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Therapeutic hypothermia after out-of-hospital cardiac arrest: experiences with patients treated with percutaneous coronary intervention and cardiogenic shock

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Background: Therapeutic hypothermia has been shown to increase survival after out-of-hospital cardiac arrest (OHCA). The trials documenting such benefit excluded patients with cardiogenic shock and only a few patients were treated with percutaneous coronary intervention prior to admission to an intensive care unit (ICU). We use therapeutic hypothermia whenever cardiac arrest patients do not wake up immediately after return of spontaneous circulation.
Methods: This paper reports the outcome of 50 OHCA patients with ventricular fibrillation admitted to a tertiary referral hospital for immediate coronary angiography and percutaneous coronary intervention when indicated. Patients were treated with intra-aortic balloon counterpulsation (IABP) (23 of 50 patients) if indicated. All patients who were still comatose were treated with therapeutic hypothermia at 32–34 °C for 24 h before rewarming. The end-points were survival and cerebral performance category (CPC: 1, best; 5, dead) after 6 months.
Results: Forty-one patients (82%) survived until 6 months. Thirty-four patients (68%) were in CPC 1 or 2, and seven (14%) were in CPC 3. Of the 23 patients treated with IABP, 14 (61%) survived with CPC 1 or 2. In patients not treated with IABP, 20 patients (74%) survived with CPC 1 or 2. Forty patients (80%) developed myocardial infarction. Percutaneous coronary intervention was performed in 36 patients (72%).
Conclusion: In OHCA survivors who reached our hospital, the survival rate was high and the neurological outcome acceptable. Our results indicate that the use of therapeutic hypothermia is justified even in haemodynamically unstable patients and those treated with percutaneous coronary intervention.

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Key words: cardiac arrest; intra-aortic balloon counterpulsation; percutaneous coronary intervention; therapeutic hypothermia.

Survival after out-of-hospital cardiac arrest (OHCA) is low (1–3), but, recently, two randomized studies have shown better outcome by the induction of mild hypothermia after cardiac arrest (4, 5). These results prompted the International Liaison Committee on Resuscitation (ILCOR) to issue guidelines on the use of therapeutic hypothermia (TH) following OHCA, when the initial rhythm is ventricular fibrillation (VF) (6).

However, the inclusion criteria of the two randomized studies were fairly strict, and patients with persistent hypotension (mean arterial pressure < 60 mmHg) (5) or systolic pressure < 90 mmHg (4) were excluded. As a consequence, the ILCOR advisory statement (6) only recommends TH after cardiac arrest for patients without 'severe cardiogenic shock' until further data become available.

In addition, of the patients included, only a few had been treated with new therapeutic options such as primary percutaneous coronary intervention (PCI) (4, 5). There is a priori no reason to believe that TH should not protect the brain in haemodynamically unstable patients after cardiac arrest, and we decided to include these patients in our hypothermia protocol.

Acute coronary angiography, followed by PCI when indicated, is routine treatment for most patients with an acute coronary syndrome. Anticoagulants in combination with inhibitors of blood platelet aggregation are routinely administered during PCI procedures, and the extent to which these drugs increase the risk of spontaneous bleeding when combined with hypothermia has not been investigated.

This paper reports the treatment, outcome and follow-up of 50 consecutive patients admitted to our hospital after OHCA caused by VF.

Materials and methods

Patients and setting

Rikshospitalet is a tertiary hospital in Norway, and the only centre offering 24-h PCI in a population of about 1 200 000. Paramedic teams resuscitate patients with OHCA. Twenty-eight of these patients were brought to a local hospital where a cardiologist decided whether or not to transfer them for primary or facilitated PCI; the other 22 patients were brought directly to Rikshospitalet. The patients' pre-arrest conditions are listed in Table 1.

This study is a retrospective investigation of the results of a newly adopted change of practice in our department. Patients were not randomized. Only routinely collected clinical data were used. The Data Inspectorate of Norway approved the collection of the data and the submission of the data to a Nordic database.

Interventions

Since April 2003, TH has been our standard treatment for OHCA survivors not regaining consciousness after cardiac arrest. Fifty-three consecutive patients with out-of-hospital VF were treated with TH between April 2003 and April 2005. Three of these were foreigners and were excluded from this report because of a lack of follow-up data. Patients suffering in-hospital cardiac arrest or OHCA with causes other than VF were also treated with TH, but are not included in this report.

Patients were brought directly from the ambulance to the angiography laboratory for immediate coronary angiography and primary or facilitated (following primary thrombolysis) PCI if indicated and feasible. If patients were haemodynamically unstable, an intra-aortic balloon counterpulsation (IABP) was established. All patients who had PCI were given aspirin, clopidogrel and (most of them) abciximab according to our PCI protocol. Following coronary intervention, patients were brought to the intensive care unit (ICU) and active cooling was implemented by means of cold infusions and a water-based external cooling system (Thermowrap®, Allon, Or Akiva, Israel). Most patients were monitored invasively, 33 of 50 with a pulmonary artery catheter.

Following communication about our cooling therapy with collaborating hospitals and emergency services, cooling by means of cold infusions and ice-packs was often started during transport. In the ICU, patients were sedated with continuous infusions of midazolam and fentanyl, paralysed with continuous infusion of cisatracurium and kept at the target temperature of 32–34 °C for 24 h. There was then a slow rewarming to 36 °C over approximately 6 h. Sedation and muscle relaxant were discontinued when normothermia was reached. During the ICU stay, most patients required an infusion of insulin to achieve blood sugar levels between 4 and 7 mmol/l.

Table 1

Patient characteristics: pre-morbid conditions.

	n (%)
Male sex	44 (88%)
Diabetes mellitus	4 (8%)
Myocardial infarction	7 (14%)
Coronary artery disease	11 (22%)
Hypertension	9 (18%)
Pulmonary disease	3 (6%)
Neurological disease	2 (4%)
Malignancy	5 (10%)
Congestive heart failure	6 (12%)
Alcoholism	1 (2%)

Outcome

The primary end-points were defined as survival and neurological outcome after 6 months following admission. The National Population Registry of Norway was used to find survivors and the date of death of the non-survivors. Survivors were contacted by telephone by one of the investigators (JH) and questioned about their daily life activities, experience of memory, psychological problems and capabilities to resume previous work. Medical reports from the local hospitals were requested when needed in order to classify the outcome of the patients. Patients were then categorized to cerebral performance categories (CPCs) 1–5 (5, 7). Patients were routinely scored at the ICU using the simplified acute physiology score "(SAPS)" (8) and global registry of acute coronary events (GRACE) score (9) for cardiological patients.

Statistics

Because of the small sample size, we decided to use mostly descriptive statistics. Proportions are expressed as percentages, continuous data are expressed as means ± standard deviation, and time

intervals and ordinal data are expressed as medians (range). For statistical calculations of the differences between the subgroups in Tables 2 and 3, the Mann–Whitney test and chi-squared test were used, employing the statistical program SPSS 12.1 (SPSS Inc., Chicago, IL).

Results

The mean age was 57.2 ± 12.4 years. The proportion of men was 88%. The median SAPS II score was 53 (minimum–maximum, 16–88) (8), and the median GRACE score was 218 (92–326) (9). In 47 of the 50 cases, the cardiac arrest was witnessed. Bystander cardiopulmonary resuscitation (CPR) was given in 80% of cases. The median interval from the emergency call to the arrival of the ambulance was 7.0 min (0–35 min), and the median time to return of spontaneous circulation (ROSC) was 15 min (4–45 min). The time from arrest until the start of cooling was 150 min. Coronary angiography was performed in 98% of patients and was followed by acute PCI in 72% of patients in this series. Eleven patients received thrombolytic therapy at the referring hospital. Eighty per cent of patients developed enzymatic signs of myocardial infarction, and 23 (46%) had an IABP inserted. Twenty of these received IABP at the angiography laboratory, two at the ICU and one at a local hospital prior to transport.

At 6 months of follow-up, there were 41 survivors (82%). Their neurological status is shown in Table 3. There were no patients in CPC 4. Three patients died of probable cardiac causes (at 2, 5 and 14 days) and five died of probable cerebral causes (at 3, 3, 7, 13 and 26 days) within 1 month, and the last patient died after 9 months of an unknown cause. The neurological status of this patient was unknown at 6 months and, in our material, the patient is counted as dead.

The use of IABP did not influence significantly the proportion of patients with CPC 1 and 2 (Table 2). The maximum levels of troponin-I and creatine kinase MB isoenzyme (CKMB) mass were higher in the IABP group, and a greater proportion of IABP-treated patients received adrenergic drugs. In the IABP group, 48% of patients received levosimendan, compared with 11% in the group not treated with IABP. When comparing the group with a good outcome (CPC 1 or 2) with that with an unfavourable outcome

Table 2

Patients treated with and without intra-aortic balloon counterpulsation (IABP).

	IABP ($n = 23$)	No IABP ($n = 27$)	*P* value
Witnessed arrest†	22 (96)	25 (93)	0.65
Ambulance arrival (min)*	6 (0–20)	10 (0–35)	0.075
ROSC (min)*	15 (4–30)	15 (5–45)	0.45
Number of defibrillations*	2 (1–20)	2 (1–12)	0.87
Start cooling (min)*	180 (60–480)	150 (30–420)	0.15
Target temperature (min)*	630 (120–1560)	400 (120–1240)	0.15
SAPS II*	52 (22–88)	58.5 (16–81)	0.38
PCI†	18 (78)	18 (67)	0.37
PCI of LAD†	15 (65)	8 (30)	0.012
PCI of CX†	3 (13)	2 (7)	0.51
PCI of RCA†	5 (22)	12 (44)	0.09
Myocardial infarction†	21 (91)	19 (70)	0.065
Max troponin-I (μg/l)*	30 (1.8–164)	5.3 (0.06–127)	0.002
Max CKMB mass (μg/l)*	382 (36–500)*	159 (7.8–500)	0.011
Alive at 6 months†	17 (74)	24 (89)	0.17
CPC 1†	12 (52)	16 (59)	0.62
CPC 2†	2 (9)	4 (15)	0.51
CPC 3†	3 (13)	4 (15)	0.86
CPC 5†	6 (26)	3 (11)	0.17
Levosimendan†	11 (48)	3 (11)	0.004
Any adrenergic drug†	20 (87)	17 (63)	0.056
Norepinephrine†	11 (48)	5 (19)	0.03
Dobutamine†	13 (57)	9 (33)	0.10
Dopamine†	3 (13)	5 (19)	0.60

CKMB, creatine kinase MB isoenzyme; CPC, cerebral performance category; CX, circumflex artery; LAD, left anterior descending artery; PCI, percutaneous coronary intervention; SAPS, simplified acute physiology score; RCA, right coronary artery; ROSC, return of spontaneous circulation.
*Median values (minimum–maximum).
†*n* (%).

Table 3

Cerebral performance category (CPC).

	CPC 1 or 2 ($n = 34$)	CPC 3 or 5 ($n = 16$)	*P* value
Age (years)*	56.5 (24–80)	61 (42–82)	0.10
Bystander CPR†	30 (88)	10 (63)	0.04
Ambulance arrival (min)*	6 (0–20)	8.5 (0–35)	0.43
ROSC (min)*	15 (4–40)	20 (10–45)	0.03
Number of defibrillations*	2 (1–8)	4 (1–20)	0.007
Start cooling (min)*	150 (30–420)	180 (60–480)	0.41
Target temperature (min)*	400 (120–1240)	525 (180–1560)	0.31
SAPS II score*	52 (16–81)	63 (42–88)	0.059
GRACE score*	207 (92–267)	248.5 (176–326)	0.01
ICU length of stay (h)*	70 (41–190)	109.5 (30–310)	0.04
PCI†	25 (74)	11 (69)	0.73
PCI RCA†	13 (38)	4 (25)	0.36
PCI CX†	2 (6)	3 (19)	0.16
PCI LAD†	15 (44)	8 (50)	0.70
Myocardial infarction†	26 (77)	14 (88)	0.36
Max troponin-I (μg/l)*	6.8 (0.06–133)	31.5 (0.53–164)	0.025
Max CKMB mass (μg/l)*	180 (7.8–500)	288 (18–500)	0.05
IABP†	14 (41)	9 (56)	0.32
Proportion adrenergic drugs†	23 (68)	14 (88)	0.14
Pulmonary artery catheter†	22 (65)	11 (69)	0.78

CKMB, creatine kinase MB isoenzyme; CPR, cardiopulmonary resuscitation; CX, circumflex artery; GRACE, global registry of acute coronary events; IABP, intra-aortic balloon counterpulsation; ICU, intensive care unit; LAD, left anterior descending artery; PCI, percutaneous coronary intervention; SAPS, simplified acute physiology score; RCA, right coronary artery; ROSC, return of spontaneous circulation.
*Median values (minimum–maximum).
†*n* (%).

(CPC 3 or 5), patients in CPC groups 3 and 5 had less bystander CPR, a longer time to ROSC and received more defibrillations before ROSC (Table 3). The group with an unfavourable outcome also had higher maximum values of CKMB mass and troponin-I.

The systemic vascular resistance index (SVRI) was higher during the first hours of cooling than during the last hours (Table 4). The pulmonary artery catheter was used to monitor SVRI and the cardiac index (CI). There was no significant difference between the IABP group and the non-IABP group with regard to CI (data not shown).

Despite the medication given to inhibit haemostasis (aspirin, clopidogrel and abciximab), no serious bleeding was observed in any patient. Autopsies were not performed, and so it is possible that some bleeding may have occurred.

The median duration of ICU stay at our hospital was 71.5 h (30–310 h). Some patients were transferred to ICUs at local hospitals.

Discussion

Our experience indicates that patients who are haemodynamically unstable after cardiac arrest, i.e. requiring support with IABP and adrenergic drugs, can be safely treated with hypothermia. Our strategy is early revascularization with PCI and a liberal use of IABP to support a failing circulation (10, 11). It is not known whether hypothermia favours the heart as well as the brain with respect to the prevention of reperfusion injury. In animal models, there are data indicating that hypothermia can reduce the extent of the area of myocardial infarction (12, 13), but others have found no evidence for such an effect (14). Whether hypothermia can reduce the size of the infarct and improve myocardial outcome is an interesting question, which should be addressed with prospective controlled studies (15).

Our patients are not representative of all those being brought alive to hospitals after OHCA caused by VF. Only those considered eligible for PCI are brought to us. Previously, an excellent outcome has been shown in OHCA patients receiving primary PCI without TH (16).

A crucial question is whether the IABP and non-IABP groups are fundamentally different. There was no difference in blood pressure on arrival between these groups, but there was a difference in the maximum levels of troponin-I and CKMB mass

Table 4

Cardiac index and systemic vascular resistance index (SVRI) during the first 32 h in the intensive care unit (ICU).

	Cardiac index (l/min/m^2)	SVRI (dyn s/cm^5/m^2)	Central venous oxygen saturation (%)
At 4 h in ICU*	2.1 (1.1–3.8) ($n = 22$)	1990 (1260–4200)	69 (56–85)
At 8 h in ICU*	2.2 (1.6–4.2) ($n = 23$)	2100 (800–3300)	76 (57–85)
At 12 h in ICU*	2.3 (1.0–3.6) ($n = 25$)	1785 (1163–4975)	75.5 (63–87)
At 16 h in ICU*	2.6 (1.1–4.3) ($n = 27$)	1650 (645–3520)	77 (61–83)
At 20 h in ICU*	2.6 (1.8–3.9) ($n = 27$)	1540 (980–3110)	77 (65–86)
At 24 h in ICU*	2.8 (1.7–5.5) ($n = 28$)	1500 (580–2810)	75 (63–85)
At 28 h in ICU*	3.15 (2.0–5.4) ($n = 26$)	1400 (860–2660)	79.5 (65–88)
At 32 h in ICU*	3.3 (2.2–5.7) ($n = 24$)	1250 (740–1860)	74 (55–85)

*Median values (minimum–maximum).

(Table 2), indicating more extensive infarction in IABP-treated patients. Most patients received IABP after becoming circulatory unstable during angiography and PCI.

Another point of discussion is the optimal sequence of interventions. Our patients were referred to our hospital for angiography and PCI, and the main focus was to achieve early revascularization by PCI. However, this strategy may increase the time from cardiac collapse to the implementation of TH. According to the results of a European multicentre study (5), TH is effective even if it is started several hours after cardiac arrest, but it seems reasonable to start cooling as early as possible. Partly as a result of the initiation of cooling during transport to our hospital, the time to the target temperature has decreased recently (J.H. Laake, unpublished data).

We did not observe any serious bleeding complications in these patients. Hypothermia may increase the risk of bleeding and, in combination with clopidogrel and abciximab, it is conceivable that the risk is enhanced. It has been shown that mild hypothermia does not augment abciximab-induced inhibition of platelet aggregation (17). To our knowledge, the combination of hypothermia and clopidogrel has not been investigated.

The proportion of patients alive after 6 months was higher in our material than in both the Australian and European multicentre studies (4, 5). One explanation is that our patients were highly selected and some were perhaps not really comatose (sedated). Possibly, the aggressive revascularization and circulatory support may have contributed to reduce the number of cardiac deaths in this group.

In conclusion, this report supports the contention that patients who are haemodynamically unstable after ROSC and PCI may benefit from TH. TH will probably be a part of CPR in the future (18).

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