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VARIOUS ASPECTS OF TREATMENT IN CARDIAC ARREST PRIOR TO HOSPITAL ARRIVAL

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VARIOUS ASPECTS OF TREATMENT IN CARDIAC ARREST PRIOR TO HOSPITAL ARRIVAL

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Background and aims:

Out-of-hospital cardiac arrest (OHCA) is a major public health issue, affecting almost 300,000 victims per year in Europe, who have an overall survival rate of about 10 per cent. In general, the current Emergency Medical Services (EMS) do not have the capacity to act quickly and effectively enough in regard to this vast group of patients. The objectives of the current work were: to study the importance of bystander cardiopulmonary resuscitation (CPR) from a national perspective; to determine the safety, feasibility and efficacy of trans-nasal evaporative cooling initiated during CPR; to investigate the effects of dual dispatch of fire-fighters and EMS on short- and long-term survival; to explore regional differences in response times and survival rates in relation to dual dispatch of fire-fighters and EMS in cases of OHCA.

Methods and results:

Study I. Observational study of 34,125 patients. From 1992 to 2005, bystander CPR significantly increased, especially when performed by laypersons, in witnessed (40% to 55%, $p<0.0001$) and unwitnessed (22% to 44%, $p<0.0001$) OHCA. Bystander CPR was associated with higher ventricular fibrillation (VF) rates (adjusted OR 1.73, 95% CI 1.62–1.86) and improved 30-day survival (adj. OR 2.20, 95% CI 1.68–2.90).

Study II. Randomised trial concerning 200 cases of witnessed OHCA. Trans-nasal evaporative cooling was feasible in pre-hospital arrests. Eighteen device-related adverse events were reported, where one case of epistaxis was defined as serious. Time to target temperature of 34°C was shorter in the treatment group for both tympanic (102 *vs.* 282 minutes, $p=0.03$) and core (155 *vs.* 284 minutes, $p=0.13$) temperature.

Study III. Intervention study (trained fire-fighters dispatched in cases of OHCA) using historical controls. When dispatched, fire-fighters were first on the scene and connected an automated external defibrillator (AED) in 41% of the cases. Thirty-day survival improved from 3.9% (control) to 7.6 % (intervention) ($p=0.001$, adjusted OR 2.8, 95% CI 1.6–4.9). Survival to 3 years increased from 2.4% to 6.5% respectively ($p<0.001$, adjusted OR 3.8, 95% CI 1.9–7.6).

Study IV. Intervention study using historical controls, assessing the regional impact of Study III in areas with different population densities. Median response times shortened significantly in all subgroups, ranging from 0.8 (downtown) to 3.2 minutes (rural). The effect on 30-day survival rates varied depending on population density, with the lowest impact in rural areas

Conclusions:

Bystander CPR, especially when performed by laypersons, increased in Sweden between 1992 and 2005 and is associated with increased VF and survival rates. Intra-arrest trans-nasal cooling in cases of OHCA is safe and feasible and it shortened the time interval required to cool patients. Implementation of a dual dispatch system (fire-fighters and EMS) in cases of OHCA was associated with increased 30-day- and 3-year survival. Shortened response times were seen in sparsely as well as in highly populated regions. The lowest impact of a dual dispatch system on survival was seen in rural areas.

Key words: out-of-hospital cardiac arrest, EMS, first responder, CPR, automated external defibrillators, hypothermia, intra-arrest cooling.

LIST OF SCIENTIFIC PAPERS

I. Nordberg P, Hollenberg J, Herlitz J, Rosenqvist M, Svensson L. Aspects on the increase in bystander CPR in Sweden and its association with outcome. Resuscitation. 2009;80:329–333.

II. Castrén M, Nordberg P, Svensson L, Taccone F, Vincent JL, Desruelles D, Eichwede F, Mols P, Schwab T, Vergnion M, Storm C, Pesenti A, Pachl J, Guérisse F, Elste T, Roessler M, Fritz H, Durnez P, Busch HJ, Inderbitzen B, Barbut D: Intra-arrest transnasal evaporative cooling: a randomized, prehospital, multicenter study (PRINCE: Pre-ROSC Intra-Nasal Cooling Effectiveness). Circulation. 2010;122:729–736.

III. Nordberg P, Hollenberg J, Rosenqvist M, Herlitz J, Jonsson M, Järnbert-Petterson H, Forsberg S, Dahlqvist T, Ringh M, Svensson L. The implementation of a dual dispatch system in out-of-hospital cardiac arrest is associated with improved short- and long-term survival. Submitted.

IV. Nordberg P, Jonsson M, Forsberg S, Ringh M, Fredman D, Riva G, Hasselqvist-Ax I, Hollenberg J. The survival benefit of dual dispatch of EMS and Fire-fighters in out-of-hospital cardiac arrest may differ depending on population density. Submitted.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AED	Automated external defibrillator
AHA	American Heart Association
ALS	Advanced life support
CA	Cardiac arrest
CI	Confidence interval
CPC	Cerebral performance category
CPR	Cardiopulmonary resuscitation
ECG	Electrocardiogram
EMS	Emergency medical service(s)
ERC	European Resuscitation Council
GIS	Geographic information system
OHCA	Out-of-hospital cardiac arrest
OR	Odds ratio
PAD	Public access defibrillation
PEA	Pulseless electric activity
ROSC	Return of spontaneous circulation
SALSA	Saving lives in the Stockholm area
SCAR	Swedish Cardiac Arrest Register
VF	Ventricular fibrillation
VT	Ventricular tachycardia

1 RATIONALE

Despite some advances in recent years, survival rates of patients suffering out-of-hospital cardiac arrest (OHCA) are poor. Several knowledge gaps remain that need to be addressed by way of pre-hospital intervention studies.

After the introduction of a dual dispatch system in the greater Stockholm area, using fire-fighters as first responders in cases of OHCA, a pilot study showed promising results (reduced response times and improved survival) in different subpopulations.[1] Furthermore, when analysing the results of the pilot study, several new issues were raised. In the current work some of these issues were addressed, including how the benefits of dual dispatch in cases of OHCA would remain over time; what effect would in-hospital factors have on survival rates during the years of the intervention; and, where does intervention with dual dispatch have the most effect from a regional perspective?

In addition to the above, this work covers the largest randomised controlled trial concerning the effects of intra-arrest cooling in cases of OHCA, where hypothermia treatment is induced during cardiopulmonary resuscitation. A new method for induction of hypothermia, trans-nasal evaporative cooling via the nasal cavity, which may be applied during resuscitation, was studied as regards safety, feasibility and cooling efficacy.

2 INTRODUCTION

"Cardiac arrest is the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation."

(Jacobs et al, Updated Utstein definition[2])

2.1 HISTORICAL GLANCE

Closed chest massage similar to the standardised chest compression used today was described as early as 1904 in anecdotal case reports. In 1958 colleagues Kouwenhoven, Knickerbocker and Jude made a pioneering discovery. While performing defibrillation studies on dogs, they accidentally discovered that a femoral artery pulse could be achieved by forcefully applying the defibrillation paddles to the chest. Subsequently, they moved further in their experimental setting and assessed where to press on the chest, how rapidly and to what depth to obtain a maximal haemodynamic effect. Shortly thereafter Jude applied this technique of closed-chest cardiac massage when treating a patient with cardiac arrest following anaesthesia, which resulted in successful outcome and complete recovery. In 1960, in a landmark study, the three investigators reported findings (in the Journal of the American Medical Association) concerning 20 cases of in-hospital cardiac arrest, where 14 patients survived.[3]

In parallel, Peter Safar developed a technique for airway management by tilting the back of the head and thereafter applying mouth-to-mouth breathing.[4] The formal connection of chest compression with mouth-to-mouth ventilation to create cardiopulmonary resuscitation (CPR) occurred when Safar, Jude, and Kouwenhoven presented their findings at the annual Maryland Medical Society meeting on September 16, 1960 in Ocean City.[5] Somewhat earlier, a landmark study was published in 1956 by Zoll, who described 4 cases in which ventricular fibrillation (VF) was terminated 11 times by externally applied electric countershocks.[6] In 1962 the use of direct-current monophasic waveform defibrillation was described,[7] and in 1966 the American Heart Association developed their first CPR guidelines.

2.2 EPIDEMIOLOGY

Out-of-hospital cardiac arrest (OHCA) is a major public health concern,[8] accountable for more than 60% of deaths from coronary heart disease.[9] The incidence of OHCA and its outcome vary substantially between countries and also within different regions in a nation.[10-13] In Europe, the incidence of OHCA (any rhythm) where the emergency medical services (EMS) have initiated resuscitation attempts is estimated to be 38 per 100,000 person-years, ranging from 17 to 53 per 100,000 depending on the setting. This translates into almost 300,000 victims annually in Europe.[14] In 2006 the corresponding incidence of EMS-treated OHCA in the US was estimated to be 55 per 100,000 person-years.[15] Recently, the number of persons affected by OHCA in the US was estimated to be around 382,000 annually.[16]

The incidence of OHCA with ventricular fibrillation (VF) as first rhythm has been estimated to be 17 per 100,000 person-years in Europe and 21 per 100,000 person-years in the US.[14, 15] In Sweden the incidence of EMS-treated OHCA varies between counties, ranging from 37 to 67 per 100,000 person-years.[17] In Stockholm County the incidence reported in the register is 46 per 100,000 person-years.

2.2.1 Survival rates

In two epidemiological studies the overall outcome in cases of EMS-treated OHCA of any rhythm, measured as OHCA to hospital discharge, has been estimated to be 10.7% in Europe and 8.4% in the US.[14, 15] Survival rates in EMS-treated OHCA with VF as first rhythm were approximated to 21.2% and 22.0% respectively. In Sweden, recent data from the Swedish Cardiac Arrest Register (SCAR) show 30-day survival rates of 10.4% (all rhythms) and 31% for patients with VF as first rhythm.[17]

2.2.2 Populations at risk

Some patient categories are identified as populations at risk of cardiac arrest (e.g. those with ischaemic heart disease, dilated or hypertrophic cardiomyopathy, severe heart failure, previous cardiac arrest and arrhythmia risk markers).[18] In these identified populations the incidence of VF is many times greater than in the general population, which make them suitable for preventive measures with an implantable cardiac defibrillator. However, the vast majority of cases of cardiac arrest occur in the general population without any known cardiac disease, which makes them difficult to predict and prevent.[18] In approximately 50% of patients with ischaemic heart disease, OHCA is the first recognized cardiac event.[19] Within hospitals various systems have been developed to recognize patients at risk of cardiac arrest and, subsequently, take preventive measures.[20, 21] In OHCA some genetically predisposed individuals may be identified by their family histories or by genetic tests. However, to find tools to identify the main populations at risk of OHCA remains a challenge.

2.3 PROGNOSTIC FACTORS IN CARDIAC ARREST

Although several of the presented predictors for survival are interdependent many of them still reflect the association between the time to effective treatment (CPR and defibrillation) and survival. The importance of time to treatment will be discussed in the next section.

2.3.1 Causes of cardiac arrest

In 1991 a consensus of opinion concerning uniform reporting in cases of cardiac arrest was achieved. This is referred to as the Utstein template, which was designed to facilitate comparison of results from different cardiac arrest studies.[22] A cardiac aetiology, mainly due to coronary artery disease,[9, 23] is the most common cause of OHCA and is associated with a better prognosis compared with OHCA due to non-cardiac causes.[24, 25] However, the cause of OHCA is usually presumed by the EMS crew or the emergency physician, often with limited information on the patients and the circumstances of the arrest. This may affect the accuracy of reporting. The Utstein definition states that an arrest is presumed to be of cardiac aetiology unless it is known or likely to have been caused by trauma, submersion, drug overdose, asphyxia, exsanguination, or any other non-cardiac cause as best determined by rescuers.[2] When comparing the assumptions of emergency physicians with retrospective analyses of clinical records and autopsy reports, Kürkciyan et al. demonstrated that cardiac origin is most common (69% of cases). These assumptions of cardiac aetiology showed a sensitivity of 95% and a specificity of 77%.[26] Pulmonary embolism, a ruptured aortic aneurysm, and intracerebral haemorrhage were frequent in patients where the assumptions of cardiac origin were incorrect. Similar findings have been reported by others.[24, 27] The various causes of OHCA are presented in Table 1.

Table 1. Causes of OHCA divided into cardiac and non-cardiac origin.

Cardiac causes of OHCA
Ischaemic cardiac disease (coronary artery disease)
Ischaemic cardiomyopathy
Dilated cardiomyopathy
Hypertrophic cardiomyopathy
Non-atherosclerotic disease of coronary arteries
Valvular heart disease
Arrhythmogenic right ventricular cardiomyopathy
Infiltrative and inflammatory myocardial disease
Congenital heart disease
Primary cardiac electrical abnormalities
Non-cardiac causes of OHCA
Pulmonary embolism
Lung disease (hypoxic cause of cardiac arrest)
Electrolyte abnormalities
Bleeding, non-traumatic (hypovolemic cause of cardiac arrest)
Subarachnoid haemorrhage
Drug overdose
Suffocation
Drowning
Sudden infant death syndrome

Adapted from Hollenberg et al., 2013[28]

2.3.2 Location of cardiac arrest

The specific location where a cardiac arrest occurred or the patient was found is most often divided into place of residence, public place, or other.[2] Most investigators report that around two thirds of cases of OHCA occur at the patient's home.[29, 30] In one observational study, OHCA outside home was associated with a threefold greater chance of survival compared with when the collapse occurred at home.[30] This may depend on several factors such as advanced age, comorbidity, more often unwitnessed arrest and lower frequency of bystander CPR compared with OHCA that occurred in a public place.[30] On the other hand, OHCAs occurring in a public place are independently associated with improved survival [31] and are associated with a greater incidence of VF compared with OHCAs occurring at home.[29] In addition, OHCAs occurring in public locations such as airports, sport facilities and malls increasingly are subjects of public access defibrillation (PAD), which has been shown to improve survival rates in these particular settings.[32, 33]

2.3.3 Witnessed cardiac arrests

A witnessed CA is defined as a CA seen or heard by another person or an arrest where the heart rhythm is monitored. Witnessed collapse, in contrast to unwitnessed collapse, has been shown to be an independent predictor of an increased chance of survival in OHCA.[34, 35] Witnessed OHCA is seen in about two-thirds of cases and is associated with a greater proportion of patients receiving bystander CPR and a higher VF incidence compared with unwitnessed OHCA.[35] A witnessed OHCA is associated with two- to threefold better survival than an unwitnessed arrest.[1, 34, 36] In many studies cases of unwitnessed OHCA are not included because of the extremely low chance of survival of these patients.

2.3.4 Age

Advanced age is associated with worse outcome in cases of OHCA.[37] The characteristics vary somewhat within different age groups and greater age is associated with a lower rate of bystander CPR, less VF as first rhythm and fewer cases with cardiac aetiology.[37] However, VF as first rhythm compared with other initial rhythms is associated with increased survival despite age.

2.3.5 First rhythm

"First rhythm" refers to the first rhythm recorded by a monitor or when a defibrillator is attached to a patient after cardiac arrest.[2] It may be defined as either shockable (i.e. ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT)) or non-shockable (pulseless electrical activity (PEA) or asystole).

These initial rhythms indicate different pathophysiological mechanisms. VF may occur as a direct effect of an acute ischemic episode or as a consequence of a previous ischemic event such as myocardial infarction. The ischemic zones trigger re-entry circuits, which may induce an electric chaos that make the myocardium to contract in an unsynchronised way (i.e. fibrillate).[38] Asystole is associated with the cessation of electric activity in the myocardium. It is associated with prolonged cardiac arrest and thus poor prognosis. It may be subsequent to VF or due to non-cardiac causes of the CA. In PEA the contractility of the heart is lost but with maintained electric activity. It is associated with non-cardiac causes of CA such as hypovolemia and pulmonary embolism.

In several studies VF or VT as first monitored rhythm has been demonstrated to be the strongest independent predictor of survival in OHCA.[34, 39-41] The proportion of cases of VF/VT as first rhythm has been assessed in several studies to be about 25–50%, but it has declined over the last few years.[15, 42, 43] There is a strong relationship between first rhythm and the time interval from collapse until the rhythm is recorded by the EMS. Thus, when the rhythm is assessed very soon after the arrest the rate of VF may be substantially higher, as fewer patients have deteriorated to asystole.[39] In studies assessing public access defibrillation in OHCA before arrival of the EMS, the VF rate has been reported to be as high as 50 to 65%. [33, 44, 45]

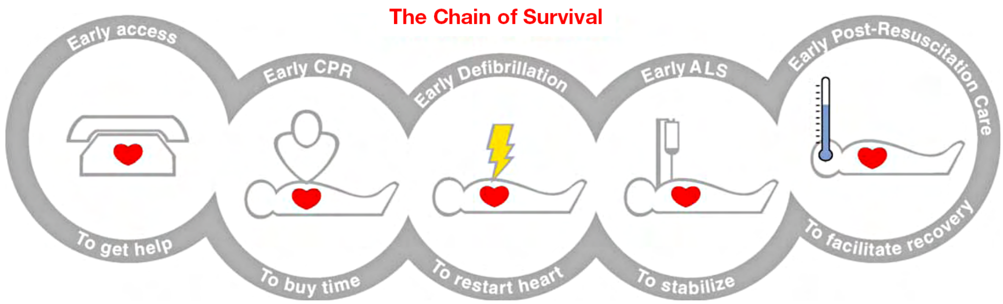
2.3.6 Gender

About a third of cases of OHCA are in women.[46, 47] The characteristics differ somewhat from those in men, as women are affected at a greater age. In women, OHCA more often occurs at home; they receive a lower rate of bystander CPR and show a lower VF rate compared with men. In some studies, when adjusting for the differences in characteristics between men and women, female sex has been associated with improved survival.[46-48]

2.4 TREATMENT STRATEGIES IN CARDIAC ARREST

The principles of treatment in OHCA follow the different links in the chain-of-survival concept, where emphasis is placed on minimizing the time to treatment (see Figure 2).[49] The five links of the chain-of-survival are: Early access; Early CPR; Early Defibrillation; Early Advanced Life Support (ALS); and Early Post-Resuscitation Care.

Figure 2. Chain-of-Survival.



2.4.1 Early Access

The first link in the chain emphasizes the importance of early recognition and recruitment of resources to the scene of the arrest by way of an emergency call. At the other end of the line it is important for the dispatcher receiving the emergency call to rapidly identify the condition, to locate the place of the event and to minimize the time delay at the emergency dispatch centre.[50, 51] When the condition is identified promptly by the dispatcher, this is associated with significantly shorter response time intervals and increased survival rates.[52] Strategies have been developed to improve the dispatchers' skills, which have reduced the time for identification and dispatching.[53] The role of the dispatcher also includes guidance in telephone-CPR to untrained bystanders.[54]

2.4.2 Early cardiopulmonary resuscitation

The second link refers to the importance of early bystander CPR. Current guidelines recommend a chest compression:ventilation ratio of 30:2 with a compression rate of 100 per minute at a depth of at least 5 cm in adults.[55] The chest should be allowed to expand before initiating the next compression. High-quality chest compression may result in cerebral and coronary perfusion of about 30% of normal blood flow.[56] Continuous CPR builds up diastolic pressure, which is necessary to increase coronary perfusion pressure and it has been suggested that a coronary perfusion pressure over 15 mmHg is needed to achieve return of spontaneous circulation (ROSC) in cases of OHCA.[57]

Cardiopulmonary resuscitation may also extend the time of VF before deterioration to asystole, thus working as a bridge to defibrillation.[58] In addition, VF amplitude when CPR is performed has been shown to be associated with the likelihood of success in defibrillation.[59]

Bystander CPR is an independent predictor of survival in cases of OHCA and immediate CPR may substantially improve survival rates in OHCA with VF as first rhythm.[60-62] However, the role of ventilation has been debated and in observational studies compression-only CPR has been associated with an outcome comparable with that in standard CPR.[63, 64] Recently, in two randomised trials in which telephone-assisted CPR carried out by untrained laypersons was assessed, it was shown that the effect of compression-only CPR was similar to that of standard CPR.[65, 66] Guidelines from the American Heart Association recommend that laypersons with no CPR training should perform compression-only CPR until EMS providers or other responders take over care of the victim.[67]

The clinical effect of mechanical devices for CPR has been debated. Although haemodynamics may be improved in experimental models,[68, 69] so far no outcome benefit has been demonstrated in randomised clinical trials.[70] One previous randomised clinical trial was disrupted because the use of an automated CPR device was associated with worse neurological outcome at discharge compared with standard manual CPR.[71] Mechanical CPR may be advantageous in prolonged resuscitation such as in cases with accidental hypothermia, intoxication, thrombolysis in pulmonary embolism, or during patient transport.

2.4.3 Early defibrillation

The third link is early defibrillation, a therapy that is limited to OHCAs with VF/VT as first rhythm and to those cases that convert to VF/VT from an initial non-shockable rhythm during resuscitation. A first rhythm of VF is one of the strongest independent predictors of survival in OHCA.[34] When defibrillation can be performed in patients with VF within minutes after collapse, the survival rate may well be over 50%. In one study, when security officers defibrillated VF arrests within 3 minutes of collapse, the survival rate was 74%.[72] The association between time interval and survival in this group of patients cannot be underrated. Predictive models for survival in witnessed OHCA with VF as first rhythm have shown that the probability of survival to hospital discharge decreases by about 10% per minute without CPR or defibrillation.[60]

2.4.3.1 *First responders and public access defibrillation*

First responders are persons who are certified to provide medical care in emergencies before more highly trained medical personnel arrive on the scene. In cases of OHCA, fire-fighters, police and security officers trained in CPR and automated external defibrillator (AED) use have been used as first responders. In several trials the use of first responders has resulted in success in shortening response times when they are dispatched in cases of suspected OHCA. [45, 73-76] In some studies, these interventions have been associated with increased survival rates in patients presenting with VF or VT.[1, 73] Few studies, however, have shown an impact of such intervention in cases of cardiac arrest with any first rhythm.[77]

Public access defibrillation is a strategy to enable defibrillation with the minimum delay, before the arrival of the EMS. Public access defibrillation programmes have been shown to improve survival rates in subgroups of patients with VF as first rhythm in different settings, often in limited geographical areas or situations.[33, 78, 79] Recently, a Japanese study showed a more than twofold increase in survival with good neurological outcome in patients with ventricular fibrillation as first rhythm who had been defibrillated with a public AED by laypersons.[32]

2.4.4 Early advanced life support

The fourth link is early ALS, meaning advanced airway management and use of intravenous drugs. Despite the recommendation in current guidelines, the use of adrenaline in cases of OHCA is under debate. It has repeatedly been associated with increased return of spontaneous circulation (ROSC) rates, but without improvements in overall survival rates.[80-82] In a randomised trial, Olasvengeen and colleagues tested the use of any intravenous drug versus no intravenous drugs and came up with similar findings.[83] Amiodarone is recommended in refractory VF and in a randomised trial (compared with placebo) significantly increased survival to hospital admission,[84] and when compared with lidocaine, increased survival to discharge.[85]

The use of advanced airway management in OHCA is controversial. Although probably needed in some cases, advanced airway techniques (i.e. endotracheal intubation or use of a supraglottic device) have in large observational studies been associated with worsened neurological outcome and decreased survival compared with bag-mask ventilation.[86, 87] On-going studies will add valuable information to this issue.

In one landmark US multicentre study the addition of ALS to a previously optimized EMS system with rapid defibrillation did not improve the rate of survival after out-of-hospital cardiac arrest.[80] In summary, intravenous drug administration and advanced airway management are included in ALS intervention, but are not prioritised compared with early defibrillation and uninterrupted CPR.

2.4.5 Early post-resuscitation care

The fifth link includes the in-hospital management of resuscitated patients (i.e. post-resuscitation care). Recently, a statement document from the ERC and the AHA defines the condition as post-cardiac arrest syndrome.[88] Although the treatment with therapeutic hypothermia has received most attention in recent years, a more comprehensive approached with combined interventions has been emphasised to improve the in-hospital management of these patients.[89]

2.4.5.1 Therapeutic hypothermia

Cooling of the human body decreases the cerebral metabolic rate for oxygen by about 6% per 1°C reduction in body core temperature.[90] In cardiac surgery deep hypothermia is routinely used for cerebral protection.[90, 91] Both experimental and clinical data indicate that mild hypothermia is neuroprotective after a period of global cerebral hypoxia-ischemia.[92, 93]

In two randomised trials with 273 and 77 unconscious patients resuscitated from a witnessed VF arrest, therapeutic hypothermia improved neurological function among survivors. In these studies patients were cooled to 33 °C for 12 to 24 hours and actively[94] or passively[95] re-warmed to normal body temperature. The primary outcome measure was survival with good neurological outcome. The cerebral performance category (CPC) was assessed, where CPC 1 and CPC 2 are considered as good neurological outcome and CPC 3 to 5 as bad (Table 2). These studies represent the scientific basis for international recommendations concerning therapeutic hypothermia, which is an established method at intensive care units for this subgroup of patients (i.e. witnessed OHCA with VF/VT as first rhythm). Recently, Nielsen et al., in a randomised trial including 950 patients, compared the temperatures of 33 °C and 36 °C for 24 hours in post-cardiac arrest patients independently of the first rhythm (excluded were unwitnessed arrests with asystole as first rhythm). No differences in survival or neurological outcome were found.[96] The clinical implications of this study have not yet been seen.

While clinical data is mainly derived from hospital cooling, started hours after collapse (eg. Nielsen et al, HACA, Bernard et al.),[94-96] most of the experimental data support the initiation of cooling very early, either during CPR (i.e. intra-arrest)[97] or after restoration of circulation (i.e. post-ROSC).[98] Despite the lack of conclusive clinical data, guidelines recommend starting cooling as early as possible. Two randomised trials concerning post-ROSC cooling with cold fluids compared with hospital systemic cooling showed no differences in survival rates or neurological function.[99, 100] In one study the use of large amounts of cold intravenous fluids was associated with severe haemodynamic side-effects, including a significantly increased number of cases of re-arrest.[100] Intra-arrest cooling in cases of OHCA has been tested in safety and feasibility trials with cold fluids.[101, 102] In animal studies, trans-nasal evaporative cooling has been shown to cool the brain primarily and thereafter the whole body. The method is described in detail below (Methods).

Table 2. Cerebral performance categories.[103]

CPC 1	Conscious, alert, able to work and lead a normal life. May have minor psychologic or neurologic deficits (mild dysphasia, non-incapacitating hemiparesis, or minor cranial nerve abnormalities).
CPC 2	Conscious. Sufficient cerebral function for part-time work in sheltered environment or independent activities of daily life (dress, travel by public transportation, food preparation). May have hemiplegia, seizures, ataxia, dysarthria, or permanent memory or mental changes.
CPC 3	Conscious. Dependent on others for daily support (in an institution or at home with exceptional family effort). Has at least limited cognition. This category includes a wide range of cerebral abnormalities, from patients who are ambulatory but have severe memory disturbances or dementia precluding independent existence, to those who are paralyzed and can communicate only with their eyes, as in the “locked in” syndrome.
CPC 4	Unconscious. Unaware of surroundings, no cognition. No verbal and/or psychologic interaction with environment.
CPC 5	Brain dead, circulation preserved.

2.4.5.2 Coronary angiography/revascularization

Although supported by a low level of evidence, current guidelines recommend immediate coronary angiography in resuscitated OHCA patients with (electrocardiographic) ST-segment elevation myocardial infarction (STEMI).[55] However, as ECG findings in OHCA patients are poor predictors of coronary occlusion,[104] it is recommended that immediate coronary angiography should be considered in all post-cardiac arrest patients with suspected coronary artery disease.[55] Several observational studies have demonstrated as association between immediate angiography and increased survival.[105, 106] However, at present there is no data from randomised clinical trials.

2.4.5.3 Other post-cardiac arrest parameters

Some in-hospital factors have been associated with poor outcome, such as fever, high blood glucose levels, elevated serum potassium, acidosis, seizures, advanced age and long delay to ROSC.[107, 108] Although there is a lack of good evidence to support intensive care measures, there are some studies where structured programmes[89] or forms of combined intervention[109] have been implemented to improve the intensive care of post-cardiac arrest patients, which have been shown to improve survival compared with historical controls. The recommendations made by the European Resuscitation Council (ERC) concerning certain parameters are presented in Table 3.[55]

Table 3. In-hospital factors/interventions that are recommended in ERC guidelines 2010.[55]

In-hospital factor/intervention	ERC recommendation
Ventilation	Target saturation 94–98%. Avoid hyperoxaemia. Normocapnia.
Circulation	No specific target mean arterial pressure (MAP). Achieve urine output 1 ml/kg/h. If vasoactive drugs are insufficient, consider intra-aortic balloon pump.
Control of seizures	Treat promptly with benzodiazepines, phenytoin, valproate, propofol or barbiturate
Glucose control	Avoid hypoglycaemia. Maintain ≤ 10 mmol/l
Temperature control	Avoid fever for at least 48 h
Therapeutic hypothermia	In VF patients. 32–34 °C for 24 h. Re-warming 0.25–0.5 °C /hour
Angiography	Immediate in STEMI. Consider immediate in Non-STEMI if coronary artery disease is suspected.

3 AIMS

The overall aim of the present work was to explore ways towards improved management of victims of OHCA. The studies embrace several aspects of treatment of cardiac-arrest patients such as the importance of bystander CPR, early defibrillation and early hypothermia. The emphasis was to assess the clinical effect of interventions carried out to improve CPR and early defibrillation by using non-health personnel as first responders in cardiac arrests in the context of pre-hospital care.

3.1 SPECIFIC AIMS

To describe changes in the proportion of bystanders performing cardiopulmonary resuscitation in cases of OHCA in Sweden, and to study the impact of bystander CPR on ventricular fibrillation and on survival over various time periods.

To determine the safety, feasibility and cooling efficacy of pre-hospital trans-nasal evaporative cooling in humans, and to explore the effects on neurologically intact survival to hospital discharge.

To determine the impact of a dual dispatch system (using fire-fighters as first responders) on short- and long-term survival in cases of OHCA, and to investigate potential differences regarding in-hospital factors and forms of intervention between patient groups.

To determine the effects on response times and 30-day survival in relation to population density after the implementation of a dual dispatch system in cases of OHCA.

4 METHODS

4.1 ETHICS

The Regional Ethics Committee approved all studies in this work. Ethical considerations for treating subjects without their express consent were in accordance with the Helsinki Declaration of 1964, revised in 2008. In Study II, informed consent was obtained from all patients, or, in cases where the patient died, the next of kin or a legal representative.

4.2 PATIENTS

As presented in Table 4, the patients in the four studies were: OHCA patients in Sweden, 1992–2005 (Study I); witnessed OHCA patients from 15 European study sites, November 2008–June 2009 (Study II); OHCA patients in Stockholm, 2004–2009 (Studies III & IV).

Table 4. Characteristics of each study population.

Study	Inclusion criteria	Exclusion criteria
I	OHCA patients in Sweden in whom CPR was attempted and who were included in the Swedish Cardiac Arrest Register.	EMS crew witnessed
II	Witnessed collapse, >18 years of age, unresponsive to external stimuli, pulseless.	EMS response time ≥ 20 min, non-cardiac causes (hypothermic, pregnancy, known coagulopathy, ROSC prior to randomisation, existing DNAR*, intra-nasal obstruction).
III	EMS-treated OHCA in Stockholm	Age <9 years, traumatic origin, EMS crew witnessed.
IV	EMS-treated OHCA in Stockholm	Age <9 years, traumatic origin, EMS crew witnessed, OHCA with no exact geographical coordinates for the arrest.

*DNAR = do not attempt resuscitation

4.3 THE SWEDISH CARDIAC ARREST REGISTER

All data for Study I and most of the data for Studies III and IV were collected from The Swedish Cardiac Arrest Register. It is a national register funded by the Swedish National Board of Health and Welfare. The register started in 1990 and is at present run by the Swedish Resuscitation Council. The register depends on voluntary participation by the EMS districts in Sweden and coverage has increased gradually from a few EMS districts in 1990 to include all districts in 2009. The EMS crews report according to the Utstein model. For each case the EMS crew complete a digital form with data on the arrest based on clinical findings and bystander information, such as: demographic information; estimated time of arrest; presumed aetiology divided into different categories (see Table 1); whether the OHCA was witnessed or not; type of resuscitation procedure and interventions; information on whether CPR was performed and which type of bystander was performing CPR (i.e. layperson, ambulance crew, police, healthcare providers or others). The first recorded rhythm is defined as VF, PEA or asystole. When AEDs have been used, the rhythms are defined as shockable (i.e. VF/VT) or non-shockable. Data on 30-day survival is completed by the rapporteur from each EMS district who monitors the outcome of the patients by merging data with the National Register of Deaths.

4.4 OBSERVATIONAL STUDY (STUDY I)

Study I was an observational study based on OHCA patients included in the Swedish Cardiac Arrest Register. The study period was from the 1st of January 1992 to the 31st of December 2005. Temporal trends of patient and baseline characteristics were assessed, as were comparisons between patients in the early period of the study (i.e. 1992–1995) versus the late period (i.e. 2002–2005).

4.5 RANDOMISED CLINICAL TRIAL (STUDY II)

Study II was designed as a prospective randomised trial conducted by EMS in 15 sites in five European countries between November 2008 and June 2009.

The randomization procedure was as follows: EMS personnel screened patients and the randomisation envelope was opened if the patient appeared to be eligible. The patient was assigned to either intra-arrest trans-nasal evaporative cooling or to no pre-hospital cooling. Trans-nasal cooling was intended to continue until systemic cooling was started in the hospital. Patients in both groups were cooled in the hospital according to institutional standards. The EMS crew completed the case report forms as regards pre-hospital data for each case. In general, the attending physician at the intensive care unit collected in-hospital data, including outcome data on survival to discharge. Neurological assessment at discharge was intended to be performed by physicians blinded to the treatment given.

4.5.1 Method of trans-nasal evaporative cooling

Trans-nasal evaporative cooling is a method used for early, non-invasive induction of hypothermia. The method was developed primarily to cool the brain and in animal studies has been shown to create a temperature gradient in which the brain is cooled faster than the rest of the body.[110, 111] In addition, in animal studies the method has also been associated with improved ROSC rate,[112] improved coronary perfusion pressure during resuscitation,[113] and improved outcome in terms of survival and neurological function.[110] In clinical trials it has been proven to be safe to use in-hospital, in cardiac-arrest patients with ROSC, when cooling was started at the emergency department.[114] In this study of post-ROSC cooling the temperature decreased by 2.3 °C per hour.

The device used for trans-nasal evaporative cooling (RhinoChill) consists of a backpack that weighs 12 kg containing a disposable nasal catheter, a control unit, a 2-litre bottle of coolant, and an oxygen tank. First, the nasal catheters are inserted through the nostrils. Second, a mixture of oxygen (or air) and an inert liquid coolant (perfluorohexane), via the nasal catheter, are sprayed into the upper surface of the nasal cavity. There the coolant evaporates and absorbs heat from the tissues, thereby cooling them and the innate vasculature that supplies blood to the brain.

The tubing set is connected to a battery-operated control unit that allows the cooling rate to be controlled by adjusting the oxygen/air flow rate. The device is automatically switched off if the pressure in the nasal cavity exceeds 60 cm H_2O. This system delivers trans-nasal evaporative cooling for 22.5 minutes at an oxygen/air flow rate of 40 L/min. Additional oxygen tanks or a connection to an ambulance or hospital oxygen supply are required for longer use. The 2-L bottle contains enough coolant for 1 hour of cooling. The equipment is easy to handle and the device can most often be applied to the patient and be ready to use within one minute.

4.6 INTERVENTION WITH HISTORICAL CONTROLS (STUDIES III, IV)

Studies III and IV were performed in Stockholm County between the 1st of January 2004 to the 31st of December 2009. On Dec. the 31st 2009 Stockholm County had a population of 2,019,182 inhabitants, of which 50.6% were female and 14.7% persons over 65 years of age.[115]

Study III is the main study of the SALSA project (Saving Lives in Stockholm Area). It was designed as a prospective, interventional trial with historical controls, conducted by the EMS and the Fire Department in Stockholm County.

Study IV had the same study population as in Study III and it was designed to assess the regional effects of the intervention. However, in Study IV, cases where the exact geographical coordinates for the arrest could not be found were excluded (3% of all cases). The patients were divided into four subgroups depending on the population density of the place of arrest. Cut-off values for population densities were decided after reviewing previous studies,[116] combined with context-specific factors. The groups were classified as: 1. Rural ($<250/km^2$), 2. Suburban ($250–2999/km^2$), 3. Urban ($3000–5999/km^2$) and 4. Downtown ($\geq 6000/km^2$).

4.6.1 Emergency Medical Services in Stockholm.

The EMS system in Stockholm is two-tiered in emergencies such as OHCA, with an advanced life-support level as the second tier (e.g. nurses specialized in anaesthesia, or an anaesthesiologist). During the study period of 2004–2009 the number of ambulances was the same. In 2004 there were four ALS vehicles manned by nurses specialized in anaesthesia. In 2007, this was changed to two ALS vehicles manned by specialised nurses and one ALS vehicle manned by anaesthesiologists.

4.6.2 Dual dispatch of first responders

During 2005, all 43 fire stations in Stockholm County were gradually equipped with AEDs as part of the SALSA project, with the main objective of shortening response times and thereby increasing survival in cases of OHCA. All fire-fighters underwent an 8-hour course in CPR and use of an AED according to ERC guidelines.[55] For all fire-fighters, the training programme was repeated once a year during the study period.

Dual dispatch of EMS and fire-fighters occurred in cases where the dispatcher suspected an OHCA. Subsequently, the dispatcher alerted the nearest available EMS and thereafter deployed the closest available fire department by using a computer-mediated alarm code.

In cases of OHCA where the fire brigade arrived first, the fire-fighters were responsible for performing the medical assessment. If the patient was unresponsive and pulseless, CPR was started and the AED was attached to the patient. Ventilation by fire-fighters was performed with a mouth-to-mouth resuscitation mask. When the EMS crew arrived, they took over responsibility for the treatment.

4.6.3 Data collection

In addition to the data from the Swedish Cardiac Arrest Register in Study III, several other data sources were used to collect additional information. Event times, such as when a call was made to a dispatch centre, dispatch and arrival of first responders and additional dispatch information were collected from the emergency dispatch centre. Data on co-morbidity was derived from registries within the National Board of Health and Welfare. Data on in-hospital measures such as therapeutic hypothermia, cardiac interventions such as angiography and percutaneous coronary intervention were collected from medical records, the Swedish Register of Intensive Care, and Swedeheart.[117, 118]

The geographical data of the OHCAs in Study IV was collected by means of a geographic information system (GIS), which is a computer-based method to integrate and analyse geographical data. A parish is the smallest administrative level for which they have shapefiles in Sweden. In Study IV, the digital spatial data (x and y coordinates of the OHCA) obtained from the emergency dispatch centre was used to locate the parish in which each OHCA had occurred. Subsequently, the cardiac arrest data was merged with the spatial data so as to be able to perform analyses.

4.7 STATISTICAL METHODS

A summary of the statistical methods used is presented in Table 5. For details, see the sections on statistical analysis in the separate studies.

Table 5. Statistical methods used in Studies I to IV.

	Study I	Study II	Study III	Study IV
Comparisons between two groups:				
Dichotomous variables:				
Fisher's exact test	X	X		
Pearson's X^2 test			X	X
Continuous variables				
Wilcoxon's rank-sum test	X			
Pitman's non-parametric permutation test		X		
The Mann–Whitney ***U*** test			X	X
Two-group ***t*** tests		X		
Multivariable analysis:				
Logistic regression	X		X	X
Trend tests:				
The Mann–Whitney ***U*** test	X			

5 RESULTS

5.1 BYSTANDER CPR IN SWEDEN – STUDY I

In total, 34,125 patients were included in the analysis. There were no differences in patient baseline characteristics between the different ambulance organisations in regard to age, sex, proportion of patients who received bystander CPR and place of cardiac arrest.

5.1.1 Main results

There was a significant increase in the proportion of patients who received bystander CPR among witnessed as well as non-witnessed cases (Figure 3). There was a significant increase in bystander CPR performed by laypersons (21% in 1992 *vs.* 40% in 2005; $p < 0.0001$) but no change as regards healthcare providers, ambulance personnel or police (Figure 4).

Bystander CPR was associated with an increased number of patients found in shockable rhythm, compared with no bystander CPR (odds ratio (OR) 1.73; 95% confidence interval (CI) 1.62–1.86; n=14,294). Bystander CPR was associated with increased survival both in the early study period, 1992–95 (OR 2.11; 95% CI 1.64–2.72) and later, 2002–2005 (OR 2.20; 95% CI 1.68–2.90).

Figure 3. Change in bystander CPR rates in witnessed and non-witnessed cases during the study period (1992–2005).

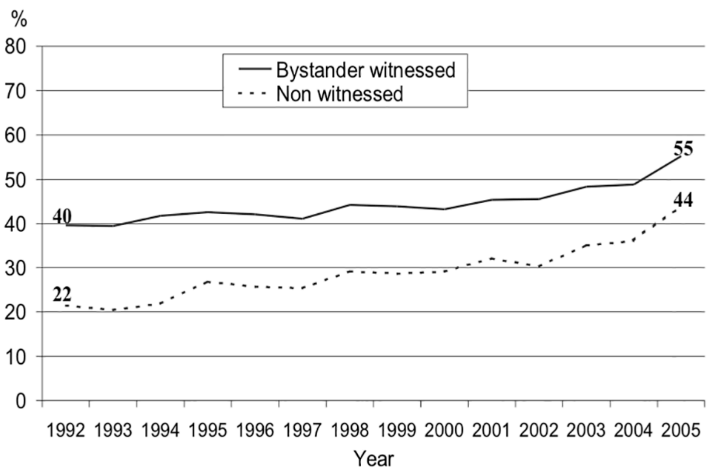
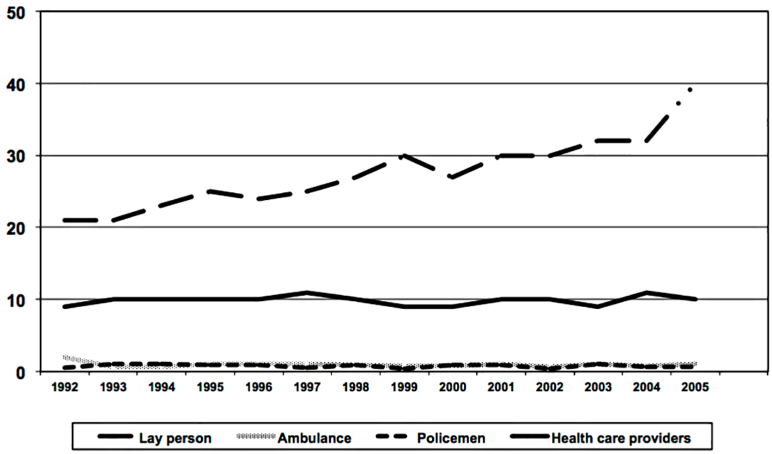


Figure 4. Change in bystander CPR among various types of bystanders.



5.2 INTRA-ARREST COOLING – STUDY II

The study period for this randomised safety and feasibility trial was November 2008 to June 2009. Out of 200 enrolments, six patients (three from the treatment group and three control subjects) had missing outcome data. One hundred and ninety-four patients, therefore, were included in the intention-to-treat analysis (93 intervention cases *vs.* 101 controls). The patient groups showed similar demographics, initial rhythms, bystander CPR rates, and intervals to CPR and arrival of ALS personnel.

5.2.1 Main results

5.2.1.1 Safety

Eighteen device-related adverse events were recorded in the intervention group (one case of periorbital emphysema, three of epistaxis, one of perioral bleeding and 13 cases of nasal discoloration; see Table 6). The nasal discoloration resolved spontaneously in all five resuscitated patients. One case of epistaxis was defined as serious (in a patient with an underlying coagulopathy). This was the only device-related serious adverse event. The total numbers of serious adverse events not related to the cooling device that occurred within seven days were seven in the treatment group and 14 in the control group.

Table 6. Adverse events in Study II.

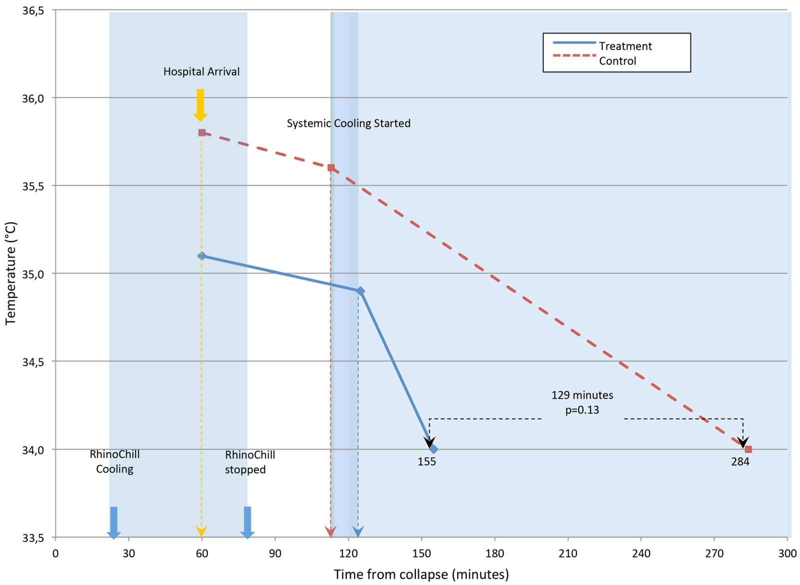
Adverse events	Intervention N=93	Control N=101
Device-related		
Nasal discoloration	13	na
Epistaxis	3*	na
Periorbital emphysema	1	na
Perioral bleed	1	na

*One serious device-related case of epistaxis in a patient with coagulopathy.

5.2.1.2 Cooling efficacy

The median time to the start of intra-arrest cooling in the treatment group was 23 minutes. On arrival at the hospital, the mean tympanic temperature was significantly lower in the treatment group (34.2 °C versus 35.5 °C, p=0.001). The median time from the arrest to target temperature (tympanic; < 34 °C) was 102 minutes in the treatment group compared with 291 minutes in control patients (p=0.03; Figure 5). The median time to target temperature (core; <34 °C) in the treatment group was 155 minutes versus 284 minutes in the controls (p=0.13).

Figure 5. Time to target temperature (core) of <34°C



5.2.1.3 Outcome

Outcome data on survival to hospital discharge, and survival to discharge with good neurological function, defined as CPC 1–2, concerning the entire group, those who received rescuer CPR within 10 minutes, and those with a presenting rhythm of VF are presented in Table 7.

Table 7. Survival to discharge and neurologically intact survival to discharge (CPC 1-2)

	Intervention	Control	p
Survival to discharge (%)			
All patients	43.8	31.0	0.26
CPR ≤ 10 minutes	56.5	29.4	0.04
VF as first rhythm	62.5	47.6	0.37
Neurologically intact survival, CPC 1–2 (%)			
All patients	34.4	21.4	0.21
CPR ≤ 10 minutes	43.5	17.6	0.03
VF as first rhythm	50.0	28.6	0.18

5.3 DUAL DISPATCH OF FIRST RESPONDERS IN OHCA – STUDY III

The period for Study III was the 1st of January 2004 to the 31st of December 2009. In total, 2,581 OHCA patients were included, of which 620 were in the historical control group (2004), and 1,961 were in the intervention group (2006-2009). Baseline characteristics were similar except for the proportion of cases of witnessed OHCA, which was significantly greater in the control group than in the intervention group.

5.3.1 Main results

5.3.1.1 EMS and first responders

When dispatched, fire-fighters were first on the scene and connected an AED in 41% of the cases. Even if not first on the scene, they assisted the EMS and performed CPR in 90% of all patients.

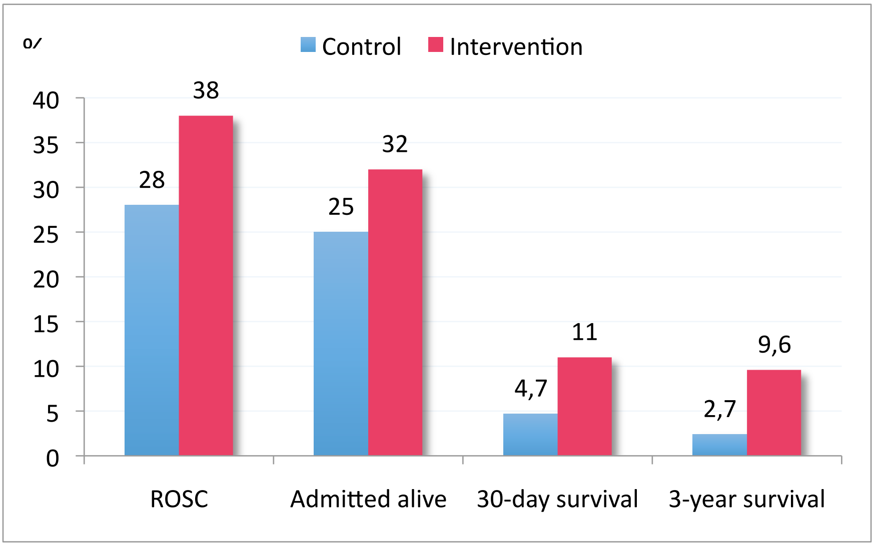
The median time interval to treatment (i.e. dispatch to arrival of EMS or fire-fighters) was significantly shorter in the intervention group than in the control group (6.7 minutes *vs*. 7.7 minutes, p<0.001).

In the intervention group, the proportion of patients with VF/VT was significantly greater than in the control group (25% *vs*. 20%, p=0.02).

5.3.1.2 Short- and long-term outcome

Thirty-day survival improved from 3.9% in the control group to 7.6% in the intervention group (adjusted OR 2.8, 95% CI 1.6–4.9, p=0.001). Survival to 3 years increased from 2.4% to 6.5% respectively (adjusted OR 3.8, 95% CI 1.9–7.6, p<0.001). As shown in Figure 6, among witnessed cases the rates of ROSC, admission alive, 30-day survival and 3-year survival were significantly greater in the intervention group than in the controls.

Figure 6. Outcome data for witnessed OHCA. All differences between groups were highly significant (p<0.01)



5.3.1.3 In-hospital factors

For the subgroup of VF/VT patients, the proportions of patients treated by means of therapeutic hypothermia were similar in the two groups (62% *vs.* 71%, p=0.35).

Among patients with ST-elevation myocardial infarction (STEMI) there was a significant difference between the control group and the intervention group in the proportion of patients who underwent immediate catheterization (39% *vs*. 69% respectively, p=0.03). However, no difference between groups was found in STEMI patients who underwent immediate reperfusion measures (i.e. acute catheterization or thrombolysis) (69% *vs.* 72%, p=0.82). There was a significant difference between the control and the intervention group in patients where angiography was performed during their hospital stay (13% *vs*. 27% respectively, p=0.001).

5.4 REGIONAL DIFFERENCES IN CASES OF OHCA - STUDY IV

The study period was the same as for Study III (2004–2009). A total of 2513 cases of OHCA were included where the exact geographic location of the arrest could be determined, 571 in the historical control group and 1942 in the intervention group. The numbers of patients (control/intervention) in each population density subgroup were: Rural (population density <250 km^2) 85/319, Suburban (population density 250–2999/km^2) 288/832, Urban (population density 3000–5999/km^2) 149/552 and Downtown (population density >6000/km^2) 49/239. No major differences were seen in baseline characteristics between the different population subgroups (see article for details). However, bystander CPR rates and the VF rate were significantly higher in the intervention group.

5.4.1 Main results

5.4.1.1 First responders and time intervals

Fire-fighters were first on the scene in 54% of cases in the Rural area compared with 27% in the Downtown area. Fire-fighters performed CPR in the majority of cases in all subgroups; lowest in the Downtown area (79% of cases) and highest in the Suburban area (94% of cases).

The response times (i.e. dispatch to arrival) were significantly shortened in all studied subgroups. The most prominent time reduction was seen in the Rural group (13.5 to 10.3 minutes, p=0.001) compared with (5.8 to 5.0 minutes, p<0.05) the Downtown group.

5.4.1.2 Population density

In logistic regression analysis, high population density (Downtown >6000/km^2) was associated with improved 30-day survival as compared with the most sparsely populated area (Rural <250/km^2), after adjusting for sex, age, place of the arrest, aetiology, witnessed status, bystander CPR and rhythm (adjusted OR 2.1, 95% CI 1.1–4.1).

5.4.1.3 30 day-survival

As seen in Table 8, overall survival improved significantly in the intervention group compared with controls in the Suburban group and the Downtown group. When comparing low- and high-density areas, the 1-month survival rates changed from 4.7 to 5.3% in the Rural area (control *vs.* intervention) and from 4.1 to 15% in Downtown.

Table 8. Outcome in all patients and in each population subgroup (n=control/intervention).

Patient population	30-day survival	
	Control	**Intervention**
All patients, (n=571/1942)	3.9	7.6*
Rural <250/km^2, (n=85/319)	4.7	5.3
Suburban 250–2999/km^2, (n=288/832)	3.1	7.0**
Urban 3000–5999/km^2, (n=149/552)	2.7	6.9
Downtown >6000/km^2, (n=49/239)	4.1	15**

*p<0.01, **p<0.05

6 DISCUSSION

6.1 DO INCREASED BYSTANDER CPR RATES IMPROVE SURVIVAL?

The association between bystander CPR and survival was recently challenged in an editorial in the New England Journal of Medicine, where considerations regarding efficacy, safety and associated costs were taken into account, suggesting that to educate persons in CPR may be counterproductive instead of leading anywhere in terms of improved survival.[119] However, despite the lack of randomised data, there is compelling evidence supporting bystander CPR as one of the key measures in the treatment of OHCA.[60-62]

In several large observational studies with patient numbers ranging from 30,000 (as in Study I) to more than 100,000, the findings are very similar.[36, 120] Bystander CPR has repeatedly been demonstrated to be an independent factor affecting survival in cases of OHCA and it is associated with a twofold or even a threefold increased chance of survival compared with no CPR. The effect of bystander CPR seems to be more marked when the delay between the arrest and the start of CPR is short.[61, 62] Bystander CPR has been associated with an increased likelihood of VF as first rhythm,[121] suggesting that CPR may prolong the duration of VF before deterioration to asystole. The results of Study I are in line with these findings, as bystander CPR was found to be an independent predictor of survival and was associated with an increased proportion of patients found in shockable rhythm.

6.2 TYPE OF BYSTANDER – DOES IT MATTER?

The category of the bystander has been shown to influence survival. Bystander CPR performed by healthcare professionals is associated with a higher proportion of VF and increased survival compared with CPR by laypersons.[62, 122] Although many factors are involved, the quality of CPR, in terms of compression rate, depth of compression and hands-off time, is probably the key factor.[123] However, even when EMS personnel deliver CPR the quality may be far from optimal, with substantial hands-off time and too shallow chest compression.[124] With a CPR feedback device these factors have been improved among EMS providers.[125] Although difficult to assess, one may assume that healthcare personnel find it easier to identify a cardiac arrest and may therefore initiate CPR more rapidly after a collapse than laypersons.

As shown in Study I, the proportion of laypersons performing CPR, trained or untrained, has increased over the last few years in Sweden. Besides the influence of educational campaigns in Sweden, one factor that may also have contributed to the increase is CPR guidance by telephone from dispatchers to untrained bystanders, which started in 1997.

In previous studies layperson CPR has been associated with a twofold increase in the chance of survival compared with no CPR.[122] However, the data is very limited as regards outcome and the level of training among lay rescuers. This has also been difficult to assess in studies involving the Swedish Cardiac Arrest Register, as this information is not required when the EMS crew fill in the register form. In some studies, survival rates have been reported to be similar when poor CPR has been performed by an untrained bystander versus no CPR.[61] In Study I, no data existed on the level of training of bystanders and therefore this could not be assessed. In addition, the quality of CPR could not be assessed in Studies II–IV, which would have been interesting for several reasons. In Study II the quality of CPR might have been affected by application of the cooling device. In Study III, CPR quality in comparison between EMS and fire-fighters may have differed. In Study IV regional differences in CPR quality carried out by EMS and fire-fighters may have had an effect.

6.3 WHAT ARE THE LIMITATIONS OF THE SWEDISH CARDIAC ARREST REGISTER?

A register is no better than the quality of data recorded. Since 2009 the Swedish Cardiac Arrest Register has included all the EMS organisations in Sweden and it thus covers the vast majority of the population. However, at the start in 1990 only a few EMS organisations reported to the register, and the number has increased gradually. In Study I this makes comparison of data from the early study period (i.e. 1992–95) with that of a more recent time (i.e. 2002–2005) somewhat difficult, as we might have been looking at slightly different populations. At the end of the study period for Study I (2005) about 70% of EMS organisations were included. Thus, when missing data from one third of the population the results are more difficult to generalise. In addition, we do not know if all cases of OHCA were included in the register. One might suggest that in cases where the EMS crew is not playing an active part in CPR (e.g. when a public AED is used and ROSC is achieved prior to ambulance arrival) the reporting rate may be lower.[126] Evaluating data in observational studies always carries a risk that some confounding factors will not be included in multivariate analyses.

6.4 WHY IS THE INITIAL RHYTHM SO IMPORTANT FOR SURVIVAL?

The presence of VF as first recorded rhythm is the strongest predictor of survival in cases of OHCA. This well-established fact was confirmed by the results in Studies I and III. To have VF as first rhythm is both an indicator of the origin (i.e. cardiac origin) and the duration (i.e. before deteriorating to asystole) of cardiac arrest. In our material the VF rate ranged from 20% to 43%. However, the VF rate at the time of cardiac arrest is probably much higher. Estimations have been made suggesting a VF incidence of 60–70% at the time of arrest.[39] In some settings, e.g. cardiac arrests occurring in aircraft or at public venues with an AED close by, the VF rate has been described as being as high as 59% to 65%.[33, 45]

In Study III the use of first responders reduced the time to quality CPR and connection of an AED by one minute. This might be the mechanism behind the increased VF incidence seen in this study. In addition, high quality CPR with short pre-shock pauses and accurate chest compression has been shown to increase the chance of successful defibrillation and it most likely has a direct impact on clinical the outcome.[127, 128]

6.5 HOW IMPORTANT IS TIME TO CPR AND DEFIBRILLATION?

The chain-of-survival concept is focused on time to treatment. Use of survival models has suggested that each minute of delay to defibrillation in VF patients reduces the probability of survival by around 10%.[60, 129] To shorten the time to high-quality CPR and defibrillation was the rationale behind Study III. In previous studies, short time intervals to CPR and defibrillation have been shown to improve survival rates.[60-62] If defibrillation can be carried out within the first 3 to 5 minutes after cardiac arrest, survival rates well over 50% have been presented.[72, 77, 79, 130] However, the findings in Study IV suggest that the relationship between time reduction and survival may not be proportional (Figure 7). A relatively small gain in time in areas with a shorter response time seems to be more important than a substantial time reduction in regions with longer response times. The implication of this finding is that there might be a breakpoint where time reduction after a certain duration is of less value. In areas with long response times of EMS and first responders, other ways need to be explored to recruit rescuers to the scene.

6.6 WHERE DO WE HAVE THE BEST USE OF FIRST RESPONDERS?

The results in Study III indicate an overall benefit of the use of a first responder system in cases of OHCA, with significantly increased 30-day- and 3-year survival. However, when assessing the different subpopulations we can see that the effect is outstanding in witnessed arrests and in patients with VF as first rhythm. This is in line with other reports and with the results of a pilot study preceding Study III, where none of the survivors were among non-witnessed arrests.[1, 35] The implication of this is that it might be useful to explore ways towards more restricted dispatching of fire-fighters, limited to only bystander witnessed cases. However, this requires a high level of expertise among dispatchers to rapidly identify the circumstances of the arrest. Furthermore, in Study III there was no benefit among patients with non-shockable rhythms in any of the outcome measures: ROSC, admitted alive, 30-day- or 3-year survival. These findings are similar to those in other first-responder studies.[73, 75, 76] To improve outcome in this patient group remains a challenge. In Study IV we saw that dual dispatch can reduce time intervals in different regions with various population densities. However, the survival rate in scarcely populated areas was unchanged, in accordance with the results of other studies.[116, 131] In this setting, other approaches to recruit resources might be needed.

6.7 DOES THE NUMBER OF PERSONS ON THE SCENE MATTER?

The optimal number of trained persons (i.e. EMS and first responders) on the scene during resuscitation in a case of OHCA is unknown. Some data exists which suggests that multiple lay rescuers on the scene of an arrest prior to EMS arrival could be associated with improved CPR quality.[132] Historically, ERC ALS teaching scenarios concern four or even five people.[133] One potential effect of the intervention in Study III was the recruitment of more skilled persons (i.e. fire-fighters in addition to EMS) to the scene of the arrest. Besides an earlier start of resuscitation, this could also mean an improved quality of ALS. Over time, one might assume that the roles of fire-fighters and EMS crews have become more established. As previously discussed, the number of persons on the scene might improve the quality of CPR.[124, 127, 134] With skilled fire-fighters on the scene, EMS crews are not restricted to performing CPR but can focus on the next step, such as drug administration and airway management.

6.8 HOW IMPORTANT ARE IN-HOSPITAL FACTORS?

Post-resuscitation care at intensive care units has improved significantly during the last decade and has most likely contributed to increased in-hospital survival. Therapeutic hypothermia has been tested in randomised controlled trials and is discussed in the next section. However, the level of evidence concerning other specific in-hospital measures following cardiac arrest is generally low and is derived mostly from observational studies, specific or combined interventional studies using historical controls, or small randomised series (e.g. concerning glucose levels).[55, 88] Some of these factors are presented in Table 4. In many aspects, this is a difficult population to investigate in observational studies. The risk of selection bias is particularly high, as many of the forms of in-hospital intervention in these patients, such as coronary angiography, will not be considered unless the patient shows signs of neurological recovery. Some in-hospital factors were considered in Study III in order to assess their potential impact on outcome during the study period. We could see a difference in the proportion of patients where angiography was performed more than 24 hours after the arrest. This may indicate a different approach between the control- and the intervention period concerning the use of coronary angiography in these patients.

Perhaps most debated over the past few years is the potential benefit of immediate angiography in patients without STEMI. As in aware patients, immediate angiography is recommended in OHCA survivors with ST elevation, which in small studies has been associated with improved outcome.[109, 135] Although the results of several studies have confirmed that significant lesions (up to 58%) and occlusions (up to 27%) may occur even in the absence of ST elevation,[104-106] the value of immediate coronary angiography in non-STEMI cases is undetermined and this needs to be tested in randomised trials. [136, 137]

6.9 HOW SHOULD THERAPEUTIC HYPOTHERMIA BE USED?

Brain injury is the cause of death in two-thirds of resuscitated cardiac arrest patients that are admitted to hospital.[138] Hypothermia has been shown to have a range of neuroprotective effects after cardiac arrest, limiting the effect of the global ischaemia/reperfusion injury by reducing the pathological mechanisms of ischaemia, decreasing cerebral metabolism, slowing the ischaemic loss of ion gradients and exerting anti-inflammatory effects.[93]

As described earlier, in-hospital therapeutic hypothermia in VF patients has been shown to improve neurological function six months after cardiac arrest.[94, 95, 139] Therapeutic hypothermia is now integrated in current guidelines and for many years has been an established treatment at intensive care units.[55] However, this approach has been challenged recently in a large randomised hospital study where fever was avoided and hypothermia to 33 °C versus 36 °C was compared.[96] In this study, with a slightly different study population in comparison with the previous studies (e.g. all rhythms included and, except for patients with asystole, unwitnessed arrests as well) no differences in outcome were seen between the treatment groups. In Study III, there was no difference in the control and intervention groups in the proportion of patients treated by means of therapeutic hypothermia. In logistic regression analysis of patients admitted alive with VF as first rhythm, therapeutic hypothermia was not associated with improved 30-day- or 3-year survival.

6.10 HOW CRUCIAL IS THE TIME TO COOLING?

In Study II we investigated the safety and feasibility of very early induction of hypothermia as early as during CPR, hours before the start of cooling in most hospital studies.[140] The pathophysiology of global ischaemic/reperfusion injury that is triggered at the time of cardiac arrest provides a strong argument for such intervention to avoid deleterious cellular damage.[92, 93] The immediate injuries induced by the global ischaemic/reperfusion response after OHCA are particularly damaging in the brain.[92, 93] The current consensus of opinion is also to initiate cooling as soon as possible. [55, 67] The existing experimental data are convincing as regards the benefit of hypothermia after circulatory arrest.[98, 141] These studies are mainly based on early cooling, induced during CPR (i.e. intra-arrest) or very soon after the circulation has been restored (i.e. post-ROSC), with clear superiority of rapid intra-arrest cooling over cooling initiated post-ROSC.[97] [142] In addition, numerous cases of severe accidental hypothermia occurring before or just after cardiac arrest have shown the potential of cooling to protect the brain from injury. [143, 144] Starting cooling at a later stage, after several hours, has not been widely tested in animals. Thus, when moving from very early cooling in an experimental setting to several hours of delay in clinical practice, we might miss the time-window for the best effectiveness of hypothermia.[145]

6.11 IS THE METHOD OF COOLING OF IMPORTANCE?

To be able to start early intra-arrest cooling in the field a safe and reliable method is needed that can be used by the EMS. The predominating method used is administration of cold intravenous (i.v.) saline, which in several smaller studies has been shown to be safe and feasible for use intra-arrest and post-ROSC and has resulted in a lowered temperature on hospital arrival (by 1.2 to 2.1 °C).[101, 102, 146] However, in two recent randomised clinical trials no benefit of early post-ROSC cooling compared with hospital cooling alone was found.[99, 100] In these studies, patients were randomised minutes after ROSC to either i.v. cooling with up to 2 litres of cold saline or to standard ALS treatment. In addition, patients randomised to pre-hospital cooling in the larger study showed an increase in haemodynamic side-effects, with a significantly increased number of re-arrests, poorer oxygenation and increased pulmonary oedema at admission. These findings suggest that an i.v. volume load directly after ROSC may be harmful.

In Study II, we assessed another method of in-field cooling of OHCA patients. The technique of trans-nasal evaporative cooling was developed primarily to cool the brain. In Study II we concluded that trans-nasal evaporative cooling is an easily applicable and effective cooling method that can be induced during cardiopulmonary resuscitation. It was safe to use, significantly lowered the patients' temperature at hospital arrival and it shortened the time to achieve the target temperature of <34°C. The method involves continuous cooling without an i.v. volume load, which most likely is advantageous compared with the use of cold i.v. fluids.[113, 147]

There are two on-going randomised clinical trials that have been set up to investigate the effect of intra-arrest cooling versus hospital cooling that will add important information to this field of research. One of them involves trans-nasal evaporative cooling [148] and the other one is involves the use of cold fluid as the pre-hospital cooling method.[149]

6.12 SOME ETHICAL ASPECTS OF CARDIAC ARREST RESEARCH

To perform high quality research within the field or resuscitation is a major challenge. Most of the studies in this field origin from experimental studies, retrospective studies, prospective observational studies or before/after studies. In general the level of evidence from these types of studies is very limited. The approaches are certainly valuable to highlight certain issues or generating hypothesis for future research. However, the need of randomised controlled trials is essential to assess new (or old) treatments, their potential benefit and whether they are cost effective or not.

There are several ethical concerns in performing research in cardiac arrest patients. One of the most debated issues is the informed consent procedure, which is impossible to perform in unconscious patients. In addition, to ask relatives for permission to enrol the person in a research study in this critical situation when the emphasis must be on the medical management is very difficult and may also delay necessary actions. Recent directives within the European Union[150] and the US[151] have made research in unconscious persons more difficult when the patient's autonomy cannot be ensured prior to enrolment. However, to improve the chances of survival at a population level, exceptions from these directives are most probably needed. In study III, the preceding pilot study showed very promising results on survival rates, which consequently made randomisation very difficult. In study II informed consent was received from all surviving patients and from next of kin in cases where the patients did not survive. To discuss with relatives about consent for a clinical study when their close relative recently died from a cardiac arrest is very challenging. To explore ways to reduce some of the barriers associated with performing research in these patients are needed to improve the quality of evidence in the treatment of cardiac arrest.

7 CONCLUSIONS

Between 1992 and 2005 there was substantial increase in bystander CPR in cases of out-of-hospital cardiac arrest in Sweden, performed by laypersons. Bystander CPR was associated with positive effects on both ventricular fibrillation and survival.

Pre-hospital intra-arrest trans-nasal cooling is safe and feasible in cases of out-of-hospital cardiac arrest and is associated with a significant improvement in the time interval required to cool patients.

The implementation of a dual dispatch system using fire-fighters as first responders in addition to EMS significantly shortened response times and was associated with substantially improved 30-day survival and survival after 3 years in cases of out-of-hospital cardiac arrest.

Dual dispatch of fire-fighters and EMS reduced response times in all studied regions, ranging from very rural areas to very densely populated areas in Stockholm. However, the effect of this intervention on 30-day survival rates varied depending on population density, with the lowest impact in the rural areas.

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