Successful early application of extracorporeal membrane oxygenation to support cardiopulmonary resuscitation for a patient suffering from severe malignant hyperthermia and cardiac arrest -a case report-

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Malignant hyperthermia (MH) may lead to metabolic crisis of skeletal muscle in susceptible individuals following exposure to triggering agents such as volatile anesthetics or depolarizing muscle relaxants. MH is a rare and a potentially lethal disease, which can lead to cardiac arrest. We report a case of severe MH, in which the rapidly evolving signs of hypermetabolism eventually resulted in cardiac arrest. Despite conventional treatments following cardiopulmonary resuscitation, the patient's vital signs did not improve. Therefore, we applied extracorporeal membrane oxygenation for providing hemodynamic support.

Key Words: Dantrolene, Desflurane, Extracorporeal membrane oxygenation, Malignant hyperthermia.
anesthetics (sevoflurane, desflurane), the face of MH is changing from fulminant to more insidious [4]. Nevertheless, MH can still be a life-threatening disease which causes cardiac arrest, especially since sudden cardiac arrest still has a low survival rate, despite the introduction of cardiopulmonary resuscitation (CPR) [8].

We report a case of severe MH, in which the rapidly evolving signs of hypermetabolism eventually resulted in cardiac arrest. Despite conventional treatments following CPR, the patient’s vital signs did not improve. Therefore, we applied extracorporeal membrane oxygenation (ECMO) for providing hemodynamic support.

**Case Report**

A 56-year-old man (height 162.3 cm, body weight 58.8 kg) presented for emergency surgery of transurethral resection for bladder tumor due to bleeding associated with bladder cancer. His medical history included hypertension, stage IV chronic kidney disease and benign prostatic hypertrophy. There was no family history of MH, and he had not been anesthetized previously.

Preoperatively, the patient had recurrent hematuria and a laboratory test revealed a hemoglobin (Hb) concentration of 4.2 g/dl. The patient received transfusion of 2 pints packed red blood cells, and the Hb concentration increased to 6.8 g/dl. Glycopyrrolate 0.2 mg was injected intramuscularly as a premedication. In the operating room, an electrocardiogram, non-invasive blood pressure measurement, and pulse oximetry were performed, and the bispectral index (BIS VISTA®, Aspect Medical Systems, Inc., Norwood, MA, USA) sensor was attached onto his forehead. The patient was preoxygenated for 2 minutes, and anesthesia was induced using 120 mg of 1% propofol and 12 mg cisatracurium. After intubation, anesthesia was maintained using desflurane in a total fresh gas flow of 3 L/min of an air/oxygen mixture via an active humidified circuit with a heated wire in the inspiratory limb. In addition, effect-site target-controlled infusion of remifentanil was adjusted between 2.5 and 4.0 ng/ml. After consultation with the surgeon for considering the possibility of a radical cystectomy, catheters were placed in the right radial artery and right internal jugular vein as a precaution.

Baseline measurements at onset of surgery were oxygen saturation (SpO2) 99%, arterial blood pressure (ABP) 115/50 mmHg, heart rate (HR) 90 bpm, end-tidal CO2 (ETCO2) 37 mmHg, and esophageal temperature 36.5°C. Approximately 120 minutes after anesthesia induction, ABP was not checked. On inspection, right arm rigidity and lower extremity rigidity were detected. Then cannulation of the right brachial artery was performed. At that time, his ABP dropped to 95/45 mmHg and ETCO2 rose to 54 mmHg. Repeated bolus injections of phenylephrine had a short duration, and hence a continuous infusion of norepinephrine was administered (0.05 μg/kg/min). The esophageal tem-

| Time after induction (h' min") | POD #1 | POD #3 | POD #7 | POD #10 | POD #2* |
|-------------------------------|--------|--------|--------|---------|---------|
| ABP (mmHg)                    | 115/50 | 95/45  | 51/28  | 37/15   | 28/15   |
| HR (beats/min)                | 90     | 87     | 121    | 64      | 34      |
| Body temperature (°C)         | 36.5   | 36.8   | 38.5   | 36.5    | 36.5    |
| ETCO2 (mmHg)                  | 34     | 34     | 28     | 34      | 37      |
| ABGA                          | 7.032  | 7.039  | 7.342  | 7.406   | 7.366   |
| pH                            | 73.1   | 90.9   | 27.4   | 31.8    | 34.7    |
| PaCO2 (mmHg)                  | 108.8  | 150.8  | 154    | 113.6   | 78.1    |
| PaO2 (mmHg)                   | 19.6   | 24.7   | 10.3   | 20.2    | 20      |
| HCO3−(mmol/L)                 | −10.8  | −6.2   | −18.3  | −3.3    | −4.2    |
| Base excess                    | 143    | 142    | 145    | 143     | 137     |
| Electrolyte Sodium (mmol/L)   | 7.4    | 6.9    | 4.7    | 4.3     | 3.5     |
| Electrolyte Potassium (mmol/L)| 29.9/2.93 | 23.0/2.11 | 30.1/2.39 | 41.3/2.21 |
| BUN/Creatinine (mg/dl)        | 136/42 | 644/183| 467/495| 83/176  |
| AST/ALT (IU/L)                | 2413   | 17779  | 9020   | 969     |
| Serum creatine kinase (IU/L)  | 145.2  | 5072   | 0.308  | 0.308   |
| Troponin I (ng/ml)            | 4.7    | 4.3    | 3.5    | 3.4     |

ETCO2: end-tidal carbon dioxide, ABGA: arterial blood gas analysis, ABP: arterial blood pressure, HR: heart rate, BUN: blood urea nitrogen, AST: aspartate transaminase, ALT: alanine transaminase. *POD #2: post-operative day 2, after the second operation. †Muscle rigidities and increasing minute volume. ‡Before dantrolene sodium administration. §After dantrolene sodium administration and cardiac arrest. ¶After application of extracorporeal membrane oxygenation (ECMO). **After radial cystectomy with an ileal-conduit.

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temperature was maintained at 36.2°C. We proceeded with manual hyperventilation to increase minute ventilation (MV) from 6.2 to 8.4 L/min; however, ETCO₂ remained above 60 mmHg. Bilateral breath sounds were clear without wheezing and the peak airway pressure remained unchanged. At this point, arterial blood gas analysis (ABGA) showed pH 7.032, PaO₂ 108.1 mmHg, PaCO₂ 73.1 mmHg and base excess (BE) −10.8 mmol/L (Table 1). Therefore, we administered sodium bicarbonate 60 mEq. The esophageal temperature increased gradually to 38.6°C. The clinical condition of the patient was suspected to be due to MH, and hence the operation was stopped and dantrolene sodium was prepared. One hundred and fifty minutes after induction of anesthesia, hypotension still persisted and the HR gradually rose to 120 bpm. Next, a continuous vasopressin infusion was initiated and both the breathing circuit and soda lime canister were changed. In spite of increasing MV to 14.5 L/min, the retention of CO₂ intensified, and so the ventilator was replaced. In addition, desflurane was discontinued and it was washed out with 100% O₂ in 18 L/min fresh gas over a period of 10 minutes. At the same time, anesthesia was switched to 2% propofol (Fresofol 2%\textsuperscript{TM}, Fresenius Kabi, Graz, Austria) and the ventilator was replaced with continuous manual hyperventilation. To cool off the patient, ice packs were placed on the head and chest areas and cold saline irrigation was administered through the Foley catheter and the Levin tube. The ETCO₂ rose to more than 80 mmHg and the SpO₂ gradually decreased to 94%. At this point, the esophageal temperature was 41.7°C and ABGA showed pH 7.039, PaO₂ 150.8 mmHg, PaCO₂ 90.9 mmHg and BE −6.2 mmol/L. Also, serum potassium and lactic acid levels were 7.37 mmol/L and 11.7 mmol/L, respectively. We administered 10 mg furosemide and a regular insulin infusion (10 IU/h). Despite administration of norepinephrine and vasopressin, his ABP dropped rapidly to 42/23 mmHg. Epinephrine 100 and 300 μg was then injected intravenously in a sequence. Dantrolene sodium arrived in the operating room and it was reconstituted with sterile water as quickly as possible and administered through the central venous line. The esophageal temperature at this point was 40.5°C, but within the first 1–2 minutes following 60 mg dantrolene sodium, a rapid decrease in the esophageal temperature to 38.5°C and a drop in ETCO₂ to 32 mmHg were noted. However, at this time, the patient suffered a cardiac arrest with asystole. Then, the infusion of dantrolene sodium was stopped and CPR was initiated immediately following chest compression and epinephrine injection. After 15 seconds of CPR, ventricular fibrillation occurred and the patient’s cardiac rhythm converted back to sinus rhythm after a single defibrillation at 200 J. Boluses of epinephrine 1 mg were injected 3 times. Despite infusion of epinephrine and vasopressin, the patient’s ABP did not improve. We made a decision to initiate ECMO for providing hemodynamic support and activated an ECMO team. Peripheral veno-

arterial ECMO was applied by using a size of 15 French (F) arterial cannula (Biomedicus\textsuperscript{®}, Medtronic, Anaheim, CA, USA) and a size of 21 F venous cannula (Biomedicus\textsuperscript{®}, Medtronic, Anaheim, CA, USA) into the right femoral artery and vein, respectively. The initial blood flow rate was 3.5 L/min and the sweep gas-flow rate was 3.0 L/min. The total down time for the first cardiac arrest was 80 minutes until ECMO was ready. After applying ECMO, the patient’s ABP improved. The patient was then transferred to the surgical intensive care unit (SICU) running an ECMO. No more dantrolene sodium was administered, because the rigidity of the right arm and the lower extremity had resolved, and ETCO₂, body temperature and ABGA had improved before the patient was transferred to the SICU. The serum creatine kinase (CK) levels were elevated upon admission (CK 2,413 IU/L) and they continued to be elevated till the following morning (CK 17,779 IU/L). MH clinical grading scale score was 73 (MH rank was 6, ‘Almost certain’). Sixty hours later, the patient was successfully weaned off ECMO. A week later, he was inevitably scheduled for a radical cystectomy with an ileal conduit due to the remnant bladder tumor, persistent hematuria in spite of arterial embolization and bladder necrosis. For general anesthesia, we performed total intravenous anesthesia using 2% propofol. The patient’s vital signs were stable during the operation and the operation was completed uneventfully. After one week, the patient displayed a hemodynamically stable state, was extubated, and then transferred to the general ward.

**Discussion**

To our knowledge, early application of ECMO in severe cases of MH accompanied by cardiac arrest in spite of immediate treatment with dantrolene sodium has not yet been reported. It is important that the prognosis of MH crisis depends on how soon MH is suspected and how rapidly an appropriate treatment is initiated; because the MH crisis including rigidity, muscle breakdown, cardiac involvement and metabolic derangement, is aggravated as time passes. However recently, the clinical manifestation of MH tended to have an insidious and delayed onset rather than a fulminant onset [4]. Therefore, the monitoring of raising ETCO₂, an early sign of MH in the perioperative period, is important for early administration of dantrolene sodium. Administration of triggering agents must be stopped immediately and anesthesia should be continued using intravenous opioids, sedatives, and, if necessary, non-depolarizing muscle relaxants. The vaporizer used for administration of volatile anesthesia should be removed from the anesthesia machine and the patient should be hyperventilated with 100% oxygen at a maximum fresh gas flow, increasing the minute volume by approximately 2–3 fold, while aiming for an ETCO₂ within the normal limits [3]. The gold standard for diagnosis of MH susceptibility is the caf-

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feine-halothane contracture test [5]. But DNA analysis, requiring only a blood sample, could be an alternative to this invasive test [7]. However, as this test is not widely available, the diagnosis of MH can be made by clinical presentation in most cases [5]. Therefore, we diagnosed MH based on clinical symptoms and the clinical symptom ceased on dantrolene administration.

In our case, administration of dantrolene sodium was stopped following 60 mg infusion. Dantrolene sodium has been known to block the Ryanodine receptors (RyRs), and it acts directly on RyR1 and RyR3 isoforms, reduces the channel activation by calmodulin, and reduces the channel sensitivity to Ca$^{2+}$ [9]. Notably dantrolene sodium does not have a negative inotropic effect on the heart because it does not block RyR2, the cardiac RyRs [9]. However, several studies have suggested that dantrolene sodium might inhibit Ca$^{2+}$ release via both RyR1 and RyR2, and it can affect cardiac function under pathophysiologic conditions [10,11]. Due to the possibility of worsening cardiac function in a hemodynamically unstable condition, we stopped the infusion of dantrolene sodium.

ECMO, as a device for cardiac resuscitation, was proposed in the early 1960s, and it has shown encouraging outcomes in patients with cardiac arrest [8]. In addition, ECMO is a therapeutic option increasingly used in the management of patients with refractory cardiorespiratory failure [12]. Advances in technology have allowed such a treatment to be deployed more rapidly, and several descriptive series investigations have shown encouraging outcomes in patients with cardiac arrest [8]. This gradual increase in the use of ECMO has also been described in the Extracorporeal Life Support Organization (ELSO) registry [13]. According to these data, patients with myocarditis and cardiomyopathy benefit more from an ECMO treatment than patients with congenital defects or those who are in cardiogenic shock [13]. In their 2005 CPR guidelines, the American Heart Association recommended the use of ECMO at institutions capable of deploying it rapidly in patients who had an in-hospital cardiac arrest, received good-quality CPR, and were thought to have a reversible cause of their cardiac arrest [14]. Despite the absence of controlled trials, there is principal support for the use of ECMO in the case of CPR in the AHA/ACC guidelines for advanced cardiac life support [15].

In cases of malignant hyperthermia accompanied by cardiac arrest in spite of immediate treatment with dantrolene sodium, early application of ECMO for providing cardiopulmonary support should be considered as a promising therapeutic option in order to improve the probability of patient survival when conventional cardiac arrest management has failed.

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