Cardiopulmonary bypass in malignant hyperthermia susceptible patients: A systematic review of published cases

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Objectives: Malignant hyperthermia susceptibility is an important risk factor during general anesthesia. Affected patients have an asymptomatic but potentially lethal hypermetabolic reaction after contact with volatile anesthetics or succinylcholine. Classic symptoms include hemodynamic instability, combined with acidosis, rigor, and hyperthermia. During cardiopulmonary bypass, these signs may be obscured, delaying correct diagnosis and lifesaving treatment. Malignant hyperthermia-susceptible individuals are more sensitive to heat and stress, so rewarming and catecholamine administration may trigger an episode, necessitating prophylactic measures.

Methods: This systematic review identified typical malignant hyperthermia symptoms during cardiopulmonary bypass and investigated other factors in cardiac surgery that might trigger an episode in susceptible individuals. Approaches used to treat and prevent malignant hyperthermia during cardiopulmonary bypass were systematically analyzed. We conducted a systematic search for reports about malignant hyperthermia and cardiopulmonary bypass. Search terms included *malignant hyperthermia* and *cardiopulmonary bypass*, *extracorporeal circulation*, or *cardiac surgery*.

Results: We found 24 case reports and case series including details of 26 patients. In 14 cases, malignant hyperthermia crises during or shortly after cardiopulmonary bypass were described. Fourteen reports discussed prevention of an episode. Early symptoms of a malignant hyperthermia episode include excessive carbon dioxide production and metabolic acidosis. Massively increased creatine kinase levels are a strong indicator of a malignant hyperthermia reaction. Rewarming is associated with development of clinical signs of malignant hyperthermia.

Conclusions: In potentially susceptible patients, apart from avoiding classic trigger substances, aggressive rewarming should not be applied. Hemodynamic instability in conjunction with the described symptoms should result in a diagnostic algorithm. (J Thorac Cardiovasc Surg 2011;141:1488-95)

Malignant hyperthermia (MH) remains an important risk factor during general anesthesia. In initially symptom-free patients, a potentially lethal hypermetabolic syndrome can develop after contact with so-called trigger substances, namely volatile anesthetics (halothane, enflurane, isoflurane, sevoflurane, and desflurane) and succinylcholine (INN suxamethonium).¹⁻⁵ The overall incidence of MH is uncertain, but it is estimated to be between 0.5 to 2 in 100,000 general anesthesia procedures.⁶⁻⁹ The prevalence of MH susceptibility could be as high as 1 in 3,000 in the general population.¹⁰ Because of the widespread use of volatile anesthetics in cardiac surgery, with or without cardiopulmonary bypass (CPB), MH remains a relevant concern.

MH primarily affects the calcium homeostasis of skeletal muscles. Contact with trigger substances leads to a massive calcium release from the sarcoplasmic reticulum in response to a defective ryanodine receptor.¹ Increased intracellular calcium levels activate contractile filaments and stimulate the cellular energy turnover. Dramatic increases in oxygen consumption and carbon dioxide production are followed by hugely increased production of lactic acid.¹¹ The ongoing stimulation finally leads to a breakdown of the cellular metabolism and integrity, and a massive release of muscle enzymes occurs. Without adequate therapy, multiorgan failure develops within hours of onset. Dantrolene blocks the calcium release from the sarcoplasmic reticulum and allows treatment.^{12,13}

Classic early symptoms of MH episodes include hemodynamic changes to meet the increased oxygen demand. The expiratory and venous Pco₂ values increase, as a result of a dramatic rise in carbon dioxide production. Lactic acidosis, the eponymous hyperthermia, and a generalized rigor develop.² During CPB, these symptoms are often obscured, in part because the MH typical increase of cellular metabolism may be mitigated by the imposed hypothermia. In MH-susceptible pigs, temperatures lower than 35°C were able to prevent MH episodes completely after exposure to

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Abbreviations and Acronyms

CPB = cardiopulmonary bypass

MH = malignant hyperthermia

halothane and succinylcholine. After systemic rewarming, the same substances induced a fulminant MH crisis in the same animals.¹⁴ Because of this effect, hypothermia was even discussed as a treatment option before dantrolene was available.¹⁵

Patients undergoing cardiac surgery often have more significant underlying medical conditions than do other surgical patients. Perioperative complications are therefore attributed to these underlying problems, and a MH diagnosis is thus often delayed or neglected. Timely treatment is essential, so early symptoms must be identified and interpreted appropriately.

Heat and exceptional stress can trigger MH episodes in susceptible individuals.¹⁶ Even if classic trigger substances are avoided, rapid rewarming and administration of catecholamine might be able to trigger a MH episode. It is therefore vital to apply appropriate prophylaxis in patients with suspected MH susceptibility.

The aim of this systematic review was to identify potential further cotriggers and early clinical symptoms during CPB that should prompt further attention. Furthermore, applied treatment and prophylactic measures are reviewed and commented on. The purpose is to describe and assess best practice for adequate management of MH-susceptible cardiac surgical patients during CPB.

MATERIALS AND METHODS

Studies focusing on MH and CPB were systematically searched with MEDLINE, EMBASE, and the Cochrane Library by 2 authors independently (T.M. and P.K.). Any type of report that described CPB in MH-susceptible individuals or a case of MH in a patient undergoing CPB was to be included, without language restriction. The free text key words were *malignant hyperthermia* or *malignant hyperpyrexia* or *dantrolene* and *cardiopulmonary bypass* or *extracorporeal circulation* or *cardiac surgery*. These were applied in conjunction with the appropriate MeSH terms (*malignant hyperthermia* and *cardiopulmonary bypass* or *extracorporeal circulation*).

Titles were evaluated for relevance and further examined if they were in accordance with the inclusion criteria. In addition, references within the identified studies were hand searched until no further new trials were identified. The last electronic search was performed in June 2010. All relevant articles were retrieved as full-text articles and analyzed in detail.

Data extraction and scoring for validity were performed with established procedures.¹⁷ Quantitative analysis, or vote counting, was not feasible because of the lack of appropriate data. All retrieved reports were tabulated in a spreadsheet and analyzed in a qualitative manner.

RESULTS

The systematic search yielded 160 potentially relevant articles. Of these articles, 136 did not deal with the investi-

gated topic and therefore were not further analyzed. Overall, 24 reports met the inclusion criteria and were included in the analysis (Table 1).¹⁸⁻⁴¹

No controlled clinical trial or epidemiologic study dealing with the topic could be found. There were 24 case reports and case series.

Unfortunately, not all case reports gave a detailed description of underlying medical conditions. Preexisting neuromuscular symptoms were described in only 1 patient. A history of cardiomyopathy was documented in only the 2 transplant recipients.

Symptoms of MH Episodes

Twelve reports described the development of an episode of MH in 14 patients (Table 2). In 3 cases, the first symptoms occurred during CPB; in the remaining 11 cases, shortly after CPB. None of the patients had MH typical symptoms in the prebypass period.

An unexplained increase of the arterial P_{CO_2} was the first symptom in 11 of the 14 cases. During bypass, only 3 patients had an elevated arterial P_{CO_2} . Within minutes after rewarming, however, this symptom was present in all patients. Despite dramatically increased minute ventilation (up to 40 L/min), values between 44 mm Hg and 67 mm Hg were documented. Metabolic acidosis was observed during CPB in only 2 cases. In 6 more cases, metabolic acidosis developed later (pH between 7.1 and 7.2). Interestingly, hemodynamic instability was considered a symptom of MH in only 5 patients. Improvement of the hemodynamic situation, however, was used in 3 of these 5 cases to monitor the treatment success with dantrolene. A rapid recovery of the patient's situation after administration of dantrolene was considered confirmation of an episode of MH. Rigor, another classic clinical sign, was observed in only 2 patients after CPB. In only 3 of the 14 patients with a marked increase in the body temperature was this interpreted as a sign of an episode of MH. In none of the described cases was hyperthermia mentioned as the first symptom.

The massive increase of muscle enzymes, resembling rhabdomyolysis, occurred in only 7 of the 14 cases. Creatine kinase levels ranged from 5000 to 38,000 U/L. Early appropriate treatment presumably prevented the development of rhabdomyolysis in the remaining 7 cases.

In 5 of the analyzed cases, a definite MH diagnosis could be made with in vitro contracture testing. In the remaining 7 cases, the clinical course and the adequate response to dantrolene were considered very strong indicators for an episode of MH.

Treatment of MH Episodes

In a total of 14 cases the treatment was described in detail (Table 3). The administration of trigger substances (if any were used) was immediately discontinued in all cases.

TABLE 1. List of relevant reports

Author(s)	Year	Type	Topic	Age (y)	Surgery	Journal citation
Byrick RJ, et al ¹⁸	1982	Case report	Prophylaxis	54	CABG	<i>Can Anaesth Soc J.</i> 1982;29:50-4
MacGillivray RG, et al ¹⁹	1986	Case report	MH crisis	2	Tetralogy of Fallot correction	<i>Can Anaesth Soc J.</i> 1986;33:509-14
Larach DR, et al ²⁰	1987	Case report	Prophylaxis	2	VSD correction	<i>J Cardiothorac Anesth.</i> 1987;1:448-53
Landymore RW, et al ²¹	1987	Case report	MH crisis	54	CABG	<i>Can J Surg.</i> 1987;30:209-11
Richardson J ²²	1987	Case report	Prophylaxis	46	CABG	<i>Anaesthesia.</i> 1987;42:1125
Marks LF, et al ²³	1988	Case report	Prophylaxis	87	CABG	<i>Anaesth Intensive Care.</i> 1988;16:482-5
Kleinman B, et al ²⁴	1990	Case series	MH crisis	57; 65	CABG; aortic-valve plus CABG	<i>Cardiothorac Anesth.</i> 1990;4:385-99
Comunale ME, et al ²⁵	1991	Case report	Prophylaxis	56	CABG	<i>J Cardiothorac Vasc Anesth.</i> 1991;5:153-5
Mongan PD, et al ²⁶	1992	Case report	Prophylaxis	3	ASD correction	<i>Can J Anaesth.</i> 1992;39:99-100
Hachenberg T, et al ²⁷	1992	Case report	Prophylaxis	27	Transplant	<i>J Cardiothorac Vasc Anesth.</i> 1992;6:386-7
Quinn RD, et al ²⁸	1992	Case report	MH crisis	41	Mitral valve	<i>Ann Thorac Surg.</i> 1992;53:1114-6
Koehntop DE, et al ²⁹	1997	Case report	Prophylaxis	14	Transplant	<i>Anesth Analg.</i> 1997;85:229-30
Abe K, et al ³⁰	1997	Case series	MH crisis	64; 69	CABG; mitral valve	<i>Can J Anaesth.</i> 1997;44:662-5
Allen GC, et al ³¹	1998	Case report	MH crisis with prophylaxis	55	CABG	<i>Can J Anaesth.</i> 1989;36:81-5
Lindholm P, et al ³²	2000	Case report	MH crisis	77	Aortic valve plus CABG	<i>J Cardiothorac Vasc Anesth.</i> 2000;14:576-8
Riess FC, et al ³³	2001	Case report	MH crisis	48	Aortic valve	<i>Anesthesiology.</i> 2001;94:355-7
Johi RR, et al ³⁴	2003	Case report	Prophylaxis	44	CABG	<i>Br J Anaesth.</i> 2003;91:744-7
Girard T, et al ³⁵	2003	Case report	Prophylaxis	55	CABG	<i>Acta Anaesthesiol Scand.</i> 2003;47:233-5
Pandya AB, et al ³⁶	2003	Case report	MH crisis	42	Mitral valve	<i>J Cardiothorac Vasc Anesth.</i> 2003;17:625-8
Jonassen AA, et al ³⁷	2004	Case report	MH crisis	56	Mitral valve plus CABG	<i>Acta Anaesthesiol Scand.</i> 2004;48:1062-5
Lichtman AD, et al ³⁸	2006	Case report	MH crisis with prophylaxis	54	CABG	<i>Anesth Analg.</i> 2006;102:372-5
Siddik-Sayyid SM, et al ³⁹	2007	Case report	Prophylaxis	75	CABG	<i>Anesth Analg.</i> 2007;104:214; author reply, 214-5
Aeschlimann N, et al ⁴⁰	2009	Case report	Prophylaxis	58	CABG	<i>J Cardiothorac Vasc Anesth.</i> 2009;23:134-5
Firstenberg M, et al ⁴¹	2010	Case report	MH crisis	69	CABG	<i>Ann Thorac Surg.</i> 2010;89:947-8

CABG, Coronary artery bypass grafting; MH, malignant hyperthermia; VSD, ventricular septal defect; ASD, atrial septal defect.

Furthermore, dantrolene was administered in all but 1 case. That patient died after development of acute renal failure caused by massive rhabdomyolysis. All other patients received dantrolene, with dosages ranging from 1.0 to 11.0 mg/kg, and survived the MH episode. The patient who received a total of 11 mg/kg dantrolene had development of a profound muscular weakness that prevented early extubation. The further clinical course was then complicated by pneumonia in conjunction with prolonged ventilation. In all other cases, no dantrolene-related side effects were observed. None of the reports mentioned any negative inotropic effects of dantrolene. To monitor the success of the causal therapy with dantrolene, both improvement of

the hemodynamic instability (3 cases), and decrease of the measured arterial P_{CO_2} (8 cases) were used.

Additional supportive care was given and included fluid administration and vasopressors for refractory hypotension. Low cardiac output was treated with inotropic agents and mechanical assist devices, such as intra-aortic balloon pump support. No complications related to the use of catecholamines or inotropic agents were observed in these individuals. Various antiarrhythmic drugs, including digoxin, lidocaine, and propranolol, were used to treat arrhythmias.

Among the 7 patients with rhabdomyolysis, only 4 developed acute renal failure and had to be treated with hemodialysis. One of these 4 patients died (the patient without

TABLE 2. Symptoms that occurred during or shortly after cardiopulmonary bypass, as described in 14 published malignant hyperthermia episodes

Symptom	No. of cases
Total	14
Unexplained increase in arterial Pco ₂	14
Metabolic acidosis	9
Unexplained hemodynamic instability	5
Rigor	2
Increased serum creatine kinase and myoglobin levels	7

dantrolene treatment); all others regained sufficient renal function.

Potential Trigger Substances

In 10 of the 14 described cases, volatile anesthetics as classic trigger substances were identified (Table 4). In one of these cases, succinylcholine was used for emergency re-intubation in the intensive care unit. This patient had an abortive MH episode develop after administration of enflurane and a fulminant MH crisis after treatment with succinylcholine. In 4 cases no classic trigger agents were used. Rapid and exaggerated rewarming was considered to be the trigger in 2 of these 4 cases. In 1 case report, enoximone, a phosphodiesterase III inhibitor, was implicated as trigger. In that case report, however, no data on the rewarming process was presented. In 1 additional case, no trigger could be identified at all. Again, no information on the rewarming process was presented.

Prevention of MH Episodes in Known Susceptible Patients During CPB

A total of 14 reports of cases described measures to prevent an episode of MH in patients known (n = 10) or suspected (n = 4) to be MH susceptible (Table 5). In 12 cases an MH episode was prevented, whereas 2 still had MH crises develop.

Trigger agents were avoided in all cases, and only decontaminated anesthesia machines and oxygenators were used. Anesthesia was induced and maintained with opiates and intravenous hypnotics. Relaxation was achieved with non-depolarizing neuromuscular-blocking agents. Dantrolene

TABLE 3. Treatment of malignant hyperthermia crisis as described in 14 published case reports

Treatment	No. of cases
Total	14
Discontinuation of trigger substances	11
Administration of dantrolene	13
Hemodynamic stabilization with volume administration, vasopressors, and inotropic agents	11
Antiarrhythmic agents	4

TABLE 4. Potential triggers of the MH malignant hyperthermia episodes in 14 published cases

Trigger	No. of cases
Total	14
Volatile anesthetics (halothane, enflurane, isoflurane, sevoflurane)	10
Succinylcholine	1
Rapid and exaggerated rewarming alone	2
Unknown (possibly enoximone or rewarming)	2

Sums to 15 because 1 patient received both enflurane and succinylcholine.

prophylaxis was applied in 5 cases, with dosages ranging from 2.0 mg/kg to 6.0 mg/kg. None of the patients who received dantrolene showed signs of hypermetabolism. Two of the 9 patients with suspected MH susceptibility who had no dantrolene prophylaxis had MH crises develop. In these 2 cases, no definite trigger could be identified. In both cases, however, no attention was paid to the rewarming process. A heat-induced MH episode therefore could not be excluded. Because of the potential danger, rewarming was done slowly and stopped at 36°C in 3 of the 14 patients. The aim was to maintain a core temperature under 36°C in the postoperative period. No MH episodes were described in any of these cases, even without dantrolene prophylaxis.

One case report even noted avoidance of inotropic agents. Hypotension and low output were instead treated with volume substitution and an intra-aortic balloon pump. In all other cases, inotropic agents were used without reported problems.

Overall, 17 patients received dantrolene in the perioperative period. A significant muscular weakness developed in 4 of these patients. Direct negative inotropic effects of dantrolene were not observed.

DISCUSSION

The current systematic review provides evidence that the nature of MH episodes observed during CPB does not markedly differ from other MH episodes. The heterogeneous picture of symptoms present as first signs, however, highlights the hypothesis that the CPB setting makes an early diagnosis and timely treatment more difficult than in other settings. MH is a potentially lethal disease. The reported outcomes in

TABLE 5. Preventive measures in cases of a known or suspected MH malignant hyperthermia susceptibility, as described in 14 published cases

Preventive measures	No. of cases
Total	14
Avoid contact with trigger substances	14
Slow and careful rewarming	3
Dantrolene	5
Avoid inotropic agents	1

the reviewed cases (only 1 patient died) cannot be viewed as indicating a less severe characteristic of MH during CPB. Cases with negative outcome may not have been published, thus creating a significant reporting bias.

Detection of MH by Classic Symptoms

All described cases document that classic MH symptoms are obscured and can be misinterpreted. It therefore must be suspected that an episode of MH could even be missed in some cases because symptoms typical of MH are attributed to other factors involved in cardiac surgery.

The earliest symptom was an unexplained increase in the arterial PCO_2 . Because of a massive increase of the cellular metabolism in MH, enormous amounts of carbon dioxide are produced.¹ Even an adaptation of the minute ventilation is often not sufficient to achieve normal values. During CPB, expiratory PCO_2 is not measured. Therefore detection of this early sensitive sign can be delayed unless frequent monitoring of the arterial PCO_2 takes place and is correlated with the applied (increased) sweep gas flow.

After depletion of the oxidative reserve, lactic acid is produced in the muscle. An increase in arterial serum lactate is seen early during MH crisis, because the metabolic capacity of the liver is reduced during an episode of MH.^{2,42} During cardiac surgery, periods of impaired tissue oxygenation may occur, with subsequent development of lactic acidosis. Point of care measurements for lactic acid would allow a timely detection of a developing mismatch in oxygenation. A profound drop in the mixed venous saturation would be another indication of the massive increase in tissue oxygen demand.⁴³

Hemodynamic instability is a further classic symptom of an episode of MH.¹ During and right after CPB, however, patients often undergo periods of arrhythmias and hypotension. Therefore the hemodynamic situation is not necessarily conducive to diagnosis of MH crisis.

After administration of dantrolene, the hemodynamic situation usually rapidly improves in MH episodes. This response can be used to confirm the working diagnosis and to monitor the success of the treatment.^{4,44} Because other causes may contribute to hemodynamic instability, however, clinicians may not be able to determine the necessary amount of dantrolene to administer without a change in the hemodynamic instability.

Rigor, another classic clinical sign of MH, is often missing during cardiac surgery. This may be because some patients receive high amounts of nondepolarizing neuromuscular-blocking agents. The profound paralysis induced by these agents attenuates the induced rigor without preventing development of MH.⁴⁵

For obvious reasons, the eponymous hyperthermia can only develop after termination of CPB with temperature control. Inhomogeneous and rapid rewarming can sometimes lead to core body temperatures above 38°C, and

may therefore be ignored as a symptom of MH. Hyperthermia was not the first symptom in any of the described cases. In fact, in general, hyperthermia is a rather late symptom in an episode of MH. Metabolic changes, in cardiac patients as well as in other patient populations, occur earlier and are more sensitive.¹¹

Another late sign of an episode of MH is the development of rhabdomyolysis.¹ Variable increases of creatine kinase and myoglobin levels are often seen in surgical patients; however, above average increases in muscle enzymes must lead to suspicion of MH. The usefulness of rhabdomyolysis as a sign for MH is further impaired by the fact that various test assays cannot distinguish between myoglobin and hemoglobin. Thus in the postcardiosurgical setting, a positive test result might be misinterpreted as indicating hemolysis related to CPB.

In the analyzed cases, MH symptoms occurred either during or shortly after CPB. An adequate diagnosis may be complicated by the delayed onset of MH symptoms. The initial presentation may even begin in the postoperative period. A recent study, however, revealed that so-called “post-operative MH” is very uncommon (<2% of all cases) and usually occurs within less than an hour after discontinuation of the trigger.⁴⁶

Treatment of Supposed MH Episodes

As a first step in managing a potential MH episode, the administration of any trigger substances used must be discontinued immediately. Anesthesia must be maintained with intravenous anesthetics and nondepolarizing neuromuscular-blocking agents.

The only treatment option is dantrolene, which blocks the calcium release from the sarcoplasmic reticulum by interfering with the activated type 1 ryanodine receptor. Early treatment of an episode of MH can decrease the mortality from greater than 80% to less than 5%.^{2,42} Current guidelines recommend the administration of 2.5 mg/kg every 5 minutes, until a clinical improvement is seen.^{2,47} Previous studies were able to show that no dosing adjustments have to be made during CPB, because only the initiation of the CPB leads to a slight decrease in blood levels, as a result of dilution.⁴⁷ After administration of 10 mg/kg, without clinical improvement, a differential diagnosis has to be considered.^{2,47}

Dantrolene can induce a profound muscular weakness by interfering with the intracellular calcium handling.¹¹ This side effect should not prevent sufficient treatment, but it must be considered. Negative inotropic effects were not described in the reviewed case reports. In previous animal studies, however, higher than recommended doses induced negative inotropic effects.^{48,49}

To improve the hemodynamic situation, supportive care should be given. Refractory hypotension is treated with volume administration and vasopressors. Low cardiac output can be treated with inotropic agents and mechanical assist

devices, such as intra-aortic balloon pump support. No complications related to the use of inotropic agents have been documented in MHS-susceptible individuals. Various antiarrhythmic drugs can be used to treat arrhythmias. The current guidelines advise the use of β -blockers, as described in the newer case reports.⁴⁴ Before the acute situation is under control, separation from CPB should not be recommended, because both hemodynamics and temperature can easily be manipulated.

Cardiac surgical patients, in general, have an increased risk of development of acute renal injury. Additionally, almost all untreated MH episodes result in rhabdomyolysis, with the risk of direct myoglobin-mediated damage to the kidney.¹ An adequate therapy to prevent kidney damage includes aggressive fluid replacement with crystalloids. Diuretics should be used to maintain an adequate urinary flow. This decreases the risk of myoglobin precipitation and flushes nephrotoxic agents through the tubules. Whether osmotic diuretics lead to a better outcome than loop diuretics is unknown. Whether alkalization has a significant benefit is also not certain. Nephroprotective effects of antioxidants or vitamins could not be demonstrated in larger trials.⁵⁰ Preventive hemofiltration or hemodialysis does not show a benefit. Renal replacement therapy should therefore be initiated according to the clinical routine.^{2,50}

Potential Trigger Agents of MH

All volatile anesthetics and also succinylcholine are considered classic trigger substances for MH.^{1,3} Further potential triggers have been discussed in the literature. Gasoline vapors and serotonin receptor agonists are considered potential trigger agents.^{51,52} The role of the body core temperature in human MH remains controversial. In MH-susceptible pigs, episodes can be induced by heat alone.¹¹ Physical activity in a hot, humid environment can trigger MH in human beings.⁵³ Patients with a preexisting fever are at a higher risk of development of an episode of MH. Whether heat itself is capable of triggering MH in human beings is not known, but the possibility cannot be excluded, and at least a modulating effect on a developing crisis must be assumed.¹ During rapid and exaggerated rewarming, body core temperatures above physiologic levels can be reached.

Inotropic agents increase the intracellular calcium level and are therefore at least theoretically capable of triggering an episode of MH. In animal studies, however, even extremely high concentrations of enoximone were not capable of triggering a hypermetabolic reaction.⁵⁴ A modulating effect of inotropes on a developing MH reaction, however, cannot be excluded. The calcium sensitizer levosimendan does not increase the intracellular calcium level,⁵⁵ so any influence on cellular calcium handling in MH-susceptible individuals seems unlikely.

Theoretically, a further trigger is possible, as 4-chloro-m-cresol, a preservative contained in heparin, can induce in

vitro a reaction similar to MH.^{43,56} In MH-susceptible swine, however, only doses 150-fold higher than those contained in preparations used clinically were able to induce a reaction in vivo. It therefore seems unlikely that this agent contributes to the occurrence of MH in human beings.^{43,57}

Prevention of MH Episodes in MH-Susceptible Patients

Basic preventive measures include the avoidance of trigger substances. The vapor has to be removed, and the tubing and the carbon dioxide absorber must be renewed. According to various guidelines, the anesthesia machines should be decontaminated with a high flow of pure oxygen for at least 10 minutes.⁴⁴ The same measures must be applied to the oxygenator of the CPB circuit.

For induction and maintenance of general anesthesia, opiates and intravenous hypnotics can be used without problems. Nondepolarizing neuromuscular-blocking agents are also considered safe.¹¹

Controversially, preoperative dantrolene prophylaxis has been discussed; however, MH episodes still occur with dantrolene prophylaxis.⁵⁸ Additionally, early signs of MH crisis may be obscured, delaying subsequent treatment. These limiting factors have to be evaluated critically in light of the potential side effects of dantrolene.⁵⁹ Namely, a considerable number of patients treated with dantrolene, especially those with preexisting neuromuscular disorders, have relevant muscular weakness develop.⁶⁰ In our view, in the 2 cases in which MH episodes occurred despite suspected susceptibility, it is possible that a MH episode could have been prevented with more attention to the rewarming process, even without dantrolene prophylaxis. Newer guidelines no longer recommend the prophylactic administration of dantrolene. Appropriate monitoring allows the early detection of symptoms, and consequent treatment prevents negative outcomes.⁴⁴

Special attention has to be paid to the rewarming process because of its potential influence on the body core temperature. Rewarming should be done slowly and stopped at 36°C. The aim is to maintain a core temperature of less than 36°C during the postoperative period in MH-susceptible patients; however, the effects of this mild hypothermia on coagulation must be considered.

Both catecholamines and phosphodiesterase III inhibitors are considered safe drugs. The placement of a complication-prone mechanical assist device simply to avoid inotropic agents seems not to be justified by the available data.

CONCLUSIONS

With the frequent use of volatile anesthetics, MH will remain a topic in cardiac anesthesia. Classic symptoms of an episode of MH are often obscured during CPB. MH as a differential diagnosis, however, has to be considered with the

occurrence of various otherwise inexplicable symptoms. Rapid rewarming could play an important role in the development of MH episodes and thus may prove a relevant cofactor in the surgical setting if CPB is applied. Treatment with dantrolene, the only curative approach, must not be delayed. The development of MH episodes in susceptible individuals, can be avoided with simple interventions. Anesthesiologists, perfusionists, and cardiac surgeons must be familiar with these measures, and warning signs should be added to respective checklists to facilitate early detection and treatment.

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