Rewarming following hypothermic cardiopulmonary bypass in the malignant hyperthermia-susceptible patient: Implications for diagnosis and peri-operative management

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A 55-year-old, malignant hyperthermia-susceptible patient underwent myocardial revascularization without incident. Six hours postoperatively, he developed what was initially diagnosed as an MH crisis, for which he received intravenous dantrolene. The resultant muscle weakness prolonged the duration of postoperative mechanical ventilation and likely contributed to the development of a postoperative pneumonia. Plasma dantrolene levels were measured for the first 48 hours postoperatively and correlated with clinical findings. On reviewing the patient's perioperative course, it was felt that the hypermetabolic state was not due to MH. The patient's pattern of rewarming following hypothermic cardiopulmonary bypass was similar to non-MH-susceptible patients. Because of the difficulty in diagnosing a MH crisis after hypothermic bypass, it is recommended that patients receive prophylactic dantrolene preoperatively and after bypass. Nondepolarizing muscle relaxants should be given postoperatively to prevent shivering and respiratory acidosis while patients rewarm.

Key words

HYPERTHERMIA: malignant; NEUROMUSCULAR RELAXANTS: dantrolene; SURGERY, cardiopulmonary bypass.

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Malignant hyperthermia (MH) is an inherited disorder of skeletal muscle that is potentially fatal, and is triggered primarily by volatile anaesthetic agents and succinylcholine. The diagnosis of an MH crisis depends on a combination of clinical and laboratory features representing a hypermetabolic state within skeletal muscle and its secondary effects on the rest of the body. We report a case of a patient susceptible to MH who, having undergone hypothermic cardiopulmonary bypass (CPB) and myocardial revascularization, developed postoperatively what was initially thought to be a MH crisis. Treatment was initiated and plasma dantrolene concentrations were measured during the postoperative period, and correlated with clinical findings. The implications of rewarming following hypothermic CPB in MH-susceptible patients and the effects of therapeutic doses of intravenous dantrolene are discussed.

Case report

A 55-year-old, 76 kg male with a family history of MH was admitted to hospital for coronary artery bypass grafts. He had suffered an inferior wall myocardial infarction three months earlier, and subsequent coronary angiography showed severe triple-vessel disease and a Class III left ventricle. On admission, he was taking no medications. The patient's maternal uncle had suffered a possible MH reaction following aortic aneurysm surgery, and was considered MH-susceptible on the basis of subsequent muscle biopsy and *in vitro* contracture responses to caffeine and halothane. The patient himself had never undergone general anaesthesia. The patient's MH status was unknown so a muscle biopsy and *in vitro* contracture studies were planned at the time of the cardiac surgery.

The anaesthetic machine had its vaporizers removed

TABLE Vital signs, blood gases, and ventilatory variables during postoperative period. Dantrolene therapy began at 6 hrs, 20 min

Time (hr postop)	HR (bpm)	SBP (mmHg)	PA Temp (°C)	Ax Temp (°C)	pHa	PaCO ₂ (mmHg)	PaO ₂ (mmHg)	BE (mEq·L ⁻¹)	SvO ₂ (%)	FiO ₂ (%)	VE (L·min ⁻¹)
0:00	90	120	34.8	33.4	7.40	40	140	+1.0	69	50	7.5
1:20	95	130	—	—	—	—	—	—	—	50	7.5
2:20	95	130	35.4	33.6	7.41	40	180	+0.8	65	45	7.5
3:20	98	135	35.8	33.7	—	—	—	—	—	45	7.5
4:20	105	140	36.3	34.2	7.35	43	179	-1.1	—	45	7.5
5:20	115	140	36.7	34.8	—	—	—	—	—	45	7.5
6:20	125	140	37.2	34.9	7.26	54	352	-3.2	72	100	7.5
7:20	100	120	37.6	35.0	7.48	36	174	+4.0	—	50	15.0
8:20	100	150	37.9	34.9	7.45	36	203	+1.9	—	50	12.0
9:20	98	100	38.2	36.2	—	—	—	—	—	50	12.0
10:20	85	140	38.1	37.0	7.50	32	201	+2.8	—	45	12.0
11:20	100	100	38.2	37.1	7.51	32	165	+3.1	—	45	10.8
12:20	85	110	37.9	36.6	—	—	—	—	—	45	10.8
13:20	90	120	37.8	36.5	7.46	33	150	+1.2	—	40	10.2
14:20	85	120	37.5	36.8	—	—	—	—	—	40	10.2
15:20	85	120	37.3	36.8	—	—	—	—	—	40	10.2
16:20	80	100	37.1	36.7	—	—	—	—	—	40	10.2
17:20	85	130	37.0	36.6	7.44	34	160	+0.2	—	40	10.2

Abbreviations: PA Temp – pulmonary artery temperature; Ax Temp – axillary temperature; FiO₂ – inspired O₂ concentration; VE – minute ventilation; BE – base excess; SvO₂ – mixed venous O₂ saturation.

and was flushed with oxygen for 15 hours. A new coaxial (Bain) circuit was also used, and all rubber parts were changed.

The patient was premedicated with lorazepam 4 mg PO and morphine 10 mg IM. No dantrolene was given since a muscle biopsy was planned. Monitors included electrocardiograph, radial arterial line, pulmonary artery catheter, pulse oximeter, capnograph, oesophageal and nasopharyngeal temperature probes, and a urinary catheter. Anaesthesia was induced with 10 µg·kg⁻¹ of sufentanil, vecuronium 0.2 mg·kg⁻¹ and 100 per cent oxygen, and maintained with intermittent boluses of sufentanil and pancuronium.

A muscle biopsy of the left sartorius muscle was obtained through the same incision made for saphenous vein harvesting. The patient was then placed on CPB using a bubble oxygenator and cooled to a nasopharyngeal temperature of 28.4°C (NP). The total time on bypass was 106 minutes. Rewarming was accomplished over 49 minutes using high pump flows and IV nitroglycerin, with subsequent weaning from CPB at a NP temperature of 37.0°C,^{1,15} and without the need for inotropic support. The operative period was described as smooth. At the conclusion of surgery, however, his temperature had decreased to 34.5°C NP. Blood drawn during and after CPB for arterial and mixed venous gas analysis did not reveal any acid/base disturbance or signs of increased oxygen demand.²

On arrival in the ICU, the patient's pulmonary artery (PA) temperature was 34.8°C. The patient was sedated as

required with morphine and diazepam, and pancuronium 2 mg IV was given to prevent possible shivering during rewarming. Five hours later the PA temperature was 36.7°C and pancuronium was discontinued (total dose 10 mg). Over the next 60 minutes, the patient's PA temperature rose to 37.2°C accompanied by an increase in heart rate to 125 beats·min⁻¹ (Table). During that time the patient had not received any blood products or additional medications, nor was there any clinical suspicion of an allergic reaction. The cardiac output was 7.0 L·min⁻¹ and the pulmonary capillary wedge pressure (PCWP) was 14 mmHg. An arterial blood gas sample showed a pH of 7.26, PCO₂ 54 mmHg, PO₂ 354 mmHg, and a base deficit of 3.2 mEq·L⁻¹ (Table).

A tentative diagnosis of MH crisis was made and treatment was begun consisting of surface cooling, hyperventilation with 100 per cent oxygen, 100 mEq of intravenous sodium bicarbonate over 30 minutes, and intravenous dantrolene. Over the next five hours, the patient received a total of 840 mg (11 mg·kg⁻¹) of dantrolene. His temperature peaked at 38.2°C six hours after treatment had begun. The heart rate remained between 85 and 100 beats per minute during those six hours. During dantrolene administration, the patient's cardiac output was 5.5 to 7.0 L·min⁻¹, with a PCWP of 10 to 15 mmHg and a central venous pressure of 4 to 6 mmHg. The patient's skin was warm and dry and there was no evidence of muscle rigidity. A mixed venous blood gas drawn from the pulmonary artery catheter showed a venous PO₂ of 48 mmHg (72 per cent

FIGURE 1 Log plasma dantrolene concentration vs time. Time 0 = end of initial IV dantrolene therapy ($11 \text{ mg} \cdot \text{kg}^{-1}$). Four IV doses of $1 \text{ mg} \cdot \text{kg}^{-1}$ were administered over the next 8 hrs. The patient's clinical condition is noted between extubation and the end of the blood sampling period.

saturated), indicating no increase in oxygen utilization. Serum creatine kinase concentration peaked at 724 international units (normal range 10–120 IU), and was negative for CK-MB isoenzyme. The peak serum lactate concentration was $1.76 \text{ mmol} \cdot \text{L}^{-1}$ (normal $< 2.2 \text{ mmol} \cdot \text{L}^{-1}$) and the urine was negative for myoglobin. With hyperventilation, the PaCO_2 ranged from 31 to 36 mmHg for the next 12 hours. Blood cultures drawn at the time were negative for bacterial growth and thyroid function tests were normal.

Overnight, the patient received $1 \text{ mg} \cdot \text{kg}^{-1}$ of intravenous dantrolene every two hours for a total of $4 \text{ mg} \cdot \text{kg}^{-1}$ to prevent recrudescence of the reaction.¹¹ Blood for the determination of plasma dantrolene concentrations was drawn after the initial $11 \text{ mg} \cdot \text{kg}^{-1}$ were given, and every six hours thereafter for the next 48 hours. Plasma dantrolene concentrations (Figure 1) were determined using a reverse phase high-pressure liquid chromatographic method.³

Because of generalized weakness, the patient was not

weaned from mechanical ventilation until the second postoperative day. Early that morning, his temperature rose to 38.0°C but the arterial blood gases were normal and no additional dantrolene was given. The patient was subsequently extubated 45.5 hours postoperatively. He felt quite weak and his muscles were flaccid. Later in the day it was noted that he was too weak to swallow oral medications; his gag reflex was still impaired, and the strength of his cough was reduced. On the third postoperative day he was subjectively and objectively weak in all limbs. The patient's postoperative course was otherwise uneventful until the seventh postoperative day when he developed a fever of 40.0°C . A chest radiograph revealed patchy atelectasis of both lower lobes and a blood culture grew *E. coli*. The patient was treated with IV antibiotics with resolution of the fever within 36 hours. He was discharged home six days later in good condition.

The muscle biopsy specimen was tested by *in vitro* contracture response to halothane and caffeine.⁴ There was no contracture response to 2.5 per cent halothane, but a 0.3 gram contracture appeared in response to $2 \text{ mmol} \cdot \text{L}^{-1}$ caffeine and the caffeine specific concentration was $2.8 \text{ mmol} \cdot \text{L}^{-1}$. The test was interpreted as equivocally positive. Muscle histology revealed mild, nonspecific myopathic changes (fibre-splitting, central nucleation, cytoplasmic bodies). The patient was informed that he should consider himself to be MH-susceptible.

Discussion

Rewarming following hypothermic CPB in the MHS patient has not been described previously, and the question arises whether it is similar to that in normal patients. There is some evidence that awake MHS individuals may have greater than normal tolerance to cold by minimizing heat loss from the body core and possibly increased heat production through alpha adrenergic mechanisms.⁵ This might lead to more rapid rewarming in the Recovery Room, and less temperature afterdrop immediately following bypass. Whether this is true in the anaesthetized, poikilothermic patient is unknown.

Sladen⁶ has documented the changes in temperature that occur over the first 12 hours postoperatively in 73 patients who had undergone cardiac surgery with hypothermic CPB (Figure 2). He found that rewarming was most rapid two to four hours postoperatively, peaking at a temperature of $38.3 \pm 0.7^\circ \text{C}$ at 8 ± 2 hours. Associated with this rise in temperature was an increase in CO_2 production and respiratory acidosis if ventilation was not increased. Documentation of the presence of shivering was not attempted and it is not stated if the patients received muscle relaxants in the Recovery Room. As can be seen from Figure 2, our patient's temperature was within the ranges reported by Sladen.

FIGURE 2 Core temperature vs time postoperatively. ■ = our patient's pulmonary artery temperature. ● = mean rectal temperature $\pm$ 1SD in 73 patients reported by Sladen.⁶ Figure reprinted with permission of author and publisher.

Donati *et al.*⁷ found that the largest rise in temperature following hypothermic CPB occurred four hours postoperatively, with a mean increase of 1.7° C per hour. Shivering was noted in all 20 of their patients coinciding with increasing temperature and CO₂ production. Twelve of 20 of their patients developed a respiratory acidosis (end-tidal CO₂ > 45 mmHg) and required frequent adjustments of minute ventilation during rewarming. The authors recommended end-tidal CO₂ monitoring for patients rewarming after cardiac surgery to help maintain normocarbida during this period of thermal instability.

Chiara *et al.*⁸ examined the metabolic and cardiovascular changes that occur during rewarming after hypothermic CPB. They found that maximal oxygen consumption and CO₂ production occurred three hours postoperatively and lasted six hours. There was a poor correlation between temperature and resting energy expenditure, especially in the first three hours ($r = 0.08$). There was little increase in cardiac index in response to the increased energy requirements, and evidence of decreased left ventricular compliance and increased afterload. The authors expressed concern that this may represent a period of high risk for cardiac decompensation. Further myocardial depression might also occur in the MHS patient due to high plasma dantrolene levels;¹³ our patient did not show any evidence of myocardial depression, as measured by cardiac output and filling pressures.

Hypercarbia during rewarming after cardiac surgery

should be avoided in the MHS patient because it can confound accurate diagnosis of MH crisis. Although hypercarbia does not appear to be a trigger of MH,⁹ it may lead to sympathetic hyperactivity adversely affecting myocardial oxygen balance. The source of the increased CO₂ is shivering in skeletal muscle which can lead indirectly to increased myocardial oxygen consumption.

The metabolic response of patients rewarming after accidental hypothermia following noncardiac surgery has been studied.¹⁰ Patients who were given metocurine to prevent shivering had lower oxygen consumption and CO₂ production, as well as lower mean arterial pressures, heart rates and rate-pressure products. The rewarming period was significantly prolonged (55 per cent). Our patient's temperature peaked at 9.5 hours postoperatively following the administration of pancuronium during rewarming which is somewhat longer than the times recorded by Sladen and Donati *et al.*

Our patient received what would be considered optimal dantrolene therapy, having had 11 mg·kg⁻¹ IV over five hours until his temperature stopped rising, then 4 mg·kg⁻¹ IV over the next eight hours.¹¹ The plasma dantrolene concentrations (Figure 1) achieved were many times higher than those considered effective for MH prophylaxis, i.e., 2.8 to 4.2 µg·ml⁻¹;¹² however, higher doses of dantrolene may be required to treat a fulminant MH crisis. The associated weakness likely contributed to the patient's prolonged time to extubation, his generalized weakness and poor ability to cough, and subsequently his development of bibasilar atelectasis and pneumonia on the seventh postoperative day.

Byrick *et al.*¹³ questioned if the muscle weakness induced by dantrolene might precipitate respiratory muscle fatigue postoperatively. In their case report of a MHS patient who underwent coronary artery bypass grafting with hypothermic CPB, the postoperative course was uneventful and there was no significant impairment of respiratory function. The patient received 10 mg·kg⁻¹ of prophylactic oral dantrolene over 2.5 days preoperatively, then 4 mg·kg⁻¹ IV dantrolene over 24 hours postoperatively; plasma dantrolene concentrations were not measured.

In a report by Larach *et al.*,¹⁴ CPB was shown to decrease whole blood dantrolene levels by 54 to 68 per cent. There was little uptake of dantrolene by the CPB circuit. Additional dantrolene after CPB may be indicated to maintain protective blood levels.

The diagnosis of a MH crisis following cardiac surgery with hypothermic CPB may prove somewhat difficult. These patients do not yet have stable cardiopulmonary function and may manifest tachycardia and/or dysrhythmias, fluid and electrolyte disturbances, renal dysfunction, sympathetic hyperactivity secondary to pain, stress or anxiety, and coagulation disturbances. Furthermore,

rewarming creates in essence a hypermetabolic state with tachycardia, shivering thermogenesis, respiratory and metabolic acidosis, and relative hypoxaemia.

In conclusion, the pattern of rewarming following hypothermic CPB in this MHS patient was similar to non-MHS patients previously reported in the literature. However, the similarities between MH and rewarming following hypothermic CPB led to the incorrect diagnosis of a MH crisis. Because of the physiologic consequences of CPB and rewarming, and subsequent difficulties in the diagnosis of MH we recommend the use of prophylactic dantrolene preoperatively and after CPB.^{11,14} Although serious muscle weakness leading to prolonged mechanical ventilation may occur, milder side-effects would be anticipated with prophylactic dantrolene.¹² Rewarming during CPB should be gradual to avoid possibly triggering MH by regional hyperthermia.^{1,14,15} In addition, these patients should be paralyzed with nondepolarizing muscle relaxants during the early postoperative period, if hypothermia is present, to prevent shivering and the associated respiratory acidosis that occurs with rewarming.

Acknowledgements

We wish to thank Dr. Jan Horrow for constructive criticism and Dr. Robert Peterson for measuring plasma dantrolene levels; the secretarial help of Mrs. Fenna Zylstra and Mrs. Lynne McHardy is also appreciated.

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Résumé

Un patient âgé de 55 ans, susceptible de développer une hyperthermie maligne a subi une revascularisation myocardique sans incident. A la sixième heure postopératoire, il a développé ce qu'on a initialement diagnostiqué comme une crise d'hyperthermie maligne pour laquelle on lui administra par voie intraveineuse du dantrolène. La faiblesse musculaire qui s'en est suivie a prolongé la durée de la ventilation mécanique postopératoire et a contribué possiblement au développement d'une pneumonie. Les niveaux plasmatiques du dantrolène ont été mesurés pour les premières 48 heures postopératoires et correspondaient aux données de la clinique. En revoyant l'histoire périopératoire de ce patient, on a jugé que l'état hypermétabolique n'était pas dû à une crise d'hyperthermie maligne. Le "pattern" de réchauffement après la CEC hypothermique de ce patient était similaire aux patients non-susceptibles de développer une crise d'hyperthermie maligne. A cause de la difficulté de diagnostiquer une crise d'hyperthermie maligne après une CEC hypothermique, il est recommandé que les patients reçoivent en période préopératoire et après la CEC du dantrolène en prophylaxie. Les relaxants musculaires non-dépolarisants doivent être administrés en période postopératoire afin de prévenir les frissons et l'acidose respiratoire lors du réchauffement.