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ABSTRACT

***Background*: Therapeutic hypothermia is recommended by international guidelines for patients after out-of-hospital cardiac arrest (OHCA) due to ventricular fibrillation. However, data for patients after in-hospital cardiac arrest (IHCA) are still scarce. Guidelines leave it to the attending physician to decide on the use of hypothermia in IHCA patients.**

***Objective*: To determine the use of therapeutic hypothermia in-hospital cardiac arrest.**

***Design*: Retrospective case series.**

***Setting*: University Hospital of colgne, intensive care units.**

***Subjects*: Seven patients admitted to the intensive care unit after peri-interventional IHCA between January and December 2009.**

***Interventions*: Therapeutic hypothermia was initiated in all patients with a median delay of five hours.**

***Results*: Four out of seven patients (57 %) survived cardiac arrest, but one of these later died due to her primary cause of hospitalisation. The other three patients were discharged without neurological sequelae. There were no serious adverse effects of therapeutic hypothermia.**

***Conclusion:* Therapeutic hypothermia after peri-interventional IHCA is safe and might benefit the patient. This treatment strategy should be taken into consideration until further data are available.**

INTRODUCTION

Two large randomised clinical trials have shown that therapeutic hypothermia improves both survival and neurological outcome in adult patients after out-of-hospital cardiac arrest (OHCA) due to ventricular fibrillation (1,2). As a consequence, therapeutic hypothermia has been recommended by the International Liaison Committee on Resuscitation (ILCOR) for these patients (3,4) and has been implemented into cardiopulmonary resuscitation (CPR) guidelines of the European Resuscitation Council (ERC) (5) and the American Heart Association (AHA) (6).

However, no randomised clinical trial on therapeutic hypothermia after in-hospital cardiac arrest (IHCA) has been published yet. As a matter of fact, it is well known that patients suffering from IHCA differ in many terms from those with OHCA. While acute myocardial infarction represents by far the leading cause of OHCA (7,9), IHCA often develops more sub-acutely, for example from arrhythmia, hypotension, or respiratory insufficiency (10,11). Further known causes are haemorrhage, deterioration of pre-existing disease, or perioperative complications. Patients with IHCA also tend to have more co-morbidities than patients with OHCA. While neurological injury due to cerebral ischaemia is the leading cause of deaths (60–70 %) after OHCA, in IHCA this is the case for 20–30 % (12). Instead, majority of the patients after IHCA seem to die from multiple organ failure (12).

It is, therefore, not possible to simply transfer results and treatment strategies obtained from OHCA studies to IHCA patients. However, there is convincing patho-physiological rationale not to withhold therapeutic hypothermia from IHCA patients (13). This view is clearly encouraged by the recent international CPR guidelines, even though this cannot be regarded as a fully accepted treatment recommendation at this time (5,6).

In 2008, we introduced therapeutic hypothermia on our post-operative intensive care unit (ICU) at the University Hospital of Cologne (*Uniklinik Köln*, Germany). Due to high specialisation with five different ICUs (anaesthesiologic/post-operative, medical, cardiologic, neurologic and paediatric), patients with IHCA in relation to anaesthesiological

or surgical procedures (peri-interventional cardiac arrest) or patients with OHCA due to trauma are treated in this department.

In the present study, we retrospectively analysed all patients who had been treated with therapeutic hypothermia after peri-interventional IHCA in our ICU from January to December 2009.

During the 12 month observation period, seven adult patients with peri-interventional IHCA were treated in the ICU. All were subjected to therapeutic hypothermia (Table 1).

Patient 1: A 62 year old female patient with a stiff total knee arthroplasty was scheduled for mobilisation under general anaesthesia. After induction of anaesthesia with 200 mg propofol, 0.3 mg fentanyl, and 10 mg cis-atracurium, bag-mask ventilation evolved to be difficult. Two attempts to intubate the trachea failed. Pulse oxymetry showed desaturation down to 30 %. Then, asystole occurred and mechanical CPR was initiated immediately. In the meantime, tracheal intubation was established by the attending anaesthesiologist. There was immediate restoration of spontaneous circulation. The patient was admitted to the ICU subsequently, where therapeutic hypothermia was initiated by ice packs, cold air and ice-cold infusions. 32–33 °C body temperature was maintained for 24 hours. During hypothermia, episodes of bradycardia were treated by atropine (0.5 mg), ipratropium bromide (0.25 mg), and dobutamine (5 mg/h). The patient was rewarmed over 12 hours and was extubated without problems. She was discharged in good neurological condition.

Patient 2: A 58 year old female patient was admitted for minimally invasive exstirpation of a left atrial myxoma. After induction of general anaesthesia and intubation of the trachea, a drainage cannula for cardiopulmonary bypass had to be introduced into the superior caval vein. Using Seldinger technique, the right internal jugular vein was punctured and dilated with a nine French sheath. After removal of the sheath, there was a sudden drop of arterial blood pressure. CPR was initiated. Tension pneumothorax was suspected due to decreased breath sounds on the right side. However, pleural puncture was unable to improve the situation. The patient was immediately transferred to the operating theatre and extracorporeal circulation was installed after 15 minutes of continuous CPR. During CPR, the patient had received a cumulative dose of 6 mg epinephrine. Upon surgical exploration, a massive haematothorax on the right side (3500 ml) due to perforation of the internal jugular vein and the subclavian artery was disclosed. After suture of these vessel lesions, exstirpation of the myxoma was performed as intended. Extracorporeal circulation was used for rapidly cooling the patient down to 28 °C. The patient was weaned off the extracorporeal circulation at 34 °C and was transferred haemodynamically stable with no signs of bleeding to the ICU. Body temperature was maintained for 24 hours by means of cold air and ice packs. After rewarming, the patient recovered well. She was discharged from hospital in good neurological condition.

Patient 3: A 58 year old female patient with chronic back pain was treated by the Department of Orthopaedics with single shot epidural anaesthesia using 20 mg ropivacaine, 20 μg sufentanil, and 20 mg triamcinolone. Five minutes after the procedure, the patient was found unconscious with no palpable pulse and dilated pupils. CPR was initiated and the second defibrillation attempt (360 J) was able to restore spontaneous circulation. No drugs were administered during CPR. Cooling was initiated at the scene using ice packs, cold air, and ice-cold infusions. 100 ml, 20 % lipid emulsion were administered due to suspected systemic local anaesthetic intoxication. The patient was admitted to the ICU two hours after cardiac arrest with 34.5 °C body temperature. Hypothermia at 33°C was maintained for 24 hours by cold infusions and cold air. During hypothermia, episodes of bradycardia required treatment with atropine (0.3 mg). Passive rewarming did not result in sufficient rise in body temperature so that a warm air system was used to facilitate rewarming. The further course was uneventful and the patient was discharged from hospital in neurologically good order.

Patient 4: A 69 year old female patient with a seven months history of Th12 vertebral fracture and consecutive spondylodiscitis was treated by corporectomy and anterior instrumentation. Following surgery, the patient was routinely admitted to the ICU. On the first day after surgery, she complained of chest pain and dyspnoea. A chest X-ray was performed, and dislocation of the pleural drainage and complete shadowing of the left hemithorax was disclosed. Before any interventions could be started, the patient became unconscious and developed bradycardia with no palpable pulse. CPR was initiated immediately. Under ongoing CPR, a new pleural drainage was installed yielding in 1700 ml haematothorax. Spontaneous circulation was restored after 45 minutes of CPR. The patient was then transferred to the operating theatre for surgical revision. However, no distinct source of bleeding could be determined. Until the operation, the patient had cooled passively to 34 °C body temperature. Hypothermia was maintained during surgery and postoperatively on the ICU for 24 hours. The patient did not regain consciousness and died of severe sepsis three days after the cardiac arrest.

Table 1
Patient overview

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Demographics	62 years, female	58 years, female	58 years, female	69 years, female	66 years, male	48 years, male	74 years, male
Cause of	Asphyxia	Haemorrhage	Differential diagnoses systemic local anaesthetic intoxication, high spinal anaesthesia	Haemorrhage Haemorrhage Differential diagnoses: myocardial infarction complete AV block	Differential	Respiratory	Haemorrhage
Initial rhythm	Asystole	PEA	VF	PEA	PEA	PEA	PEA
Duration of CPR	1 minute	15 minutes	10 minutes	45 minutes	50 minutes	20 minutes	20 minutes
Cooling device	Ice packs, cold air cold infusions	Extracorporeal circulation, ice packs, cold air	cold, infusions, cold air	Passive cooling, cold infusions	cold infusions, ice packs	cold infusions, ice packs endovascular cooling catheter	cold infusions, ice packs
Temperature	32-33^{0}C	34^{0}C	33^{0}C	34^{0}C	33-34^{0}C	33^{0}C	33-34^{0}C
Delayed to hypthermia (<34^{0}C)	5 hours	30 minutes	2 hours	2 hours	5 hours	21 hours	12 hours
Duration of hypothermia (34^{0}C)	24 hours	24 hours	24 hours	24 hours	Died after 16 hours	36 hours	spontaneous rewarming after 16 hours
Cranial nerve reflexes 24 hrs after cardiac arrest	Good puillary response good corneal reflex	Good pupillary response good corneal reflex	Good pupillary response good corneal reflex	Dilated pupils delayed pupillary response, absent corneal reflex	Good pupillary response absent corneal reflex	Dilated pupils, absent absent pupillary response, absence corneal reflex	Good pupillary, response good corneal reflex
Serum NSE peak after cardiac arrest	15.1μg/l	Not ditermined	56.5μg/l	50.5μg/l	21.6μg/l	326μg/l	23.6μg/l
Final outcome	Good neurologic outcome (CPC 1)	Good neurologic outcome (CPC 1)	Good neurologic outcome (CPC 1)	Died	Died	Died	Died

VF = Ventricular fibrillation; PEA = pulseless electrical activity; NSE = neuron-specific enolase; CPC = cerebral performance category.

Patient 5: A 66 year old male patient was admitted for drainage of an epidural abscess after craniotomy due to cerebellar haemorrhage. During emergence from anaesthesia and turning the patient from the prone to the supine position, he suddenly developed bradycardia and hypotension. CPR was initiated, but was unable to restore spontaneous circulation. Without mechanical CPR, the patient presented a heart rate of 30 bpm, a blood pressure of 35/20 mmHg, and broad QRS complexes. Under ongoing CPR, a transjugular pacemaker was installed. Despite good electrical stimulation, cardiac output did not improve. After 50 minutes of CPR (10 mg epinephrine, 200 mmol $NaHCO_3$, 3 × 200 J defibrillation attempts), we discussed discontinuation of therapy. At this time, however, heart rate and blood pressure suddenly increased and the patient showed spontaneous breathing. Hypothermia was induced on the ICU by ice-cold infusions and ice packs. Catecholamine therapy was necessary for stabilisation of haemodynamics. 24 hours after the cardiac arrest, under ongoing hypothermia therapy, the patient developed ventricular fibrillation and died after unsuccessful CPR efforts.

Patient 6: A 48 year old male patient was surgically treated for submandibular abscess. The patient was morbidly obese (263 kg body weight, 196 cm, BMI 68 kg/m^2) and reported smoking fifty cigarettes and drinking two beer and 300 ml vodka each day. Before induction of anaesthesia, a peripheral oxygen saturation of 86 % was noted. Induction of anaesthesia was uneventful, blind nasal intubation was performed by an experienced anaesthesiologist. After surgery, the patient was extubated and transferred to the ICU for further monitoring. He complained of dyspnoea despite peripheral oxygen saturation of 98 % (nasal oxygen insufflation 2 l/min). There were no signs of bleeding or stridor. In the evening, four hours after surgery, he suddenly became unconscious and showed bradycardia and hypotension. CPR was initiated. Bag-mask ventilation as well as tracheal intubation attempts failed. With a laryngeal mask airway, minimal ventilation could be established. Emergency tracheotomy was performed leading to immediate normalisation of heart rate and blood pressure (20 minutes of CPR, 10 mg epinephrine, 1 mg atropine). Immediately after restoration of spontaneous circulation, the patient was cooled with cold infusions and ice packs. However, these means proved unsuccessful in lowering the body temperature. Therefore, on the next day, an endovascular cooling catheter was introduced into the femoral vein. Now, body temperature was successfully lowered to 33 °C and hypothermia was maintained for 36 hours. The patient presented with instable circulation and complete absence of cranial nerve reflexes. Three days after the cardiac arrest, physical examination revealed clinical brain death, yet final diagnosis was impossible due to residual midazolam blood levels. On the next day, the patient died after several episodes of ventricular tachycardia and ventricular fibrillation.

Patient 7: A 74 year old female patient with sepsis due to L3–5 spondylodiscitis was subjected to percutaneous dilation tracheostomy on the ICU under analgosedation. During the procedure, suddenly massive bleeding at the puncture site developed leading to severe hypotension. CPR was initiated. A maxillofacial consultant was able to identify an abnormally medially positioned internal jugular vein as the source of bleeding. He ligated the vessel immediately under resuscitation conditions. Spontaneous circulation was restored after 20 min of CPR and a total dose of 5 mg epinephrine and 100 mmol $NaHCO_3$. The patient was cooled by cold infusions and ice packs. After approximately 16 hours of hypothermia, it was no longer possible to maintain hypothermia by non-invasive means. The patient was allowed to rewarm spontaneously to 35 °C. In the further course, the patient recovered to a state of reduced vigilance which was comparable to that before cardiac arrest and CPR. She finally died 16 days later in multiorgan failure due to her primary cause of hospitalisation.

DISCUSSION

This study for the first time presents clinical data on the application of therapeutic hypothermia in patients resuscitated from peri-interventional IHCA. During the observation period of this study, seven patients were treated after peri-interventional IHCA with therapeutic hypothermia. Three patients survived without any neurological sequelae. In addition, one patient initially recovered well from cardiac arrest before she died from a non-cardiac arrest related cause of death.

Two randomised clinical trials have shown a benefit from therapeutic hypothermia for comatose adult patients after OHCA due to ventricular fibrillation (1,2). However, data for patients after IHCA are still scarce. Several observational studies report increasing use of therapeutic hypothermia in patients after ICHA (14-18). The studies by Rittenberger *et al*. and Arrich *et al*. also present outcome variables (14,17). In both studies, survival of patients after IHCA was not improved (neither deteriorated) by therapeutic hypothermia. However, the significance of these studies suffers from their limited number of patients (n = 101 and n = 40, respectively) and particularly from not clearly (i.e. prospectively) defined inclusion criteria for therapeutic hypothermia. Wolfrum *et al*. currently perform a randomised clinical trial of therapeutic hypothermia after IHCA (n = 440), patient recruitment is still ongoing (19).

Despite this limited evidence, we have decided to introduce therapeutic hypothermia after IHCA on our ICU. Due to high specialisation with five different

ICUs at our university hospital, we are confronted with the very distinct sub-group of patients after peri-interventional IHCA. Since cardiac arrest in these cases occurs during medical procedures, there is usually minimal delay to the initiation of CPR. On the other hand, the causes of cardiac arrest are often particularly serious and life-threatening, for example severe iatrogenic haemorrhage. This study shows that therapeutic hypothermia is feasible after peri-interventional IHCA. However, we cannot decide conclusively whether therapeutic hypothermia affected outcome in our patients.

The largest body of data on IHCA is currently provided by the National Registry of Cardiopulmonary Resuscitation (NRCPR) of the American Heart Association (11). Covering more than 86 000 patients with IHCA, Peberdy *et al*. report an overall survival to hospital discharge of 18 %. Two European multi-center studies on IHCA report similar survival rates of 17 and 18 %, respectively (20,21).

Several factors are known to influence survival of patients with IHCA. Similar to OHCA, age of the patient, initial ECG rhythm, and duration of CPR clearly affect the outcome (20-25). Furthermore, the time of the day when cardiac arrest occurred plays a role in IHCA, with better outcomes reported during the office hours (11,20,22,23,26,27). Arrests occurring in critical care areas show better outcome as compared to general wards (20,21,23,26,28,29). Our study shows an initial survival rate of 57 % (four out of seven) and therefore confirms these data.

One might argue that Patient 1 would have had a particularly good prognosis even without therapeutic hypothermia because of the short cardiac arrest time. However, we feel that this can not be an argument to withhold therapeutic hypothermia in such cases, especially as we have neither specific clinical parameters nor other markers to guide the decision to apply or withhold therapeutic hypothermia. Application of therapeutic hypothermia is rarely associated with severe complications. Two of our patients developed bradycardia during hypothermia, but this could be well treated with vagolytic or β-adrenergic agents. There might be an increased risk of infection or bleeding during hypothermia, but this could not be confirmed by the two large randomised clinical trials mentioned above (1,2). Neither did a more recent observational study in 462 cardiac arrest patients treated with therapeutic hypothermia find any risks for patient safety (14).

In nearly all of our cases, hypothermia was induced and maintained by non-invasive means such as cold infusions, ice packs and cold air. Additional ice-water gastric lavage could have been used for further facilitating hypothermia induction (30), but this technique had not been established in our ICU at the time of the study. Due to the distinct subgroup of peri-interventional IHCA in our study, median delay to hypothermia (defined as body temperature < 34 °C was five hours after onset of cardiac arrest. This is even faster than in the HACA trial where the median delay was eight hours (2). Patient two was initially cooled by extracorporeal circulation, reaching hypothermia after only 30 minutes. However, this approach is surely not practicable for the vast majority of patients. Non-invasive cooling failed to successfully induce hypothermia only in Patient 6. This patient suffered from morbid obesity with a body mass index of 68 kg / m^2. Here, hypothermia was finally induced after installation of an endovascular cooling catheter. However, reaching the goal temperature was possible only after almost one day. Experimental data suggest that hypothermia is the more effective the earlier it is achieved after the onset of cardiac arrest and return of spontaneous circulation, respectively (31,32). It is therefore tempting to speculate whether fatal outcome could have been avoided in this presented case, if effective cooling had been established earlier. Peri-interventional cases of IHCA provide the special opportunity to induce therapeutic hypothermia with minimal delay; this goal should be pursued vigorously.

In conclusion, therapeutic hypothermia is a promising therapeutic strategy in patients after IHCA. Our study, for the first time, presents data on the subgroup of patients with peri-interventional IHCA, that is, in-hospital cardiac arrest during medical procedures. As compared to other IHCA cases, forexample on general wards, which often occur unwitnessed, peri-interventional IHCA is associated with immediate CPR and rapid induction of therapeutic hypothermia. Our data indicate that therapeutic hypothermia after peri-interventional IHCA seems to be safe. Further clinical trials are needed to support that hypothermia is able to improve these patients' outcome. Until such data is available, therapeutic hypothermia should be taken into consideration in suitable patients after IHCA, particularly in such a critical setting like peri-interventional cardiac arrest. All treatment options available have to be discussed and used at low threshold to the benefit of the patient.

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