasing Hct intraoperatively was blood transfusion this correlation would suggest that blood transfusion was responsible for the increase in both Hct and plasma [K^+]. However, blood transfusion was unlikely to have been the only factor influencing the plasma [K^+]. For instance, patient #8 showed a poor correlation between the Hct and blood transfusion. Other factors including changes in acid base status and fluctuation in the amount of tissue trauma might be expected to influence plasma [K^+] during surgery.

TABLE III

	pH		*PCO_2 (torr)*		*Plasma $[K^+]$ ($mmol \cdot L^{-1}$)*	
Patient	*Prepeak*	*Peak*	*Prepeak*	*Peak*	*Prepeak*	*Peak*
#1	7.37	7.42	33.0	36.0	4.5	6.7
#2	7.38	7.41	35.0	36.0	4.8	5.7
	7.39	7.37	39.0	42.0	4.0	5.9
#3	7.41	7.36	35.0	40.0	3.1	4.3
#4	7.41	7.42	33.0	36.0	4.5	5.2
#5	7.43	7.43	28.0	29.0	3.8	5.1
#6	7.38	7.35	31.0	44.0	3.6	4.9
	7.48	7.29	35.0	57.0	3.9	5.4
#7	7.30	7.38	36.0	36.0	3.6	5.0
	7.44	7.50	32.0	30.0	4.8	5.9
#8	7.47	7.49	31.0	30.0	3.8	5.1
	7.49	7.50	32.0	29.0	4.7	5.6
#9	7.34	7.33	37.0	40.0	4.8	6.0
#10	7.43	7.42	26.0	31.0	3.7	4.4

Table outlines the acid base status (pH and PCO_2) in the ten patients who experienced an increase in plasma $[K^+]$. Only patient #6 had a decrease in pH at the time of an increase in plasma $[K^+]$ (See text).

Values for the arterial pH and PCO_2 (Nova Biomedical Stat Profile 4 Analyzer) at the time of the increase in $[K^+]$ are presented in Table III. The arterial pH preceding the peak in plasma $[K^+]$ is given for comparison. Only patient #6 experienced a decrease in pH at the time of the increase in plasma $[K^+]$. The remaining nine patients either had no change in arterial pH or an increase in pH. The relationship between an acute change in acid base status has been the subject of recent investigation. It was once taught, as a rule of thumb, that a 0.1 change in pH units resulted in a reciprocal 0.6 $mmol \cdot L^{-1}$ change in plasma $[K^+]$. This seems to be true only for acute inorganic metabolic acidosis such as during HCl infusion. Acute organic metabolic acidosis and acute respiratory acidosis have been shown to cause minimal increase in plasma $[K^+]$.[10–13] A change in acid base status cannot explain the increase in plasma $[K^+]$ seen in these patients.

Units of RBCconc aged two to five days had a plasma $[K^+]$ between 14 and 23 $mmol \cdot L^{-1}$, while those ≥ two weeks of age had plasma $[K^+]$ ranging from 35–117 $mmol \cdot L^{-1}$. These values of plasma $[K^+]$ are in agreement with the range of values reported in the literature.[6–8]

The increase on plasma $[K^+]$ is expected during storage as the erythrocytes lose potassium through the processes of haemolysis and diffusion.[14–15] The energy-dependent membrane ionic pumps which maintain the transmembrane ionic gradients are inhibited during storage allowing potassium to diffuse out of erythrocytes. Since the whole blood donation is separated into its specific components very soon after donation, the erythrocytes in a unit of RBCconc have a near normal amount of intracellular (ICF) potassium. The ICF $[K^+]$ (RBC$[K^+]$) in erythrocytes is 100 $mmol \cdot L^{-1}$ and the donor plasma $[K^+]$ is about 4 $mmol \cdot L^{-1}$.[16] Therefore a considerable concentration gradient for diffusion of potassium from cells exists. The plasma $[K^+]$ seemed to plateau after 20 days of storage. This tendency to plateau was supported by the spread of data points in the papers by Michael[7] and Degowin.[14] A plateau in the plasma $[K^+]$ implies a limit to the value that the plasma $[K^+]$ may rise during storage. If the RBC and plasma volumes are assumed to remain constant then the concentration equilibrium between the intracellular (ICF) and plasma compartments can be determined.

Given that a donor unit of 450 ml of whole blood, with 63 ml of CPDA-1 preservative, has a Hct of about 0.45, the total unit contains 210 ml of erythrocytes and 21 mmol of intracellular potassium. This volume of erythrocytes can be stored either as a unit of whole blood (PV = 290 ml) or RBCconc (Hct 0.7, PV = 90 ml). The potassium which diffuses out of the donor erythrocytes (Kdec) into the plasma fraction of the unit of blood will increase the plasma $[K^+]$ such that:

$$\text{Plasma } [K^+] = \frac{((Ko \cdot PV) + Kdec)}{PV}$$

where K_o, the initial plasma $[K^+]$, is assumed to be 4 $mmol \cdot L^{-1}$ and PV is the plasma volume of the unit of blood. Diffusion of potassium from cells would decrease the RBC$[K^+]$ such that:

$$\text{RBC } [K^+] = \frac{((100\ mmol \cdot L^{-1} \cdot 210\ cc) - Kdec)}{210\ cc}$$

$$= \frac{(21\ mmol - Kdec)}{210\ cc}$$

Potassium will continue cells by diffusion until the intracellular and extracellular $[K^+]$ are in concentration such that:

$$\text{plasma}[K^+] = \text{RBC}[K^+]$$

$$\frac{((Ko \cdot PV) + Kdec)}{PV} = \frac{(21\ mmol - Kdec)}{210\ cc}$$

Figure 4 shows that if the 210 ml of donor erythrocytes were stored as RBCconc (Hct = 0.7, PV = 90 ml), a concentration equilibrium between the ICF and plasma $[K^+]$ is reached at about 70 $mmol \cdot L^{-1}$ when roughly 30 per cent of the intracellular RBC potassium has diffused from the cells. In contrast, if the 210 ml of donor erythrocytes were stored as whole blood (Hct = 0.4, PV = 290 ml), the concentration equilibrium would occur at 45 $mmol \cdot L^{-1}$, when the RBCs have lost about half of their intracellular potassium. It is curious that the diffu-

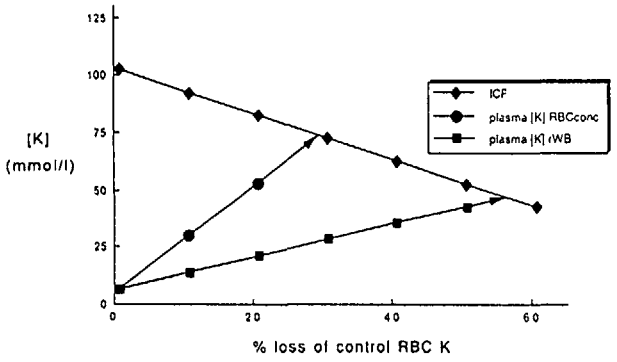

FIGURE 4 The plasma [K^+] plotted against per cent decrease in intracellular potassium content for 210 ml of donor erythrocytes representing 21 mmol of intracellular potassium, when stored either as RBCconc (Hct 0.7, PV 290 ml) or as whole blood (Hct 0.4, PV 90 ml). Concentration equilibrium in the unit of RBCconc occurs at 70 mmol · L^{-1} when about one-third of the intracellular potassium has diffused from the donor erythrocytes. Concentration equilibrium in the unit of whole blood occurs at 45 mmol · L^{-1} when about half of the intracellular potassium has diffused out of the donor erythrocytes (See text).

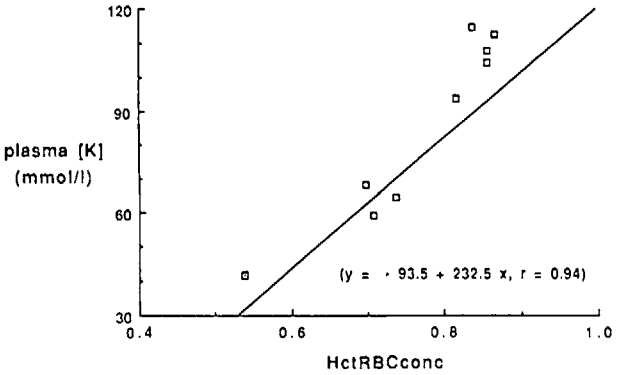

FIGURE 5 The relationship between plasma [K^+] and Hct in the eight units of RBCconc > three weeks of age.

sion of potassium from erythrocytes during storage appears to occur slowly over several weeks because the Na^+-K^+ ATPase probably fails within days following blood donation. It may imply that not all of the intracellular potassium is in a readily exchangeable pool.

It is evident that storage time is an important factor influencing the amount of extracellular potassium in a unit of RBCconc.[6-8,14-16] However, Figure 3 shows that even units of similar storage age have a wide variability in plasma [K^+] with a coefficient of variation of approximately 25 per cent. The variation in haematocrit can explain some of this variability. For instance, if the 210 ml of erythrocytes are stored in plasma such that the haematocrit is 0.6, then a 4.2 mmol decrement in intracellular potassium will result in a plasma [K^+] of 34 mmol · L^{-1}. Whereas if this same volume of erythrocytes is stored with a haematocrit of 0.8, then a 4.2 mmol decrement will result in a plasma [K^+] of 84 mmol · L^{-1}. Figure 5 shows the relationship between Hct and plasma [K^+] for the eight units of RBCconc ≥ 21 days of age. The relationship is well described by simple linear regression ($y = -93.5 + 232.54\ x$, $r^2 = 0.89$).

Five units of RBCconc had a plasma [K^+] in excess of 100 mmol · L^{-1} (Figure 3). This may imply that other processes besides diffusion cause potassium to be released into the plasma fraction. During storage erythrocytes lose intracellular anions. This may result in a less negative intracellular charge relative to the plasma fraction. This would create an electrical gradient between the intracellular and plasma compartments which could repel potassium from the intracellular space.[17]

Transfusion of RBCconc delivers an obligatory intravenous potassium load. The magnitude of the potassium load depends on (1) the age of the unit of RBCconc, (2) its plasma volume and (3) its plasma [K^+]. Following transfusion, erythrocytes are expected to recover their intracellular potassium. However, full recovery requires several days.[16,17] Valerie *et al.*[17] showed this in an elegant study which involved the transfusion of type O donor erythrocytes into non-O recipients. The time course of recovery of the transfused red blood cell intracellular potassium was followed for two weeks. The intracellular potassium content of the stored erythrocytes was decreased 20–30 per cent from the control value. There was minimal recovery of intracellular potassium at eight hours post-transfusion and a slight increase at 24 hr post-transfusion. Full recovery of intracellular potassium in the donor erythrocytes required upwards of one week. Therefore the free potassium contained in the plasma portion of transfused blood must be disposed of as if it were an exogenous potassium load.

Massive blood loss in these children was replaced with reconstituted whole blood (rWB). This was prepared by suspending a unit of RBCconc in a unit of plasma prior to transfusion. From the anaesthetic records the transfusion rate of rWB given to each patient and the age of the unit of RBCconc which had been used in the unit of rWB were known. To assess the amount of free potassium delivered with the blood transfusion, it was necessary to estimate the amount of extracellular potassium delivered per unit of rWB (plasma $K_{mass_{rWB}}$). We recognize that the unit of plasma used to suspend the unit of RBCconc must also have contained potassium. However, the plasma [K^+], in units of stored plasma, has been measured at about 5 mmol · L^{-1} (unpublished observations) and therefore was assumed to be negligible. Four patients received a $K_{dose} <$ 0.3 mmol · kg^{-1} · hr^{-1}.

It is curious that this small K_{dose} was associated with a

TABLE IV

Patient	Time (hrs)	K_{load} ($mmol \cdot kg^{-1} \cdot hr^{-1}$)	$[K^+]$ ($mmol \cdot L^{-1}$)	K_p ($mmol \cdot L^{-1}$)	K_0 ($mmol \cdot L^{-1}$)	%Exit
7	1	0.80	5.0	8.0	1.4	82.5
4	1	0.64	5.2	3.2	0.7	78.0
9	1	1.23	6.0	6.2	1.4	77.2
1	1	1.06	6.7	5.3	2.1	60.4
6	1	0.63	5.4	3.2	1.5	53.0
10	2	0.21	4.4	2.1	1.2	44.0
5	2	0.29	5.1	2.9	1.9	34.0
2	1	0.25	5.9	1.2	0.9	27.0
3	1	0.21	4.4	1.1	1.3	−18.2

The K_{dose}, K_p, K_0 and per cent Exit for the nine patients demonstrating an acute increase in plasma $[K^+]$ during blood transfusion of a significant amount of blood over a period of two hours. Patients are listed in order of descending value for per cent Exit. The plasma $[K^+]$ is also given.

significant increase in plasma $[K^+]$. One explanation may be an inaccuracy in the methodology because the units of RBCconc were grouped according to age by week and a mean value was used for determining the K_{dose}. If a patient received a unit of RBCconc containing a high K load, then the mean value used to estimate the K_{dose} would have underestimated the actual dose. A second explanation may be the physiological response to a potassium challenge. The immediate response to an increase in plasma $[K^+]$ is predominantly extrarenal and consists of (1) redistribution of potassium within the extracellular space and (2) translocation of potassium into the intracellular space.[18–21]

Redistribution and dilution of potassium are important to the maintenance of a normal plasma $[K^+]$. Certainly there is a time requirement for a potassium load to circulate and distribute within the ECF and to shift into the ICF. Rapid bolus transfusion, particularly into an hypotensive hypovolaemic circulation, may give rise to important mixing inhomogeneities in plasma $[K^+]$.[22,23] However, our review did not document any significant episodes of hypotension. It is unlikely that important mixing inhomogeneities of potassium concentration were present in these patients.

The ability to translocate potassium intracellularly can be estimated if one assumes that the difference between the observed change in plasma $[K^+]$ (K_o) and the predicted one (K_p) was due to the amount of potassium which is removed from the ECF:[21]

$$\% \text{ Exit} = 100 \times \left(1 - \frac{Ko}{Kp}\right)$$

where

$$Kp = \frac{K_{dose}}{ECF}$$

and ECF is assumed to equal to 200 $ml \cdot kg^{-1}$.

Table IV gives the values for per cent Exit in nine patients in descending order of per cent Exit. In addition the K_{dose} and plasma $[K^+]$ at the time of the potassium spike are given. Four of the nine patients had a per cent Exit of < 50 per cent, which may indicate an impairment in the ability to translocate potassium into cells. One might speculate that during anaesthesia, the movement of potassium across cell membranes is altered because several factors, which influence this ion flux, namely (1) anaesthetic drugs, (2) hormonal milieu, (3) acid–base status, (4) metabolic rate and (5) previous potassium intake, may be influenced perioperatively.[24–31]

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