International Clinical and Medical Case Reports Journal
Case Report (ISSN: 2832-5788)

Aortic Root Surgery with Hypothermic Circulatory Arrest in a Patient with Malignant Hyperthermia and Osteogenesis Imperfecta: A Case Report

Serena Errichiello[1], Fatima Zohra Taleouine[1], Ottavia Borghese[1], Wael I Awad[1,2*]

[1]Department of Cardiac Surgery, Barts Heart Centre, St Bartholomew's Hospital, London, UK

[2]William Harvey Research Institute, Queen Mary University of London, UK

Citation: Serena Errichiello, Fatima Zohra Taleouine, Ottavia Borghese, Wael I Awad. Aortic Root Surgery with Hypothermic Circulatory Arrest in a Patient with Malignant Hyperthermia and Osteogenesis Imperfecta: A Case Report. Int Clinc Med Case Rep Jour. 2026;5(11):1-8.

Received Date: 08 November 2026; **Accepted Date:** 13 November 2026; **Published Date:** 16 November 2026

***Corresponding author:** Wael I Awad, Department of Cardiac Surgery, Barts Heart Centre, St Bartholomew's Hospital, London, UK

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ABSTRACT

Malignant hyperthermia (MH) is a rare and life-threatening disorder of skeletal muscle most often triggered by volatile anaesthetic gases and succinylcholine that can lead to a dramatic increase in body temperature with possible fatal outcomes. It has also been reported in patients undergoing surgeries involving cardiopulmonary bypass (CPB) but only 30 cases have been described so far in the current literature. Osteogenesis imperfecta (OI), also Known as “brittle bone disease” is a rare disorder of connective tissue characterized by fragile bones that can easily break, often from little or no apparent trauma. While musculoskeletal abnormalities are well described in osteogenesis imperfecta, cardiovascular involvement is rare. When the heart is involved in osteogenesis imperfecta, aortic root dilation is the most common cardiovascular manifestation. Here we present a patient with confirmed malignant hyperthermia, osteogenesis imperfecta, a bicuspid aortic valve and associated aortic aneurysm, who underwent aortic root surgery with hypothermic circulatory arrest (HCA). Despite avoidance of known triggering agents, recommended peri-operative management and subsequently, active cooling, intravenous dantrolene administration and multiorgan support, the patient succumbed from complications most likely associated with the combination of malignant hyperthermia and osteogenesis imperfecta. The outcome of this case raises critical questions about the optimal management of malignant hyperthermia-susceptible patients requiring major cardiovascular interventions. Further research is needed to better understand the relationship between malignant hyperthermia and osteogenesis imperfecta, allowing tor more ettective

strategies to enhance patient safety in high-risk surgery scenarios.

Keywords: Malignant Hyperthermia, Osteogenesis Imperfecta, Cardiac Surgery, dantrolene, Cardiopulmonary bypass, Case report

INTRODUCTION

Malignant Hyperthermia is a rare, life-threatening, autosomal dominant disorder triggered by certain anaesthetic agents, particularly volatile gases and depolarizing muscle relaxants like succinylcholine. It is caused by mutations affecting the

type 1 ryanodine receptor (RYR1) gene on Chromosome 19, leading to uncontrolled calcium release from the sarcoplasmic reticulum, resulting in sustained muscle contraction, excessive heat production, metabolic acidosis, and 1 untreated, multi-organ failure. Though uncommon, MH has been reported in patients undergoing cardiac surgery requiring cardiopulmonary bypass (CPB), with only 30 documented cases in the literature. CPB complicates MH recognition and management, as active rewarming can serve as a potential trigger, and hypothermia may mask early symptoms [1].

The diagnosis of MH is primarily clinical, with early signs including sinus tachycardia, hypercarbia, metabolic acidosis, and muscle rigidity, particularly following administration of succinylcholine [2]. The definitive diagnostic test involves a muscle biopsy to assess the skeletal muscle response to halothane and caffeine [3]. In the perioperative setting, a high suspicion is necessary, particularly in patients with a personal or family history of MH.

Osteogenesis imperfecta is a rare inherited connective tissue disorder caused by mutations in COL1A1 or COL1A2, which encode type 1 collagen. While OI is primarily associated with skeletal fragility and frequent fractures, it can also affect extra-skeletal structures, including the cardiovascular system. The most frequently reported cardiac manifestations involve left-sided heart valves, particularly aortic and mitral regurgitation, as well as aortic root dilation. Additionally, OI has been linked to perioperative hyperpyrexia, metabolic acidosis, and an increased risk of respiratory and coagulation dysfunction, all of which pose significant anaesthetic and surgical challenges [4].

The co-existence of MH and OI In a single patient undergoing aortic root replacement with hypothermic circulatory arrest (HCA) presents an exceptionally rare and complex clinical scenario. Hypothermia during CPB creates unique challenges as it may both mask and exacerbate MH-associated complications. Furthermore, the fragile vasculature in OI also increases the risks of aortic surgery, while respiratory and metabolic instability in both conditions raises concerns for postoperative recovery.

Here, we present a case of a 62-year-old male with biopsy-confirmed MH, OI, a bicuspid aortic valve, and an ascending aortic aneurysm, who underwent aortic root surgery involving HCA at 25 °C.

CASE REPORT

A 62-year-old gentleman presented with progressive shortness of breath and exertional chest heaviness over a six months period that had significantly limited his exercise tolerance. He was an ex-smoker, and his past medical history included hypertension, osteogenesis imperfecta and malignant hyperthermia, which had been confirmed by muscle biopsy. His MH susceptibility was particularly significant, with five of his family members having died from MH-related crises during surgery. He had also suffered a previous ischemic stroke, for which he was on 75 mg/day clopidogrel, and had a long-standing history of suicidal depression, managed with 75 mg/day venlafaxine. Given his diagnosis of malignant hyperthermia, he previously underwent a total knee replacement and spinal surgery under spinal anaesthesia to avoid any potential risks of general anaesthesia.

Physical examination revealed a harsh, crescendo–decrescendo systolic heart murmur, radiating to the neck, as well as bilateral basal lung crackles, indicating incipient heart failure. No pedal edema, jugular distension or hepatomegaly was found.

The patient underwent a transthoracic echocardiogram that revealed a dilated left ventricle (end-diastolic diameter 62 mm, end-diastolic volume 180 mL) with a low-to-moderate reduction of systolic function (ejection fraction ot 45%) due

to global hypokinesia, a dilated aortic root (40 mm) and ascending aorta (50 mm) and a severely degenerated bicuspid aortic valve (type 0) with both moderate stenosis (mean gradient 28 mmHg, peak gradient 47 mmHg, aortic valve area y, 1.44 cm^2, Doppler Velocity Index 0.30) and regurgitation (regurgitant Volume 55 mL, regurgitant fraction 40%). A computed tomography (CT) scan further confirmed the presence of aortic dilation, with specific measurements (Figure 1) showing an annulus diameter of 38 x 28 mm, a sinus of Valsalva diameter of 40 x 36 mm, a sino-tubular junction of 45 mm, and a mid-ascending aortic dimension of 50 mm. The distal ascending aorta was also 50 mm in diameter, while the mid-arch measured 30 mm.

Coronary angiogram did not show obstructive coronary artery disease in any epicardial vessel.



Figure 1: Axial scan of ascending aorta revealing a preoperative maximum diameter of 50 mm.

Following a multidisciplinary discussion, the consensus was that the patient required aortic valve replacement (AVR) and aortic root/ascending aorta replacement (AAR), in accordance with ES valvular heart disease [5].

The patient was reviewed in our High-Risk Anesthetic Clinic in view of his complicated clinical picture. It was agreed that anaesthesia would be managed using propofol and non-depolarizing muscle relaxants, while careful temperature control would be ensured with slow rewarming on cardiopulmonary bypass. Furthermore, dantrolene would be readily available in the event of an MH crisis.

Anesthesia was successfully induced using non-triggering agents. Anaesthesia was conducted with Midazolam, Fentanyl, Propofol, rocuronium and during the entire surgery the patient was haemodynamically stable. As a distal anastomosis of the tube graft to the arch of the aorta was required, hypothermic circulatory arrest was deemed necessary to facilitate the procedure. Standard cardiopulmonary bypass was established and the patient was cooled to 25 °C. The heart was arrested with St Thomas' cardioplegia solution anterogradely with further doses administered at 20-minute intervals via direct coronary intubation.

At operation, the aortic valve was confirmed to be bicuspid (type 0). The aortic root was grossly dilated and the sinuses and ascending aorta were very thin. An aortic root replacement was thus deemed necessary. The native aortic valve was excised and the ascending aorta was resected and sent for histology. A Bentall de Bono surgery was performed: the root was replaced with a Carbomedics (Corcym, Italy) composite valve and tube graft with reimplantation of the coronary buttons. A 9-minute period of circulatory arrest allowed for the distal anastomosis to be completed, the total aortic cross-

clamp time was 139 minutes, while cardiopulmonary bypass duration was 248 minutes. Considering his susceptibility to MH, the patient was gently rewarmed to 34 °C (core temperature) before being weaned off CPB in a stable condition. Throughout the procedure, near-infrared spectroscopy (NIRS) monitoring showed no significant decreases in cerebral oxygenation.

On postoperative day one, the patient was successfully weaned from vasopressor support. First post-surgical echocardiogram revealed initial reverse remodeling Ot left ventricle, with stable ejection fraction and normal function ot aortic valvular conduit. By day seven, he developed worsening respiratory distress, necessitating reintubation due to type 1 respiratory failure with high oxygen requirements (FiO_2 0.7-1.0). He underwent broad-spectruin antibiotic therapy (Linezolid 600 mg and Cettazidime 2 g three times daily), Nigh-dose methylprednisolone (40 mg/day) and ventilation in the prone position with only small ventilatory improvements. During this period, he also developed hemodynamic instability, requiring inotropic and vasopressor support and several DC cardioversions for atrial fibrillation and ventricular tachycardia.

A transesophageal echocardiogram (TOE) identihed a collection around the aortic root. Chest CT (Figure 2) confirmed bilateral lung consolidation and a small hematoma collection around the aortic root in keeping with recent surgery. As it was possible that the cardiac arrhythmias and hemodynamic instability were related to the peri-aortic hematoma, the decision was made to proceed with a re-sternotomy and drainage. This was performed on postoperative day thirteen with drainage of a moderate serous pericardial effusion and evacuation of the periaortic hematoma.

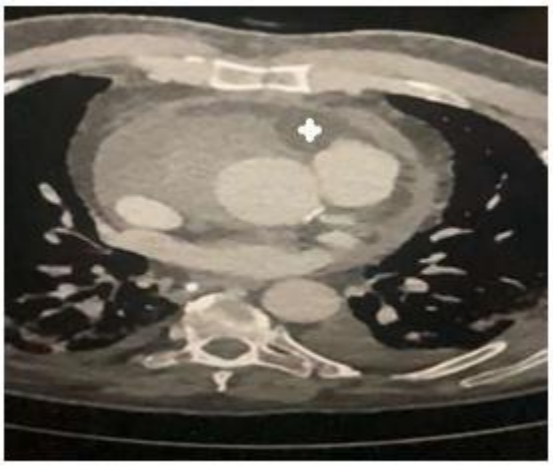


Figure 2: Chest CT showing hematoma collection around the aortic root (white star).

His respiratory failure persisted despite these interventions with no signiticant positive microbiology, prompting a suspicion of acute Respiratory Distress Syndrome (ARDS). His condition further deteriorated with the onset of renal failure, requiring replacement therapy for severe acidosis and hyperkalemia. A repeat echocardiogram on postoperative day 15 confirmed the aortic valve was functioning satisfactorily, with no aortic regurgitation and preserved LV function. Throughout this period his temperature had not exceeded 37.8°C, then spiked suddenly to 40°C on nasal probe and 42°C on LUE probe). In response, dantrolene (2.5 mg/kg) was administered intravenously, and active cooling with the Arctic Sun Temperature Management systein (Medivance/Bard) was initiated, successfully lowering his body temperature to 35°C and vasopressors were weaned off.

Despite these measures, he remained critically unwell, with severe respiratory failure requiring escalating ventilator support, worsening renal failure, and new-onset sinus bradycardia without AV block. He was deemed unsuitable for veno-venous extracorporeal membrane oxygenation (VV-ECMO) due to prolonged mechanical ventilation. By postoperative day 33, his oxygen requirements had turther escalated to FiO_2 1.0 and following discussions with tamily, a decision was made to withdraw life-sustaining treatment and the patient passed away.

DISCUSSION

This case highlights the extraordinary complexity of managing a patient with both malignant hyperthermia and osteogenesis imperfecta undergoing major cardiac surgery with hypothermic circulatory arrest. Despite comprehensive preoperative planning and meticulous intraoperative management, the patient developed late-onset hypermetabolic state, multi-organ failure, and ultimately succumbed to complications.

MH is a rare but life-threatening disorder that has traditionally been considered a perioperative event, primarily triggered by exposure to volatile anaesthetic agents or depolarizing neuromuscular blockers such as succinylcholine and halogenated hydrocarbon anaesthetic vapor [6]. However, it has also been reported among patients undergoing cardiac surgeries involving cardiopulmonary bypass, raising concerns about its unique presentation and management challenges in this setting. Diagnosing MH can be difficult, as symptoms may present subtly and the underlying trigger 1s not always identifiable. Without prompt intervention, mortality can reach up to 75% [7].

Due to its rarity, the management of MH-susceptible patients in cardiac surgery is largely derived troin a limited number ot case reports. Standard recommendations include avoiding triggering agents, active cooling, and intravenous dantrolene administration. However, even when these measures are successfully implemented, severe complications such as renal failure, heart failure, and bowel ischemia can still occur, as seen in this case.

Malignant hyperthermia has been reported in patients undergoing surgeries involving cardiopulmonary bypass, though cases remain rare. Butala et al. recently reviewed the diagnosis and treatment of MH during cardiac surgery requiring cardiopulmonary bypass [6]. They identified 17 cases of newly diagnosed or presumed MH. Of this group, the majority were treated with dantrolene and a survival rate Ot 88% (15 Out Of 17 patients) was observed. Additionally, 13 cases Ot Known malignant hyperthermia-suscepuble patients were also 1dentitied, all of whoin received tailored management that included the use of non-triggering agents, meticulous preparation of mechanical ventilators, close multiparametric monitoring, avoidance of hypothermia during cardiopulmonary bypass, slow rewarming after cardiopulmonary bypass, off-pump coronary artery bypass graft when possible, continued high-level vigilance throughout the postoperative period, and in many cases dantrolene prophylaxis.

Supportive treatment also ininvolved optimization of oxygenation and ventilation, discontinuation of triggering agents, correction Of hyperkalemia and metabolic acidosis, cooling as necessary with cold 1sotonie crystalloid and ice packs, and cardiovascular support as needed.

Dantrolene functions as a postsynaptic muscle relaxant that plays a crucial role in the treatment and prevention of MH. It exerts its effect by directly inhibiting the release of calcium ions from the sarcoplasmic reticulum in skeletal muscle cells, thereby preventing the uncontrolled calcium accumulation that leads to sustained muscle contraction, hypermetabolic state, and excessive heat production. By blocking RYR1 channels, dantrolene effectively reduces intracellular calcium levels, which in turn helps to relax the muscles, counteract the hypermetabolic state, and stabilize cardiovascular and

respiratory function. Its mechanism of action specifically targets skeletal muscle, without affecting cardiac or smooth muscle, making it the only pharmacologic agent capable of reversing an MH crisis. However, its prophylactic use remains controversial, even among patients with confirmed MH susceptibility or a strong family history [8]. Current guidelines do not routinely recommend preemptive administration, as there is insufficient evidence to justify its use in all cases. Furthermore, Butala et al noted inconsistencies in dantrolene's pharmacokinetics in the CPB setting [6], highlighting existing gaps in knowledge regarding its optimal use in cardiac surgery. In our case, dantrolene was not given prophylactically but was administered once MH was suspected in the late postoperative period. Whether earlier intervention could have improved the outcome remains uncertain.

Hypothermia during cardiopulmonary bypass introduces additional challenges, particularly in MH detection and management. Cooling may suppress early metabolic warning signs, potentially delaying diagnosis, while active rewarming has been implicated as a potential MH trigger. For this reason, it is recommended that MH-susceptible patients undergo slow, controlled rewarming, maintaining core temperatures below 36°C[g]. In this case, the patient was rewarmed slowly to only 34 °C, yet still developed a delayed hypermetabolic crisis, suggesting CPB-associated temperature shifts alone may not fully explain MH activation in this context.

While MH is well-recognized as a hypermetabolic disorder, osteogenesis imperfecta has also been associated with perioperative hyperpyrexia, metabolic acidosis, and respiratory complications, though the exact mechanism remains unclear. In contrast to fulminant MH, OI-related hyperthermia is often self-limiting and does not present with generalized rigidity or severe hypercarbia. [10]. Some patients with OI have exhibited intraoperative hyperthermia and tachycardia, yet muscle biopsy testing ruled out MH, supporting the hypothesis that OI may involve a separate, distinct metabolic dysregulation [11].

During the aortic multidisciplinary meeting, concerns were raised regarding the need for hypothermic circulatory arrest to facilitate the procedure in this patient. However, the consensus was that surgery was strongly indicated based on current guidelines. Despite an appropriate pre-operative work-up, meticulous intraoperative monitoring, gentle rewarming on cardiopulmonary bypass, and the administration of dantrolene, the outcome was ultimately fatal. It is possible the combination of hypothermic circulatory arrest, malignant hyperthermia, and Osteogenesis imperfecta is a bridge too far and avoidance of surgery in these patients might be warranted.

CONCLUSIONS

This case highlights the complex challenges of managing a patient with both MH and OI undergoing major cardiac surgery with hypothermic circulatory arrest. Despite extensive perioperative precautions, the patient experienced a delayed hypermetabolic crisis, ultimately leading to multi-organ failure and a fatal outcome. The interplay between MH and OI in this setting remains poorly understood, raising important considerations regarding perioperative metabolic stability, temperature modulation strategies, and tailored anaesthetic management in high-risk patients.

Although malignant hyperthermia is primarily recognized as a pharmacogenetic disorder of skeletal muscle, its occurrence in patients undergoing cardiopulmonary bypass suggests that temperature shifts and metabolic stress may serve as additional triggers. The role of hypothermia in masking early signs of MH, as well as the potential for rewarming to precipitate a crisis, emphasizes the importance of intraoperative temperature control and prolonged postoperative monitoring.

The outcome of this case raises critical questions about the optimal management of MH-susceptible patients requiring major cardiovascular interventions. Given the high perioperative risk associated with both MH and OI, alternative approaches should be explored. Additionally, while prophylactic administration of dantrolene is not routinely recommended, its potential role in reducing the risk of late postoperative MH warrants further investigation in patients at high risk of developing MH.

In conclusion, this case calls for the need for a highly individualized approach when managing patients with complex metabolic disorders undergoing major cardiac surgery. A multidisciplinary collaboration between surgeons, anesthesiologists, and intensivists is essential to anticipate potential complications, optimize perioperative management, and improve overall outcomes, further research is needed to better understand the relationship between MH, OI, and metabolic crises, allowing for more effective strategies to enhance patient safety in similar high-risk scenarios.

FUNDING

There are no sources of funding to declare.

AUTHOR CONTRIBUTIONS:

Conceptualization, S.E. and W.A.; methodology, W.A.; software, S.E.; validation, S.E., O.B. and W.A.; formal analysis, S.E.; investigation, W.A.; resources, W.A.; data curation, S.E.; writing—original draft preparation, S.E, F.Z.T. and writing—review and editing, S.E, O.B. and W.A.; visualization, S.E.; supervision, W.A.; project administration, W.A.; funding acquisition, W.A.

All authors have read and agreed to the published version of the manuscript.”

CONFLICT OF INTEREST

The authors declare no conflict of interest. Data availability statement:

Data supporting these findings are available within the article or upon request.

INSTITUTIONAL REVIEW BOARD STATEMENT

Ethical review and approval were waived for this study due to the retrospective nature of the case report and the lack of identifiable patient data involved.

INFORMED CONSENT STATEMENT

Written informed consent has been obtained from the patient's closest relative to publish this paper.

SAMPLE AVAILABILITY

The author(s) declare that no physical samples were used in this study.

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