Perioperative management of malignant hyperthermia during general anesthesia: A report of two cases

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Abstract
Malignant hyperthermia (MH) is a lethal complication associated with general anesthesia characterized by sudden onset, rapid progression, and high mortality. We present two seemingly typical cases of intraoperative MH development, with details on perioperative assessment and rescue. Postoperative genetic test showed mutations in the ryanodine receptor type 1 gene.

KEYWORDS
dantrolene, general anesthesia, hypermetabolic crisis, idiopathic scoliosis, malignant hyperthermia, tetralogy of Fallot

1 | INTRODUCTION

Malignant hyperthermia (MH) is a rare genetic skeletal muscle disease usually induced by inhaling anesthetics or depolarized skeletal muscle relaxants. This potentially lethal hypermetabolic crisis is associated with a rapid and uncontrolled increase in sarcoplasmic Ca2+ in the skeletal muscle cells.1 This instigates strong contractions of systemic muscles, a rapid increase in body temperature, and progressive circulatory failure.2 MH has a sudden onset, rapid progression, and high mortality rate. This retrospective, single-center case series describes two patients who were admitted to the hospital for congenital idiopathic scoliosis and congenital tetralogy of Fallot and developed MH intraoperatively. Postoperative genetic testing of the patients and close relatives showed mutations in the RYR1 gene. Our department successfully rescued the two patients who developed MH under general anesthesia. This report outlines the diagnosis and treatment process.

2 | CASE REPORT

Between March 2013 and June 2020, two patients who developed MH during general anesthesia were rescued at our hospital.

Written informed consent was obtained from the families of both patients for the collection of samples and the publication of medical data.

2.1 | Case 1

A 16-year-old, 48-kg man was admitted to the hospital for idiopathic scoliosis and underwent transposterior spinal osteotomy orthopedic surgery. There was no notable medical or family history. First- and second-degree relatives with a history of surgical anesthesia had not experienced any adverse events. Physical examination revealed dysplasia, spinal deformity, and thoracic deformities. The muscle strength of both lower limbs was normal. On standing,
the heights of bilateral iliac spines and shoulders were unequal. Kyphosis and scoliosis were seen on the back. Auxiliary examination showed scoliosis upon radiography. The levels of serum phosphocreatine kinase (CK) were enhanced (1158.3 U/L; normal range, 24–195 U/L). There were no abnormalities in the electrocardiogram, blood routine, creatinine and urea, and coagulation functions. The patient was classified as grade 1 according to the American Society of Anesthesiologists (ASA) guidelines.

On the day of the surgery, penehyclidine hydrochloride (0.5 mg) and dexamethasone (10 mg) were administered intravenously 30 min before anesthesia induction. General anesthesia was induced at 8:30 AM with intravenous midazolam (3 mg), sufentanil (20 μg), cis-atracurium benzoate (10 mg), and propofol (60 mg). Tracheal intubation and mechanical ventilation were performed. The intraoperative ventilation mode comprised tidal volume (VT) of 8 ml/kg; respiratory rate (RR) of 16 times/min, and inspiration:expiration (I:E) ratio of 1:2. After anesthesia induction, the end-expiratory carbon dioxide pressure (PetCO₂) was 38 mmHg.

General anesthesia was maintained with inhaled sevoflurane, propofol, and remifentanil. The surgery was initiated at 9:45 AM. At 9:50 AM, PetCO₂ suddenly increased to 59 mmHg, heart rate (HR) increased to 100 beats/minute (bpm), and the operator complained of muscle tension. The anesthesiologist suspected that the anesthesia was shallow and, thus, it was deepened. Additional muscle relaxants (cis-atracurium) were administered, soda lime was replaced, and minute ventilation was increased. At 10:00 AM, PetCO₂ increased to 144 mmHg, HR increased to 135 bpm, and nasopharyngeal temperature increased to 38.3°C. The blood gas analysis (Table 1) showed severe acidosis, hypercarbia, and hyperkalemia.

Combined with the following features: unexplained and unexpected increases in PetCO₂, HR, temperature, and no history of medication use, the differential diagnosis of malignant syndrome of antipsychotics was excluded. In addition, an assessment of the limbs for swelling, muscle softness, and peripheral pulses or peripheral oxygen saturation was performed. No predisposing factors led to compartment syndrome.

Malignant hyperthermia was suspected, and an emergency plan was immediately activated. Dantrolene was urgently requested from the regional medical center. Sevoflurane was discontinued, and soda lime and the respiratory circuit were replaced. The patient was hyper-ventilated with a maximum flow of 100% oxygen and 2–3 times the average minute ventilation to correct hypercapnia and acidosis. The surgeon discontinued surgery and placed the patient in the supine position, at which time the patient was found to have flexed limbs and muscle rigidity. Cooling measures included using ice caps, ice packs, alcohol baths, and saltwater infusions. We used 5% sodium bicarbonate and glucose (50 ml of 50%) with insulin (10 units) to treat acidosis and hyperkalemia. Amiodarone was administered to treat the arrhythmias (supraventricular tachycardia). Methylprednisolone (500 mg) was administered intravenously.

At 10:45 AM, the patient’s HR suddenly dropped to 20 bpm, blood pressure (BP) decreased to 60/40 mmHg, and SpO₂ was 77%, and we immediately performed cardiopulmonary resuscitation to treat cardiac arrest. The patient recovered sinus rhythm after 150 J of asynchronous

| Time  | PH   | PCO₂ (mmHg) | PO₂ (mmHg) | BE (mmol/L) | Na (mmol/L) | K⁺ (mmol/L) | iCa²⁺ (mmol/L) |
|-------|------|-------------|------------|-------------|-------------|-------------|----------------|
| 08:20 | 7.445| 38.8        | 100        | 2           | 137         | 3.8         | 1.21           |
| 10:00 | 6.748| >130        | 277        | −a          | 145         | 6.4         | 1.46           |
| 10:30 | 6.687| >130        | 134        | −a          | 145         | 7.2         | 1.45           |
| 10:45 | 6.918| 115.5       | 335        | −9          | 144         | 7.7         | 1.40           |
| 11:00 | 7.068| 77.5        | 331        | −8          | 142         | 6.7         | 1.20           |
| 11:20 | 7.235| 61.4        | 410        | −1          | 138         | 6.5         | 1.05           |
| 11:40 | 7.363| 45.9        | 432        | 1           | 140         | 6.4         | 0.95           |
| 11:50 | 7.389| 40.5        | 262        | 0           | 140         | 5.7         | 0.98           |
| 12:10 | 7.323| 42.3        | 237        | −4          | 142         | 4.1         | 1.32           |
| 12:30 | 7.298| 42.0        | 255        | −6          | 143         | 3.6         | 1.27           |
| 12:50 | 7.309| 43.5        | 255        | −4          | 144         | 3.5         | 1.22           |

Abbreviations: BE, base excess (normal range, −3 to 3 mmol/L); iCa²⁺, ionic calcium comparison (normal range, 1.10–1.34 mmol/L); K⁺, blood potassium comparison (normal range, 3.5–5.5 mmol/L); Na, blood sodium comparison (normal range, 135–145 mmol/L); PCO₂, arterial carbon dioxide pressure (normal range, 35–45 mmHg); PH, potential hydrogen (normal range, 7.35–7.45); PO₂, arterial oxygen pressure (normal range, 80–100 mmHg).

*The result is abnormal and cannot be measured.
electric defibrillation. At 11:00 AM, vital signs showed a HR of 94 bpm; BP, 76/46 mmHg; SpO₂, 99%; PetCO₂, 88 mmHg; and nasopharyngeal temperature, 41.6°C. Sequential arterial blood gas measurements revealed sustained metabolic and respiratory acidosis despite adequate ventilatory support.

Dantrolene (120 mg) was administered intravenously at 11:10 AM. Meanwhile, the above-mentioned rescue measures were continued. At 11:40 AM, the nasopharyngeal temperature dropped to 38.0°C, PetCO₂ was reduced to 45 mmHg, and muscle rigidity was relieved. At 11:50 AM, vital signs showed a HR of 127 bpm; BP, 106/57 mmHg; SpO₂, 100%; PetCO₂, 36 mmHg; and nasopharyngeal temperature, 36.5°C. Vital signs became more stable. The patient was transported to the intensive care unit (ICU) at 1:00 PM and continued to receive circulatory and nutritional support, prophylaxis, and continuous renal replacement therapy when myoglobinuria occurred. Additional dantrolene (60 mg) was administered intravenously every 6 h until 120 mg. The patient’s condition stabilized over the next 24 h. He was extubated 2 days postoperatively, transferred to the general ward 6 days later, and discharged 35 days postoperatively. The patient’s body temperature and PetCO₂ trends are shown in Figures 1 and 2, respectively, and the patient’s myoglobin (MYO) and creatine kinase (CK) levels are shown in Table S1 in the Supporting Information.

2.2 | Case 2

A 49-year-old, 69-kg man was admitted to the hospital for surgical correction of tetralogy of Fallot. The patient complained of heart palpitations, dyspnea, and cyanosis after physical activity. Cardiac color ultrasonography revealed ventricular septal defect, aortic straddling, right ventricular outflow tract stenosis, and right ventricular hypertrophy, thus confirming tetralogy of Fallot. Additional findings included ventricular level left-to-right two-way shunt, left atrial enlargement, and left ventricular hypertrophy. Coronary angiography revealed moderate stenosis of the left coronary artery (50% stenosis of the proximal left anterior descending artery) and mild stenosis of the right artery (30% stenosis of the middle right coronary artery). The ASA classification suggested grade 3.

At 08:25 AM on the day of surgery, general anesthesia was induced with intravenous midazolam (2 mg), sufentanil (25 μg), etomidate (14 mg), and rocuronium (60 mg). Tracheal intubation and mechanical ventilation were...
performed. The intraoperative ventilation mode was VT of 8 ml/kg, RR of 12 times/min, and I:E of 1:2. The PetCO2 was 35 mmHg after anesthesia induction. General anesthesia was maintained with inhaled sevoflurane, propofol, sufentanil, and rocuronium.

The surgery was initiated at 9:32 AM. At the beginning of the cardiopulmonary bypass (CPB), sevoflurane was stopped, and intravenous anesthesia was maintained during CPB. Dobutamine and milrinone infusions were initiated at the end of surgery and during rewarming. Heparin was reversed with protamine after separation from CPB. Sevoflurane inhalation was restarted and combined with intravenous anesthesia after CPB. At 02:27 PM, the blood gas analysis (Table 2) showed that pH decreased to 7.286, PCO2 increased to 48.1 mmHg, and nasopharyngeal temperature increased to 37.3°C. The patient was hyperventilated with 100% oxygen and high-minute ventilation to correct hypercapnia and acidosis.

Approximately 1.5 h after discontinuing CPB, the patient rapidly developed hyperthermia (39.1°C via a nasopharyngeal probe), hypercarbia (PCO2, 58–67.2 mmHg), and tachyarrhythmia (HR 135–145 times/min).

Sevoflurane was discontinued, ice packs were placed, and soda lime and the respiratory circuit were replaced. We continued to supply adequate ventilatory support while administering dantrolene (70 mg) and sodium bicarbonate (5%). At 05:00 PM, the patient’s nasopharyngeal temperature dropped to 38.1°C. Additionally, his blood gases and vital signs stabilized. He was transported to the ICU at 05:35 PM for continued circulatory and nutritional support and prophylaxis. The patient’s condition stabilized over the next several hours. He was extubated 2 days postoperatively, transferred to the general ward 2 days later, and discharged 11 days postoperatively. The patient’s body temperature and PCO2 trends are shown in Figures 3 and 4, respectively. Table S2 in the Supporting Information shows the patients’ MYO and CK levels.

### TABLE 2  The arterial blood gas analysis results of Patient 2

| Time  | PH   | PCO2 (mmHg) | PO2 (mmHg) | BE (mmol/L) | Na (mmol/L) | K+ (mmol/L) | iCa2+ (mmol/L) |
|-------|------|-------------|------------|-------------|-------------|-------------|---------------|
| 08:15 | 7.400| 38.2        | 252        | –1          | 144         | 4.0         | 1.33          |
| 10:20 | 7.323| 45.9        | 322        | –2          | 143         | 4.9         | 1.30          |
| 10:55 | 7.222| 53.1        | 200        | –6          | 145         | 4.7         | 1.20          |
| 11:10 | 7.264| 54.9        | 198        | –5          | 142         | 6.1         | 1.21          |
| 11:50 | 7.410| 35.5        | 153        | –2          | 142         | 5.6         | 1.23          |
| 12:20 | 7.440| 29.6        | 132        | –3          | 141         | 6.5         | 1.19          |
| 12:40 | 7.347| 41.9        | 134        | –3          | 142         | 6.4         | 1.22          |
| 14:27 | 7.286| 48.1        | 216        | –4          | 144         | 5.0         | 1.35          |
| 15:15 | 7.189| 58.4        | 124        | –6          | 146         | 5.2         | 1.06          |
| 15:40 | 7.096| 64.8        | 152        | –10         | 145         | 5.3         | 1.32          |
| 16:10 | 7.217| 67.2        | 196        | 0           | 156         | 5.3         | 1.28          |
| 17:00 | 7.265| 47.7        | 292        | –1          | 1445        | 5.4         | 1.17          |

Abbreviations: BE, base excess (normal range, −3–3 mmol/L); iCa2+, ionic calcium comparison (normal range, 1.10–1.34 mmol/L); K+, blood potassium comparison (normal range, 3.5–5.5 mmol/L); Na, blood sodium comparison (normal range, 135–145 mmol/L); PCO2, arterial carbon dioxide pressure (normal range, 35–45 mmHg); PH, potential hydrogen (normal range, 7.35–7.45); PO2, arterial oxygen pressure (normal range, 80–100 mmHg).

**FIGURE 3** Perioperative body temperature changes in Patient 2. CPB, cardiopulmonary bypass; Cs, starts CPB; Ic, skin incision; It, endotracheal intubation; L, leave ICU; W, weaning from CPB.
2.3 | Genetic test results

In Patient 1, postoperative peripheral blood analysis for MH susceptibility gene detection showed RYR1 gene nucleotide c.742G > A/C site mutation with a GG genotype. No mutations occurred at any of the other sites. In Patient 2, the results showed RYR1 gene nucleotide c.7361G > A site mutation with an AG genotype. No mutations occurred at any of the other sites. The genetic test results of the patients and their immediate relatives are shown in Table 3.

3 | DISCUSSION

The two patients we describe were admitted to the hospital for idiopathic scoliosis (Patient 1) and congenital tetralogy of Fallot (Patient 2). The intraoperative conditions were highly indicative of MH during general anesthesia. The postoperative genetic test results of the two patients and their immediate relatives showed mutations in the RYR1 gene. Genetic testing of Patient 1 and his father showed the RYR1 gene nucleotide in position 742nd G mutation for A or C. The genetic test results of Patient 2 and his son showed the RYR1 gene nucleotide in position 7361st G mutation for A. These results indicated that the families were susceptible to MH.

Malignant hyperthermia susceptibility is commonly considered monogenic with locus and allelic heterogeneity. Genetic testing and the caffeine-halothane contracture test (CHCT) are two alternatives for investigating MH susceptibility, with the reference standard being the CHCT skeletal muscle contracture test in vitro. Three genes—RYR1, calcium voltage-gated channel subunit alpha1 S, and SH3 and cysteine-rich domain 3—are associated with MH susceptibility and the extreme dysregulation of skeletal muscle Ca\(^{2+}\) homeostasis that produce the clinical features of MH under anesthesia.

Anesthesiologists must increase awareness of MH susceptibility. Although large-scale CHCT and gene mutation detection may be difficult to achieve, these tests can identify patients with diseases that increase MH risk. Before surgery, at-risk patients should undergo neurological examinations and biochemical tests, such as CK, CK-MB, and MYO. The preoperative CK values of both our patients were nearly 6–10 times higher than those of normal individuals (Tables S1 and S2); unfortunately, these anomalies were overlooked preoperatively. Inhalation anesthetics and depolarizing muscle relaxants should be avoided in such patients. Calcium channel blockers should not
be used along with dantrolene since hyperkalemia and profound hypotension may occur due to this drug combination. Continuous relevant monitoring needs to be strengthened.

Malignant hyperthermia can occur anytime during anesthesia induction, intraoperatively, or after anesthesia. The speed of progression tends to be more rapid in those whose reactions occur soon after triggering agent administration. The time and severity of MH after exposure to anesthetics in the two patients in this study were different. Compared with Patient 2, MH occurred earlier, progressed faster, and was more severe in Patient 1. However, in both patients, an unexplained, unexpected increase in PCO₂ or PetCO₂ was the first symptom (Figures 2 and 4). PetCO₂ is a sensitive index for the early detection of MH; however, this is not monitored during CPB. Arterial blood gas analysis of Patient 2 showed that PCO₂ was increased at the beginning of CPB, decreased to the normal range when the temperature dropped below 35°C and increased again after rewarming. Additionally, the patient's rewarming time was shorter than usual (Figures 3 and 4). When the patient's ventilation volume was higher than normal, PetCO₂ or PCO₂ increased continuously, and the core body temperature exceeded 40°C.

The initial signs and symptoms of MH during CPB differ from those of MH during routine surgery. Hypothermic CPB was established soon after anesthesia induction and rewarming itself increases body temperature; this could easily mask the body temperature increase during MH attacks. Low temperature (32°C) and rewarming can mask or trigger the MH reaction. Hyperthermia, tachycardia, chills, and acidosis caused by rewarming also interfere with MH diagnosis.

Delayed treatment can result in death within hours from severe acidosis, hyperkalemia, intractable arrhythmia, and circulatory failure. Treatment primarily aimed to reverse the reaction and treat complications and may include termination of possible trigger drugs, replacement of the soda lime and respiratory circuits, provision of 100% oxygen at maximum flow, increasing minute ventilation to 2–3 times the normal limit, cooling the body's surface, and administration of dantrolene sodium.

Dantrolene sodium is an antidote to MH. The initial dose of dantrolene is 2–3 mg/kg, and additional doses of 1 mg/kg are required every 5 min (cumulative maximum dose, 10 mg/kg) until the treatment goals (PetCO₂ < 6 kPa, with normal minute ventilation, core temperature < 38.5°C) are achieved. Because of its limited availability, dantrolene was only administered 1 h after MH in Patient 1. This delay may have contributed to the faster progression and a stronger reaction of MH in Patient 1.

Direct or indirect inhibition of the RYR is hypothesized to be fundamental to the molecular action of dantrolene, decreasing intracellular calcium concentrations. Therefore, dantrolene should be used as soon as possible before the dissolution damage of the skeletal muscle occurs.

Malignant hyperthermia management should focus on prevention and early detection, and clinicians should know emergency protocols for managing complex situations. This situation may be improved with the domestic production of dantrolene. Comprehensive treatment measures, such as physical cooling and correction of homeostatic imbalance should be immediately implemented. Renal replacement therapies such as hemofiltration and plasma exchange may also improve the comprehensive treatment of MH.

Fortunately, both patients with MH described above were successfully rescued. Given its rarity, complexity, and high mortality rate, knowledge of and preparation for the possibility of MH can facilitate rescue, as with the described cases.

AUTHOR CONTRIBUTIONS
Xiaowei Chi involved in supervision and writing—original draft. Yi Xu involved in writing—original draft. Hongbing Liao, Tao Chen, and Qiang Li involved in writing—review and editing. Qiang Fu involved in conceptualization and writing—review and editing.

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None.

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

DATA AVAILABILITY STATEMENT
The data used to support the findings of this study are available from the corresponding author upon request.

IRB NUMBER
This study was approved by the Medical Ethics Committee of The Third People’s Hospital of Chengdu and was conducted in accordance with the Declaration of Helsinki.

ETHICAL APPROVAL
This study was approved by the Medical Ethics Committee of The Third People’s Hospital of Chengdu and was conducted in accordance with the Declaration of Helsinki.

CONSENT
Written informed consent was obtained from the families of all patients for the collection of samples and the publication of medical data.
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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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