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Massive Rhabdomyolysis Following Cardiopulmonary Bypass

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Here, we report a case of massive rhabdomyolysis following an uncomplicated repair of a ventricular septal defect in a five-month-old baby. Postoperatively, the patient was hemodynamically stable but metabolic acidosis continued, accompanied by fever and delayed mental recovery. The next day, he became comatose and never regained consciousness thereafter. The computed tomography of the brain revealed a diffuse brain injury. The patient followed a downhill course and eventually died on postoperative day 33. An unusually high level of creatine phosphokinase was noticed, peaking (21,880 IU/L) on postoperative day 2, suggesting severe rhabdomyolysis. The relevant literature was reviewed, and the possibility of malignant hyperthermia obscured by cardiopulmonary bypass and hypothermia was addressed.

Key words: 1. Rhabdomyolysis
2. Malignant hyperthermia
3. Cardiopulmonary bypass

CASE REPORT

A five-month-old male infant (weight, 6 kg; height, 64 cm) underwent elective repair of a large perimembranous-type ventricular septal defect (VSD). He had no discernible anomaly other than VSD; his preoperative routine laboratory values were all within normal limits, and he had no family history of genetic disease including malignant hyperthermia (MH)-susceptible trait (which was inquired later). The echocardiography revealed a large VSD of the perimembranous type with pulmonary hypertension.

Premedication was not given. Upon anesthetic induction, fentanyl sodium and ketamine were administered intravenously, followed by rocuronium bromide for intubation. Anesthesia was maintained with nitrous oxide and sevoflurane, along with incremental doses of fentanyl and ketamine. End-tidal PCO_2 ($ETCO_2$) and oxygen saturation were monitored continuously with an intermittent analysis of the arterial blood gases. The operation was carried out under standard hypothermic cardiopulmonary bypass (CPB). The patient's body temperature was normal (36.8°C) before the induction of anesthesia, but it increased to 38.7°C just before the bypass; no specific measures were taken as he was going to be on hypothermic CPB soon. Systemic cooling was applied shortly after the initiation of the bypass, and the temperature was maintained around 26°C throughout the intracardiac procedure. The flow rate was appropriately controlled according to the body temperature, and there was no episode of a significant fall in the mean blood pressure during the entire course of CPB. The blood gas profiles were also in the normal range. Upon rewarming, although the standard rewarming protocol was applied, a very rapid and excessive elevation of the temperature

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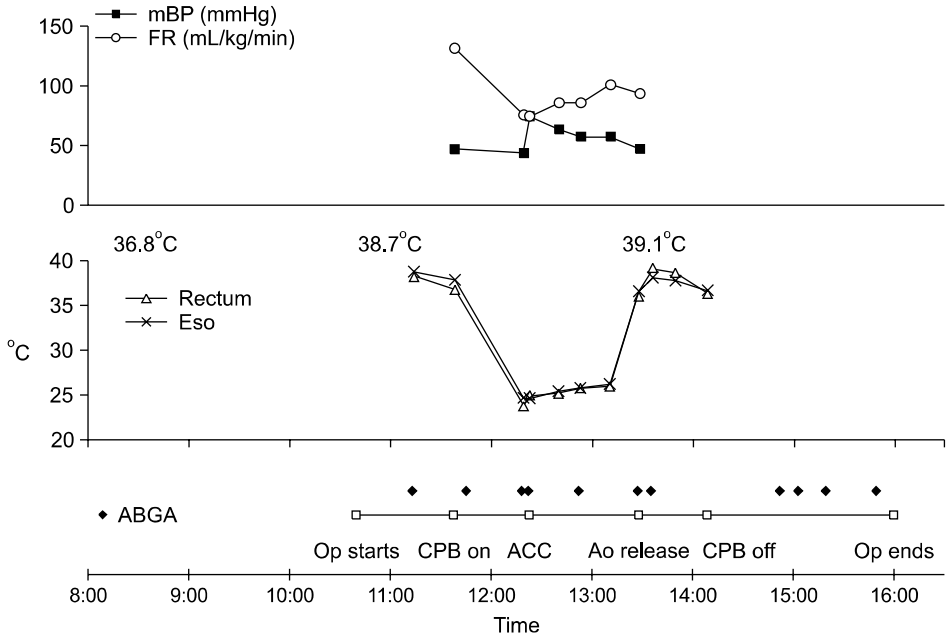


	ABGA
11:46	7.35-33-320-18
12:19	7.38-37-363-33
12:53	7.42-28-234-18
13:36	7.44-31-235-21
14:53	7.21-49-49-20
15:04	7.27-41-247-19
15:20	7.31-38-195-19
15:50	7.29-43-136-21

Fig. 1. Schematic drawing of the timeline of the operation; blood pressure, flow rate, body temperature and blood gas profiles were chronologically displayed. mBP, mean blood pressure; FR, flow rate; Eso, esophagus; ABGA, arterial blood gas analysis; Op, operation; ACC, aortic clrss clamp; CPB, cardiopulmonary bypass; Ao, aorta.

was noted; it took only 17 minutes for the temperature to reach 36.6°C/36.2°C (esophageal/rectal), and then, the temperature continued to rise and peaked at 38.2°C/39.1°C 12 minutes later. Cooling measures were applied, and the temperature fell gradually to the normal level 35 minutes after peaking. The CPB weaning was smooth. Urine dropped well without any noticeable color change. The first sign of metabolic acidosis, along with hypoxia and hypercapnia, was noted in the blood gas sample drawn 44 minutes after the CPB weaning. Hypoxia and hypercapnia were corrected by the manipulation of the ventilator; however, a mild degree of metabolic acidosis persisted (Fig. 1). Nevertheless, the hemodynamic parameters were quite stable. The chest was closed, and the patient was transferred to the intensive care unit (ICU) in a stable condition. Initially, in the ICU, the only sign against normal recovery was metabolic acidosis, which continued until postoperative day 2. Intermittent pyrexia was managed conservatively. The initial profile of the cardiac enzyme (creatine kinase [CK]/CK-myocardial band [MB]/troponin-I: 1,100/190/98.7) was unusually elevated, showing results that did not match the clinical findings at that time. Mental recovery was delayed; the patient opened his eyes late in the evening. Nonetheless, he was sedated again overnight mainly because of the unexpected metabolic acidosis. The next day, sedation was stopped, but the patient's movement was rather sluggish. He opened his eyes, but his eye contact was uncertain. The ventilator weaning was not successful. The serum concentrations of the cardiac enzymes continued to increase. The patient's mental status deteriorated rapidly over time, and he became comatose. The computed tomogram of the brain taken on postoperative day 2 revealed a diffuse brain injury pattern. The CK level continued to rise, peaking at 21,880 IU/L on postoperative day 2; it gradually fell afterwards (Fig. 2). Nonetheless, the urine output was well main-

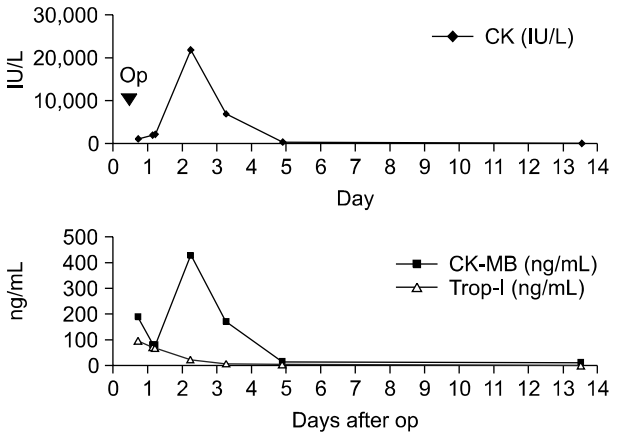
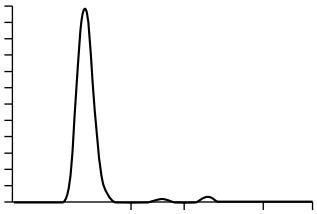


Fig. 2. Graphs showing change of CK, CK-MB and troponin-I postoperatively. Op, operation; CK, creatine kinase; MB, myocardial band; Trop, troponin.



Fraction		Result 1 (%)	Result 2 (U/L)	Reference	Unit
MM		97.20	335.34	97.00-100.00	%
MB		1.20	4.14	0.00-3.00	%
BB	High	1.60	5.52	0.00-0.00	%
Total CPK		100	345	32-294	U/L

Fig. 3. The result of isoenzyme electrophoresis of creatine kinase.

tained, without any noticeable color change and without a significant elevation of the serum blood urea nitrogen or creatinine. Neither was observed as a significant abnormality in the chest X-ray. Echocardiography showed good postoperative results; the VSD was closed well without a residual shunt, and cardiac contractility was preserved. Metabolic acidosis also resolved after postoperative day 2. However, the patient fell into full coma and never regained consciousness. The isoenzyme study of CK from a blood sample taken on postoperative day 5 revealed a significant elevation of the MM fraction (Fig. 3). The family did not approve a tracheostomy. Thereafter, the patient followed a gradual downhill course and eventually died on postoperative day 33.

DISCUSSION

At first, upon reviewing this complicated and unhappy case, malperfusion came to our mind first as a culprit for the diffuse brain injury and massive rhabdomyolysis leading to death. However, according to the perfusionist's record, the pump speed and the flow rate were maintained within the acceptable range throughout the run of the bypass, and the blood gas profiles were absolutely within the normal limits. Moreover, the extent of rhabdomyolysis as represented by the CK elevation was too severe to be simply attributed to malperfusion [1]. It would be logical to conclude that the initial excessive elevation of serum CK-MB was only a reflection of the elevation of the total CK amount. As for MH, we were not aware of it until we were reminded by a text that MH was supposed to be the number-one disease to be ruled out in the differential diagnosis of rhabdomyolysis [2].

MH is a genetic disorder of the skeletal muscle that presents a high fever, usually after operation, as a result of the hypermetabolic state to the volatile anesthetic agents, such as halothane, sevoflurane, desflurane, and the depolarizing muscle relaxant succinylcholine, and rarely to stresses such as vigorous exercise and heat. This disorder is characterized by massive rhabdomyolysis and is likely to be fatal unless recognized early and treated appropriately. The classic signs of MH include hyperthermia to a marked degree, tachycardia, tachypnea, increased carbon dioxide production, increased oxygen consumption, acidosis, and muscle rigidity. The early diagnostic clue of the disorder is known to be elevated $ETCO_2$. However, the presentation of the symptoms is highly variable: The fever can be a mild one and even totally omitted, and the interval from the exposure to the symptom onset can be highly variable. Thus, MH is a disease of exclusion; a variety of conditions may resemble MH during anesthesia. Similarly, when severe rhabdomyolysis is encountered postoperatively, MH should be considered in the first line [3].

In this context, we scrutinized the case again and came up with the notion that the earlier abnormal pattern of rewarming, which was once thought to be insignificant, might be an early sign of MH. The ensuing events such as acidosis and rhabdomyolysis corresponded well to the clinical features of MH as described earlier. It might be argued that careless and

very rapid rewarming was the principle cause of death. We insisted that the temperature had increased abruptly although we had followed the general guideline of rewarming. In addition, we believed that if MH had developed in the setting of CPB, one could hardly have detected the early signs largely because of the symptoms obscuring hypothermia. Thus, we systematically searched the literature focusing on MH and CPB and found some relevant articles.

Recently, Metterlein et al. [4], in their review article, have described 14 patients experiencing an episode of MH associated with cardiopulmonary bypass in 12 reports over nearly three decades. In general, when MH develops in patients undergoing cardiac surgery under cardiopulmonary bypass, the situation becomes more complicated. Classical clinical features are obscured by the effect of hypothermia, rendering the early recognition and timely management of MH extremely difficult [5,6]. They also pointed out that putting aside volatile anesthetics, rewarming per se can be a triggering factor or at least have a modulating effect on the development of a crisis [7].

The definite diagnosis of MH is currently made by an *in vitro* contracture test [3], which unfortunately was not carried out in this patient because of the rapidly declining clinical course. Dantrolene, which is currently accepted as an effective treatment regimen [3], was also not administered in time because clinical suspicion was lacking at that time.

General measures for the management of MH are usually supportive and symptom-specific. All potent inhalation agents and muscle relaxants should be stopped immediately, and minute ventilation should be increased to lower $ETCO_2$. Cooling measures such as ice pack application and/or nasogastric lavage with an iced solution should be carried out. Measures to maintain the urine output should be encouraged, and the treatment of hyperkalemia, arrhythmia, and potential disseminated intravascular coagulation should be undertaken as needed [3].

In summary, although we could not explain the cause of the brain injury, the occurrence of MH was very probable in this case; the abnormal pattern of temperature rise upon rewarming, which was transient and did not draw much attention at that time, might have been an early sign of MH. The ensuing metabolic acidosis that was hard to correct and massive rhabdomyolysis also tied in very closely with the clinical situation in the case of MH. We might have missed the first sign of MH—the increase in $ETCO_2$ by a simple manipulation of the ventilator, as pointed out by others [8].

One should be aware of the possibility of MH, although it rarely occurs, when unexplained metabolic acidosis and rhabdomyolysis develop and continue in association with CPB and rewarming.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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