

Rare postoperative delayed malignant hyperthermia after off-pump coronary bypass surgery and brief review of literature

Monish S. Raut, Sibashankar Kar¹, Arun Maheshwari, Ganesh Shivnani¹, Arun Kumar, Elvin Daniel, Sandeep Joshi, Amit Motihar, Priyanka Gupta²

Departments of Cardiac Anaesthesiology and ¹Cardiac Surgery, Sir Ganga Ram Hospital, New Delhi, ²Department of Cardiac Anaesthesiology, Amrita Institute of Medical Sciences, Kochi, Kerala, India

ABSTRACT

Postoperative malignant hyperthermia (MH) is a very rare phenomena. It is generally observed within less than an hour after discontinuation of the anesthetic trigger. Present case describes rare delayed postoperative presentation of MH after off-pump coronary bypass surgery. Prompt recognition and immediate treatment with dantrolene can effectively treat the fatal syndrome. Family education and genetic counseling should be encouraged.

Received: 29-10-15
Accepted: 29-02-16

Key words: Hyperthermia; Malignant hyperthermia; Rigidity; Triggering anesthetic agents

INTRODUCTION

Malignant hyperthermia (MH) is pharmacogenetic syndrome inherited in an autosomal dominant way. Mutations in genes coding for calcium channel proteins (RYR1) and receptors (dihydropyridine) are responsible for MH susceptibility in 30–50% of the cases.^[1,2] The incidence of MH episodes in the general population is estimated as 1:100,000 administered anesthetics.^[3] This may be an underestimated prevalence as unrecognized, mild, or atypical reactions occur due to variable penetrance of the inherited trait.^[4,5] The occurrence of MH has been reported in all ethnic groups in all parts of the world. About 45–52% of reported events has been seen in children below 19 years of age.^[4,6]

surgery. Preoperative history was not suggestive of any use of antipsychotic medications nor any medical illness or any previous anesthesia exposure. There was no history suggestive of any muscle disorders in his family. Anesthesia induction was done with intravenous (IV) injection fentanyl 2 mcg/kg, midazolam 0.03 mg/kg, and propofol 2 mg/kg with inhalation agent sevoflurane. The patient was intubated by using IV injection of rocuronium 1 mg/kg. Anesthesia was maintained by inhalational agent isoflurane 2–3% keeping bispectral index 40–60. Intraoperatively, dexmedetomidine infusion 0.5 mcg/kg/h along

Address for correspondence: Dr. Monish S. Raut, Department of Cardiac Anaesthesiology, Sir Ganga Ram Hospital, New Delhi, India. E-mail: drmonishraut@gmail.com

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

Cite this article as: Raut MS, Kar S, Maheshwari A, Shivnani G, Kumar A, Daniel E, *et al.* Rare postoperative delayed malignant hyperthermia after off-pump coronary bypass surgery and brief review of literature. *Ann Card Anaesth* 2016;19:357-62.

Access this article online

Website: www.annals.in

DOI:
10.4103/0971-9784.179620

Quick Response Code:



CASE REPORT

Sixty-eight-year-old gentleman presented with retrosternal chest discomfort since 10 days. He was evaluated thoroughly at our center and found to have severe triple vessel coronary artery disease. He was scheduled for coronary artery bypass grafting (CABG)

with intermittent fentanyl doses were used for analgesia. Muscle relaxant vecuronium was used intermittently. Off-pump CABG was done successfully. Total surgical duration was 3.5 h. Patient's temperature remained between 35°C and 36°C intraoperatively. End-tidal carbon dioxide (ETCO₂) was between 30 and 35 mm Hg with mechanical ventilation at tidal volume 10 ml/kg and respiratory rate of 12/min. Intraoperatively, metabolic or respiratory acidosis or electrolytes imbalance was not noticed with lactate level of 0.5 mmol/L. After the skin closure, isoflurane inhalation was stopped and propofol infusion 150 mcg/kg/min was started for sedation before shifting the patient to the cardiac recovery room. Patient's ETCO₂ started rising from 35 to 65 mmHg with the same ventilatory setting 60 min after the completion of surgery. Temperature showed rising trend from 36°C to 38.8°C. Generalized muscle rigidity was observed including masseter muscle spasm despite using vecuronium. Arterial blood gas analysis revealed mixed respiratory and metabolic acidosis with raised lactate level of 5 mmol/L (pH 7.20, PaCO₂ 62 mmHg, and base excess - 9 mEq/L). Heart rate was 110/min and mean arterial blood pressure of 70 mmHg was maintained with an infusion of noradrenaline 0.5 mcg/kg/min. Electrocardiogram showed sinus tachycardia with intermittent appearance of premature ventricular contractions. Serum potassium increased from 3.8 to 4.9 mEq/L. Any fault in ventilator machine and breathing circuit were checked and ruled out. Ventilator settings were adjusted to normalize ETCO₂. Cooling blanket and cold saline were used to decrease the core body temperature. IV frusemide 1 mg/kg was injected to augment urine output to decrease the probability of acute tubular necrosis induced by suspected myoglobinuria. Considering clinical suspicion of

MH, IV dantrolene 1 mg/kg was administered within 30 min of noticing the symptoms. Patient's limb rigidity decreased to some extent and temperature dropped to 38.2°C. Oral dantrolene 50 mg qid was started due to nonavailability of IV dantrolene. Patient's creatinine phosphokinase (CPK) enzyme level was raised. The patient was mechanically ventilated for another 2 days. Patient was extubated on the 3rd postoperative day, as the muscle rigidity reduced significantly and temperature normalized with good hemodynamic stability without any inotropic support. Oral dantrolene was stopped after the 3rd day. CPK enzyme showed decreasing trend [Figure 1]. Postoperative course after the event was stable and smooth. Patient and his family members were counseled about the event occurred and advised about genetic testing for MH. Patient was given anesthesia summary at the time of discharge stating MH occurrence and its management.

Closest differential diagnosis with features of muscle rigidity and hyperthermia is a neuroleptic malignant syndrome, which was ruled out in the present case due to the absence of history of antipsychotic medications. Our patient had a rise in CPK more than 5000 IU/L. Normal increase in CPK after cardiac or great vessel surgeries can be up to 1100 IU/L.^[7] As per the clinical grading scale (CGS), clinical features of the present case scored 58 which suggests it was an almost certain case of MH [Figure 2]. MH in the present case is diagnosis by exclusion, and it was reaffirmed by the disappearance of symptoms after dantrolene therapy. We could not perform muscle biopsy to confirm the diagnosis. Liver function tests were monitored and found to be normal during dantrolene therapy.

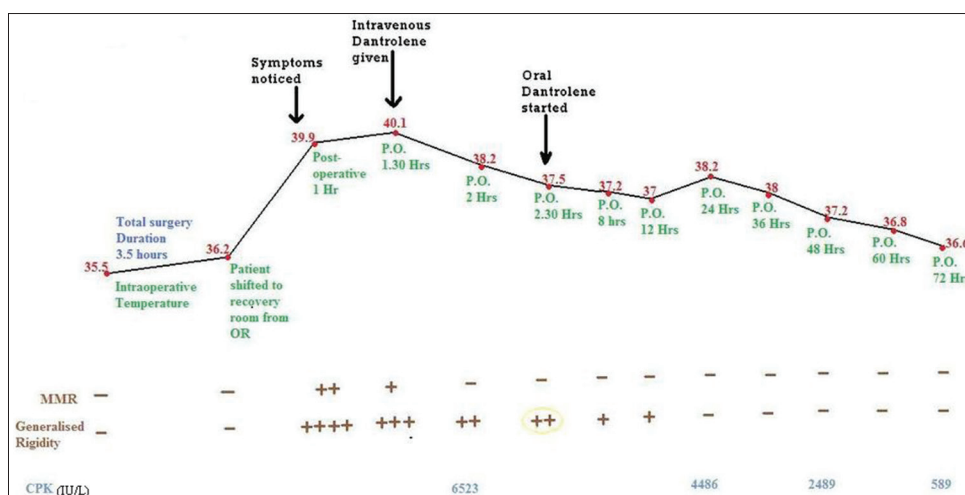






Figure 1: Course of the events

Figure 2: Malignant hyperthermia clinical grading scale

Parameters	Points
Rigidity	
Generalized muscular rigidity	15 
Masseter spasm following succinylcholine	15
Muscle breakdown	
Ck >20,000 IU (with succinylcholine)	15
Ck >10,000 IU (without succinylcholine)	15
Cola colored urine in perioperative period	10
Myoglobin in urine >60 mcg/L	5
Myoglobin in serum >170 mcg/L	5
Blood/plasma/serum K >6 mEq/L	3
Respiratory acidosis	
ETCO ₂ >55 mmHg	15 
PaCO ₂ >60 mmHg with appropriate controlled ventilation	15
ETCO ₂ >60 mmHg on spontaneous respiratory	15
PaCO ₂ >65 on spontaneous respiratory	15
Inappropriate hypercarbia (in anesthesiologist judgment)	15
Inappropriate tachypnea	10
Temperature increase	
Inappropriate rapid rise in temp (in anesthesiologist judgment)	15 
Inappropriate increased temperature >38.8°C in the perioperative period	10
Cardiac involvement	
Inappropriate sinus tachycardia	3
Ventricular tachycardia or ventricular fibrillation	3
Others	
Arterial base excess >-8 mEq/L	10
Arterial pH <7.25	10 
Rapid reversal of signs with IV dantrolene	5

Score	MH rank	Description of likelihood
0	1	Almost never
3-9	2	Unlikely
10-19	3	Somewhat less than likely
20-34	4	Somewhat greater than likely
35-49	5	Very likely
50+	6	Almost certain

Malignant hyperthermia clinical grading scale given by Larach *et al.* Clinical features seen in this patient are marked by green arrows. The total score is calculated as 58 which suggests almost certain of malignant hyperthermia. MH: Malignant hyperthermia, ETCO₂: End-tidal carbon dioxide, IV: Intravenous

In the present case, features of MH appeared 1 h postoperatively. The case was managed successfully using IV dantrolene initially followed by the oral form of dantrolene.

DISCUSSION

MH susceptible (MHS), patient when exposed to triggering anesthetic agents, causes uncontrolled intracellular release

of calcium in skeletal muscle with resultant sustained muscle contraction. Such muscular hypermetabolic state produces rigidity, hyperthermia, and acidosis [Figure 3].

Intraoperative clinical diagnosis of MH may be difficult due to the nonspecific nature of MH clinical signs and symptoms. Larach *et al.* devised the CGS as a set of clinical diagnostic criteria for MH.^[8] As per the scale, clinical features of the present case scored 53 which suggests it was an almost certain case of MH. Cases developing MH during cardiopulmonary bypass (CPB) in cardiac surgery have been reported.^[9,10] However, classical features of MH are obscured and disguised by the hypothermic CPB.^[11]

Postoperative MH is very rare (<2% of all cases) and generally observed within less than an hour after discontinuation of the anesthetic trigger.^[12] After reviewing published cases of MH, North American Malignant Hyperthermia Registry (NAMHR) found postoperative MH is a rare event which happened in 10 of 528 suspected MH cases (1.9%) reported to the NAMHR. None of these cases had hyperthermia as an initial presenting sign.^[12] NAMHR suggested that initial postoperative fever without signs of hypermetabolism is unlikely to be MH. Postoperative MH cases presenting more than 1 h after discontinuation of anesthesia should warrant investigation of alternative diagnoses.^[12] Firstenberg *et al.* reported a successfully treated case of delayed MH after 4.5 h of isoflurane inhalational anesthesia in a case of on-pump CABG.^[13] MH cases have presented in a delayed or atypical manner with a latency of 0–40 min in the postoperative period.^[12,14]

Considering rapidly, progressive, and fulminant course of MH, it is essential for the anesthesiologist to diagnose the condition as early as possible to minimize mortality and MH-related complications. Visoiu *et al.* have reported shorter MH onset time in the presence of halothane and after succinylcholine in all anesthetics. MH onset time was shorter during sevoflurane anesthesia than during isoflurane or desflurane in the human cohort of MH cases.^[15] Larach *et al.* observed cardiac dysfunction and level of consciousness change as the most common MH-related complications.^[16] More the time period between the first clinical sign and dantrolene administration, higher complication rate was observed. Other studies also suggested early dantrolene use can reduce the MH-related complications.^[16,17] Riazi *et al.* reported more than 50 min delay in the administration of dantrolene raised complication rate to 100%. The most common complication in this study

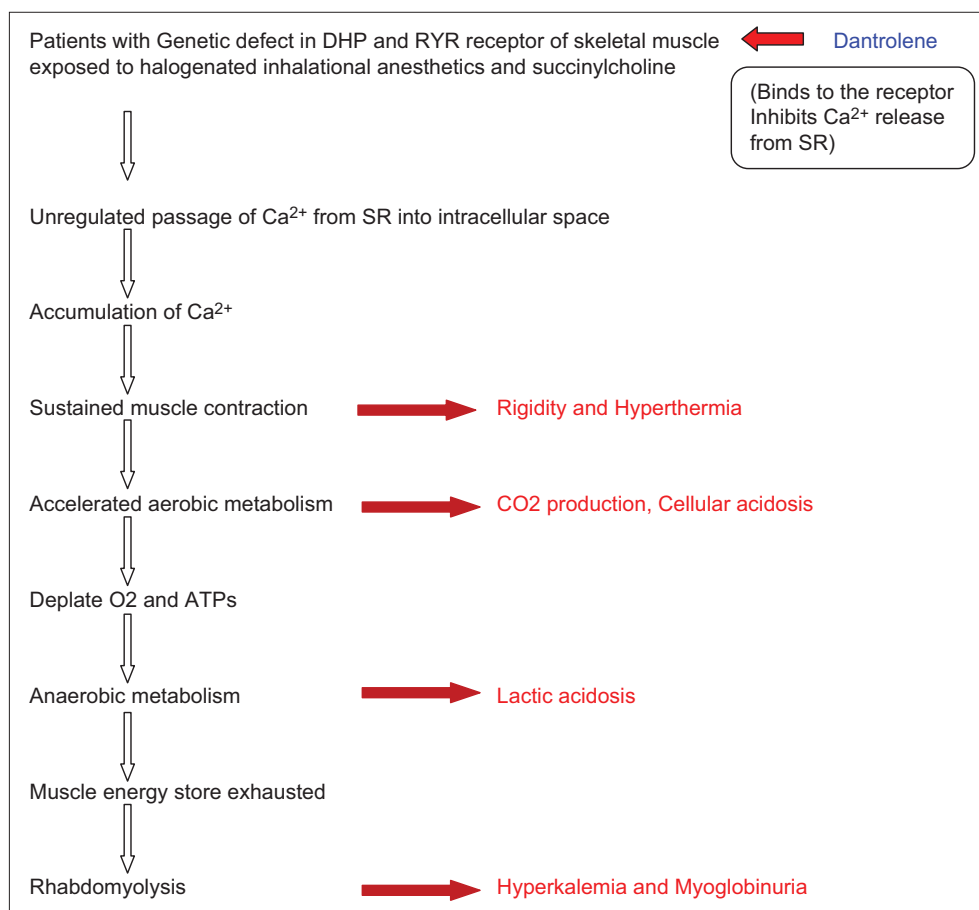


Figure 3: Pathophysiology of malignant hyperthermia

was renal dysfunction (14.7%).^[18] In the present case, we managed to administer dantrolene in 30 min after diagnosing the symptoms.

Dantrolene is recommended in the dose of 2.5 mg/kg every 5 min until a clinical improvement is seen.^[19,20] Previous studies suggested that no dosing adjustments need to be made during CPB, as there is only a slight decrease in blood levels due to dilution.^[20] Improvement in symptoms is generally observed within 30–60 min. No clinical improvement even after administration of 10 mg/kg warrants a review of differential diagnosis.^[19,20] Recrudescence of symptoms is observed in up to 25% of patients after successful treatment at a mean of 13 h (standard deviation, 13 h) after the initial reaction^[21] and commonly in patients with increased muscle mass.^[21,22] Hence, it is suggested to continue dantrolene in maintenance doses (1 mg/kg IV every 4–6 h) for 24–48 h after the last noticed sign of acute MH.^[21,23]

Dantrolene can cause a profound muscular weakness by interfering with the intracellular calcium handling.^[23,24] Higher than recommended doses has been reported to

have negative inotropic effects in animal studies.^[25,26] Dantrolene can also cause fatal and nonfatal hepatic failure after long-term use.^[27,28] Shih *et al.* described that intraoperative administration of low-dose dantrolene, 1.2 mg/kg, was effective in treating hyperthermia, hypercapnia, and hyperkalemia.^[29] In the present case, we also used IV dantrolene in the low dose of 1 mg/kg successfully and oral dantrolene for 48 h to prevent the recurrence.

Use of oral dantrolene in MH has been reported anecdotally.^[30-32] Oral dantrolene sodium is well absorbed and achieves peak blood levels 3–6 h after ingestion.^[33] Oral dantrolene 5 mg/kg (divided 3–4 times a day) can attain acceptable plasma level of the drug.^[31]

Dantrolene was stopped in our case when the following criteria were met: Core temp is <38°C, metabolic stability for 24 h, muscle is no longer rigid, creatine kinase is decreasing, and no evidence of myoglobinuria.

Complications such as hypercarbia, hyperthermia, electrolyte abnormalities, and arrhythmias should be

managed with conventional measures, like mechanical ventilation, systemic cooling, and anti-arrhythmic drugs.^[13] Cardiac surgical patients are generally prone to develop an acute renal injury. Rhabdomyolysis in untreated MH can cause myoglobin-induced kidney damage.^[6] Aggressive fluid replacement with crystalloids and adequate diuresis can decrease the risk of myoglobin precipitation in renal tubules.^[34] Excessive physical activity in a hot, humid environment can trigger MHS human beings.^[35] Patients with a preexisting fever are more prone to develop an episode of MH.^[34] Role of heat in triggering MH in human beings is not known, however a modulating effect on a developing crisis must be presumed.^[7] Rapid and exaggerated rewarming during CPB can be a potential risk factor. Slow rewarming till 36°C is advisable. Core temperature should be maintained <36°C during the postoperative period in MHS patients.^[34] Gasoline vapors and serotonin receptor agonists are also said to be potential trigger agents.^[36,37] Usefulness of CPB has been reported in noncardiac surgery patients who had MH episode during general anesthesia. The advantages of CPB in MH patients include ultrafiltration, temperature control, normalization of electrolytes, control of acidosis, cytokine removal, and supporting the circulation of the patient.^[38] Witherspoon have reported the use of extracorporeal membrane oxygenation for cardiac failure due to hypermetabolic episode possibly caused by MH.^[39]

Anesthesia can be safely given to MHS patients with nontriggering agents. Close monitoring of minute ventilation, ETCO₂ levels, and core body temperature should be done in MHS patients. MH triggering agents are inhalational halogenated anesthetics (e.g., sevoflurane, desflurane, isoflurane, enflurane, and halothane) and depolarizing muscle relaxant like succinylcholine. Safe agents that can be safely administered to MHS patients include - all IV sedatives and anesthetic including propofol, dexmedetomidine, ketamine, etomidate, and barbiturates. All local anesthetics (e.g., ropivacaine, lidocaine, and bupivacaine), nondepolarizing neuromuscular blockers (e.g., atracurium, vecuronium, and rocuronium), analgesics and anxiolytics (opioids and benzodiazepines), and inhalational agents limited to nitrous oxide and xenon are safe. Perioperative dantrolene for prophylaxis is not recommended by the Malignant Hyperthermia Association of the United States.^[40]

After recovery from MH episode, all details should be noted in anesthesia discharge summary and patient and family should be counseled specifically about

the following points - avoid anesthesia with triggering agents, avoid exercise in excessive heat which can be a triggering event. Inform family members of the possible MH reaction, as MHS is a genetic condition.

Recognizing these genetically-susceptible individuals is the mainstay of prevention.

Avoiding anesthetic triggers and prompt use of dantrolene during acute event occurs have decreased the mortality due to MH from historic rates of 70% to about 5%.^[41,42] The present case describe a rare delayed postoperative presentation of MH after off-pump coronary bypass surgery. Prompt recognition and immediate treatment with low dose IV dantrolene followed by oral form can effectively reverse potentially fatal syndrome. Family education and genetic counseling should be encouraged.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Davis PJ, Brandom BW. The association of malignant hyperthermia and unusual disease: When you're hot you're hot or maybe not. *Anesth Analg* 2009;109:1001-3.
2. Carpenter D, Robinson RL, Quinnett RJ, Ringrose C, Hogg M, Casson F, et al. Genetic variation in RYR1 and malignant hyperthermia phenotypes. *Br J Anaesth* 2009;103:538-48.
3. Brady JE, Sun LS, Rosenberg H, Li G. Prevalence of malignant hyperthermia due to anesthesia in New York State, 2001-2005. *Anesth Analg* 2009;109:1162-6.
4. Larach MG, Gronert GA, Allen GC, Brandom BW, Lehman EB. Clinical presentation, treatment, and complications of malignant hyperthermia in North America from 1987 to 2006. *Anesth Analg* 2010;110:498.
5. Bendixen D, Skovgaard LT, Ording H. Analysis of anaesthesia in patients suspected to be susceptible to malignant hyperthermia before diagnostic *in vitro* contracture test. *Acta Anaesthesiol Scand* 1997;41:480-4.
6. Rosenberg H, Davis M, James D, Pollock N, Stowell K. Malignant hyperthermia. *Orphanet J Rare Dis* 2007;2:21.
7. Yousef MA, Vaida S, Somri M, Mogilner J, Lanir A, Tamir A, et al. Changes in creatine phosphokinase (CK) concentrations after minor and major surgeries in children. *Br J Anaesth* 2006;96:786-9.
8. Larach MG, Localio AR, Allen GC, Denborough MA, Ellis FR, Gronert GA, et al. A clinical grading scale to predict malignant hyperthermia susceptibility. *Anesthesiology* 1994;80:771-9.
9. Pandya AB, O'Leary CE. Development of malignant

- hyperthermia post-cardiopulmonary bypass during surgery for mitral valve replacement. *J Cardiothorac Vasc Anesth* 2003;17:625-8.
10. Franklin AD, Lorinc AN, Donahue BS. Malignant hyperthermia-like manifestations in a two-month-old child with Holt-Oram syndrome undergoing cardiac surgery. *J Cardiothorac Vasc Anesth* 2014;28:1326-7.
 11. MacGillivray RG, Jann H, Vanker E, Gemmell L, Mahomed AE. Development of malignant hyperthermia obscured by cardiopulmonary bypass. *Can Anaesth Soc J* 1986;33:509-14.
 12. Litman RS, Flood CD, Kaplan RF, Kim YL, Tobin JR. Postoperative malignant hyperthermia: An analysis of cases from the North American Malignant Hyperthermia Registry. *Anesthesiology* 2008;109:825-9.
 13. Firstenberg M, Abel E, Blais D, Andritsos M. Delayed malignant hyperthermia after routine coronary artery bypass. *Ann Thorac Surg* 2010;89:947-8.
 14. Papadimos TJ, Almasri M, Padgett JC, Rush JE. A suspected case of delayed onset malignant hyperthermia with desflurane anesthesia. *Anesth Analg* 2004;98:548-9.
 15. Visoiu M, Young MC, Wieland K, Bandom BW. Anesthetic drugs and onset of malignant hyperthermia. *Anesth Analg* 2014;118:388-96.
 16. Larach MG, Gronert GA, Allen GC, Bandom BW, Lehman EB. Clinical presentation, treatment, and complications of malignant hyperthermia in North America from 1987 to 2006. *Anesth Analg* 2010;110:498-507.
 17. Migita T, Mukaida K, Kawamoto M, Kobayashi M, Yuge O. Fulminant-type malignant hyperthermia in Japan: Cumulative analysis of 383 cases. *J Anesth* 2007;21:285-8.
 18. Riaz S, Larach MG, Hu C, Wijesundera D, Massey C, Kraeva N. Malignant hyperthermia in Canada: Characteristics of index anesthetics in 129 malignant hyperthermia susceptible probands. *Anesth Analg* 2014;118:381-7.
 19. Steinfath M, Wappler F, Scholz J. Malignant hyperthermia. General, clinical and experimental aspects. *Anaesthesist* 2002;51:328-45.
 20. Comunale ME, DiNardo JA, Schwartz MJ. Pharmacokinetics of dantrolene in an adult patient undergoing cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 1991;5:153-5.
 21. Burkman JM, Posner KL, Domino KB. Analysis of the clinical variables associated with recrudescence after malignant hyperthermia reactions. *Anesthesiology* 2007;106:901-6.
 22. Nelson P, Litman RS. Malignant hyperthermia in children: An analysis of the North American malignant hyperthermia registry. *Anesth Analg* 2014;118:369-74.
 23. Podranski T, Bouillon T, Schumacher PM, Taguchi A, Sessler DI, Kurz A. Compartmental pharmacokinetics of dantrolene in adults: Do malignant hyperthermia association dosing guidelines work? *Anesth Analg* 2005;101:1695-9.
 24. Wappler F. Malignant hyperthermia. *Eur J Anaesthesiol* 2001;18:632-52.
 25. Saltzman LS, Kates RA, Corke BC, Norfleet EA, Heath KR. Hyperkalemia and cardiovascular collapse after verapamil and dantrolene administration in swine. *Anesth Analg* 1984;63:473-8.
 26. Meyler MJ, Wesseling H, Agoston S. The effects of dantrolene sodium on cardiac and skeletal muscle in rats. *Eur J Pharmacol* 1976;39:127-31.
 27. Chan CH. Dantrolene sodium and hepatic injury. *Neurology* 1990;40:1427-32.
 28. Utili R, Boitnott JK, Zimmerman HJ. Dantrolene-associated hepatic injury. Incidence and character. *Gastroenterology* 1977;72 (4 Pt 1):610-6.
 29. Shih TH, Chen KH, Pao YY, Yang SC, Chen CL, Huang CJ, et al. Low-dose dantrolene is effective in treating hyperthermia and hypercapnia, and seems not to affect recovery of the allograft after liver transplantation: Case report. *Transplant Proc* 2010;42:858-60.
 30. Kang BJ, Song J, Kim SK, Yoo JH. A suspected case of malignant hyperthermia that was successfully treated with dantrolene administration via nasogastric tube. *Korean J Anesthesiol* 2012;63:378-80.
 31. Allen GC, Cattran CB, Peterson RG, Lalande M. Plasma levels of dantrolene following oral administration in malignant hyperthermia-susceptible patients. *Anesthesiology* 1988;69:900-4.
 32. Nagase M, Naganuma Y, Ryo K, Sato N, Kawashima Y. Treatment of malignant hyperthermia by dantrolene sodium administered through a nasogastric tube. *Masui* 1984;33:1021-6.
 33. Krach LE. Pharmacotherapy of spasticity: Oral medications and intrathecal baclofen. *J Child Neurol* 2001;16:31-6.
 34. Metterlein T, Zink W, Kranke E, Haneya A, Graf B, Kranke P. Cardiopulmonary bypass in malignant hyperthermia susceptible patients: A systematic review of published cases. *J Thorac Cardiovasc Surg* 2011;141:1488-95.
 35. Wappler F, Fiege M, Steinfath M, Agarwal K, Scholz J, Singh S, et al. Evidence for susceptibility to malignant hyperthermia in patients with exercise-induced rhabdomyolysis. *Anesthesiology* 2001;94:95-100.
 36. Wappler F, Roewer N, Köchling A, Scholz J, Steinfath M, Rumberger E, et al. Effects of serotonin 2 receptor agonists on skeletal muscle preparations in patients with a disposition toward malignant hyperthermia. *Anaesthesist* 1995;44:538-44.
 37. Anetseder M, Hartung E, Klepper S, Reichmann H. Gasoline vapors induce severe rhabdomyolysis. *Neurology* 1994;44:2393-5.
 38. Edwards JH, Siwek L. Successful use of cardiopulmonary bypass and ultrafiltration for metabolic resuscitation of a moribund child with acute perianesthetic rhabdomyolysis; a case report of unsuspected malignant hyperthermia. *J Extra Corpor Technol* 2000;32:103-6.
 39. Witherspoon KA. ECMO for resuscitation of an infant immediately post-op VSD closure and RVOT repair: A case report of possible malignant hyperthermia. *Prog Pediatr Cardiol* 2008;24:131-5.
 40. Available from: <http://www.mhaus.org/healthcare-professionals/be-prepared/post-operative-procedure>. [Last accessed on 2015 Oct 18].
 41. Larach MG, Bandom BW, Allen GC, Gronert GA, Lehman EB. Cardiac arrests and deaths associated with malignant hyperthermia in North America from 1987 to 2006: A report from the North American malignant hyperthermia registry of the malignant hyperthermia association of the United States. *Anesthesiology* 2008;108:603-11.
 42. Rosero EB, Adesanya AO, Timaran CH, Joshi GP. Trends and outcomes of malignant hyperthermia in the United States, 2000 to 2005. *Anesthesiology* 2009;110:89.