─Case Reports─

Fatal Hyperkalemia Due to Rapid Red Cell Transfusion in a Critically Ill Patient

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Abstract

A 60-year-old woman in severe hemorrhagic shock underwent urgent laparotomy to control massive hematemesis. Severe metabolic acidosis due to hemorrhagic shock and hyperkalemia as well as hypocalcemia associated with rapid blood transfusion were aggressively corrected with administration of sodium bicarbonate, insulin, and calcium chloride. Following rapid transfusion of the last 8 units of red cell concentrate (RCC), however, cardiac arrest occurred because of hyperkalemia and did not respond to cardiopulmonary resuscitation. Blood gas analysis revealed that the serum K^+ concentration had increased from 4.05 to 8.24 mEq/L over a 7-minute period, while the Ca^{2+} concentration had decreased from 1.43 to 0.53 mmol/L. Rapid transfusion of irradiated RCC containing a high concentration of K^+, an extreme decrease in the circulating blood volume to dilute the exogenously administered K^+ and citrate, and severe metabolic acidosis impeding the intracellular shift of K^+ seemed to have contributed to the extremely rapid development of fetal hyperkalemia accompanied by hypocalcemia. Anesthesiologists must be aware that hyperkalemia due to rapid blood transfusion can develop extremely rapidly in patients in severe hemorrhagic shock.
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Key words: hemorrhagic shock, blood transfusion, hyperkalemia, hypocalcemia, cardiac arrest

Introduction

Rapid transfusion of blood products is often required in patients with massive bleeding. Hyperkalemia and citrate intoxication causing ionic hypocalcemia are complications of rapid blood transfusion[1,2]. In most cases, however, these complications are self-limited and not life-threatening[1].

We describe a case of fatal hyperkalemia and hypocalcemia, which developed extremely rapidly following rapid transfusion of irradiated red cell concentrate (RCC), leukocyte-reduced (Nisseki, Japan Red Cross Society, Tokyo), in a patient in severe hemorrhagic shock.

Case Report

A woman, aged 60 years and weighing 60 kg, required immediate hospitalization because of severe back pain and hematemesis of sudden onset. Before

Time (h:m) 13:00 13:15 13:30 13:45 14:00 14:15 14:30 14:45 15:00 15:15

Fentanyl (mg) 0.1 .... 0.1
Rocuronium (mg) 50
Dopamine (μg/kg/min) 20--/
Noradrenaline (μg/kg/min) 0.3----------------0.2--------------
Phenylephrine (mg) 0.1 0.2 0.2 0.2 0.2
Noradrenaline (mg) 2
Adrenaline (mg) 1 2 3   2 2 4
Lidocaine (mg) 100
Insulin (units) 10 10   10   10 10 10
2%CaCl2 (ml) 20 20 20   20   20   20 20 20
7%NaHCO3 (ml) 375-----------------------/ 125---/ 250-------------
Infusion (ml) 5000---------------------------------------/
5%Albumine (ml) 2750-----------------------------/
RCC (units) 10---------------------------/ 8-------/
FFP (units) 4--------/   8--------------------/

200

Cardiac massage ←→
Direct cardioversion ■■■

150

HR
SAP
MAP
DAP
(mmHg/bpm)

100

50

Blood gas analysis #   G1   G2   G3   G4 G5 G6

0

Time (h:m) 13:00 13:15 13:30 13:45 14:00 14:15 14:30 14:45 15:00 15:15
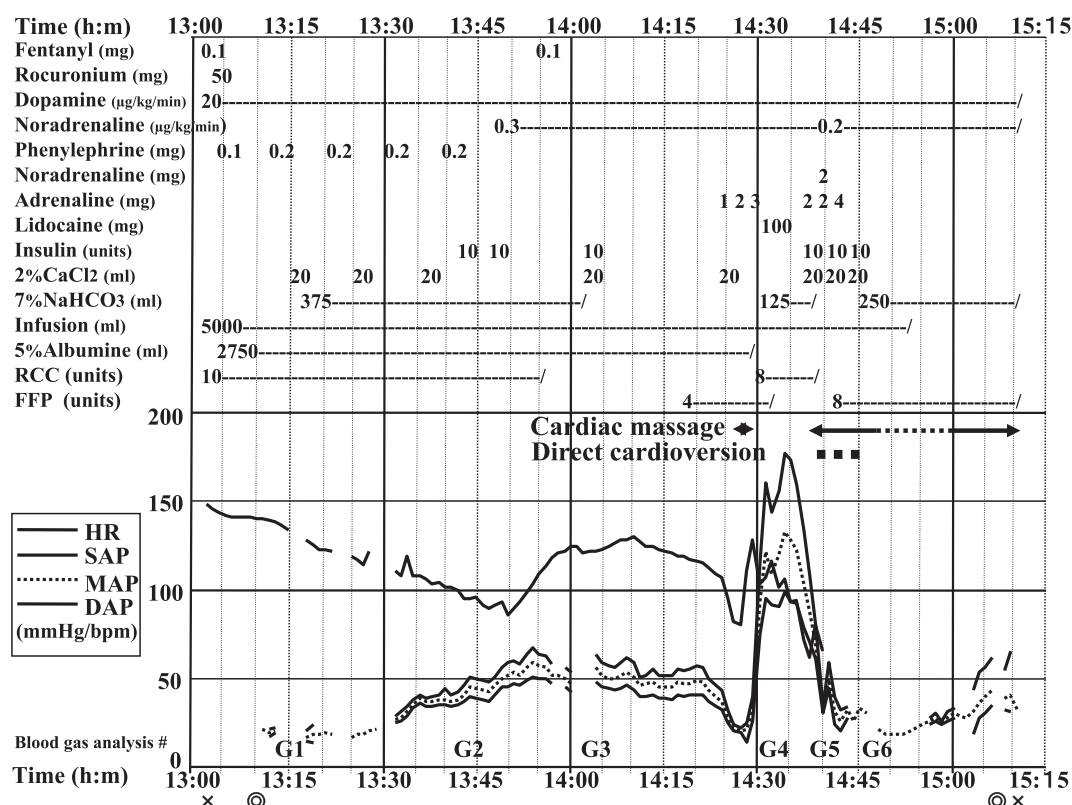× ◎   ◎ ×

Fig. 1 Anesthesia management, changes in heart rate and arterial pressure, and time points of blood gas analyses during the operation.
RCC=Irradiated Red Cells Concentrates-Leucocytes Reduced, "Nisseki"®; FFP=Fresh frozen plasma, "Nisseki"®; HR=heart rate; SAP=systolic arterial pressure; MAP=mean arterial pressure; DAP=diastolic arterial pressure; G1 to G6=Time points of arterial blood gas analyses (see also Table 1)

the present hospitalization, she had undergone cholecystectomy for gallbladder cancer (20 months earlier) and pylorus-preserving pancreaticoduodenectomy for local recurrence of cancer (19 days earlier) and had been uneventfully discharged from the hospital (5 days earlier). During the endoscopic examination performed in an attempt to control gastrointestinal bleeding, the patient required awake tracheal intubation because of continuing massive hematemesis and the rapid development of hemorrhagic shock. After this attempt to control bleeding failed, the patient was transferred to the operating room for urgent laparotomy and given a transfusion of the first 2 units of RCC and an infusion of dopamine via the 22-gauge venous cannula placed on the dorsum of the hand (Fig. 1).

When the patient arrived at the operating room, a large amount of blood was flowing from her mouth. The patient was unresponsive. Blood pressure was unmeasurable with an automated blood pressure cuff, and the heart rate was 150 beats per minute (Fig. 1). General anesthesia was induced with 0.1 mg of fentanyl and 50 mg of rocronium. Intraoperatively, 0.1 mg of fentanyl was added. The electroencephalographic bispectral index remained at 30 during the operation. The operation started immediately after the induction of anesthesia, while transfusion of RCC via the 22-gauge venous cannula was continued. A radial intra-arterial line could be established after several attempts. Initially, invasive mean blood pressure measured only 23 mmHg (Fig. 1), and arterial blood gas analysis showed severe metabolic or lactic acidosis, severe anemia, and moderate hypocalcemia (Table 1: G1). Sodium bicarbonate was infused and calcium chloride was injected in an attempt to correct the metabolic acidosis and hypocalcemia (Fig. 1). Because of the severe vasoconstriction of superficial veins, including the external jugular veins, a 4.5-cm 16-gauge venous cannula was inserted directly into the right internal

Table 1 Results of arterial blood gas analyses during the operation

Time (analysis number)	13 : 13 (G1)	13 : 41 (G2)	14 : 02 (G3)	14 : 30 (G4)	14 : 37 (G5)	14 : 47 (G6)
pH	**6.83**	**ND**	7.34	**7.21**	7.40	7.26
pCO_2 (mmHg)	**22.1**	**ND**	60.1	37.2	46.7	35
pO_2 (mmHg)	472	465	227	247	208	89
HCO_3^- (mEq/L)	**3.6**	**ND**	31.5	**14.4**	28.1	15.3
Base Excess (mEq/L)	**− 27.7**	**ND**	5.4	**− 12.7**	3	− 10.7
Na^+ (mEq/L)	148	141	160	146	152	142
K^+ (mEq/L)	4.43	**6.54**	4.96	4.05	**8.24**	**6.99**
Ca^{2+} (mmol/L)	**0.79**	1.53	**0.82**	1.43	**0.53**	1.49
Hematocrit (%)	**15**	21	**13**	ND	21	24
Hemoglobin (g/dL)	**5.1**	7.3	**4.4**	ND	7.1	8
Glucose (g/dL)	224	289	194	217	241	194
Lactate (mmol/L)	**17.8**	**ND**	**16.7**	**13.5**	**14.1**	**12.3**

Results of blood gas analyses at 13 : 13 (G1) immediately after establishment of the arterial line, at 13 : 41 (G2) when the first ten units of RCC were being tansfused, at 14 : 02 (G3) several minutes after completion of transfusion of the first ten units of RCC, at 14 : 30 (G4) shortly after successful cardiopulmonary resuscitation after the first cardiac arrest, at 14 : 37 (G5) when the additional eight units of RCC were being transfused, immediately before the occurrence of the second cardiac arrest, and at 14 : 47 (G6) when cardiac massage was continued.
ND; Not determined because of data values out of measurement ranges. Extremely abnormal data are shown in bald types.

jugular vein under echographic guidance during the operation. Afterwards, rapid infusion and transfusion was possible. Transfusion of 10 units of RCC, preoperatively prepared, was completed within 1 hour (**Fig. 1**). Although the blood pressure gradually increased while the heart rate gradually decreased in response to blood transfusion at a moderate rate and rapid crystalloids/colloids infusion, the metabolic or lactic acidosis worsened and hyperkalemia developed (**Fig. 1**, **Table 1: G2**). Infusion of sodium bicarbonate was continued, and insulin was injected repeatedly to correct the metabolic acidosis and hyperkalcemia (**Fig. 1**). Even after 10 units of RCC had been infused, anemia persisted due to the continuing hematemesis and massive surgical bleeding (**Fig. 1**, **Table 1: G3**).

Cardiac arrest occurred because of severe anemia after the transfusion of the preoperatively prepared RCC was discontinued, immediately before 15 units of uncrossmatched autologous B-positive RCC arrived from the blood bank (**Fig. 1**, **Fig. 2A−B**, **Table 1: G4**). Cardiac resuscitation was immediately performed with cardiac massage and intravenous infusion of epinephrine (**Fig. 1**, **Fig. 2C−D**). After the heart was successful resuscitated, rapid transfusion of additional units of RCC was started. When the

transfusion of the eighth additional unit of RCC had almost been completed within 9 minutes of the resumption of RCC transfusion, however, cardiac arrest occurred again due to slow ventricular fibrillation (**Fig. 1**, **Fig. 2J**) following the extremely rapid development of widening of the QRS complex (**Fig. 2E−I**). Cardiac resuscitation was unsuccessful despite direct cardioversion, cardiac massage, and intravenous administration of epinephrine, norepinephrine, calcium chloride, insulin, and sodium bicarbonate (**Fig. 1**). Blood gas analysis revealed that the serum K^+ concentration had increased extremely rapidly, during a 7-minute period, from 4.05 mEq/L after the successful resuscitation following the first episode of cardiac arrest, immediately before resumption of RCC transfusion, to 8.24 mEq/L immediately before the second episode of cardiac arrest following rapid RCC transfusion, while the Ca^{2+} concentration decreased from 1.43 to 0.53 mmol/L (**Table 1: G4, G5**).

The abdominal wall was closed, and the patient was transferred to the intensive care unit. The operation time and anesthesia time were 121 minutes and 132 minutes, respectively. The patient was declared dead shortly after she arrived on the ward. A postoperative investigation revealed that
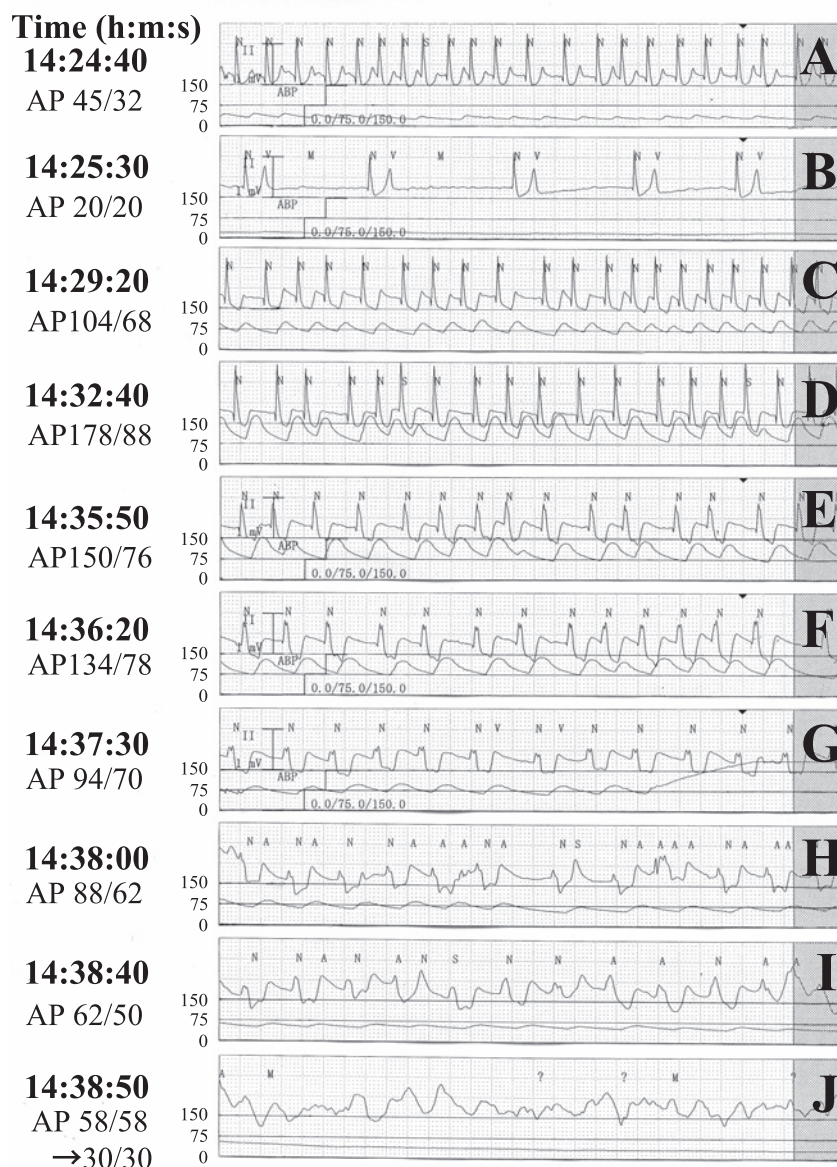
Fig. 2 Changes in electrocardiogram (ECG) and invasive arterial pressure (AP) immediately before and during two episodes of cardiac arrest.

Shown in Fig. 2 are ECG and AP at 14 : 24 (A) when severe hypotension of sudden onset occurred due to severe anemia (note that hemoglobin and hematocrit levels at 14 : 02 [G3] were very low and those at 14 : 30 [G4] were unmeasurable as shown in Table 1); at 14 : 25 (B) when pulseless electrical activity (severe bradycardia) developed, which was immediately followed by cardiac massage and repeated bolus adrenaline injections; at 14 : 29 (C) after successful cardiopulmonary resuscitation and immediately prior to resumption of RCC transfusion (also note that serum concentrations of K^+ and Ca^{2+} at 14 : 30 [G4] were 4.05 mEq/L and 1.43 mmol/L as shown in Table 1); at 15 : 32 (D) when transfusion of the additional second unit of RCC was completed; at 14 : 35 (E) when the additional sixth unit of RCC was being transfused and widening of the QRS complex began to develop; at 14 : 36 (F) when transfusion of the additional eighth unit of RCC was begun and widening of QRS complex worsened; at 14 : 37 (G) when wide QRS complex worsened and hypotension began to occur, immediately before discontinuation of RCC transfusion (note that serum concentrations of K^+ and Ca^{2+} at 14 : 37 [G5] were 8.24 mEq/L and 0.53 mmol/L as shown in Table 1); and at 14 : 38 (H–J) when widening of QRS complex and hypotension worsened further and rapidly led to pulseless gross ventricular fibrillation, which was unresponsive to resuscitation.

the 8 units of RCC transfused immediately before the second episode of cardiac arrest had been irradiated 6 to 8 days before transfusion.

Discussion

Hyperkalemia and citrate toxicity following blood transfusion can occasionally cause severe complications, including cardiac arrest[1-3], although the documentation included with RCC states that the estimated incidence of cardiac arrest associated with RCC transfusion is less than 0.1%[2]. Our patient showed an extremely rapid increase in the serum K^+ concentration and an extremely rapid decrease in the Ca^{2+} concentration during rapid RCC transfusion which eventually led to irreversible cardiac arrest. Hyperkalemia following blood transfusion is multifactorial, with the three most important factors being the transfused blood products, the mode of blood transfusion, and the condition of the patient[3].

First, loading of the large amount of K^+ contained in blood products is the primary cause of hyperkalemia[3]. In stored red cell products, the extracellular release of potassium continues due to failure of the cell-surface sodium/potassium ATPase pump. Furthermore, the K^+ concentration is higher in suspensions of irradiated red cell products than in unirradiated products due to damage to erythrocyte membranes induced by gamma-ray irradiation[2,4]. According to the documentation included with RCC, the K^+ concentration in RCC suspensions, irradiated with 15 Gy on the day of collection, increases from almost 0 on the day of collection to approximately 37 mEq/L on the seventh day after collection and is higher than the K^+ concentration of 20 mEq/L in unirradiated RCC[2]. The 8 units of RCC transfused immediately before the second and fatal episode of cardiac arrest had been irradiated approximately 1 week before transfusion, and therefore, the K^+ concentration of these products could have been extremely high.

Second, a higher rate of blood transfusion is associated with a higher risk or incidence of hyperkalemia and citrate intoxication causing ionic hypocalcemia[1,2]. Clinically significant hyperkalemia and cardiovascular changes due to citrate

intoxication can occur when citrated banked blood is given at a rate of 120 mL/70 kg/minute or more and at a rate of 150 mL/70 kg/minute or more, respectively[1]. The rate of transfusion of an additional volume of nearly 8 units of RCC (a total volume of nearly 1,040 mL) over 9 minutes (116 mL/60 kg/minute) in our patient was near these critical rates. Therefore, it was likely that the high transfusion rate caused the extremely rapid increase in the serum K^+ concentration and the decrease in the Ca^{2+} concentration. Ionic hypocalcemia due to citrate intoxication can lead to impaired cardiovascular function, as manifested as hypotension, narrowed pulse pressure, and elevated intraventricular end-diastolic pressure[5]. In our patient, the serum Ca^{2+} concentration decreased extremely rapidly when the hyperkalemia-induced cardiac arrest occurred, and, therefore, it was possible that the concurrent ionic hypocalcemia exacerbated the direct cardiac depressant effect of hyperkalemia[5]. Furthermore, the RCC was transfused mainly via the internal jugular vein in our patient. This route of transfusion, in addition to the high rate of transfusion, might have shortened the time required for K^+ equilibration and have facilitated the direct delivery of undiluted K^+ to the heart[6].

Third, a state of severe hypovolemic shock in our patient could have contributed to the accidental hyperkalemia. At the time of rapid transfusion, massive hemorrhage continued. Therefore, it was likely that the rapid increase in the serum K^+ concentration and the decrease in the Ca^{2+} concentration occurred at least in part because the volume of circulating blood had been markedly reduced and, thus, its capacity to dilute exogenously loaded K^+ and citrate was limited. Furthermore, due to the continuing state of shock the metabolic acidosis progressed in our patient despite the administration of a large dose of bicarbonate (see **Table 1: G1, G2, G4, G6**). The acidosis should have exacerbated the rapid increase in serum K^+ concentration by impeding the transcellular shift of K^+ from the extracellular fluid to the intracellular fluid through exchange of $H^+/K^{+[5,7]}$.

In our patient, the possibility cannot be excluded that factors other than rapid blood transfusion

contributed to fatal hyperkalemia. A potentially lethal hyperkalemia can occur with reperfusion of a large vascular bed after a period of ischemia (usually more than 4 hours)[5]. Ischemia results in significant acidosis in the affected area which causes an outflow of intracellular potassium. When the area is reperfused, the body receives a large bolus of potassium, resulting in potentially fatal hyperkalemia. While the blood pressure in our patient was being increased through a massive infusion of crystalloids/colloids solution and the transfusion of the first 10 units of RCC, transient hyperkalemia developed while metabolic or lactic acidosis was exacerbated despite RCC transfusion at a moderate rate and bicarbonate infusion (**Fig. 1**, **Table 1: G2**). Transient hyperkalemia and exacerbation of acidosis in this early phase might have resulted not only from blood transfusion but also from reperfusion of organs after an initial state of severe shock. It was unlikely, however, that reperfusion of ischemic vascular beds resulted in hyperkalemia that caused the second episode of cardiac arrest, because blood samples obtained shortly after successful resuscitation following the first episode of cardiac arrest, immediately before the resumption of RCC transfusion, did not show hypokalemia or hypocalcemia (**Fig. 1**, **Fig. 2C-D**, **Table 1: G4**), whereas blood samples obtained after the rapid RCC transfusion, immediately before the second episode of cardiac arrest, showed both severe hyperkalemia and hypocalcemia (**Fig. 1**, **Fig. 2E-J**, **Table 1: G5**). Therefore, rapid RCC transfusion was considered the primary cause of the fatal hyperkalemia.

The propriety of administration of a large dose of bicarbonate must be discussed. Because carbon dioxide that is produced enters the cells freely, unlike administered bicarbonate ions, the inside of the cells may initially become even more acidic, a phenomenon known as "paradoxical acidosis"[5,8], although direct studies with nuclear magnetic resonance have not confirmed this phenomenon[5]. Therefore, bicarbonate therapy is usually reserved for emergencies and situations in which the indications for therapy are compelling[5]. We believe that urgent bicarbonate therapy was indicated in

our patient, because she presented with extreme metabolic or lactic acidosis (**Table 1: G1**) and had hyperkalemia during two sessions of RCC transfusion (**Fig. 1**, **Table 1: G2, G5**). The treatment of hyperkalemia involves stabilization of the heart from the effects of K^+ by means of intravenous Ca^{2+} and redistribution of K^+ from the plasma into cells with intravenous glucose, insulin, bicarbonate, and hyperventilation[5]. The administration of 10 units of insulin lowers serum K^+ levels only after 10 to 20 minutes[5]. In this regard, the correction of metabolic acidosis with intravenous bicarbonate might more rapidly decrease the serum K^+ concentration. The necessity for treating metabolic acidosis is judged largely on clinical grounds, with the metabolic acid level base excess used to determine the correct dose of bicarbonate, as: dose (mEq) = 0.3 × weight (kg) × base excess (mEq/L)[5]. A bicarbonate dose required to completely correct initial metabolic acidosis is estimated to be 500 mEq (= 0.3 × 60 × 27.7) (**Table 1: G1**), which corresponds to 600 mL of a 7% sodium bicarbonate solution. We did not aim to achieve the immediate and complete correction of metabolic acidosis with a bicarbonate bolus but aimed for gradual correction of metabolic acidosis through slow bicarbonate infusion and adjusted the dose on the basis of the results of intermittent blood gas analyses (**Fig. 1**, **Table 1**). Given these conditions, we believe that the bicarbonate infusion therapy we employed was appropriate for correcting the severe metabolic acidosis and hyperkalemia.

In many instances requiring rapid transfusion, it is difficult to transfuse blood slowly with sequential monitoring of the serum K^+ concentration or to measure the K^+ concentration in each RCC suspension before transfusion. To avoid rapid transfusion, we should have transfused heterologous O-positive RCC at a slower rate before the first episode of cardiac arrest without waiting for the arrival of homologous B-positive RCC from the blood bank[1]. In addition, we should have started infusion of norepinephrine earlier, instead of continuing high-dose dopamine infusion, to achieve earlier stabilization of hemodynamics. However, it is questionable whether we could have saved the patient's life even if we had slowly transfused O-

positive RCC or had started the norepinephrine infusion earlier, because the patient was near death at the start of the operation and because the failure of surgical hemostasis likely indicated severe coagulopathy associated with consumption, dilution, acidosis, hypocalcemia, anemia, hypothermia, and other factors[9,10].

In conclusion, we have reported a case of fatal hyperkalemia, which developed immediately after rapid RCC transfusion. The rapid transfusion of irradiated RCC products with a high K^+ concentration, a marked decrease in the circulating blood volume to dilute exogenously administered K^+, and severe metabolic acidosis that should have impeded the transcellular shift of K^+ seemed to have contributed to the extremely rapid development of fetal hyperkalemia in our patient. Our experience indicates that anesthesiologists must be aware that hyperkalemia due to rapid blood transfusion can occur extremely rapidly in patients in a state of severe hemorrhagic shock.

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