Hyperthermia after cardiac surgery

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Purpose: To describe two cases of hyperthermia occurring after cardiac surgery.

Clinical features: At the end of cardiopulmonary bypass, protamine was injected to reverse heparin. Following protamine, hypotension, pulmonary hypertension and hypoxia developed, but protamine induced hypotension recovered after administration of methyl prednisolone and catecholamines. Rectal temperature increased to 41°C in the first case and 40°C in the second after recovery from protamine induced hypotension. Arterial blood gas analysis, breathing 100% oxygen, showed severe acidosis and hypercapnia (pH 6.96, PaCO₂ 73 mmHg, PaO₂ 45 mmHg, BE -18 in the first case, and pH 7.13, PaCO₂ 59.9, PaO₂ 52.8, BE -11 in the second). At the same time, creatine phosphokinase levels showed 8400 u·L⁻¹ in the first case and 4369 u·L⁻¹ in the second. Serum and urine myoglobin concentrations were 334.2 ng·mL⁻¹ and 1085 ng·mL⁻¹, and 468 ng·mL⁻¹ and 885 ng·mL⁻¹, respectively. Efforts to cool the patients using alcohol were made. Following dantrolene (400 mg and 200 mg), the hyperthermia, acidosis, hypoxaemia and hypercarbia subsided (temperature 37.5 and 37.5°C, PaO₂ 220 mmHg and 180 mmHg with 100% oxygen, PaCO₂ 35 mmHg and 41 mmHg respectively). Postoperatively, 20 mg·hr⁻¹ dantrolene infusion were administered for 24 hr. In the first case, an anaphylactoid reaction was confirmed by increased plasma tryptase.

Conclusion: We report two cases of hyperthermia after cardiac surgery in whom dantrolene was very effective in reducing the high rectal temperature.

Objectif : Rapporter deux cas d'hyperthermie survenus après une chirurgie cardiaque.

Éléments cliniques : La neutralisation de l'héparine était accomplie avec de la protamine administrée après l'arrêt de la circulation extracorporelle. Par la suite, de l'hypotension, de l'hypertension pulmonaire et de l'hypoxie apparaissaient. L'administration de méthylprednisolone et de catécholamine permettait de corriger l'hypotension induite par la protamine. Après ce traitement, la température rectale augmentait à 42°C dans le premier cas et à 40°C dans le deuxième. La gazométrie artérielle révélait, sous oxygène pur, une acidose et une hypercapnie sévères (pH 6.96, PaCO₂ 73 mmHg, PaO₂ 45 mmHg, BE -18 dans le premier cas et pH 7.23, PaCO₂ 59.9, PaO₂ 52.8 et BE -11 dans le second). En même temps, la créatine phosphokinase atteignait 8 400 u·L⁻¹ dans le premier cas et 4 369 u·L⁻¹ dans le second. Les concentrations sériques et urinaires de myoglobine étaient respectivement de 334.2 ng·mL⁻¹ et de 1085 ng·mL⁻¹ dans le premier cas et de 468 ng·mL⁻¹ et de 885 ng·mL⁻¹ dans le second. Le refroidissement était entrepris avec de l'alcool. Après l'administration de dantrolène sodium, (400 et 200 mg), l'hyperthermie, l'acidose, l'hypoxémie, l'hypercarbie et l'hypertension renaissaient dans l'ordre (température 37.5°C dans les deux cas, et respectivement, PaO₂ 200 mmHg et 180 mmHg sous 100% O₂, PaCO₂ 35 mmHg et 41 mmHg). Du dantrolène sodium 20 mg·h⁻¹ était administré pendant 24 h. Dans le premier cas, l'augmentation de la tryptase plasmatique confirmait la réaction anaphylactoïde.

Conclusion : Le dantrolène sodium a permis de réduire une température rectale élevée après une chirurgie cardiaque chez deux patients.

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THESE are reports^{1,2} of anaphylactoid reactions, including hyperthermic episodes, to protamine after the end of extracorporeal circulation during cardiac surgery. On the other hand, malignant hyperthermia (MH) is an inherited disorder of skeletal muscle that is catastrophic. Anaesthetic drugs that can trigger MH include halothane, enflurane, isoflurane, desflurane, sevoflurane as well as succinylcholine. The diagnosis of MH depends on a clinical and laboratory features represented by a hypermetabolic state within skeletal muscle. However, it is difficult to confirm the diagnosis of MH during cardiac surgery because of the hyperdynamic state. We report two cases of hyperthermia occurring after protamine induced hypotension.

Case report

Case #1

A 64-yr-old, 169 cm, 70-kg man was scheduled for mitral valve replacement and subaortic myectomy for hypertrophic obstructive cardiomyopathy (HOCM). Medical history included diabetes mellitus treated with diet and oral hypoglycaemic agents until four months earlier, when NPH insulin was added.

The patient was premedicated with 0.4 mg atropine sulfate and 50 mg hydroxyzine *im*. Monitors included ECG, radial artery line, pulmonary artery catheter (thermodilution catheter, Baxter Edward Swan Ganz Model), pulse oximeter, capnograph, rectal temperature. Anaesthesia was induced with 15 mg diazepam, 0.5 mg fentanyl and muscle relaxation with 8 mg vecuronium, and maintained with 100% oxygen, 70 $\mu\text{g}\cdot\text{kg}^{-1}$ fentanyl and pancuronium. After induction of anaesthesia, a transoesophageal echocardiography probe was inserted. Cardiac output and mixed venous oxygen saturation were continuously monitored using Vigilance Monitor Model VGS (Baxter USA). Mitral valve replacement and subaortic myectomy were performed. Cardiopulmonary bypass (CPB) time was 160 min and aortic clamp time was 105 min. Rewarming was accomplished over 30 min using high pump flows with subsequent weaning from CPB at a rectal temperature of 37.0. Ten minutes after CPB, systolic arterial blood pressure (SABP) was 100 mmHg, heart rate 80 beats $\cdot\text{min}^{-1}$, central venous pressure (CVP) 12 mmHg, pulmonary artery pressure (PAP) 22/14 mmHg, pulmonary capillary wedge pressure (PCWP) 14 mmHg, cardiac output (CO) was 5.4 L $\cdot\text{min}^{-1}$, mixed venous oxygen saturation was 75% under continuous infusion of 0.1 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ noradrenaline and 5 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ dopamine. About 20 min after CPB, 150 mg protamine (protamine sulphate, 10 mg $\cdot\text{ml}^{-1}$, Shimizu) were administered slowly via the central vein. Within 10 min,

SABP decreased from 110 to 50 mmHg, CVP increased from 12 to 20 mmHg, PAP increased from 22/12 to 65/45 mmHg, PCWP increased from 12 to 33 mmHg, and CO decreased from 5.0 to 2.2 L $\cdot\text{min}^{-1}$. Heart rate was maintained at about 110 beats $\cdot\text{min}^{-1}$ under atrial pacing. Arterial blood gas analysis revealed; pH 7.20, PaCO₂ 46.1 mmHg, PaO₂ 60 mmHg, BE -11, oxygen saturation (SaO₂) 91%. Based on these observations, an anaphylactoid reaction was suspected and methylprednisolone (500 mg) was injected. Blood was sampled about one hour after protamine and centrifuged, and the serum was frozen for later tryptase measurement. In order to treat pulmonary hypertension, 0.02 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ prostaglandin E₁ (PGE₁) was infused and, PAP decreased from 65 to 30 mmHg, PCWP from 35 to 12, but hypotension (SABP 50-60 mmHg) and low cardiac output (CO 2.2-2.5 L $\cdot\text{min}^{-1}$) continued despite 0.2 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ noradrenaline and 7 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ dopamine infusion. Dopamine and PGE₁ were discontinued. About 10 min after discontinuation of these drugs, SAP increased to 100 mmHg, CO increased to 4.0 L $\cdot\text{min}^{-1}$ and SaO₂ recovered to 100%. Infusion of 60 mg $\cdot\text{hr}^{-1}$ lidocaine was started for the treatment of premature ventricular contraction. Myoglobinuria developed and rectal temperature increased from 37.0 to 41°C within 60 min of the start of lidocaine. The SABP decreased to 50 mmHg, CO decreased to 2.0 L $\cdot\text{min}^{-1}$ and PAP increased to 70 mmHg, and mixed venous oxygen saturation decreased from 85% to 50%. Arterial blood gas analysis revealed hypoxaemia, hypercarbia and severe metabolic acidosis (pH 6.96, PaCO₂ 73 mmHg, PaO₂ 45 mmHg, BE-18 with 100% oxygen). Creatine phosphokinase (CPK) concentration was 8400 u $\cdot\text{L}^{-1}$. Serum myoglobin and urine myoglobin concentrations were 334.2 ng $\cdot\text{ml}^{-1}$ (normal value; 23-30 ng $\cdot\text{ml}^{-1}$) and 1085 ng $\cdot\text{ml}^{-1}$ (normal; none). Malignant hyperthermia was suspected. Dantrolene 400 mg was injected and surface cooling using alcohol was commenced. About 60 min after dantrolene injection, rectal temperature decreased to 37.5 and, while breathing 100% oxygen, PaO₂ returned to 220 mmHg and PaCO₂ to 35 mmHg. Haemodynamic variables recovered (CO increased to 4.0 L $\cdot\text{min}^{-1}$, SAP increased to 100 mmHg, PAP decreased to 25 mmHg and mixed venous oxygen saturation increased to 85%). On postoperative day one, serum and urine myoglobin concentrations were 197.6 ng $\cdot\text{ml}^{-1}$ and 313 ng $\cdot\text{ml}^{-1}$. Postoperatively, a dantrolene infusion of 20 mg $\cdot\text{hr}^{-1}$ was administered for 24 hr in the intensive care units. Tracheostomy was performed on the third postoperative day for the anticipated long term ventilatory support. Although the patient had been stable, haemodynamically, hepatic and renal failure

developed. Serum tryptase concentration was 18.0 ng·ml⁻¹ (normal < 2.0 ng·ml⁻¹, RIA method, Mitsubishi Yuka BCL, Osaka Japan).

Case #2

A 69-yr-old, 162 cm, 67-kg man was scheduled for total arch replacement and coronary artery bypass graft to right coronary artery (4 PD) for thoracic aortic aneurysm (DeBakey type 1) and coronary artery disease (#1 90% stenosis, #2 90% stenosis, #4 50% stenosis). Medical history included diabetes mellitus treated with diet and an oral hypoglycaemic until six months earlier, when NPH insulin had been added.

The patient was premedicated with 0.4 mg atropine sulphate and 50 mg hydroxyzine *im*. Monitors included ECG, radial artery and pulmonary artery catheters, pulse oximeter, capnograph, and rectal temperature. Anaesthesia was induced with 15 mg diazepam, 0.5 mg fentanyl and 8 mg vecuronium bromide, and maintained with 100% oxygen, 40 µg·kg⁻¹ fentanyl and pancuronium. After induction, a transoesophageal echocardiography probe was inserted. Cardiac output and mixed venous oxygen saturation were continuously monitored using Vigilance Monitor Model VGS (Baxter USA). Anaesthesia time was 615 min and operation time was 480 min.

Cardiopulmonary bypass time was 130 min. Rewarming was accomplished over 30 min using high pump flows with subsequent weaning from CPB at a rectal temperature of 37.0°C. At 10 min after CPB, SABP was 110 mmHg, heart rate was 96 beats·min⁻¹, CVP was 8 mmHg, PAP was 25/12 mmHg, PCWP was 9 mmHg, CO was 3.4 L·min⁻¹, mixed venous oxygen saturation was 84 % under continuous infusion of 0.1 µg·kg⁻¹·min⁻¹ adrenaline, 10 µg·kg⁻¹·min⁻¹ dopamine and dobutamine. About 20 min after CPB, protamine (protamine sulfate, 10 mg·ml⁻¹, Shimizu) 170 mg were administered slowly via the central vein. Within 10 min, SABP decreased to 60 mmHg, CVP increased to 24 mmHg, PAP increased to 75/45 mmHg, PCWP increased to 43 mmHg, CO decreased to 1.9 L·min⁻¹. Arterial blood gas analysis revealed; pH 7.29, PaCO₂ 47.2 mmHg, PaO₂ 54.8 mmHg, BE -7, oxygen saturation (SaO₂) 90%. An anaphylactoid reaction was suspected and methylprednisolone (500 mg) was given. Within an hour, the rectal temperature increased to 40°C. Arterial blood gas analysis revealed hypoxaemia, hypercarbia and severe metabolic acidosis (pH 7.13, PaCO₂ 59.9 mmHg, PaO₂ 52.8 mmHg, BE -11 with 100% oxygen). The CPK concentration was 4369 u·L⁻¹. Serum myoglobin and urine myoglobin levels were 468 ng·ml⁻¹ and 885 ng·ml⁻¹. Malignant hyperthermia was suspected. Dantrolene

sodium, 200 mg, was given and surface cooling using alcohol was commenced. About 60 min after dantrolene, rectal temperature decreased to 37.5°C and breathing 100% oxygen, PaO₂ returned to 180 mmHg and PaCO₂ to 41 mmHg. At postoperative day one, CPK levels reduced to 1194 u·L⁻¹. Postoperatively, a dantrolene infusion of 20 mg·hr⁻¹ was administered for 24 hr in the intensive care units. At the fifth postoperative day, tracheostomy was done for long term ventilatory support.

Discussion

In these two patients, hyperthermia developed after recovery from protamine induced hypotension. Myoglobinuria, high serum myoglobin concentration, high rectal temperature, increased CPK concentration, hypoxaemia, metabolic acidosis and hypercapnia suggested the possibility of MH, but we could not confirm the diagnosis. There are many possible causes of hyperthermia, hypoxaemia, hypercapnia and increase of enzyme concentrations in patients after cardiac surgery. Catastrophic reactions to protamine are rare (0.13%)³ but in patients with diabetes mellitus treated with NPH insulin which contains protamine, the incidence is 50 times greater than in the nondiabetic population.² In our cases, the patient had been treated with NPH insulin (10–20 U·day⁻¹) and appeared to have developed allergy to protamine before surgery. Serum tryptase is an indicator of mast cell involvement and anaphylactoid reaction.^{4,5} The increased serum tryptase concentration observed one hour after the protamine injection in this case, together with hypotension, hypovolaemia, pulmonary hypertension, hypoxaemia and hypercarbia suggested an anaphylactoid reaction. In the second case, serum tryptase concentration was not measured, so we could not confirm the diagnosis of anaphylactoid reaction to protamine. These patients developed hyperthermia after recovery from protamine induced hypotension.

Malignant hyperthermia is a genetically predisposed, potentially fatal disorder triggered by anaesthetic agents.⁶ Early diagnosis and treatment of MH is necessary, but when the patient is undergoing CPB, MH may be difficult to recognize. In our first case, hyperthermia developed after the administration of lidocaine. Previously, it was believed that amide local anaesthetics, such as lidocaine, could trigger MH⁷ but they do not. An infusion of lidocaine 2% was started after CPB for the treatment of arrhythmia and lidocaine 1% had been injected several times for local anaesthesia in cardiac catheterization before surgery when the patient's condition was stable. In the first case, sevoflurane 1% was administered for about 20

min before CPB to control hypertension. In the second case, sevoflurane 1% was administered for two hours before CPB. There are some reports of sevoflurane induced MH.^{8,9} In both of the present cases, sevoflurane was administered before CPB, so that sevoflurane is unlikely to have been a trigger of hyperthermia in either case. Diagnosis of MH during and after CPB may be difficult because of the hypermetabolic state induced by extracorporeal circulation. Rewarming following hypothermic CPB may produce conditions similar to MH episodes in the postoperative period with rapid increases in temperature and carbon dioxide production.^{10,11} It is not possible to determine whether these cases are of MH or rewarming following hypothermic CPB. Since muscle biopsy testing was not undertaken, clinical features must be used to assess the likelihood of an MH episodes. Hypercapnia may be attributed to inadequate ventilation. Elevation of CPK concentration and myoglobinuria may accompany cardiac surgery. Although there are several possibilities for hyperthermia and increased serum enzyme concentration, the combination of hyperthermia, acidosis, myoglobinuria, elevated CPK, and temperature reduction after dantrolene support the clinical diagnosis of MH. Dantrolene, a directly acting skeletal muscle relaxant, interrupts skeletal muscle hypermetabolism by uncoupling calcium transport from myofibrilla contraction. Administration of dantrolene early in an MH episode generally halts the progression of this syndrome.¹²

In conclusion, we report two cases of hyperthermia which developed after recovery from anaphylactoid reactions to protamine during cardiac surgery. Although the diagnosis of MH could not be confirmed, dantrolene was effective in reducing the high rectal temperatures.

References

- 1 Takenoshita M, Sugiyama M, Okuno Y, Inagaki Y, Yoshiya I, Shimazaki Y. Anaphylactoid reaction to protamine confirmed by plasma tryptase in a diabetic patient during open heart surgery. *Anesthesiology* 1996; 84: 233-5.
- 2 Levy JH, Zaidan JR, Faraj B. Prospective evaluation of risk of protamine reactions in patients with NPH insulin-dependent diabetics. *Anesth Analg* 1986; 65: 739-42.
- 3 Stewart WJ, McSweeney SM, Kellett MA, Faxon DP, Ryan TJ. Increased risk of severe protamine reactions in NPH insulin-dependent diabetics undergoing cardiac catheterization. *Circulation* 1984; 70: 788-92.
- 4 Schwartz LB, Yunginger JW, Miller J, Bokhari R, Dull D. Time course of appearance and disappearance of human mast cell tryptase in the circulation after anaphylaxis. *J Clin Invest* 1989; 83: 1551-5.
- 5 Laroche D, Vergnaud M-C, Sillard B, Soufarapis H, Bricard H. Biochemical markers of anaphylactoid reactions to drugs. *Anesthesiology* 1991; 75: 945-9.
- 6 Britt BA. Recent advances in malignant hyperthermia. *Anesth Analg* 1972; 51: 841-50.
- 7 Gronert GA. Malignant hyperthermia *Anesthesiology* 1980; 53: 395-423.
- 8 Ducart A, Adnet P, Renaud B, Riou B, Krivosic-Horber R. Malignant hyperthermia during sevoflurane administration *Anesth Analg* 1995; 80: 609-11.
- 9 Ochiai R, Toyoda Y, Nishio I, *et al.* Possible association of malignant hyperthermia with sevoflurane anesthesia. *Anesth Analg* 1992; 74: 616-8.
- 10 Allen GC, Cattran CB. Rewarming following hypothermic cardiopulmonary bypass in the malignant hyperthermia-susceptible patient: implications for diagnosis and perioperative management *Can J Anaesth* 1989; 36: 81-5.
- 11 Sladen RN. Temperature and ventilation after hypothermic cardiopulmonary bypass. *Anesth Analg* 1985; 64: 816-20.
- 12 Kolb ME, Horne ML, Martz R. Dantrolene in human malignant hyperthermia. *Anesthesiology* 1982; 56: 254-62.