THERAPEUTIC HYPOTHERMIA

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Dedication

This book is dedicated to our wives and children, who tolerate our long hours and dedication to our patients and our research. We are also indebted to Peter Safar who inspired so many of us to care for the critically ill and to pursue research in resuscitation.

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PREFACE

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The use of hypothermia for a variety of therapeutic purposes has a long and erratic history. Hippocrates recommended the use of topical cooling to stop bleeding. Fay used cooling of the extremities for patients with tumors in the 1930s. It wasn't until the 1950s, when the effects of hypothermia on systemic oxygen metabolism became better defined, that systemic hypothermia became a commonly used modality, particularly for cardiac surgery. Hypothermia was used for *protection* (treatment before the insult) and *preservation* (treatment during the insult) of the heart and entire organism during planned operative ischemia. Shortly thereafter, attempts were made to use hypothermia for *resuscitation* (treatment after the insult) from cardiac arrest and for management of head trauma. At that time, it was felt that moderate hypothermia (28-32°C) was needed. This was difficult to achieve and manage. Multiple complications were noted. Consequently, therapeutic, resuscitative hypothermia lay dormant for many years while mild (32-35°C) to moderate hypothermia became common for many cardiothoracic and neurosurgical procedures.

In the early 1990s, it was found that mild hypothermia, even after cardiac arrest, had benefit for the brain. Similar results were found with head trauma. This lead to a burst of enthusiasm for research into resuscitative hypothermia for a variety of insults, most of which have tissue ischemia as a major component. These laboratory studies demonstrated significant improvement in outcome (survival, neurologic function). In addition, the mechanisms of the beneficial effects of hypothermia were explored in greater detail. It is clear that the effects are not just related to suppression of oxygen demands of tissues. Multiple deleterious chemical cascades are attenuated by hypothermia while beneficial responses are enhanced, or at least decreased to a lesser degree.

These promising laboratory studies have lead to clinical trials for cardiac arrest, head trauma, and stroke. The results for cardiac arrest are extremely encouraging, while those for head trauma are difficult to interpret. Data for stroke are too preliminary. Clinical studies of resuscitative hypothermia for other insults should not be far away.

Peter Safar deserves much of the credit for the use of hypothermia for resuscitation. Even when cardiopulmonary resuscitation was first described as the ABCs (airway, breathing, circulation), Dr. Safar added 'D' for drugs defibrillation, 'E' for EKG (defibrillation), 'F' for fluids, 'G' for gauge (determine and treat the cause of arrest), and *'H' for hypothermia*. With his fellow, Sven Erik Gisvold, he conducted one of the first controlled animal studies utilizing hypothermia as part of a multifaceted therapy after global brain ischemia. He later made the observation that relatively small differences in pre-ischemia brain temperature had significant effects on neurologic outcome. This led to work by Safar's group and others demonstrating that mild hypothermia had beneficial effects after cerebral ischemia. His encouragement led to clinical trials of resuscitative hypothermia, particularly the successful studies of mild hypothermia after cardiac arrest.

This book is designed to review the current state of knowledge regarding therapeutic hypothermia, particularly resuscitative hypothermia, including known mechanisms of action and results from laboratory studies (both mechanistic and outcome) and clinical trials. Cooling methods and potential side effects of hypothermia will be addressed. Unanswered questions and recommendations for future laboratory and clinical research will be presented. This is meant to serve both the researcher interested in therapeutic hypothermia, as well as the clinician interested in the potential use of therapeutic hypothermia in his or her patient population.

Chapter 1

GLOBAL BRAIN ISCHEMIA: ANIMAL STUDIES

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INTRODUCTION

This chapter will describe the background of therapeutic hypothermia with regard to animal models with cardiac arrest or vessel occlusion that led to the recent trials of therapeutic hypothermia after cardiac arrest in humans (1-7). In addition, future potentials of intra-ischemic hypothermia (suspended animation) are discussed.

The history of induced hypothermia began in the 1950s with elective moderate hypothermia (28-32°C) of the brain, introduced under anesthesia, for protection-preservation during brain ischemia needed for surgery on the heart or brain (8, 9) *Protective* hypothermia, induced before cardiac arrest, has to be differentiated from *preservative* hypothermia, induced during cardiac arrest, and from *resuscitative* hypothermia, induced during resuscitation after cardiac arrest. The first animal studies of *resuscitative* hypothermia after cardiac arrest were reported in the 1950s (10, 11). Already in the early 1960s, Peter Safar recommended the use of therapeutic resuscitative hypothermia for humans in his cardiopulmonary-cerebral resuscitation algorithm (12). Resuscitative hypothermia research was then given up for 25 years, because experimental and clinical trials had been complicated by the injurious systemic effects of total body cooling, such as shivering, vasospasm, increased plasma viscosity, increased hematocrit, hypocoagulation, arrhythmias (including ventricular fibrillation when temperatures dropped below 30°C), and lowered resistance to infection during prolonged moderate hypothermia (13-16). At that time, it was felt that moderate hypothermia was required for brain protection.

PROTECTIVE-PRESERVATIVE HYPOTHERMIA

It was in the mid-1980s, when therapeutic hypothermia was re-discovered. Hossmann (17) reported the beneficial effect of mild hypothermia (35-36°C), unintentionally induced before the experiment, on electroencephalogram recovery in cats subjected to one hour of global brain ischemia followed by blood recirculation for 3 h or longer. At the same time, Safar analysed the outcome data of several cardiac arrest dog studies and found that dogs that were mildly hypothermic at the beginning of the experiment had better neurologic outcome than dogs that were normothermic at the beginning of the experiment (18). These observations were followed by controlled, randomized animal studies in various laboratories. In dogs (19), ventricular fibrillation cardiac arrest of 12.5-min no-flow was accompanied by head immersion in iced water (which reduced brain temperature by only 1°C during no flow) and followed by reperfusion cooling with brief cardiopulmonary bypass to 34°C for one hour. Functional and morphologic brain outcome variables were significantly improved in the hypothermic groups four days after the insult. Busto, et al (20), found in a 20-min four-vessel occlusion rat model that small increments of intra-ischemic brain temperature (33, 34, 36, or 39°C) markedly accentuated histopathological changes following 3-day survival, despite severe depletion of brain energy metabolites during ischemia at all temperatures. Siesjö, et al (21, 22), confirmed the beneficial effects of intraischemic hypothermia in a two-vessel occlusion rat model with various durations of ischemia. Intentional lowering of brain temperature from 37 to 35°C markedly reduced, and to 33°C virtually prevented, neuronal necrosis.

Importantly, the benefit of intra-ischemic mild to moderate hypothermia on neuronal death is regarded as long lasting. Green, et al (23), found in a 12.5-min four-vessel occlusion rat model that intra-ischemic hypothermia to 30°C provided protection from behavioural deficits as well as neuronal injury up to 2 months. This long lasting effect of intra-ischemic hypothermia was confirmed by the same group in a 10-min two-vessel occlusion rat model (24), and by Corbett, et al (25), in a 5-min global ischemia gerbil model with brain temperature of 32°C.

The critical finding in these studies was that mild hypothermia (33-35°C), which is safe, could have a significant impact on the brain. Cooling to moderate hypothermia levels, which is difficult to achieve and maintain, and is associated with many extracerebral complications, may not be needed.

RESUSCITATIVE HYPOTHERMIA

The re-discovery of protective-preservative mild to moderate hypothermia in brain ischemia led to widespread research of *resuscitative* mild to moderate hypothermia in several animal models in the 1990s. Safar and colleagues conducted a systematic series of major outcome studies in dogs of prolonged normothermic cardiac arrest followed by *mild resuscitative* cerebral hypothermia (34°C), induced immediately after reperfusion and maintained for 2-3 h (26-28) or 12 h (29). In these studies, controlled ventilation was maintained for 24 h, and intensive care was provided for three to four days, with final evaluation of neurologic outcome and histologic damage in various brain regions. In one study (26), ventricular fibrillation cardiac arrest of 10 min no-flow was reversed by standard external cardiopulmonary resuscitation. Cooling to 34°C for 2 hours was with a combination of head-neck-trunk surface cooling, plus cold fluid loads administered intravenously, intragastrically, and nasopharyngeally; in one group induced at the beginning of resuscitation, in another group induced after restoration of spontaneous circulation. In both hypothermia groups, neurologic recovery in terms of functional outcome and histologic damage was improved compared to normothermic control animals. In the next study (27), ventricular fibrillation cardiac arrest of 12.5 min no-flow was reversed with brief cardiopulmonary bypass. Immediate post-arrest mild (34°C) or moderate (30°C) hypothermia improved functional and morphologic brain outcome, but deep post-arrest hypothermia (15°C) did not improve function and worsened brain histology. In the same model (28), delaying cooling (to 34°C for one hour) until 15 mins after normothermic reperfusion did not improve functional outcome, but did improve histologic damage, compared to normothermia. In the last study of this series (29), after ventricular fibrillation cardiac arrest of 11 min, reversed by brief cardiopulmonary bypass, a combination treatment of mild hypothermia induced by head-neck-surface cooling plus peritoneal instillation of cold Ringer's solution to keep brain temperature 34°C from reperfusion until 12 h, plus cerebral blood flow promotion by induced moderate hypertension until 4 h and colloid induced hemodilution until 12 h, led to the best functional outcome with least histologic damage ever achieved in dogs. Mild cooling in all dog studies caused no cardiovascular or other side effects.

At the same time, resuscitative hypothermia was studied in rodent ischemia models as well. First, Busto, et al (30), reduced hippocampal CA1 injury with 3 h of immediate, but not 30-min delayed, post-ischemic hypothermia to 30°C in a two-vessel occlusion rat model with 10 min of ischemia and survival to 3 days. Buchan, et al (31), reduced hippocampal CA1 injury with 8 h of immediate hypothermia to 34.5°C in gerbils after 5

min of ischemia and survival to 5 days. Coimbra, et al (32), reduced hippocampal CA1 injury after 5 h of immediate hypothermia to 29°C in gerbils with 5 min of ischemia and survival to 7 days. Chopp, et al (33), reduced hippocampal CA1 injury with 2 h of immediate hypothermia to 34°C in a in a two-vessel occlusion rat model after 8 min of ischemia, but not 12 min of ischemia, and survival to 7 days. Carroll, et al (34), progressively reduced hippocampal CA1 injury with immediate hypothermia to 28-32°C for 1/2, 1, 2, 4, and 6 hours in gerbils after 5 min of ischemia, and survival to 4 days; 6 h of hypothermia delayed for 1 hour after reperfusion resulted in protection as well, delayed for 3 h was not effective. In another study by Coimbra, et al (35), hippocampal CA1 injury was reduced with 5 h of hypothermia to 33°C, delayed for 2 h after reperfusion, in a two-vessel occlusion rat model after 10 min of ischemia and survival to 7 days. The same group (36) reduced hippocampal CA1 injury with 5 h of hypothermia to 33°C, delayed for 2, 6, and 12 h, but not for 24 and 36 h, after reperfusion in a two-vessel occlusion rat model after 10 min of ischemia and survival to 7 days; 3.5 h of hypothermia delayed for 2 h after reperfusion was less effective, and 30 min of hypothermia delayed for 2 h after reperfusion was ineffective in the same model.

While the benefit of intra-ischemic hypothermia on preventing neuronal death seems to be long lasting (23, 25), long lasting effects of post-ischemic hypothermia have been more controversial. Dietrich, et al (24), found hippocampal CA1 protection in a in a two-vessel occlusion rat model with 10 min of ischemia and post-arrest immediate hypothermia to 30°C for 4 h, when histologic evaluation was at 3 days after the insult. This protection significantly declined by 7 days and was completely absent by 60 days after the insult.

Colbourne, et al (37-39), conducted a series of studies in gerbils to systematically explore factors affecting neuro-protection of hypothermia. In the first study (37), two experiments were performed. In experiment 1, after 3 min of ischemia, 12 h of hypothermia (32°C), delayed for 1 h after reperfusion, attenuated the early (<10 days) ischemia-induced open-field habituation impairments and substantially reduced hippocampal CA1 necrosis when assessed at 10 and 30 days. Hypothermia was only partially effective after 5 min ischemia. In experiment 2, prolonged hypothermia (32°C) for 24 h, delayed for 1 h after reperfusion, resulted in near total preservation of CA1 neurons at 30 days even after 5 min of ischemia. In the second study, with ischemia of 5 min (38), the observation period was extended to 6 months. Hypothermia (32°C) for 24 h delayed for 1 h after reperfusion, provided substantial CA1 protection at 6 months, although there was less protection than at 1 month. Delaying hypothermia (32°C, 24 h) to 4 h after reperfusion also provided significant protection at 6 months survival,

but significantly less than that found with delaying hypothermia for only 1 h. In the third study, with ischemia of 5 min (39), increasing the duration of hypothermia to 48 h resulted in long lasting protection of neurons at 1 month, even when hypothermia was delayed to 6 h after reperfusion. The long lasting effect of delayed (6 h), prolonged (48 h) hypothermia (32-34°C) on functional and histologic outcome at 1 month was confirmed in rats after 10 min of severe four-vessel occlusion ischemia (40).

The studies described above suggest that minimal delay and longer durations of hypothermia are of critical importance to extend the therapeutic window and to provide permanent protection.

SUSPENDED ANIMATION

About one half of out-of-hospital resuscitation attempts for sudden cardiac death fail to restore heartbeat. Resuscitation of these patients is often given up in the field (41). It is suspected that many of these deaths occur in patients with potential for complete cardiac and cerebral recovery if oxygen delivery could be rapidly restored. For example, initiation of cardiopulmonary bypass before loss of cerebral viability could support the heart until it recovers from stunning or it can be repaired or replaced (42, 43). Cardiopulmonary bypass is not currently available in the field. Therefore preservation of the organism is needed until cardiopulmonary bypass can be initiated in the emergency department. In 1984, Colonel Ronald Bellamy and Professor Peter Safar introduced the concept of "suspended animation for delayed resuscitation", starting with a focus on rapidly exsanguinating trauma patients. Suspended animation is hypothermic and pharmacologic "preservation of the organism during transport and surgical hemostasis, under prolonged controlled clinical death, followed by delayed resuscitation to survival without brain damage" (44).

Preservative hypothermia, induced and reversed with cardiopulmonary bypass before cardiac arrest, has been shown to preserve the organism for up to 15 min by mild hypothermia (33°-36°C) (18), for up to 20 min by moderate hypothermia (28°-32°C) (8), for up to 30 min by deep hypothermia (11°-27°C) (45, 46), and for up to 60 min by profound hypothermia (6°-10°C) (47). To rapidly preserve the brain with mild to moderate hypothermia until more prolonged preservation with profound hypothermic circulatory arrest could be induced and reversed by cardiopulmonary bypass (43, 47, 48), the use of an aortic cold saline flush, via a balloon catheter, was introduced (49-52). In a clinically realistic exsanguination cardiac arrest dog outcome model, the induction of suspended animation by use of cold (4°C) saline aortic flush within the first 5 min of CA, has shown to preserve brain

viability for a cardiac arrest time of 15 min (49), 20 min (50), 30 min (51), 90 min, and, perhaps, 120 min (52).

This approach of preserving the organism with rapidly induced mild to moderate cerebral hypothermia to buy time for transport to the hospital needs to also be explored for normovolemic cardiac arrest patients who are temporarily resistant to conventional resuscitation attempts (42, 44). The clinical scenario might be (modified after [42]): After cardiac arrest, a bystander will initiate basic life support and already induce cooling by exposure; ambulance personnel arrives at the scene and begins advanced life support with hypothermic intravenous infusion with a vasoconstrictor and defibrillation attempts; if restoration of spontaneous circulation can not be achieved within 10 min, the emergency physician will further attempt cooling to achieve systemic temperatures as low as possible to preserve the brain and heart, leaving the patient in cardiac arrest for transport to the emergency department, where cardiopulmonary bypass will be initiated. This suspended animation hypothermic no-flow scenario during transport should be compared with hypothermic low-flow, i.e. continued external cardiac massage after cold aortic flush, and with normothermic low-flow, i.e. conventional external cardiac massage, in a large animal outcome study.

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Chapter 2

GLOBAL CEREBRAL ISCHEMIA: CLINICAL STUDIES

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INTRODUCTION

The single most important clinically relevant cause of global cerebral ischemia is cardiac arrest. Other causes like hanging will not be covered in this chapter. The estimated rate of sudden cardiac arrest lies between 40 to 130 cases per 100,000 people per year in industrialized countries (1,2). Unfortunately full cerebral recovery is still a rare event. Almost 80% of patients who initially are resuscitated from cardiac arrest remain comatose for more than one hour. One year after cardiac arrest only 10-30% of these patients survive with good neurological outcome (3). Current therapy after cardiac arrest has concentrated on resuscitation efforts (4) but until recently no specific therapy for brain resuscitation was available.

The ability to survive anoxic no-flow states is dramatically increased with protective (before the insult) and preservative (during the insult) hypothermia (5). Intraischemic hypothermia for brain protection has been used for several years in combination with particular surgical procedures and circulatory arrest states. Experimental results showed a marked neuroprotective effect of hypothermia also if started after ischemic situations (resuscitation) (6).

NON-RANDOMIZED TRIALS

The first experiences with therapeutic hypothermia after cardiac arrest were gained by Williams and Spencer (7) in 1958; they presented a case series of two children and two middle-aged adults after cardiac arrest (Tables 2-1, 2-2). The cardiac arrests were due to respiratory failure and traumatic injury of the heart. They cooled their patients with a water-cooled mattress to a temperature of 30 to 34°C until the patients regained consciousness (24 to 72 hours). Only one individual had a residual moderate neurological defect (visual impairment). One year later Benson and coworkers (8) compared hypothermia treatment in 12 patients to 7 normothermic controls after in-hospital cardiac arrest in the operating room. All patients had moderate to severe neurological dysfunction prior to cooling. A blanket containing circulating coolant was used to reduce the temperature to 30-32°C until improvement of neurological function was observed. Patients treated with hypothermia had a favorable neurological recovery in 50% compared to 14% in the control group.

Although the target temperature was lower and the method and duration of cooling also differed compared to recent studies, the results of these pioneering studies were similar. However, the once common use of prolonged hypothermia as a therapeutic tool in cardiac arrest patients was largely abandoned until the 1990s. A review of the literature did not give a satisfactory explanation for this change in practice, but inconclusive findings and the rate of cardiovascular problems with temperatures below 30°C might have been important factors (9). Moderate hypothermia (28-32°C) can cause coagulopathy and risk of infection if prolonged. Furthermore, reports on the detrimental effect of hypothermia in experimental stroke might have also intensified this change in practice (10).

Studies in the late 1980s found that mild hypothermia (32-34°C), which should have fewer side effects than moderate hypothermia, provided significant benefit during and after global cerebral ischemia. This led to renewed interest in the efficacy of therapeutic hypothermia after localized and global ischemia in the 1990s and to the first modern clinical studies of mild (32-34°C) therapeutic hypothermia after cardiac arrest.

Bernard and colleagues (11) studied 22 consecutive patients who were comatose after an out-of-hospital cardiac arrest, excluding trauma, drug overdose or stroke. In contrast to the studies of the 1950s all patients were intubated, mechanically ventilated, sedated and relaxed. They cooled the patients by surface cooling with ice packs to 33°C core temperature for 12 hours and compared the results to a group of historical controls fulfilling the same inclusion and exclusion criteria. The target temperature in the hypothermia group was reached within 74 min. Hypothermia caused

reduction of pulse during cooling and an increase in cardiac index and decrease in systemic vascular resistance during rewarming. Compared to historical controls, patients who were cooled for 12 hours had better functional neurological recovery as measured with the Glasgow Outcome Coma Scale (normal/moderate disability: 11 of 22 vs. 3 of 22).

Table 2-1. Non Randomized trials of hypothermia after cardiac arrest - Inclusion

Study	Year	N	Cause of cardiac arrest	VF(%)	ROSC(min)
Williams (7)	1958	4	respiratory and trauma	0	5-14
Benson (8)	1959	12	respiratory		
Bernard (11)	1997	22	all	77	17
Yanagawa (12)	1998	13	all	54	31
Zeiner (13)	2000	27	cardiac	100	21
Nagao (14)	2000	23	all	91	58
Felberg (15)	2001	9	all	78	24
Holzer (16)	2002	19	all	63	21
Bernard (17)	2003	22	Cardiac	63	26

VF, rate of ventricular fibrillation; ROSC, time to return of spontaneous circulation

Table 2-2. Non Randomized trials of hypothermia after cardiac arrest - Cooling

Study	Year	Method	T_{targ}(°C)	t_{targ}(min)	t_{cool}(h)
Williams (7)	1958	Blanket	30-34	n.a.	24-72
Benson (8)	1959	Blanket	31-32	n.a.	3-192
Bernard (11)	1997	ice-pack	33	74	12
Yanagawa (12)	1998	Blanket	33-34	414	48
Zeiner (13)	2000	cold-air	32-34	276	24
Nagao (14)	2000	blood cooling by hemodialysis coil	34	360	72
Felberg (15)	2001	Blanket	32-34	378	24
Holzer (16)	2002	cooling catheter	32-34	95	24
Bernard (17)	2003	ice cold saline; ice	33	~ 30	12

T_{targ}, target temperature, t_{targ}, time until target temperature was reached; t_{cool}, duration of cooling

A combination of water filled cooling blankets and topical alcohol was used by Yanagawa and co-workers (12) to cool cardiac arrest survivors to a core temperature between 33 and 34°C over 48 hours. The patients had to be hemodynamically stable on admission. Cardiac arrest due to trauma or central nervous disease was excluded. One of 15 patients in the historical control group survived without severe disabilities (Glasgow outcome scale 1 and 2) as compared to 3 of 13 patients in the hypothermia group. Among the patients who survived, the duration of no cerebral perfusion was longer in the cooled patients.

Table 2-3. Blood Chemical Values, Hematologic and Coagulation Values, and Arterial Blood Gas Values Uncorrected for Temperature in the 27 patients cooled in the pilot study of Zeiner et al. (13)

	Admission	24 hours	36 hours	P
Potassium, mmol/l	3.8 (3.5 – 3.9)	3.7 (3.6 – 4.0)	4.2 (3.9 – 4.8)	NS
Sodium, mmol/l	139 (138 – 139)	139 (138 – 142)	139 (135 – 142)	NS
Creatinine, µmol/L	122 (113 – 116)	73 (60 – 97)	83 (73 – 88)	<0.05
Urea nitrogen, mmol/L	7.0 (5.8 – 7.9)	5.7 (4.5 – 8.2)	4.8 (3.3 – 6.0)	NS
Total bilirubin, µmol/L	10 (7 – 14)	16 (11 – 34)	15 (7 – 18)	NS
Asparate aminotransferase, U/l	53 (30 – 88)	72 (32 – 98)	55 (24 – 126)	NS
Alanine aminotransferase, U/l	53 (35 – 73)	38 (35 – 58)	37 (26 – 102)	NS
Amylase, U/l	87 (80 – 118)	190 (45 – 397)	187 (48 – 362)	NS
Lipase, U/l	82 (66 – 124)	35 (10 – 234)	33 (10 – 109)	<0.05
Glucose, mmol/L	14.9 (11.8 – 17.8)	6.9 (6.6 – 10.3)	7.1 (6.6 – 10.1)	<0.05
C-reactive protein, mg/dl	0.05 (0.05 – 0.05)	4.59 (3.22 – 5.40)	9.28 (7.54 – 11.80)	<0.05
Lactate, mmol/l	8.6 (6.5 – 11.0)	1.8 (1.0 – 4.7)	1.6 (0.8 – 3.0)	<0.05
White-cell count, G/l	13.4 (11.9 – 14.9)	8.0 (6.4 – 11.4)	7.2 (6.2 – 1.32)	NS
Platelet count, G/l	227 (211 – 300)	157 (118 – 100)	157 (125 – 178)	<0.05
Hemoglobin, g/L	144 (138 – 148)	129 (114 – 133)	120 (114 – 135)	<0.05
Fibrinogen, g/L	3.1 (2.6 – 3.6)	3.5 (3.0 – 3.6)	4.0 (2.4 – 4.4)	NS
Prothrombin Time, s	0.79 (0.51 – 0.99)	0.57 (0.16 – 0.77)	0.54 (0.07 – 0.66)	NS
PH	7.28 (7.19 – 7.35)	7.38 (7.34 – 7.44)	7.40 (7.36 – 7.44)	<0.05
PaO_2, mmHg	335 (212 – 461)	89 (83 – 95)	90 (80 – 102)	<0.05
$PaCO_2$, mmHg	38.5 (33.0 – 45.0)	34.0 (32.0 – 39.0)	38.9 (35.0 – 41.0)	NS
$Pa0_2/FiO_2$	396 (230 – 470)	243 (175 – 275)	225 (175 – 287)	NS
Base excess, mmol/l	-8.30 (-13.40 - -4.70)	-1.55 (-2.70 - -1.00)	0.00 (-2.70 – 1.40)	<0.05

Values are median (95% CI). n=27

Adapted with kind permission from the American Heart Association, Stroke 2000; 31:86-94.

Zeiner and colleagues (13) included 27 comatose patients with ventricular fibrillation (VF) cardiac arrest in a pilot trial (Table 2-3). A water filled blanket and cold air were used to surface cool the patients within 62±33 minutes after cardiac arrest. After 287±145 minutes the target temperature of 33±1°C was reached, which was maintained for an additional 24 hours. The patients were passively rewarmed within 7±4 hours to a temperature above 35°C. The laboratory results did show a decrease in

platelet counts, but this was within the physiologic range. All other values changed as expected after a cardiac arrest of this severity.

After six months good neurological recovery (cerebral performance category score 1 and 2), was achieved by 14 (52%) patients; 2 (7%) had poor neurological recovery and 11 (41%) died before discharge. Compared to historical controls this was a two-fold improvement of outcome.

In a small feasibility study of therapeutic hypothermia after cardiac arrest Felberg (15) and associates cooled 9 patients with water filled cooling blankets, ice bags and cold gastric lavage to 33°C. This temperature was maintained for 24 hours and neurologic function on discharge was recorded. Three of the included patients (33%) had a favorable neurological outcome.

A different approach was used by Nagao and co-workers (14). A combined cardiac and cerebral resuscitation strategy with emergency cardiopulmonary bypass and the intra-aortic balloon pump for patients in cardiac arrest on arrival to the emergency department (40% of included patients) was used in this study. Comatose survivors after successful resuscitation were subjected to hypothermia therapy, which was performed by direct blood cooling (34°C) via a coil over a minimum of 48 (71±49) hours. Thirteen of 23 (57%) patients treated with hypothermia had a favorable neurological recovery. Factors for good neurological outcome were higher cardiac index and oxygen delivery during cooling.

In a recent study, the feasibility of using a central venous cooling catheter was evaluated (16). In these cooling system cold fluid is pumped through a balloon at the tip of the catheter (Icy®, Alsius Corp., Irvine, USA) when inserted in the superior or inferior vena cava. Nineteen comatose patients after witnessed cardiac arrest were included, 16 were of cardiac origin, and in 12 patients the first recorded rhythm was VF. The 'no-flow-time' was 5 (1-11) minutes. Time to return of spontaneous circulation was 21 (15-28) minutes. Within 95 (70-134) minutes after start of cooling the patients were cooled to a temperature below 34°C, which led to a cooling rate of 1.4 (1.0-1.9)°C/h. In patients with VF, favorable neurological recovery at 1 month occurred in 67% of patients; 1 of 3 patients with pulseless electrical activity and 1 of 4 with a primary rhythm of asystole also achieved good neurological recovery.

A very simple and cost effective way of induction of hypothermia was used by Bernard (17) and colleagues. In this study the effectiveness and safety of rapid infusion of large volume, ice-cold intravenous fluid for induction of hypothermia was investigated. With an infusion of 30 ml/kg of ice-cold (4°C) lactated Ringer's solution over 30 minutes, 22 comatose survivors of out-of-hospital cardiac arrest were cooled. This infusion resulted in a rapid decrease in median core temperature from 35.5 to 33.8°C (cooling rate 3.4°C/h). This reduction in temperature was accompanied by