Case report

Therapeutic hypothermia with immunosuppressive drugs for a comatose renal transplant patient who survived out-of-hospital cardiac arrest

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KEYWORDS
Resuscitation; Ventricular fibrillation; Compromised host

Summary A 31-year-old man suddenly collapsed at work. His colleagues witnessed the event, applied basic life support, and called for an ambulance. After the ambulance arrived, the initial rhythm was confirmed as ventricular fibrillation (VF) and he was defibrillated with an automated external defibrillator. Spontaneous circulation was regained at 8 min after collapse. He was thought to be a good candidate for therapeutic hypothermia because he was comatose and had survived outside hospital VF cardiac arrest due to cardiac etiology. However, he was taking immunosuppressive drugs after undergoing a kidney transplant. We obtained written, informed consent from the patient’s family to start therapeutic hypothermia at 33.5—34.5 °C for 48 h, although he was at high risk for such induction. Serious complications and neurological deficits did not develop and the patient was referred to another hospital on day 42 for implantation with a cardioverter defibrillator.

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Introduction

Randomized controlled trials in Europe and Australia during 2002 revealed that therapeutic mild hypothermia improves the neurological outcomes of patients with ventricular fibrillation (VF) cardiac arrest due to cardiac causes \cite{1,2}. However, therapeutic mild hypothermia was also associated with a relatively high incidence of infectious diseases such as...
sepsis or pneumonia [1,2]. Therefore, immunocompromised hosts can be at high risk in the induction of therapeutic mild hypothermia. We describe a patient on immunosuppressive drugs after renal transplantation who underwent therapeutic mild hypothermia for prolonged coma after VF and who was revived without neurological deficits and serious complications.

Case report

A 31-year-old man suddenly collapsed at work. His colleagues witnessed the event, applied basic life support, and called an ambulance. At the time the ambulance arrived, VF was detected as the initial rhythm and he was defibrillated with an automated external defibrillator. He regained spontaneous circulation at 8 min after collapse and was transported to Osaka Mishima Emergency and Critical Care Center. Upon admission, his vital signs were as follows: blood pressure 102/77 mmHg, regular pulse rate of 102 beats, and Glasgow coma scale 3. Heart sounds were normal but respiratory sounds were coarse on all lung fields. A chest X-ray showed a butterfly shadow. Transthoracic echocardiography demonstrated only slightly impaired left ventricular contractility and coronary angiography was normal. We diagnosed idiopathic VF complicated with pulmonary congestion. We considered him as a good candidate for therapeutic hypothermia but he had undergone a kidney transplant to treat chronic renal failure due to a congenital urinary obstruction so he was taking cyclosporine 75 mg/day, mycophenolate mofetil 1000 mg/day, and methyl-prednisolone 4 mg/day. Consultation with his family physician indicated that therapeutic hypothermia was an option under continued cyclosporine and methyl-prednisolone based on the general consensus regarding invasive therapy for renal transplant patients. The advantages and disadvantages of therapeutic hypothermia were explained to his family, who then provided written, informed consent to the procedure. Thus, the elapsed time between collapse and the start of therapeutic hypothermia was 224 min, which was 210 min from admission. The target body temperature as urine temperature and duration of cooling were 33.5–34.5 °C and 48 h, respectively. Body temperature was decreased and maintained using iced saline gastric lavage and 1 or 2 cooling blankets, and the target temperature was reached at 806 min after admission and 820 min after collapse (Fig. 1). The 48-h cooling period was completed on day 3, and then the patient was warmed at a rate of 1 °C per day (Fig. 1). Body temperature increased beyond 38 °C at day 5 after warming was completed despite preventive ampicillin (2 g/day) being administered for 3 days since day 1 (Fig. 1). We considered this as rebound hyperthermia because an infectious focus was absent although his white blood cell count (WBC) and C-reactive protein (CRP) levels were slightly elevated. Thereafter, his body temperature fell naturally to the normal range (Fig. 1). Sedation was discontinued on day 6. Phenytoin was administered for seizure on day 7 and he recovered consciousness and could answer questions on the same day.

Immunosuppressive drugs included 120 mg/day of cyclosporine delivered transvenously on day 1 and the dose was decreased to 60 mg/day on day 5 as blood levels increased to 540 ng/ml (therapeutic range: 150–300 ng/ml) (Fig. 2). Cyclosporine was returned to the standard dose of 75 mg/day p.o. and 1000 mg/day of mycophenolate mofetil was started on day 6 (Fig. 2). Methyl-prednisolone (500 mg) administered as steroid cover on day 1 was reduced to the standard dose of 4 mg on day 6 (Fig. 2). We also administered 20 mg/day of prednisolone from days 1 to 8 and 10 mg/day on days 9 and 10 (Fig. 2). Although WBC and CRP level had elevated from day 7 to 10 and his body temperature went over 38 °C at day 7 immediately after oral immunosuppressive drugs were started, he was in a good general condition without local symptoms of infectious disease and his body temperature immediately went down to 37.5 °C at day 8, so we continued immunosuppressive drugs without administration of antibiotics (Fig. 2). Thereafter, the patient remained free of serious

![Figure 1](image-url)

**Figure 1** Clinical course of body temperature during therapeutic mild hypothermia.
infection and decreased renal function (Fig. 1). Moreover, cranial magnetic resonance imaging revealed no abnormal intensity. He was referred to another hospital on day 42 for implantation with a cardioverter defibrillator. Stress electrocardiogram and gallium scintigraphy demonstrated normal findings, but electrophysiological study was refused. Therefore, a cardioverter defibrillator was implanted with final diagnosis of the idiopathic ventricular fibrillation.

Discussion

Various adverse events are associated with therapeutic mild hypothermia, and among them, pneumonia and sepsis are the most frequent and serious [1,2]. Patients on immunosuppressive drugs after renal transplantation are presumed to be at high risk from therapeutic mild hypothermia. In fact, one feasibility study of mild hypothermia excluded patients who had undergone renal transplantation [3]. Therefore, our effort to induce mild therapeutic hypothermia for a patient on immunosuppressive drugs presented a significant challenge. We adopted 48 h as the cooling period, 1 °C per day as the warming rate, and 33.5–34.5 °C as the target temperature. Others [4,5] have demonstrated that cooling periods beyond 24 h increase the incidence of complications and current guidelines for therapeutic hypothermia recommend cooling periods of 12–24 h [6]. The warming period should also be modified from 1 °C/day to beyond 8 or 12 h according to two randomized controlled trials [1,2]. Moreover, given that the elapsed time from cardiac arrest to return of spontaneous circulation was relatively short and immunosuppressive treatment had been taken in this case, a cooling time of 12–24 h might be sufficient and safe. That is, shortening the cooling and warming periods might be advantageous. However, an experimental study [7] revealed the efficacy of cooling period beyond 24 h particularly in cases where induction of therapeutic hypothermia was delayed, so 48 h of cooling might be warranted in this case because the time from collapse to initiation of therapeutic hypothermia was as long as 224 min. The ideal cooling duration remains unclear, much less in compromised hosts, so we cannot conclude an adequate cooling duration at present.

The body temperature of our patient briefly fell below the target temperature, which should have been more strictly managed, since such overrun is related to the incidence of complications [4,5]. The Arctic Sun (a surface cooling system) [8], or endovascular [9] or nasopharyngeal [10] cooling systems can be used to strictly control body temperature. Among these systems, the Arctic Sun system should have been considered for our patient because extracorporeal circulation or endovascular cooling might facilitate infection through blood access and the nasopharyngeal cooling system is not widely available in clinical settings.

Only cyclosporine and methyl-prednisolone were continued for immunosuppression during the acute phase and mycophenolate mofetil was restarted at day 6 according to the general consensus regarding invasive therapy for patients after renal transplantation. Adequate types or doses of immunosuppressants during therapeutic mild hypothermia remain unknown and more patients undergoing this procedure will need to be studied.

Another concern is the influence of hypothermia upon the function of the transplanted kidney. Hypothermia is rel-
atively protective towards various organs by reducing their metabolic rates [11]. Thus therapeutic mild hypothermia is unlikely to negatively influence the transplanted kidney. However, further investigation is required to prove this assertion.

Conclusion

We described the case of a 31-year-old man on immunosuppressive drugs after renal transplantation who underwent 48h of mild therapeutic hypothermia for prolonged coma after out-of-hospital cardiac arrest. He survived without neurological deficits and serious complications. Hypothermic therapy might be safe for patients on immunosuppressive drugs, although further investigation and experience are warranted.

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References