MANAGEMENT OF A MALIGNANT HYPERTHERMIA PATIENT DURING CARDIOPULMONARY BYPASS

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ABSTRACT

The anaesthetic management of cardiopulmonary bypass (CPB) for a patient with biopsy-proven malignant hyperthermia is reported. Specific changes in the technique used, such as venting the oxygenator before use, monitoring mixed venous Po_2 and Pco_2, as well as the safety of cold hyperkalaemic cardioplegia are described. Controversial aspects of malignant hyperthermia management such as the safety of calcium and catechol inotropes are discussed in relationship to the successful use of cardio-pulmonary bypass in our patient. We chose to treat left ventricular dysfunction by aggressive vasodilator (nitroglycerine) therapy. We detected no myocardial or respiratory depression secondary to dantrolene therapy either before or after operation.

KEY WORDS: CARDIAC SURGERY, COMPLICATIONS, malignant hyperthermia.

MALIGNANT HYPERTHERMIA (MH) is a pharmacogenetic myopathy[1] involving both skeletal[2] and cardiac muscle.[3] Affected patients are susceptible to acute hyperthermia and/or myotonic reactions triggered by several specific drugs, potent inhalational anaesthetics, some muscle relaxants, and the amide type of local anaesthetics. Reactions can be aggravated by sympathomimetics, parasympatholytics, cardiac glycosides and calcium salts.[4] Stressful environmental situations such as high temperatures, infections, muscle injury, exercise and emotional excitement may also precipitate a reaction. The pathophysiology of the hyperthermic crisis has been investigated and recently reviewed.[4] The clinical and laboratory findings of human and porcine MH support the theory that the control of myoplasmic ionized calcium levels is lost, causing an increase in aerobic and anaerobic metabolism which characterizes the respiratory and metabolic acidosis of this syndrome.

The purpose of this report is to outline the anaesthetic implications in a patient with MH and coronary artery disease requiring cardiopulmonary bypass (CPB) for coronary artery surgery.

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CASE REPORT

A 54 year old male who had incapacitating angina at rest (Canadian Cardiovascular Society Class IV)[6] despite medical therapy (propranolal 160 mg/day) was admitted for coronary arteriography and elective triple aortocoronary bypass grafting. This patient had a strong family history of hyperthermic anaesthetic catastrophes and previously had been studied by muscle biopsy. The result [7] of both the caffeine contracture test and the ATP depletion test on the muscle biopsy specimen confirmed the diagnosis of MH.

Cardiac catheterization was done using procaine for local anaesthesia while the patient was sedated with diazepam given intravenously. Temperature, electrocardiogram and arterial pressure were recorded continuously and precautions were taken to prevent and, if necessary, to treat an MH crisis during the heart catheterization. The selective coronary arteriograms showed severe triple vessel coronary artery disease including a lesion (>90 per cent occlusion) of the left main and right coronary artery. Left ventricular end diastolic pressure was 1.46 kPa (11 mm Hg) and the left ventricular ejection fraction was 67 per cent. The patient tolerated this procedure without any changes in temperature or cardiac status.

Before surgical revascularization the possible risks were explained to the patient. For two days he was pretreated with dantrolene 50 mg q.i.d. (2 $mg \cdot kg^{-1}$ per day), since he noted significant skeletal muscle weakness with a 100 mg dosage. The dose of dantrolene was then gradually increased to 4 $mg \cdot kg^{-1}$ per day for the thirty-six hours before the operation. Non-invasive indices of left ventricular performance (Table I) were measured before dantrolene treatment and again after two days of therapy to evaluate the effects of this drug on ventricular function. Preoperative sedation was achieved with diazepam 10 mg per os at 0600 hours, followed by intramuscular morphine 15 mg and perphenazine 5 mg one hour later. An oral dose of dantrolene 100 mg was given with the diazepam two hours before operation.

TABLE I

NON-INVASIVE MEASURES OF VENTRICULAR PERFORMANCE

	Predicted normal	Pre dantrolene	Post dantrolene
Systolic Time Intervals:			
PEP (msec)	106	129	131
LVET (msec)	308	262	275
QS_2 (msec)	414	391	406
PEP/LVET		0.49	0.48
Echocardiogram:			
Shortening fraction	28–46%	41.3%	42.2%
Muga Scan (Tc 99m):			
Ejection fraction	0.45–0.6	0.58	0.58

A halothane vaporizer had been removed from the extra-corporeal membrane oxygenator (Travenol Teflo) four days before the operation. The oxygenator system was continuously vented with oxygen for 48 hours before operation. Precautionary measures included ice, cold intravenous solutions and a warming blanket. Intravenous dantrolene sodium, verapamil and procainamide were also available. A vapour free anaesthetic machine was used with fresh soda lime in the carbon dioxide absorber.

Monitors included the electrocardiogram (lead V_5), radial artery cannula for pressure monitoring and blood gas sampling as well as a central venous pressure catheter. A left atrial catheter was inserted before discontinuing CPB. The rectal and oesphogeal temperatures were monitored continuously. Cardiographic leads for the intra-aortic balloon pump were placed before induction of anaesthesia.

Fentanyl 50 $\mu g \cdot kg^{-1}$ was used for induction of anaesthesia supplemented with diazepam 10 mg intravenously. Pancuronium was used to provide muscular relaxation for tracheal intubation and the patient was ventilated with oxygen (FI_{O_2} = 1.0). Further fentanyl was administered intermittently to a total dose of 70 $\mu g \cdot kg^{-1}$. No lidocaine was used either to lubricate the tracheal tube or as a local anaesthetic during insertion of monitoring catheters.

The membrane oxygenator was primed with normal saline (2 litres) and potassium chloride (KCl 4 $mmol \cdot l^{-1}$) and sodium bicarbonate 50 mmol was added. Lactated Ringer's solution was avoided because it contained small amounts of calcium. Mannitol (50 ml of 20 per cent) and one gram of methyl prednisolone sodium succinate were added to promote a diuresis and to enhance membrane stability.

Moderate hypothermia (to 30° C) was accomplished during CPB. Re-warming was started early during the procedure, taking care not to exceed 37° C, thus avoiding temperature fluctuations (high or low) in the peri-operative period. Vasodilator (nitroglycerine) treatment was used during the re-warming phase to maintain arterial pressure greater than 7.98 kPa (60 mmHg) with increased pump flows (80 $ml \cdot kg^{-1}$). Vasodilation during the re-warming phase has been shown to minimize the post CPB decrease in temperature.[8]

Cardioplegia (induction of electromechanical arrest) using a cold solution containing magnesium sulphate 1.5 mmol, tromethamine 1 mmol, KCl 10 mmol and sodium chloride 13.5 mmol in each 500 ml of 5 per cent dextrose in water was used. We encountered no difficulty using 1,500 ml of this solution and electromechanical activity returned shortly after the aorta was unclamped. The procedure was performed with a 130 minute pump time and an aortic cross-clamp time of 60 minutes.

During CPB the acid-base state of the patient was monitored every 15 minutes by analyzing blood obtained from both the arterial and venous cannulae (Table II). No unusual metabolic acidosis or elevated venous carbon dioxide values were noted. Serum potassium (K^+) levels decreased significantly and supplemental KCl was given. This mild acidosis (base excess of −4) is not unusual during CPB.

The initial attempt to wean from CPB failed when the left atrial pressure increased to 5.32 kPa (40 mmHg) and the systemic blood pressure

TABLE II

CPB Time min	ARTERIAL SAMPLE							VENOUS SAMPLE								
	$[H^+]a$ nmol/l	pHa	Pa_{CO_2} kPa	Pa_{CO_2} mmHg	Pa_{O_2} kPa	Pa_{O_2} mmHg	Total CO_2 mmol/l	$[H^+]v$ nmol/l	pHv	Pv_{CO_2} kPa	Pv_{CO_2} mmHg	Pv_{O_2} kPa	Pv_{O_2} mmHg	Total CO_2 mmol/l	K^+ mmol/l	Temp °C
15	39.81	7.40	3.86	29	14.63	110	19	40.74	7.39	4.39	33	4.12	31	20	3.9	29
30	36.02	7.42	4.66	35	16.09	121	24	36.02	7.42	4.92	37	4.92	37	25	3.9	30
45	40.74	7.39	4.66	35	27.93	210	22	43.65	7.36	4.99	37.5	4.39	33	23	5.1	30
60	42.66	7.37	5.32	40	22.74	171	25	39.81	7.40	5.05	38	5.25	39.5	25	5.0	34
75	36.31	7.44	4.12	31	36.18	272	21	36.02	7.42	5.19	39	4.52	34	22	5.6	35
90	39.81	7.40	4.39	33	26.33	198	20	39.81	7.40	4.99	37.5	4.72	35.5	22	5.5	37
Post CPB	45.71	7.34	4.79	36	20.75	156	21	—	—	—	—	—	—	—	4.0	37

Arterial and mixed venous blood samples were analyzed during CPB to detect any increase in carbon dioxide production or metabolic acidosis. The values shown have been temperature corrected.

fell to 9.31/5.32 kPa (70/40 mmHg). Neither intravenous calcium salts nor catecholamine infusions were used to assist in discontinuing CPB. Full flow on CPB was reinstituted for fifteen minutes. Using an intravenous nitroglycerine infusion, we then weaned the patient easily from CPB, while maintaining left atrial pressures of 2–2.66 kPa (15–20 mmHg) and systemic arterial pressures of 15.96–18.62/10.64 kPa (120–140/80 mmHg).

The postoperative course was uneventful. Dantrolene sodium 1 $mg \cdot kg^{-1}$ was given intravenously every six hours for 24 hours following admission to the intensive care unit. Morphine and diazepam were used for sedation. The trachea was extubated without reversal of neuromuscular block after 12 hours of ventilation. No respiratory or cardiovascular depression was noted following extubation. This patient's temperature was monitored in I.C.U. for 48 hours after dantrolene was discontinued and no evidence of MH was noted.

Discussion

There are several aspects of anaesthesia requiring CPB which represent a potential risk to an MH-susceptible patient. One concern preoperatively is the possible risk entailed by the avoidance of inotropic agents,[3,4] including digoxin, calcium salts and catechol infusions. Also there are some data which suggest that cardiac muscle may be involved in the MH disease process.[3,10] Episodes of sudden death in members of known families, unexplained nonspecific cardiomyopathies and abnormal thallium scans are suggestive of a direct myocardial involvement in MH patients.[3,4] The dramatic haemodynamic response to aggressive vasodilator therapy using intravenous nitroglycerine in this case emphasizes that there are treatment modalities which are acceptable for MH patients. If cardiac failure should persist, in spite of vasodilator therapy, one must consider the respective risks of mechanical intra-aortic balloon counterpulsation and inotropic support. The use of inotropic agents in MH susceptible individuals remains controversial. We planned to use mechanical support to improve coronary perfusion and assist the left ventricle if vasodilator therapy was inadequate. Bradycardia associated with low cardiac output can be treated by pacemaker implantation.

When these interventions fail to facilitate weaning from CPB the anaesthetist is forced to consider the use of inotropic agents. Sympathetic agonists have been shown to trigger an MH reaction in susceptible swine.[4] Although there is only one clear report[11] of a sympathomimetic agent (phenylephrine) initiating an MH reaction, the safety of pure beta agonists is not clear. The mechanism of MH activation by alpha agonists may be secondary to reduced muscle perfusion[4] and hypoxia. Thus, when confronted with an MH susceptible patient who requires inotropic support unrelated to the MH condition, the anaesthetist may have to accept a significant but unkown risk when considering the potential benefits of weaning from CPB.

An associated concern was the effect of dantrolene sodium on the inotropic state of the diseased heart.[12] There is evidence[12] that dantrolene may depress the myocardium in animals but no studies have documented the effect of this drug on human cardiac muscle. We noted no significant change in left ventricular performance as assessed by systolic time interval measurements and radionuclide angiography, during dantrolene treatment with 4 $mg \cdot kg^{-1}$ per day (Table I). Further study of the effect of this agent on normal and ischaemic human heart muscle is needed before the risk of treatment can be determined.

Dantrolene frequently causes significant skeletal muscle weakness,[4] as it did in this patient. In the post-operative period, when many patients have respiratory complications, the significance of this weakness in precipitating respiratory muscle fatigue following tracheal extubation is unknown. We noted no significant impairment of respiratory function while dantrolene was being administered to this patient. However, a controlled study of pulmonary function testing before and after dantrolene therapy could clarify the degree of impairment caused by dantrolene.

The initiation of an MH crisis is in proportion to the susceptibility of the patient and the total dose of triggering agent(s) and other environmental stresses. Although triggering drugs and calcium salts can be avoided, the stress response to CPB can be considerable, resulting in significant elevation of stress-related hormones (endogenous cortisol and catecholamines).[13] The use of a technique with pancuronium and "high dose fentanyl"[13] would appear to offer the advantage of a reduced endogenous catechol response to CPB.

One interesting facet of CPB is the ability to monitor the acid-base status in mixed venous blood frequently from the extracorporeal oxygenator. An acute MH reaction would also be preceded by increasing oxygen consumption

with a decrease in $P\bar{v}_{O_2}$. One effect of crystalloid haemodilution on the content of carbon dioxide in the mixed venous blood would be a reduction in the buffering capacity (protein and haemoglobin) of the blood. Similarly hypothermia would reduce the solubility of carbon dioxide in blood. Therefore if a patient whose blood is diluted and cooled develops an MH reaction, one would expect the $P\bar{v}_{CO_2}$ to rise rapidly. In this patient there was no evidence of either increased lactate production (decrease in bicarbonate) or any rise in mixed venous P_{CO_2} ($P\bar{v}_{CO_2}$) during CPB[4] (Table II).

In summary, we have successfully managed a patient with biopsy-proven MH during CPB. The anaesthetic management of the potential problems that we considered important is outlined. Taking these factors into consideration, the risk of CPB in patients known to be susceptible to MH may be increased. This serves to emphasize that the diagnosis of malignant hyperthermia must not be made indiscriminately. Precision of the in vitro diagnostic tools used to make this diagnosis is essential to avoid needless concern among patients and physicians who are contemplating the operative risk of cardiac surgery. More clinical data is necessary to evaluate the significance of Malignant Hyperthermia in increasing this operative risk.

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RÉSUMÉ

Nous rapportons la conduite de l'anesthésie lors d'une intervention à cœur ouvert effectuée chez un patient susceptible à l'hyperthermie maligne; la susceptibilité à l'hyperthermie avait été démontrée par biopsie musculaire. Du point de vue technique, on cite entre autres, l'enlèvement du vaporisateur d'halothane habituellement fixé à l'appareil cœur-poumon et la ventilation de l'oxygénateur au moyen d'oxygène durant 48 heures avant l'intervention; on cite également les vérifications des P_{O_2} et des P_{CO_2} veineuses centrales au cours de la circulation extracorporelle. On rapporte l'emploi sans problème d'une solution de cardioplégie au potassium. L'emploi d'agents inotropes comme le calcium et les catécholamines en chirurgie à cœur-ouvert dans un contexte de susceptibilité à l'hyperthermie maligne est commenté. Dans le cas rapporté, une défaillance ventriculaire gauche survenue à la sortie de C.E.C. a pu être traitée avec succès au moyen de vasodilatateurs (nitroglycérine). Nous n'avons pas observé de dépression respiratoire ou circulatoire à la suite de l'administration de dantrolène avant et après l'intervention.