Anaesthetic management of coronary artery bypass grafting in a patient with central core disease and susceptibility to malignant hyperthermia on statin therapy

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Central core disease and malignant hyperthermia (MH) are both associated with mutations in the RYR1 gene. We report the anaesthetic management of one such patient presenting for coronary artery bypass grafting. Her medication included aspirin 75 mg, atorvastatin 20 mg, isosorbide mononitrate 60 mg, atenolol 25 mg and glyceryl trinitrate sublingual spray as required. The use of aprotinin, statins and moderate hypothermia in patients with central core disease and known susceptibility to MH has not been documented.

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susceptible to MH by \textit{in vitro} contracture testing. She presented for coronary artery bypass grafting, and we document the uneventful use of aprotinin, statins and hypothermia during her management. The use of aprotinin, a statin and hypothermia in a patient with central core disease susceptible to MH has not been reported before.

Case report
A 44-yr-old morbidly obese lady (body mass index 39.72) with a 13-yr history of ischaemic heart disease presented with unstable angina and underwent acute coronary artery bypass grafting. Risk factors for ischaemic heart disease included heavy smoking, hypercholesterolaemia and morbid obesity. There was a strong family history of premature coronary artery disease and severe hypercholes- terolaemia. The ECG showed left ventricular hypertrophy and the angiogram revealed severe coronary disease affecting the coronary ostia and a left ventricular ejection fraction of 50%. Her routine medications, consisting of atenolol 25 mg daily, atorvastatin 20 mg daily, isosorbide mononitrate 60 mg twice daily and aspirin 75 mg daily were continued up to the day of surgery.

Two years previously, she had been referred for investigations after the diagnosis of central core disease and malignant hyperthermia susceptibility (MHS) in her sister and niece. Her skeletal muscle histology was typical of central core disease while the \textit{in vitro} muscle contracture tests, carried out according to the protocol of the European Malignant Hyperthermia Group,\textsuperscript{9} were abnormal for both halothane (3 mM tension at halothane 2% v/v) and caffeine (6 mM at caffeine 2 mM) tests. None of the \textit{RYR1} mutations currently used for diagnostic purposes\textsuperscript{10 11} is present in this family. Our patient had undergone tonsillectomy and adenoidectomy as a child under general anaesthetic without any reported complications. Her myopathy was mild and restricted to minimal weakness of the legs. Her ventilatory function was normal, with an FVC (forced vital capacity) of 2.69 (88% predicted) and an FEV\textsubscript{1} (forced expiratory volume in 1 s) of 2.10 (80% predicted). Preoperative full blood count, LFTs, serum creatinine kinase (CK), sodium, potassium, urea and creatinine were normal.

After ensuring full precautions to prevent and treat MH (Table 1) were in place, she was premedicated with i.m. morphine 15 mg and metoclopramide 10 mg and oral lorazepam 3 mg, 1 h before surgery. Anaesthesia was induced with midazolam 7 mg, fentanyl 20 \(\mu\)g kg\(^{-1}\) and pancuronium 16 mg. Anaesthesia was maintained using a propofol infusion at 300–400 mg h\(^{-1}\). Other infusions included dopamine 4–24 mg h\(^{-1}\) and glyceryl trinitrate 1–10 mg h\(^{-1}\). Aprotinin 2 000 000 U was given at sternotomy, followed by another 2 000 000 U during bypass. Anticoagulation was achieved with heparin (total dose 45 000 IU). The patient was cooled to 32°C on cardiopulmonary bypass and the aortic cross-clamp time was 45 min. After bypass, the residual effects of heparin were reversed with protamine 375 mg. Four units of platelets and two units of fresh frozen plasma were transfused perioperatively. The decision to transfuse blood products was made on account of increased microvascular bleeding. No allogenic blood was transfused at any time. After surgery, the patient was transferred to the intensive care unit and her trachea was extubated after 12 h. Postoperative recovery was uneventful. Our patient did not show any sign of muscle weakness at any time in the postoperative period and was discharged from hospital after 8 days. Lung function tests and determination of serum CK concentration were not repeated.

Discussion
Cardiac surgery using cardiopulmonary bypass for patients susceptible to MH,\textsuperscript{12} and a patient with central core disease for cardiac transplantation\textsuperscript{13} have been reported. There are, however, novel and interesting aspects to this case.

It is well known that statins can be associated with rhabdomyolysis and myopathy.\textsuperscript{14} The risk of myopathy is increased when statins are combined with drugs that inhibit hepatic cytochrome P450 enzymes (e.g. fibrates, cyclosporin, macrolide antibiotics and azole antifungals)\textsuperscript{15} and when high doses are given, or in the presence of acute viral infections, major trauma, surgery or hypothyroidism. The incidence of myopathy with individual statins varies widely. Simvastatin and cerivastatin are known to produce the highest incidences (35.8 and 31.9%, respectively), and the incidence with atorvastatin is 12.2%.\textsuperscript{14} The potential for a greater likelihood of rhabdomyolysis induced by statins in

### Table 1
Precautions recommended for the prevention and treatment of MH. These should be readily available before anaesthesia is induced

<table>
<thead>
<tr>
<th>Equipment and monitoring</th>
<th>Cooling aids</th>
<th>Drugs</th>
</tr>
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<tbody>
<tr>
<td>Vapour-free anaesthesia machine (no vaporizers attached) Fresh circuit and reservoir bag Capnography ECG and pulse oximetry Core and peripheral temperature monitor Intra-arterial pressure</td>
<td>Hypothermia blanket Cold saline for irrigation and i.v. infusion Crushed ice Bypass team on stand-by</td>
<td>Intravenous dantrolene 50% dextrose with insulin to treat hyperkalaemia Sodium bicarbonate 8.4% β-blockers: esmolol Diuretics: mannitol 10%, frusemide</td>
</tr>
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patients with pre-existing muscle disease is not known, but we are aware of a patient diagnosed as susceptible to malignant hyperthermia who presented with marked rhabdomyolysis after therapy with statins.\textsuperscript{16} It would seem prudent for patients receiving statins who have a known muscle disorder to have serum CK concentration measured routinely during their follow-up visits. Our patient, who was on long-term atorvastatin therapy, had had a normal serum CK concentration before cardiac surgery and also before muscle biopsy 2 yr earlier. She showed no sign of aggravation of her myopathy at any time during the perioperative period. However, in the postoperative period, CK measurements can cause diagnostic confusion as surgery itself can cause CK elevation. We did not measure CK concentration in the postoperative period.

This patient was obese and taking aspirin for its antiplatelet effect until the day before surgery. These factors are both associated with an increased risk of perioperative bleeding after coronary artery bypass grafting. Aprotinin is commonly used in these circumstances to reduce perioperative bleeding after coronary artery bypass. Animal experiments, in susceptible pigs, have also been performed to test the potential ability of aprotinin to trigger MH in a susceptible individual.\textsuperscript{17} It was not triggered in our patient, we cannot conclude that aprotinin administration to outweigh the risk of it triggering MH, despite no previous documentation of its use in MHS patients. Furthermore, we believed the risk of triggering MH to be sufficiently small. However, although an MH reaction was not triggered in our patient, we cannot conclude that aprotinin does not trigger MH in a susceptible individual. We recognize that exposure of susceptible individuals to triggering drugs does not always lead to an MH reaction. It is also conceivable that an MH reaction was prevented by the hypothermia (32°C) induced during cardiopulmonary bypass. Animal experiments, in susceptible pigs, have shown that hypothermia is protective against precipitating MH.\textsuperscript{22}

In summary, although our patient had an uneventful procedure, there were many potential problems. It is recommended that patients suffering from a myopathy and on statin therapy should have their CK levels measured routinely as they are at risk of developing rhabdomyolysis. Hypothermia as a means of preventing an MH reaction needs more evaluation.

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