

Malignant hyperthermia upon re-exposure to sevoflurane after an uneventful identical anesthetic in a patient with negative RYR1 and CACNA1S genetic testing: a case report

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Case Report

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Abstract

Background

Malignant hyperthermia (MH) is a rare but potentially fatal hypermetabolic crisis triggered by volatile anesthetics. Mortality rises sharply when dantrolene is delayed. MH upon re-exposure to volatile anesthetics is documented. Yet it is uncommon to encounter MH after a prior uneventful identical anesthetic, with onset beyond 2 hours, negative RYR1 and CACNA1S testing, and no on-site dantrolene.

Case presentation:

A male patient underwent laparoscopic resection of a recurrent adrenal lesion. He had received the same sevoflurane-based anesthetic at the same hospital four months earlier without incident. In this laparoscopic resection of a recurrent adrenal lesion, hypermetabolic signs initiated at approximately 2.0 hours after induction. The clinical diagnosis of MH was made at 2.5 hours after induction. The peak crisis of MH reached at 3.25 hours after induction, manifested by abrupt hypercapnia (EtCO₂ 95 mmHg), hyperthermia to 40.5°C, hyperkalemia (6.5 mmol/L) and metabolic acidosis. Blood pressure fell to 75/40 mmHg and heart rate rose to 165 beats per minute. Masseter spasm was absent. The Clinical Grading Scale score was 63 ("almost certain"). Sevoflurane was stopped immediately. The breathing circuit and soda lime were replaced. Management included hyperventilation, active cooling, correction of acidosis and electrolytes, and norepinephrine infusion. Our institution did not maintain an on-site dantrolene supply. Definitive therapy was delayed for 2 hours while the drug was retrieved from an outside facility. Postoperative targeted sequencing of RYR1 and CACNA1S revealed no pathogenic variants. The patient ultimately recovered without residual complications after ICU admission.

Conclusion

This case demonstrates that MH can occur despite a prior uneventful anesthetic, despite negative RYR1/CACNA1S screening, and a 2-hour delay onset of MH. It underscores the necessity of maintaining institutional dantrolene stocks and sustained intraoperative vigilance regardless of anesthetic duration or prior unremarkable exposures.

Introduction

Malignant hyperthermia (MH) is a rare but potentially fatal hypermetabolic crisis of skeletal muscle, classically triggered by volatile anesthetics, in susceptible patients^{1, 2}. The classic presentation includes abrupt hypercapnia, hyperthermia, muscle rigidity, and severe metabolic acidosis³. Dantrolene is the only specific treatment^{2, 3}. Early recognition and prompt treatment are essential to improve outcome due to the rapid progress in MH^{2, 3}.

Most cases link to variants in *RYR1* and *CACNA1S*⁴. However, these two genes do not explain all patients. Current panel-based screening detects only approximately 50% of susceptible individuals, leaving a substantial proportion of cases genetically unexplained⁴. The heterogeneity of MH-related mutations mean that some individuals may tolerate one or more anesthetics before experiencing a fulminant crisis upon re-exposure^{5,6}.

We report an adult male who developed MH upon re-exposure to an identical sevoflurane-based regimen 4 months after a completely uneventful laparoscopic procedure at the same institution. The onset of MH was markedly delayed, with initial signs at approximately 2.0 hours, clinical diagnosis at 2.5 hours, and peak crisis at 3.25 hours. Postoperative targeted sequencing of *RYR1* and *CACNA1S* revealed no pathogenic variants. The institution did not stock dantrolene on site and specific therapy was delayed for 2 hours. This case reinforces that MH demonstrates variable penetrance, and a prior uneventful anesthetic, irrespective of interval, does not exclude susceptibility.

Case presentation

A 56-year-old man, height 170 cm, weight 85 kg, BMI 29.4 kg/m², ASA physical status II, presented with hypertension. There was no personal or family history suggestive of MH susceptibility. The patient was scheduled for laparoscopic resection of a recurrent adrenal lesion. Four months earlier, he had undergone surgery under sevoflurane-based balanced anesthesia at the same hospital. That anesthetic was entirely uneventful. Anesthesia was induced with remimazolam 0.2 mg/kg, propofol 1.5 mg/kg, sufentanil 0.5 µg/kg, rocuronium 0.6 mg/kg and methylprednisolone 40 mg. Anesthesia was maintained with inhaled sevoflurane (1.5-2.0% end-tidal), continuous remifentanil infusion (0.2 µg/kg/min) and intermittent rocuronium. Mechanical ventilation was adjusted to maintain normocapnia.

For the first 2 hours after induction, the anesthetic course was stable. Thereafter, the patient's heart rate began to rise, end-tidal carbon dioxide (EtCO₂) progressively increased from 39 mmHg to 53 mmHg despite increased minute ventilation, and core temperature climbed rapidly from 37.3°C to 39.1°C. At 2.5 hours after induction, the anesthesiologists realized that the patient might be experiencing MH, so they immediately discontinued sevoflurane and switched to total intravenous anesthesia, including propofol infusion (6 mg/kg/h), remifentanil continuous infusion (0.2 µg/kg/min) and intermittent rocuronium. The patient developed abrupt hypercapnia (EtCO₂ 95 mmHg) and hyperthermia to 40.5°C approximately 3.25 hours after induction. Meanwhile, blood pressure was decreasing to 75/40 mmHg, while heart rate was increasing to 165 beats per minute. Arterial blood gas analysis revealed mixed acidosis (pH 7.18, PaCO₂ >100 mmHg, base excess – 8.0 mmol/L) and hyperkalemia (6.5 mmol/L). No masseter spasm was observed. Preoperative plasma and urinary metanephrines and catecholamines were negative, making pheochromocytoma crisis unlikely. We systematically excluded airway obstruction (endotracheal tube kinking, mucus plugging, breathing circuit disconnection or kinking), restrictive ventilatory impairment from excessive pneumoperitoneum pressure, ventilator mis-settings (inadequate tidal volume or respiratory rate, inappropriate I:E ratio, prolonged inspiratory plateau), and anesthesia circuit failure (exhausted CO₂ absorbent, malfunctioning unidirectional valves). The persistence of hypercapnia,

hyperthermia, hyperkalemia, and metabolic acidosis despite correction of these factors, together with complete replacement of the breathing circuit and soda lime, rendered MH the leading diagnosis. Final histopathology confirmed the resected lesion as recurrent adrenal cortical adenoma, definitively excluding pheochromocytoma.

The team initiated active surface cooling with a forced-air cooling blanket set at 28°C, an ice cap and ice packs to the axillae, groin, and neck. The operating room ambient temperature was reduced. Ice-cold intravenous fluids were administered. Hyperventilation was applied with 100% oxygen at high fresh gas flows. They gave sodium bicarbonate to correct acidosis and insulin-glucose therapy to treat hyperkalemia. Norepinephrine infusion was initiated at 0.5-1.0 µg/kg/min, titrated to maintain mean arterial pressure > 65 mmHg, starting at approximately 2.5 hours after induction when significant hypotension developed. It was continued through the rest of the intraoperative period and into the ICU, where it was gradually weaned as hemodynamics stabilized.

Our institution did not have dantrolene on site. Emergency procurement from an external facility required approximately 2 hours, during which the patient's hemodynamics and acid-base status were managed entirely with the supportive therapies (before dantrolene's arrival, blood pressure was maintained at 95/52 mmHg with heart rate 140 beats per minute). Once dantrolene reached the operating room, an initial intravenous bolus of 2 mg/kg (170 mg) was administered at 4.5 hours after induction. One hour after the first dose, EtCO₂ normalized to approximately 38 mmHg and temperature gradually decreased to 40.0°C. At this point, the surgery was completed and the patient was transferred to the intensive care unit (ICU). Immediately upon arrival in the ICU (at 5.5 hours after induction), a second dose of 2 mg/kg (170 mg) dantrolene was given, bringing the accumulative dose to 340 mg. Four hours after the second dose, EtCO₂ reached 32 mmHg and temperature dropped to 38.2°C.

The patient remained intubated for ventilatory and hemodynamic support after the admission to ICU. Laboratory studies demonstrated that intraoperative peak of CK was 15,100 U/L and serum myoglobin was 422 ng/mL, measured during the MH crisis while awaiting dantrolene. CK declined to 1,091 U/L by the evening of surgery (approximately 6 hours post-dantrolene), and further to 472 U/L on postoperative day 1. Troponin I was 0.91 ng/mL on the evening of surgery and 0.60 ng/mL on postoperative day 1. BNP was 171 on postoperative day 1. Renal function remained preserved (peak creatinine 83 µmol/L) with aggressive hydration and urine alkalinization. No acute kidney injury developed. Coagulation studies on the evening of surgery showed PT 15.7 s, APTT 29.8 s, INR 1.36, fibrinogen 1.01 g/L, FDP 13.4 mg/L, and D-dimer 2.14 DDU mg/L. Thromboelastography (TEG) was normal and there was no evidence of disseminated intravascular coagulation (DIC). ALT 387 U/L and AST 502 U/L on postoperative day 1 indicated transient hepatic transaminitis secondary to hyperthermia. In the ICU, he received supportive care including aggressive intravenous hydration and mechanical ventilation until extubation criteria were met. The patient was successfully extubated at about 20 hours postoperatively once hemodynamics, temperature (36.9°C), and acid-base status had normalized. Finally, he was discharged on postoperative day six without neurological or organ damage. The changing trends of physiological parameters

following anesthetic induction were shown in Fig. 1. The progression of MH crisis was summarized in Table 1.

Table 1
Timeline of clinical events following anesthetic induction.

Time after induction	Events and clinical findings	Managements
0 h	Induction. EtCO ₂ 30 mmHg, T 36.8°C, BP 140/80 mmHg, HR 80 bpm.	Induced with remimazolam, propofol, sufentanil, rocuronium and methylprednisolone.
0–2.0 h	All parameters were stable.	Maintained with sevoflurane, remifentanil and rocuronium.
2.0-2.5 h	Onset of MH. EtCO ₂ from 39 to 53 mmHg, T from 37.3 to 39.1°C, BP from 130/72 to 108/60 mmHg, HR from 90 to 99 bpm.	Increased fresh gas flow; enhanced minute ventilation.
2.5 h	MH clinically diagnosed. EtCO ₂ 53 mmHg, T 39.1°C, BP 90/45 mmHg, HR 136 bpm.	Sevoflurane discontinued; breathing circuit and soda lime replaced; 100% oxygen; urgent request for dantrolene (not available on site); active surface cooling.
3.25 h	Peak crisis. EtCO ₂ 95 mmHg, T 40.5°C, BP 75/40 mmHg, HR 165 bpm, pH 7.18, PaCO ₂ >100 mmHg, base excess – 8.0 mmol/L and hyperkalemia (6.5 mmol/L)	Aggressive fluid resuscitation; vasopressor support; hyperventilation; continued cooling; acidosis correction and insulin-glucose therapy.
4.5 h	Post-peak stabilization begins. EtCO ₂ 55 mmHg, T 40.3°C, BP 95/52 mmHg, HR 140 bpm.	First dantrolene administration.
5.5 h	Post-peak stabilization. EtCO ₂ 38 mmHg, T 40.0°C, BP 120/70 mmHg, HR 125 bpm.	ICU admission; Second dantrolene administration ; supportive care.
9.5 h	Recovery phase. EtCO ₂ 32 mmHg, T 38.2°C.	Supportive care
20 h	Normal hemodynamics and T (36.9°C).	Extubation

EtCO₂ = end-tidal carbon dioxide; T = core temperature; BP = blood pressure; HR = heart rate; MH = malignant hyperthermia; ICU = intensive care unit.

Using the Malignant Hyperthermia Clinical Grading Scale (CGS)⁷, the patient scored 63 points (generalized muscle rigidity excluded, as it was not present; points derived from hypercapnia, hyperthermia, hyperkalemia, acidosis, markedly elevated creatine kinase, myoglobinuria, tachycardia, and rapid response to dantrolene), corresponding to Level 6 (“almost certain”). Postoperative genetic counseling and testing were performed. Targeted next-generation sequencing of the major MH-associated loci, *RYR1* and *CACNA1S*, detected no pathogenic variants, likely pathogenic variants, or

variants of uncertain significance. The patient was counseled to permanently avoid volatile anesthetics and succinylcholine. Family members were informed of the diagnosis and advised to undergo genetic counseling and, if indicated, specialized diagnostic workup (e.g., in vitro contracture testing)^{8,9} because MH susceptibility can be familial. However, the patient and his family did not perform contracture testing (IVCT) or the caffeine-halothane contracture test (CHCT), the diagnostic gold standard for MH susceptibility^{8,9}, because they declined invasive muscle biopsy.

Discussion

This case illustrates a rare and clinically challenging presentation of MH combines four unusual features: re-exposure after 4 months at the same hospital, markedly delayed onset, entirely negative targeted genetic testing, and survival despite the absence of immediate dantrolene. Each feature carries distinct implications for perioperative safety.

It is a misconception among clinicians that a previous uneventful general anesthetic reliably excludes MH susceptibility. However, MH demonstrates variable penetrance, and susceptible individuals may undergo multiple unremarkable anesthetics before a crisis is triggered^{5,10}. Geng et al. recently reported MH upon re-exposure to sevoflurane within 4 days during limb debridement surgery⁶. This case reinforces that prior safety data cannot be used to justify withholding MH precautions, and constant vigilance is mandatory during every exposure to volatile agents.

MH is usually described as occurring shortly after induction or intraoperatively within the first hour of volatile anesthetic exposure^{1,2}. However, delayed-onset MH, particularly with sevoflurane, has been reported from 30 minutes to over an hour after induction¹¹. In our patient, initial hypermetabolic signs manifested approximately 2.0 hours after induction, with clinical diagnosis at 2.5 hours and peak crisis at 3.25 hours. This unusually prolonged latency challenges the clinical habit of relaxing vigilance after an unremarkable first or second hour of anesthesia. It reinforces the necessity of continuous core temperature and capnography monitoring throughout the entire duration of any sevoflurane anesthetic, irrespective of how uneventful the preceding hours have been.

Genetic screening for MH susceptibility has traditionally focused on *RYR1* and *CACNA1S*⁴. However, a negative result in these two genes cannot exclude MH susceptibility, as known pathogenic variants account for only approximately 50–70% of susceptible individuals⁴. In the recently published case by Geng et al., targeted sequencing identified *RYR1* variants of uncertain significance (VUS), leaving the genetic diagnosis unresolved⁶. Our case identified no VUS, no likely pathogenic, and no pathogenic variants in either *RYR1* or *CACNA1S*. This represents a clear example of phenotype-positive, genotype-negative MH, which demonstrates that a negative genetic panel must not be interpreted as a green light for volatile anesthetics in patients with suggestive clinical histories or family backgrounds. Definitive MH susceptibility testing by IVCT or CHCT, the diagnostic gold standard^{8,9}, was not performed because the patient declined invasive muscle biopsy. Definitive MH susceptibility testing by contracture study is

recommended for the proband and first-degree relatives at a specialized referral center if they reconsider.

Dantrolene is the only specific therapeutic agent for acute MH and is recommended to be available wherever volatile anesthetics or succinylcholine are used¹². Our institution did not maintain an on-site supply, resulting in a 2-hour delay before specific therapy could be administered. The patient survived this interval without irreversible organ damage, but this outcome was attributable to the eventual administration of dantrolene combined with temporary supportive measures, not to supportive therapy alone. This case underscores the life-threatening risks of inadequate institutional preparedness. Wherever volatile anesthetics or succinylcholine are used, dantrolene must be immediately available on site. Supportive measures can only serve as a temporary bridge and should never be considered an acceptable substitute for prompt specific treatment.

Following this event, the patient was counseled to avoid all volatile anesthetics and succinylcholine permanently. For future surgeries, a total intravenous anesthetic regimen is indicated. Notably, the induction agent used in this case, remimazolam besylate, is not known MH triggers. The use of non-triggering anesthetic techniques, combined with clear documentation and patient education, forms the cornerstone of long-term management¹³.

Conclusion

This case contributes a rarely reported combination of clinical features to the MH literature: an unusually delayed onset exceeding 2 hours, entirely negative *RYR1/CACNA1S* sequencing, and survival despite a 2-hour dantrolene delay managed with aggressive supportive care. It directly challenges three clinical misconceptions: that prior uneventful anesthetics confer protection, that negative genetic testing for the two major loci excludes susceptibility, and that MH cannot present late in the course of a sevoflurane anesthetic. We recommend that anesthesiologists sustain peak vigilance for hypercapnia and hyperthermia throughout the entire perioperative period, regardless of anesthetic duration or historical unremarkable exposures.

Declarations

Ethics and consent to participate

Written informed consent was obtained from the patient. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Consent to publish:

Written informed consent was obtained from the patient for publication of this case report and any accompanying clinical data.

Competing interests:

The authors declare that they have no competing interests.

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Author Contribution

Tao Jiang and Qionghui Zhan, performed anesthesia, collected data and wrote the original draft. Xiao Shi and Shuyu Zhang assisted in data collection. Jie Xiao reviewed the manuscript. Qionghui Zhan, supervised clinical management and critically revised the manuscript. All the authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

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Not applicable.

Data Availability

All data generated or analyzed during this study are included in this published article. Further inquiries can be directed to the corresponding author.

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Figures

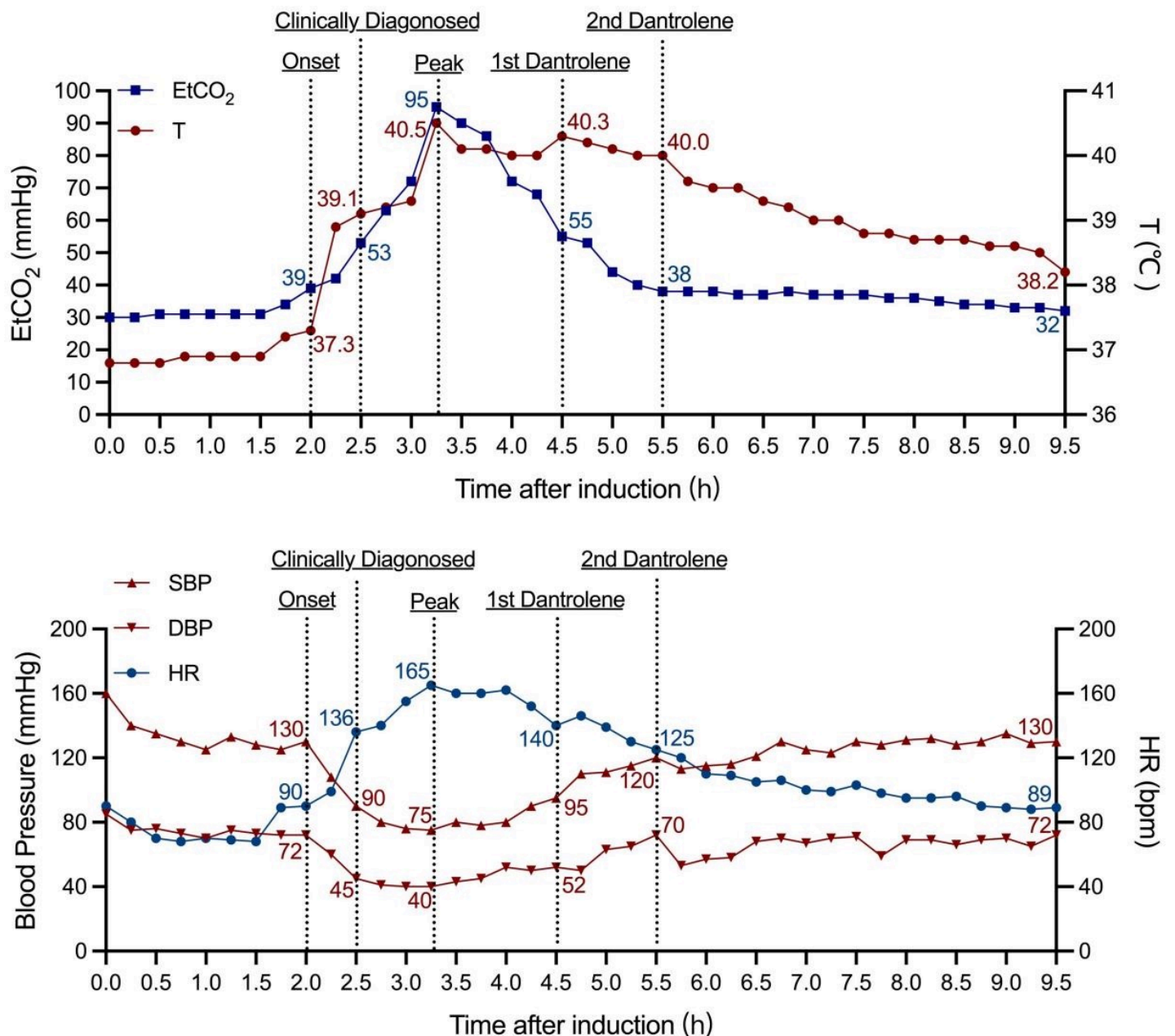


Figure 1

Temporal trends of physiological parameters following anesthetic induction. The upper panel shows end-tidal carbon dioxide (EtCO₂, blue squares) and core temperature (T, red circles). The lower panel shows systolic blood pressure (SBP, red upward triangles), diastolic blood pressure (DBP, red downward triangles), and heart rate (HR, blue circles). The dashed line represents the onset of MH (2.0 h), MH clinically diagnosed (2.5 h), the peak crisis of MH (3.25 h), the first dose of dantrolene (4.5 h) and the second dose of dantrolene (5.5 h). Peak values were EtCO₂ 95 mmHg and temperature 40.5 °C, along with HR 165 beats/min and blood pressure 75/40 mmHg.

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