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CASE REPORTS

Malignant Hyperthermia Associated with Hypocalcemia

RICHARD A. POLLOCK, CAPTAIN, MC,* AND ROBERT L. WATSON, MAJOR, MC †

Hyperthermia following anesthesia has been a matter of concern for decades. Typically the rise in temperature was slow and progressive, and usually it was attributed to elevated room temperature, heavy draping, or prolonged surgery. Recent reports from Australia, Canada, the United States, Great Britain, and South Africa have described a more alarming type of hyperthermia, which occurs during anesthesia.¹⁻²² This condition, which occurs in both man and animals, appears to be biphasic. The initial phase is characterized by an insidious,

progressive rise in temperature, accompanied by appropriately profuse sweating. A prodrome of progressive muscular rigidity may be present but is often unrecognized because of surgical draping.

The early phase, which occurs 30 to 90 minutes after induction, is followed by a more rapid rise in temperature accompanied by inability to sweat and mottling of the skin. Studies made immediately upon recognition of the syndrome reveal severe metabolic and respiratory acidosis and extreme alterations in arterial-to-mixed venous oxygen ratios. Bradycardia progressing to cardiac arrest usually follows; on occasion, this has responded to intravenous calcium chloride. Disseminated intravascular coagulation may be detected fol-

* Anesthesia and Operative Service.

† Assistant Chief, Anesthesia and Operative Service.

Received from the Walter Reed General Hospital, Washington, D. C. 20012.

lowing the rise in temperature. The syndrome has been called malignant hyperthermia.

Malignant hyperthermia, in both man and animals, appears to have a genetic basis.^{1-4, 12, 13, 16-19, 23-27} Inheritance is thought to be autosomal dominant, with reduced penetrance and variable expressivity.³⁴ A recent study³³ estimates the incidence to be 1:10,000, with a range of 1:5,000 to 1:70,000. Patient ages have ranged from 6 months¹⁷ to 58 years.³² The earliest reported cases may have occurred as early as 1922,³ but recent case-reporting suggests that the increased incidence of malignant hyperthermia has paralleled the development and use of more potent anesthetics. The mechanism by which the potent anesthetics "trigger" this condition is unknown; several etiologies will be considered. Hyperpyrexia associated with nonanesthetic (*i.e.*, psychotropic) drugs may offer some insight.

In all cases of malignant hyperthermia, electrolyte abnormalities have been found. The following case history will present the rarely seen association of hypocalcemia and hyperkalemia.

REPORT OF A CASE

A 23-year-old Caucasian man was admitted to the hospital with a history of chronic anterior dislocation of the right shoulder. The remainder of the history was negative except for a history of drug abuse involving agents described only as "pot," "LSD," and "speed." Preoperative examination and laboratory studies, including determination of calcium and phosphorus, disclosed no abnormalities (table 1).

The patient was given atropine, 0.4 mg, and meperidine (Demerol), 50 mg, intramuscularly and taken to the operating room for a Putti-Platt repair of the right shoulder. Anesthesia was induced with thiopental sodium (Pentothal), 375 mg (fig. 1). Despite intravenous injection of 100 mg succinylcholine, relaxation of the mandible was incomplete and intubation somewhat difficult. Anesthesia was maintained with a mixture of halothane and 50 per cent nitrous oxide-oxygen. Approximately 45 minutes after induction, the heart rate and respiratory rate began a steady increase. Ninety minutes after induction, the patient became markedly tachypneic and was noted to have a cape-like distribution of cyanotic color, with distention of the neck and forehead veins. Breath sounds over the left anterior chest appeared diminished, and the endotracheal tube was removed. Ventilation seemed to improve.

The patient remained tachypneic, however, and the soda-lime canister was changed. Systolic

TABLE 1. Laboratory Data, Electrolytes

	Ca ⁺⁺ (mEq/l)	PO ₄ (mg/100 ml)	K ⁺ (mEq/l)
Preoperative	(9.5 mg/ 100 ml)	4.3	
At peak of temperature rise	3.8	11.3	7.4
After cooling			6.1
	3.8	6.8	5.8
			6.2
	3.5	8.2	6.4
			6.4
	3.7		7.2

blood pressure was 90 mm Hg. Two attempts at reintubation were made, of which the second was successful. A total of 0.8 mg atropine and 120 mg succinylcholine, in divided dosage, was needed. During auscultation of the chest to assess the effect of intubation, the skin was noted to be hot, and the soda-lime canister was found to be markedly heated. The drapes were quickly removed, to reveal the lower extremities in a severe state of extensor hypertonus and the hands clenched in fists. The anesthetic was discontinued and 100 per cent oxygen given. A rectal thermistor probe revealed a temperature of 106.5 F.

Cooling procedures were begun immediately, with iced Ringer's lactate solution given intravenously and gastric lavage with iced saline solution. A polyethylene sheet was placed under the patient and he was "covered" with crushed ice. The temperature continued to rise, and the patient developed profound bradycardia and hypotension. The blood pressure and pulse were unresponsive to ephedrine and mephentermine, but returned after 400 mg CaCl₂.

Blood samples taken at the peak of the temperature rise, after removal of the soda-lime canister and administration of five ampules (220 mEq) of sodium bicarbonate, had a P_{aCO}₂ of 65 mm Hg, a P_{aO}₂ of 350 mm Hg, and pH of 7.2. Serum electrolytes at that time showed marked hyperkalemia (7.4 mEq/l), hyperphosphatemia (11.3 mg/100 ml), and hypocalcemia (3.8 mEq/l) (table 1).

The temperature fell rapidly to 100 F (fig. 1). Within an hour, the temperature was 99 F, and meperidine (Demerol) and chlorpromazine (Thorazine) were given to prevent shivering. During cooling, supraventricular arrhythmias were encountered, but they responded readily to four doses of 0.5 mg each of propranolol, given intravenously.

Blood began to ooze from the surgical incision, the nose, and the sites of intravenous and intramuscular puncture. Clotting studies revealed no clotting at one hour; prothrombin time 27 sec; partial thromboplastin time 93 sec; fibrinogen 77

mg; factor II 30 per cent, factor V 8 per cent, factor VIII 15 per cent, factor X 15 per cent, and factor XI 4 per cent; platelet count 159,000. The patient was given heparin intravenously at four-hour intervals and the bleeding progressively diminished. Hypotension, accompanied by low central venous pressure (0-3 cm H₂O) and low cardiac (3.2 l/min), necessitated the administration of blood and other fluids. The central venous pressure was kept between 8 and 16 cm H₂O.

Electrolytes in serially sampled blood (table 1) revealed persistent hyperkalemia, hyperphosphatemia, and hypocalcemia. Treatment consisted of regular insulin intravenously, Kayexalate enemas, and calcium chloride intravenously. The hands, still clenched, responded to 900 mg of CaCl₂ at hour 16, but the general state of hypertonus persisted.

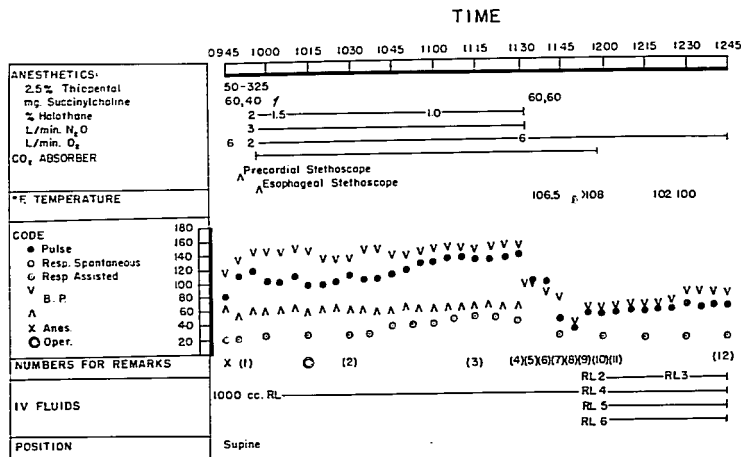
About 24 hours after induction, bleeding at the sites of puncture and surgical incision increased, accompanied by gastrointestinal hemorrhage and

hemoptysis. Additional heparin, blood and plasma were administered and, because of the suspected presence of fibrinolysis, a single injection of ethylaminocaproic acid (Amicar), 5.0 g, was given.

Pulmonary inspiratory pressures progressively increased to a preterminal level of 60 cm H₂O. Prior to death, PaO₂ fell to 40 mm Hg (FiO₂ 1.0), and the patient died following a ventricular arrhythmia.

Analysis of the halothane in this case showed the presence of nitrous oxide and a large amount of thymol (44 times normal). Vapor-phase chromatography revealed no single minor impurity present to an extent greater than five parts per million.

Pathology Report. Gross examination revealed diffuse muscular edema and hemorrhage, hemorrhagic tracheitis, pulmonary congestion and hemorrhage, and melena. Microscopic studies revealed only a few widely scattered fibrin thrombi; there was no evidence of muscular destruction.



REMARKS (1) Relaxation of mandible incomplete, intubation somewhat difficult. (2) Skin warm. (3) Noted to have a cape-like sulfocyanotic color with distention of the neck veins (4) Breath sounds over left anterior chest appeared diminished. The endotracheal tube removed. Ventilation appeared to improve. (5) Soda lime canister changed (6) Patient remained tachypneic, and two attempts at re-intubation were made, the second attempt was successful (8 mg atropine and 120 mg succinylcholine, divided dosage) (7) Patient and soda lime canister noted to be hot, hypergidity present, rectal probe revealed temperature 106.5 F. (8) Ephedrine 25 mg i.v. meperidine 15 mg i.v. (9) 400 mg calcium chloride. 3000 cc wood roger's Lactate started i.v. Polyethylene sheet placed under patient, covered with ice (10) Five ampules sodium bicarbonate. Put on non-rebreathing system. (11) blood gases, electrolyte studies drawn. (12) meperidine (50 mg) and chlorpromazine (25 mg) i.v. to prevent shivering Patient transferred to recovery room.

23 year old male with chronic anterior dislocation of right shoulder. Wt. 167 lbs., hematocrit 46, I.M. pre op medication 0.4 mg atropine and 50 mg meperidine

Agent and technique: Halothane - N₂O₂; Endotracheal tube 3mm with Ecc cuff, oral airway.

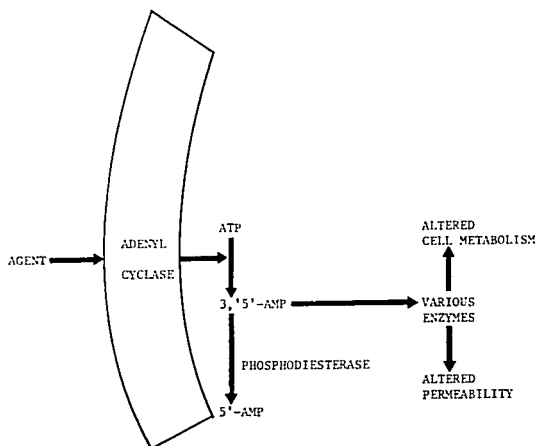
Operation: Putti platt repair, right shoulder

Total Fluids: 900 cc RL, 4400 cc iced RL

EBL: 300 cc

FIG. 1. Anesthetic record.

FIG. 2. Cyclic AMP: formation and cellular effects (after Sutherland).



DISCUSSION

The case history illustrates some of the classic signs and metabolic derangements found in malignant hyperthermia. The history of drug abuse and the presence of hypocalcemia deserve particular comment; a prerequisite, however, is a discussion of the possible etiologies of malignant hyperthermia.

Malignant hyperthermia appears to be a metabolic disorder, the specific defect remaining unknown. Wilson and co-workers³⁸ suggested that the defect lies in the coupling of oxidative phosphorylation. They used as a model an uncoupling agent, 2,4-dinitrophenol (DNP),³⁹ thought to act at the mitochondrial membrane.⁴⁰ Wilson³⁸ showed, in the dog, that the uncoupling produced by the administration of DNP is enhanced by halothane-oxygen but not by pentobarbital-oxygen. Similarly, Snodgrass incubated a number of hydrocarbons with normal rat liver mitochondria and demonstrated uncoupling of oxidative phosphorylation by chloroform, diethyl ether, and halothane.⁴¹

Other investigators question the association between uncoupling and malignant hyperthermia.^{33, 42-45} They suggest that other pathways are involved instead. One pathway, not previ-

ously mentioned, involves adenosine 3',5'-monophosphate (3',5'-AMP, cyclic AMP, cAMP). Cyclic AMP is formed from ATP (fig. 2)⁴⁶; the reaction is catalyzed by adenylyl cyclase, an enzyme "fixed" to the cell membrane^{47, 48} and found in all animal tissues, including muscle, liver, and brain.⁴⁹ Adenylyl cyclase is activated by numerous hormones, including the catecholamines and the xanthenes; activation by other agents is suspected.^{46, 50}

Cyclic AMP, if not inactivated by phosphodiesterase, acts as a "messenger" within the cell, stimulating a number of enzyme systems and altering cellular metabolism and cell permeability.⁴⁶

The effect of some psychotropic drugs on the cyclic AMP system is now established. A recent report by Abdulla and Hamadah clearly demonstrates that dibenzazepine (tricyclic) antidepressants (table 2) inhibit the degradation of cyclic AMP. They suggest that these drugs are potent competitive inhibitors of phosphodiesterase and exert their antidepressive effect by increasing intracellular levels of cyclic AMP.⁵¹ Monoamine oxidase inhibitors (MAOI; table 2) also appear to increase intracellular cyclic AMP, elevating catecholamines, which in turn stimulate adenylyl cyclase.

TABLE 2. Some Antidepressant Drugs,
Many Associated with Hyperpyrexia

Dibenzazepine compounds
Amitriptyline (Elavil)
Desmethylinipramine (Norpramin)
Imipramine (Tofranil)
Nortriptyline (Aventyl)
Protriptyline (Vivactil)
Monoamine oxidase inhibitors (MAOI's)
Isocarboxazid (Marplan)
Nialamide (Niamid)
Phenelzine (Nardil)
Tranylepromine (Parnate)

By increasing intracellular cyclic AMP, these drugs might in some instances be expected to produce a hypermetabolic state. Indeed, several cases of hyperpyrexia and muscular rigidity have followed the combined use of tricyclic antidepressants and MAOI.⁵²⁻⁶⁰ Usually the patient is in his late twenties. About 6-36 hours after the administration of combined therapy, delirium, sweating, and hyperpyrexia develop, followed or accompanied by muscular hyperrigidity, coma and, occasionally, spasm. Mortality is high; about 60-70 per cent do not survive.

The syndrome induced by psychotropic drugs appears similar to that which follows administration of potent anesthetics. A common metabolic pathway may be involved. In psychotropic drug-induced hyperpyrexia, phosphodiesterase activity apparently is depressed in the presence of increased adenylyl cyclase activity. In patients susceptible to malignant hyperthermia, phosphodiesterase may be abnormal in amount or structure. The administration of potent general anesthetics may further depress phosphodiesterase activity or may stimulate adenylyl cyclase activity, possibly triggering some of the manifestations of malignant hyperthermia.

Serum electrolytes in antidepressant-induced hyperpyrexia have not been determined, but in malignant hyperthermia, hyperkalemia is a frequent finding. Hypocalcemia, less frequently reported but suspected on clinical grounds, is also reported. Purkis¹⁸ describes a 44-year-old woman with carpopedal spasm, ECG changes, bradycardia, and hypotension following the development of malignant hyperthermia; calcium levels were within normal

limits, but the patient responded favorably to administration of calcium chloride. Still other case reports describe the presence of bradycardia, frequently amenable to calcium chloride,^{10, 18, 19, 24, 25} Hypocalcemia, though minimal, and hyperphosphatemia were first documented by Cody.²² Abnormal calcium and phosphate levels were present in our patient (table 1) from immediately following recognition of the syndrome to death 27 hours following induction. Recently, Denborough⁶¹ reported marked hypocalcemia and hyperphosphatemia in a 54-year-old man with malignant hyperthermia. The presence of hypocalcemia is not readily explained and, in fact, conflicts with data recorded during studies of the Landrace pig.^{45, 62} Jones and Burnap, however, studying an inbred strain of Poland China swine have found lowered levels of plasma calcium and magnesium on the *in vitro* exposure of this susceptible breed's muscle to halothane.⁶⁷ Recent studies have elucidated the role of cyclic AMP in the metabolism of calcium and, in turn, the role of calcium in muscle contractility^{63, 66}; clarification of the changes in malignant hyperthermia will require further study.

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Vasospasm with an Indwelling Radial Artery Cannula

BRIAN DALTON, M.D.,* AND MYRON B. LAVER, M.D.†

Prolonged cannulation of the radial artery is used in the management of critically ill patients and patients undergoing extensive surgery.¹⁻⁵ The purposes and advantages include: 1) it is less traumatic to the vessel than repeated punctures when serial blood samples

are necessary; 2) accurate measurement of arterial pressure is obtainable, especially when the use of a pneumatic cuff is unsatisfactory, e.g., with hypothermia, extracorporeal circulation; 3) it may be less disturbing to the patient where apprehension may alter values to be studied, e.g., arterial blood gases, cardiac output. The value of prolonged cannulation may be enhanced by minimizing its complications. This communication reports the response to intra-arterial lidocaine with interruption of blood flow of a hand which showed signs of inadequate circulation distal to the indwelling radial cannula.

* Associate Anesthetist, Massachusetts General Hospital; Instructor in Anaesthesia, Harvard Medical School.

† Anesthetist, Massachusetts General Hospital; Professor of Anaesthesia, Harvard Medical School.

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