ANTTI KÄMÄRÄINEN

Prehospital Cardiac Arrest and Induction of Mild Hypothermia

Studies on epidemiology and feasibility

ACADEMIC DISSERTATION
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Introduction

Cardiac arrest is defined as the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation (Jacobs et al. 2004). Among adult population, it is the leading cause of death in Western Countries (Kesteloot et al. 2006; Priori et al. 2001). In the majority of cases a structural abnormality or ischaemia has a triggering role in the onset of cardiac arrest but in 5 % of cases cardiac arrest occurs in a structurally normal heart and in some cases cardiac arrest is the first symptom of an underlying disease (Anonymous 1997; ERC 2005; Huikuri et al. 2001; Myerburg et al. 1993).

The concept of cardiopulmonary resuscitation (CPR) is an attempt to prevent premature death due to an unanticipated cardiac arrest. Resuscitative measures have been practiced throughout the history of mankind (Cooper et al. 2006), but the components of modern CPR such as chest compressions, defibrillation and artificial ventilation were introduced in the late 1950's and early 1960's (Kouwenhoven et al. 1960; Safar et al. 1958; Zoll et al. 1956). Currently the process of resuscitation consists of a chain of interventions provided by laypersons and numerous medical professionals (Nolan et al. 2006). Whether the links in this chain of survival were strong or not, resuscitation is unsuccessful in 70 to 95 % of cases (ERC 2005). Hence, the attempt of resuscitation is not always justified and due to futility CPR should not be initiated in certain cases of cardiac arrest.

Even when initial resuscitation is successful and spontaneous circulation is restored, survival to hospital discharge is poor. Approximately only 11 % of out-of-hospital cardiac arrest victims in Europe eventually survive to hospital discharge (Atwood et al. 2005). In the United States, overall survival rates have ranged from 2 to 33 % depending on EMS system configuration and patient characteristics (Becker et al. 1991; Eisenberg et al. 1990; Lombardi et al. 1994). Of those who die during post-resuscitation care in the intensive care unit, the cause of death in two thirds is neurological injury (Laver et al. 2004). Recent advances in post-resuscitation treatment include the introduction of mild therapeutic hypothermia. Decreasing core temperature between 32 to 34 °C for 12 to 24 hours has been shown to improve the neurological outcome and overall survival of successfully resuscitated comatose victims of out-of-hospital cardiac arrest (Bernard et al. 2002; HACA 2002). Current resuscitation guidelines recommend the use of mild induced hypothermia in cases of out-of-hospital cardiac arrest with ventricular fibrillation as initial rhythm. Additionally, the treatment should be considered in cases of non-shockable initial rhythms and in cases of in-hospital arrest also (ERC 2005). Preferably, the treatment should be initiated as soon as possible (ERC 2005; Safar and Kochanek 2002b) such as in the prehospital setting. Furthermore, reports from experimental studies

have suggested that delay to cooling diminishes the beneficial effects of induced hypothermia and that ideally cooling should occur already during resuscitation (Abella et al. 2004; Nozari et al. 2006).

The purpose of this study was to prospectively investigate the epidemiology of out-of-hospital cardiac arrest in the city of Tampere, Finland and the grounds of the EMS personnel to withhold resuscitative efforts. The feasibility and effects of cooling using infusion of ice-cold fluid was investigated in prehospital cardiac arrest after return of spontaneous circulation and in a smaller patient population already during CPR.

Tiivistelmä

Äkillinen sydänperäinen kuolema sepelvaltimotaudin seurauksena on aikuisväestön merkittävin kuolinsyy teollistuneissa maissa. Sydänpysähdys voi olla piilevän sepelvaltimotaudin ensimmäinen oire tai tapahtua yllättävästi aiemmin terveelle ihmiselle rytmihäiriön pohjalta. Elvytystoimin pyritään palauttamaan elimistön oma verenkierto. Hoidon kulmakivinä ovat tehokas painelu-puhalluselvytys sekä varhainen rytmihäiriöiden hoito defibrillaatiolla. Verenkierron palauduttua toipumista tuetaan elvytyksen jälkeisellä tehohoidolla.

Elvytyksellä ei aina saavuteta potilaan verenkierron palautumista tai elvytyksen jälkeen potilaan toimintakyky ei palaudu mielekkäälle asteelle. Taustalla on usein palautumaton sydänpysähdyksen syy, pitkittynyt elottomuus tai vaikea perussairaus. Näissä tapauksissa on pidättäydyttävä elvytystoimista.

Uusin elvytyksen jälkeinen hoitomuoto on elimistön viilentäminen 32–34 °C:een ydinlämpöön 12–24 tunnin ajaksi. Tämä hoitomuoto parantaa sydänpysähdyspotilaiden hengissä selviytymisen ennustetta ja neurologista toipumista. Hoidon teho perustuu vähentyneeseen metaboliaan ja hapen tarpeeseen sekä solutason suojamekanismeihin. Alustava tieteellinen näyttö tukee viilennyshoidon aloittamista mahdollisimman varhaisessa vaiheessa. Viitteitä on hoidon tehon heikentymisestä, mikäli viilennyksen aloitus viivästyy.

Väitöstutkimuksen tarkoituksena oli selvittää äkillisen sairaalan ulkopuolisen sydänpysähdyksen ja elvytyksen ilmaantuvuutta Tampereen kaupungin ensihoitojärjestelmän alueella. Tutkimus toteutettiin vuoden ajalla suoritettuna prospektiivisena tiedonkeruuna kattaen kaikki sydänpysähdystilanteet, joissa elvytystoimenpiteet aloitettiin tai näitä harkittiin ensihoitohenkilöstön toimesta. Tiedonkeruu toteutettiin kansainvälisten Utsteinin kriteerien mukaisesti. Erityistä huomiota kiinnitettiin tilanteisiin, joissa ensihoitohenkilöstö pidättäytyi elvytystoimista.

Lisäksi tutkittiin terapeuttisen viilennyshoidon varhaista aloitusta kylmällä laskimonsisäisellä nesteinfuusiolla. Hoito aloitettiin sairaalan ulkopuolella välittömästi spontaaniverenkierron paluun jälkeen infusoimalla +4 °C:sta Ringerin liuosta. Viilennyksen tehoa ja turvallisuutta verrattiin tavanomaiseen elvytyksenjälkeiseen hoitoon satunnaistetussa tutkimusasetelmassa.

Jatkotutkimuksena selvitettiin terapeuttisen viilennyshoidon aloitusta jo elvytyksen aikana kylmin infuusionestein. Viilennyshoidon tavoitteeksi asetettiin ydinlämpö 33 °C nenänielusta mitattuna. Viilennyksen tehon lisäksi arvioitiin hoidon turvallisuutta spontaaniverenkierron paluun ja hemodynaamisen vakauden suhteen.

Epidemiologisessa selvityksessä todettiin sairaalan ulkopuolisen elvytyksen ilmaantuvuudeksi 46 tapausta 100 000 henkeä kohden vuodessa. Kokonaisselviytyminen elvytyksestä aineistossa oli 13 %, joka on kansainvälisiin raportointeihin nähden keskitasoa eurooppalaisten selviytymislukujen ollessa 5.6 - 19.6 %. Kansainvälisiin raportointeihin verrattuna Tampereen kaupungin ensihoitohenkilöstö aloitti elvytystoimet harvemmin. Tarkempi selvitys elvytyksestä pidättäytymisen syistä osoitti, että selvät huonon ennusteen merkit vaikuttivat päätöksen tekoon. Syistä merkittävimpiä olivat sekundääristen kuolonmerkkien ilmentyminen, havaitsematon sydänpysähdyksen alku ja asystole ensimmäisenä rekisteröitynä rytminä.

Interventiotutkimuksissa todettiin kylmän Ringerin liuoksen infuusio sekä elvytyksen aikana että spontaaniverenkierron paluun jälkeen turvalliseksi ja tehokkaaksi menetelmäksi aloittaa terapeuttinen viilennyshoito. Spontaani jäähtyminen elvytyksen aikana ja sydämen käynnistymisen jälkeen ei laskenut ydinlämpötilaa terapeuttiselle tasolle (32–34 °C). Viilennyshoito ei selvästi heikentänyt spontaaniverenkierron palautumisen todennäköisyyttä tai aiheuttanut verenkierrollisia ongelmia tämän jälkeen. Elvytyksen aikaisen viilennyksen osalta kontrolliryhmän puuttuminen edellyttää kuitenkin jatkotutkimuksia hoidon tehon ja turvallisuuden tarkemmaksi määrittämiseksi.

Väitöstyön päätelminä voidaan todeta sairaalan ulkopuolisen elvytyksen ilmaantuvuus ja sydänpysähdyksestä selviytyminen kansainvälisesti vertaillen. Ensihoitohenkilöstön päätökset pidättäytyä elvytyksestä ovat nykytietoon pohjautuen perusteltuja. Terapeuttinen viilennyshoito voidaan aloittaa turvallisesti ja tehokkaasti jo sairaalan ulkopuolella kylmin infuusionestein.

Abstract

Aim: To study the epidemiology of prehospital cardiac arrest in Tampere, Finland with a focus on patients in whom resuscitation was not attempted. Additionally, the application of induction of mild hypothermia using infusion of ice-cold intravenous fluid in the prehospital setting was investigated. This method of intervention was carried out both as a randomized, controlled trial of cooling after return of spontaneous circulation as well as a feasibility trial of intra-arrest cooling.

Materials and methods: The epidemiological investigation was carried out in the city of Tampere, Finland, with a population of 203 000. The incidence and outcome of out-of-hospital cardiac arrest was assessed according to the Utstein guidelines during a prospective, twelve month study period.

A randomized, controlled trial of prehospital induction of therapeutic hypothermia using infusion of ice-cold fluid was conducted in the physician staffed helicopter emergency medical service of the Helsinki area. A weight-adjusted volume of +4 °C Ringer's solution with a target nasopharyngeal temperature of 33 °C was infused after return of spontaneous circulation.

The feasibility, effects and safety of intra-arrest cooling were studied in paramedic-treated victims of prehospital cardiac arrest. Paramedics infused +4 °C Ringer's solution during cardiopulmonary resuscitation with a target temperature of 33 °C. Changes in nasopharyngeal temperature and the haemodynamic effects such as the rate of rearrest, pulse rate and blood pressure were assessed.

Results: In the observational study, 191 patients were considered for resuscitation. In 98 cases (51 %), resuscitation was not attempted due to estimated futility in 97 cases and a do not attempt resuscitation- order in one case. The grounds of futility were the presence of secondary signs of death in 60% of the cases. Additionally, 97 % had asystole as the initial cardiac rhythm and 98% had suffered an unwitnessed cardiac arrest. The incidence of prehospital cardiac arrest mandating resuscitation was 46 per 100 000 per year. The overall survival after attempted resuscitation was 13 %.

In the randomized, controlled trial of prehospital cooling we observed a significantly pronounced cooling in the intervention group receiving a calculated mean volume of 30ml/ kg of ice-cold fluid; -1.5 (SD ± 0.8, range -2.8 to -0.2) °C vs. -0.1 (SD ± 0.6, range -1.5 to +1.5) °C in the control group, $p < 0.001$. Spontaneous cooling alone in the control group did not decrease nasopharyngeal temperature to the level of therapeutic hypothermia (32 to 34 °C). No immediate adverse effects such as increased rate of

rearrest, haemodynamic instability or pulmonary oedema were observed in the treatment group as compared to standard fluid regimen.

Intra-arrest induction of therapeutic hypothermia was found feasible and effective as regarding to the decrease in core temperature. In comparison to previous reports on prehospital cardiac arrest, the rate of return of spontaneous circulation and the rate of rearrest were comparable. Therefore this approach to early cooling seems safe, although the lack of control group does not permit definitive conclusions.

Conclusions: The incidence and overall survival of prehospital cardiac arrest in Tampere, Finland is similar to the majority of previous trials. However, the proportion of attempted resuscitations (51%) is lower than in some study centres with resuscitation attempted in up to 96 % of emergency medical service (EMS) attended cardiac arrests. The difference in attempted resuscitation proportions might reflect dissimilar EMS dispatch criteria or resuscitation protocols. More likely, however, this might be explained by non-uniform methods of reporting such as excluding cases where resuscitation has been considered but not attempted instead of including all cases of considered for resuscitation as the denominator. In most cases in this study, the decision to withhold resuscitation was based on strong indicators of negative outcome such as signs of irreversible death.

Induction of mild hypothermia after return of spontaneous circulation significantly lowered core temperature compared to spontaneous cooling alone. In this small study sample, this method of cooling was comparable to conventional post resuscitation treatment in terms of safety. Early cooling using infusion of large volume ice-cold intravenous fluid was also found feasible during ongoing cardiopulmonary resuscitation. In comparison to previous reports on standard resuscitation treatment, intra-arrest cooling did not reduce the rate of return of spontaneous circulation or increase the rate of rearrest. However, e.g. due to the lack of control group and small sample size, further studies evaluating the safety and benefits of early cooling are necessary, but seem justified.

Contents

Abbreviations

AED	Automated external defibrillator
ALS	Advanced life support
ASY	Asystole
ATP	Adenosine triphosphate
BLS	Basic life support
CPC	Cerebral performance category
CPR	Cardiopulmonary resuscitation
DIC	Disseminated intravascular coagulation
DNAR	Do not attempt resuscitation
ED	Emergency department
ECG	Electrocardiogram
EMS	Emergency medical service
EMT	Emergency medical technician
ERC	European Resuscitation Council
FRU	First responding unit
HEMS	Helicopter emergency medical service
ICU	Intensive care unit
ILCOR	International Liaison Committee on Resuscitation
LVICF	Large-volume ice-cold fluid
OOHCA	Out-of-hospital cardiac arrest
PEA	Pulseless electrical activity
RCT	Randomized controlled trial
ROS	Reactive oxygen species
ROSC	Return of spontaneous circulation
TCRA	Traumatic cardiorespiratory arrest
TOR	Termination of resuscitation
VF	Ventricular fibrillation
VT	Ventricular tachycardia
WHO	World Health Organization

List of Original Publications

This thesis is based on the following original publications, which will be referred to in the text by their Roman numerals I to IV.

I. Kämäräinen A, Virkkunen I, Yli-Hankala A, Silfvast T. Presumed futility in paramedic-treated out-of-hospital cardiac arrest: An Utstein style analysis, in Tampere, Finland. Resuscitation 2007;75:235-243.

II. Kämäräinen A, Virkkunen I, Tenhunen J, Yli-Hankala A, Silfvast T. Prehospital therapeutic hypothermia for comatose survivors of cardiac arrest – A randomized controlled trial. Acta Anaesthesiologica Scandinavica 2009; *in press*. DOI: 10.1111/j.1399-6576.2009.02015.x

III. Kämäräinen A, Virkkunen I, Tenhunen J, Yli-Hankala A, Silfvast T. Prehospital induction of therapeutic hypothermia during CPR: A pilot study. Resuscitation 2008;76:360-363.

IV. Kämäräinen A, Virkkunen I, Tenhunen J, Yli-Hankala A, Silfvast T. Induction of therapeutic hypothermia during prehospital CPR using ice-cold intravenous fluid. Resuscitation 2008;79:205-211.

Review of the Literature

Cardiac arrest

The cessation of cardiac activity, i.e. cardiac arrest, is an inevitable part of natural death. Manifestations include unresponsiveness, lack of detectable pulse and apnea or agonal respirations (Jacobs et al. 2004). If untreated, this condition inexorably leads to death. The circumstances under which cardiac arrest and subsequent death are considered sudden of nature have been debated for decades (Biorck and Wikland 1972; Engdahl et al. 2002). A task force of the European Society of Cardiology recommends defining sudden cardiac death as an unexpected event occurring within one hour of the onset of acute symptoms (Priori et al. 2001). Notable is that cardiac death can be sudden regardless of a pre-existing heart disease, but that traumatic aetiology needs to be excluded.

In 1985, a scientific work group of the World Health Organization (WHO) estimated that in industrialised countries approximately 30 sudden cardiac deaths occur per million persons weekly (Anonymous 1985). Calculated according to the 2005 population in Europe of approximately 728 million, this would translate to over a million annual sudden cardiac deaths in Europe alone. However, since the 1970's and until 2000, an annual ~1.3 % decrease in mortality due to cardiovascular diseases has occurred in Western Europe countries (Kesteloot et al. 2006). Although a significant decrease in the mortality due to ischaemic heart disease has occurred especially in the Western Europe, it remains to be the most important cause of sudden death in the adult population in industrialized countries (Kesteloot et al. 2006; Priori et al. 2001).

Aetiology

In the majority of cases of sudden out-of-hospital cardiac arrest (OOHCA), the aetiology is of cardiac origin (Fischer et al. 1997; Kuisma and Määttä 1996). Specifically, coronary artery disease accounts for up to 80% of sudden cardiac deaths with heart failure as the second most important cause (Chugh et al. 2004; Gorgels et al. 2003; Myerburg 1987). The underlying pathophysiology is considered to consist of an acute thrombosis of a coronary artery or a pre-existing myocardial scar giving rise to a malignant arrhythmia (Bayes de Luna et al. 1989; Davies et al. 1989; Davies and Thomas 1984; Uretsky et al. 2000).

However, sometimes cardiac arrest occurs in otherwise previously healthy and young persons and the subsequent death is unanticipated (de Vreede-Swagemakers et al. 1997). In a four year prospective study of prehospital cardiac arrest conducted in the Maastricht area, only 46 % of the victims had a history of cardiac disease (Gorgels et al. 2003). Cardiac arrest may thus be the first manifestation of an underlying undiagnosed pathologic condition such as coronary artery disease or, in structurally normal hearts, an inherited predisposition to malignant arrhythmia (Chugh et al. 2000; Huikuri et al. 2001; Kannel et al. 1985).

Non-cardiac causes of cardiac arrest include trauma, hypovolemia, intoxication, pulmonary embolism, suffocation, near drowning, severe neurological insults and pulmonary diseases (Claesson et al. 2008; Engdahl et al. 2002; ERC 2005; Hess et al. 2007; Kuisma and Alaspää 1997a; Nichol and Baker 2007; Silfvast 1991; Virkkunen et al. 2008). Reflecting the critical process of the initial insult eventually leading to cardiac arrest, these aetiologies are associated with lower survival rates than cases of cardiac origin (Huber-Wagner et al. 2007; Kuisma and Alaspää 1997a). Also the preferred treatment may differ from standard resuscitation protocol, e.g. in cases of traumatic cardiorespiratory arrest (ERC 2005; Huber-Wagner et al. 2007).

Cardiac arrest is considered to be of cardiac origin if no other obvious aetiological factors are present (Cummins et al. 1991). Thus, the cause of arrest is a working hypothesis involving the risk of false diagnosis regarding the aetiology (Kurkciyan et al. 1998). However, the initial cardiac rhythm at the time of arrest is reflective of the cause of arrest (Kurkciyan et al. 1998).

Initial cardiac rhythm

In arrests of cardiac origin, the initial malignant arrhythmia in the majority (60 to 70%) of cases is estimated to be ventricular fibrillation (VF) (Holmberg et al. 2000a). However, this rate is only estimation as it is not possible to identify the true initial cardiac rhythm in all cases of OOHCA for monitoring has not been commenced prior to collapse. Nevertheless, in 157 patients suffering sudden cardiac death during ambulatory monitoring of cardiac rhythm the cause of death was ventricular arrhythmia in 84 % (Bayes de Luna et al. 1989) with VF being the most frequent arrhythmia. VF may be triggered directly due to a pre-existing medical condition such as long QT-syndrome, or it may be preceded by a brief run of pulseless ventricular tachycardia (VT) - an initial rhythm of cardiac arrest met only seldom. The lifespan of VF consists of an initial high amplitude coarse electrical activation of cardiomyocytes which over time deteriorates into lesser amplitude and eventually no electrical activity in the myocardium is detected (Guyton and Hall 2000). This conversion of VF to asystole occurs relatively slowly as of patients met in VF after OOHCA, this arrhythmia is present in approximately 40% of patients even after 25 to 30 minutes following the onset of arrest (Holmberg et al. 2000a).

The treatment of choice in VF and pulseless VT is the rapid delivery of an electric countershock, i.e. defibrillation, which carries the potential of terminating the chaotic

electrical activity in the myocardium and thus allowing for normal cardiac rhythm to take place (ERC 2005; Zoll et al. 1956). If the initial triggering cause is of reversible nature, such as transient arrhythmia, or if ischaemic myocardial irritation has subsided to sufficient extent, it is possible that return of spontaneous circulation (ROSC) will be maintained and post-resuscitation care initiated.

Due to dissimilar aetiology and pathophysiology compared to arrests of cardiac origin, in the cases of arrest due to non-cardiac causes the initial cardiac rhythm is commonly other than VF or pulseless ventricular tachycardia (VT) (Hess et al. 2007; Silfvast 1990). The cardiac rhythms commonly observed are pulseless electrical activity (PEA) and asystole. PEA and asystole are non-shockable rhythms as they do not respond to defibrillation. Underlying PEA and asystole, commonly a non-cardiac cause needs to be identified and treated to achieve ROSC. This aetiology may well be of such severity that treatment is futile.

According to the current definition, PEA reflects the cardiac state in which organized electrical activity is detectable in the ECG but no palpable pulse is present (ERC 2005; Stueven et al. 1989). There might be some degree of myocardial contractions present, but no circulation is generated and thus the condition represents the most severe form of cardiogenic shock. Other possible conditions include the presence of blood flow obstruction or restriction of cardiac contractions such as pulmonary embolism or pericardial tamponade (Kurkciyan et al. 2000; Varriale and Maldonado 1997). In asystole, no electrical activity is present in the ECG and cardiac function is in complete cessation. This is considered to reflect the state of a dying or dead heart. If left untreated, all other malignant arrhythmias eventually degrade to asystole and therefore asystole as the initial monitored cardiac rhythm may be the result of a prolonged period without circulation. Due to these reasons, asystole and PEA are associated with worse survival than VF as the initial rhythm in cardiac arrest. Other factors related to cardiac arrest outcome and epidemiological aspects are discussed below.

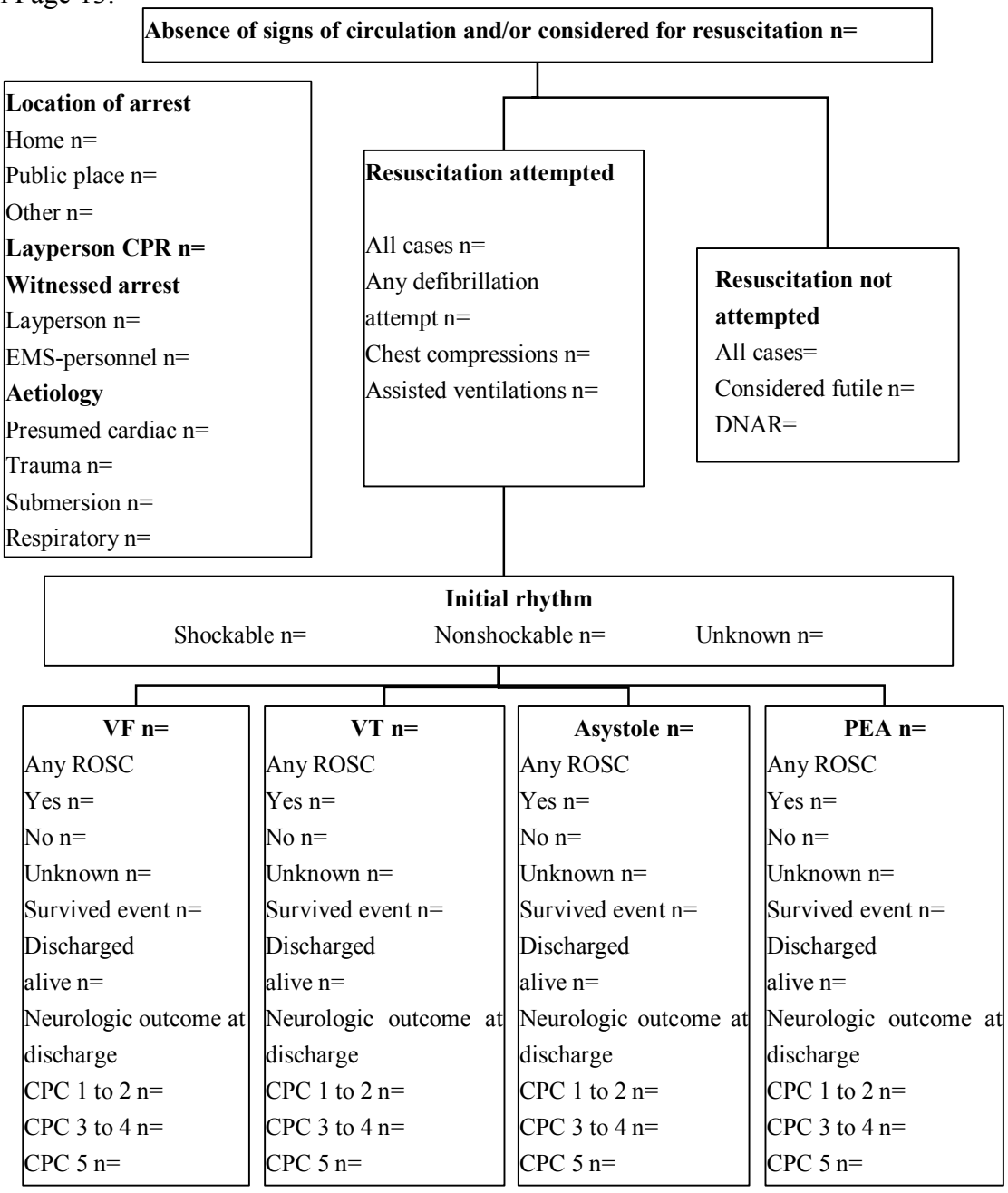
Incidence and survival after out-of-hospital cardiac arrest

To counteract sudden out-of-hospital cardiac arrest, resuscitative measures have been provided by emergency medical service (EMS) systems since the late 1960's (Pantridge and Geddes 1967). Following this, several reports on the epidemiology of prehospital cardiac arrest have been published with a varying degree of survival. In 1990, Eisenberg and colleagues shed light on the problem of non-uniform reporting. In one of their studies from 29 cities the overall survival rate ranged from 2 to 25% (Eisenberg et al. 1990). A significant cause for differing survival rates was the variability in basic definitions.

In 1991, guidelines for uniform data reporting from out-of-hospital cardiac arrest were published. These guidelines were entitled "Utstein style" based on the location in which the consensus meeting producing the guidelines was held – the Utstein abbey in Stavanger, Norway (Chamberlain et al. 1991). The guidelines provide a template for

recording of cardiac arrest data such as resuscitation characteristics, treatment and time intervals. Also specific definitions to certain basic terms such as cardiac arrest, return of spontaneous circulation and time intervals in cardiac arrest are presented. After 13 years in 2004, an updated and simplified version of these guidelines was published to provide a more accurate and practical tool for resuscitation research applicable also to the in-hospital and paediatric cardiac arrests (Jacobs et al. 2004). The purpose of these guidelines is to facilitate resuscitation research and to enable inter-system comparison of cardiac arrest variables and outcome such as survival and neurological status at the time of hospital discharge. The 2004 Utstein template is presented in Figure 1.

Figure 1. The Utstein template. Modified from Jacobs et al. 2004. Abbreviations as listed on Page 13.



In Europe, the annual incidence of sudden cardiac arrest treated by emergency medical service (EMS) systems is approximately 38 per 100 000 persons (Atwood et al. 2005). This is an overall incidence observed across 37 different European communities and excludes patients in whom resuscitation was not attempted. However, the actual incidence of sudden cardiac arrest and attempted resuscitation in a particular community is highly variable, ranging from 37 to 66 per 100 000 person-years (Atwood et al. 2005; Herlitz et al. 1999). Although a uniform template for data reporting is available, differences in exclusion and inclusion criteria exist in studies performed according to the Utstein style. This might partially explain the variability in incidence of sudden cardiac arrest in the prehospital setting (Fredriksson et al. 2003).

In Finland, the epidemiology of out-of-hospital cardiac arrest has been studied in Helsinki (Kuisma and Määttä 1996; Silfvast 1990). In the study by Kuisma and Määttä, resuscitation was considered in 79.8 patients and attempted in 66.7 per 100 000 persons per year. In addition to this, during the study period the EMS personnel were dispatched to 484 (93.8/100 000/year) cardiac arrest patients in whom irreversible signs of death were observed and resuscitation was not considered.

Of attempted resuscitations, approximately 10.7 % of the patients survive to hospital discharge in Europe (Atwood et al. 2005). Several factors associated with outcome from out-of-hospital cardiac arrest have been identified.

In some studies increasing age is associated with reduced survival (Herlitz et al. 2003; Herlitz et al. 2008). Specifically, among prehospital patients found in a non-shockable rhythm, survival decreased by 2 % per each year of increase in age (Herlitz et al. 2008). Survival to hospital admission is better in women (Herlitz et al. 2004; Mahapatra et al. 2005), but long term survival and quality of life have been observed to be equal among sexes (Mahapatra et al. 2005). Survival is decreased in cardiac arrests due to non-cardiac aetiology (Engdahl et al. 2003; Kuisma and Alaspää 1997a) as well as among patients suffering from OOHCA with a non-shockable initial cardiac rhythm (PEA or ASY) (Engdahl et al. 2001; Herlitz et al. 2008; Väyrynen et al. 2008a; Väyrynen et al. 2008b).

Better survival is observed if the onset of the cardiac arrest is witnessed and occurs in a public location (Herlitz et al. 2008). This usually promotes rapid activation of the EMS system and increases the chance of the victim to receive bystander CPR, factors associated with improved survival (Calle et al. 1997; Valenzuela et al. 1997). Improved survival is more likely if the delay to advanced life support (ALS) consisting rapid defibrillation is short (Herlitz et al. 2008; Valenzuela et al. 1997). After return of spontaneous circulation the quality of post-resuscitation care such as control of temperature, acid-base balance, seizures, blood glucose and potassium, and haemodynamics may also influence the outcome (Langhelle et al. 2005; Skrifvars et al. 2003).

In Table 1 are presented the incidence and survival rates of prehospital cardiac arrests in 13 European communities. Included were arrests of cardiac aetiology in which EMS personnel attempted resuscitation. Overall survival rates ranged from 5.6 to 19.6 % (Bottiger et al. 1999; Giraud et al. 1996; Hanche-Olsen and Nielsen 2002; Hassan et al. 1996; Hoeven et al. 1994; Kuisma and Määttä 1996; Rewers et al. 2000; Schneider et al.

1994; Skogvoll et al. 1999; Soo et al. 1999; Tadel et al. 1998; Weston et al. 1997). As discussed by Atwood et al in their review evaluating these results, the differences in survival rates may be due to differences in layperson or EMS response to cardiac arrest as well as due to treatment related factors (Atwood et al. 2005).

Community	Population served	All-rhythm arrests	All-rhythm incidence	All-rhythm survivors	Survival (%)	VF arrests	VF incidence	VF Survival (%)
Nottinghamshire UK (Soo et al 1999)	1,000, 000	1547	38.68	94	6.1	728	18.20	11.7
Leicestershire, UK (Hassan et al 1996)	900,000	159	17.67	19	12.0	85	9.44	22.4
St-Etienne, France (Giraud et al 1996)	571,191	113	19.78	8	7.1	45	7.88	17.8
Helsinki, Finland (Kuisma and Määttä 1996)	516,000	255	49.42	50	19.6	126	24.42	32.5
Copenhagen, Denmark (Rewers et al 2000)	465,000	703	50.39	82	11.7	414	29.68	17.9
South Glamorgan, UK (Weston et al 1997)	407,300	712	66.47	45	6.3	264	24.65	16.3
Ljubljana, Slovenia (Tadel et al 1998)	397,306	337	28.27	19	5.6	120	10.07	12.5
Heidelberg, Germany (Bottiger et al 1999)	330,000	338	34.14	48	14.2	106	10.71	34.0
Bonn, Germany (Fischer et al 1997)	240,000	464	48.33	74	16.0	210	21.88	26.7
Leiden, Netherlands (Hoeven et al 1994)	196,193	309	45.00	42	13.6	200	29.13	20.0
Mainz, Germany (Schneider et al 1994)	180,000	211	82.55	19	9.0	90	35.21	16.7
Trondheim region, Norway (Skogvoll et al 1999)	154,000	442	57.40	52	11.8	255	33.12	18.8
Bodo, Norway (Hanche-Olsen and Nielsen 2002)	34,500	123	50.93	23	18.7	62	25.67	32.3

Table 1. Incidence of EMS-treated all-rhythm and ventricular fibrillation cardiac arrest. Incidence is reported per 100,000 person-years. Modified from Atwood et al. 2005.

Withholding a resuscitation attempt

Withholding resuscitation in a victim of sudden cardiac arrest embraces aspects related to ethical, medical, legal and economical issues (Naess et al. 1997; Næss and Steen 2004; Pawl 2007; Suchard et al. 1999). Especially ethical standpoints are prone to subjectivity (Baskett and Lim 2004) that can and need not to be dictated on scientific basis only (Baskett et al. 2007; Baskett and Lim 2004). However, the generally accepted four principles of biomedical ethics – beneficence, non-maleficence, justice and autonomy – can be recognized in association with considered resuscitation also (Baskett et al. 2007; Beauchamp and Childress 2001; Beauchamp 2003; ERC 2005). Beneficence may represent an attempt to overcome premature death due to sudden cardiac arrest with resuscitative measures in one individual, whereas in other it may equal withholding these efforts – regarding both beneficence and non-maleficence, withholding a resuscitation attempt in a severely ill patient with no chance of reasonable recovery is to avoid prolongation of inevitable death and suffering (Baskett et al. 2007). Justice stands for righteousness of the resuscitation attempt, provided to all those who are considered to benefit from it but only for those and within the available resources so as not to compromise the care of others by wasting efforts in futile circumstances. Finally, autonomy addresses respecting the opinions and wishes of the individual patient, which, in the case of a sudden cardiac arrest, may remain unknown if advance orders are not available (Baskett et al. 2007; Schears et al. 2004).

However, even though the above discussed principlism of biomedical ethics might be generally agreed upon among healthcare professionals (Baskett et al. 2007) there still exists variability in ethical attitudes between similarly trained resuscitation professionals (Baskett and Lim 2004). Complicating the issue of withholding a potentially lifesaving treatment are the unrealistically optimistic expectations of the lay public regarding resuscitation preferences and survival (Adams and Snedden 2006; Marco and Larkin 2008; Nava et al. 2008; Van den Bulck 2002) even in cases of malignant disease or low functional status (Marco and Schears 2002).

Not all patients benefit of attempted resuscitation, as in survival or meaningful recovery can not be expected in all cases of sudden cardiac arrest (Baskett et al. 2007; Nichol and Baker 2007). Albeit futility and the concept of meaningful recovery being subjective grounds to evaluate the appropriateness of a resuscitation attempt (Baskett et al. 2007; Baskett and Lim 2004; Duchateau et al. 2008; Ferrand et al. 2006), current resuscitation guidelines acknowledge resuscitation to be futile in cases of a mortal injury, such as decapitation, hemicorporectomy, known prolonged submersion, incineration, rigor mortis, dependent lividity and fetal maceration (ERC 2005). Resuscitation is also recommended to be withheld in cases of unwitnessed arrest with initial cardiac rhythm of asystole, excluding cases of hypothermia and near-drowning (Kuisma and Jaara 1997b; Silfvast and Pettilä 2003; Väyrynen et al. 2008a; Wyatt et al. 1999). Otherwise EMS personnel generally initiate resuscitation in all prehospital cases of sudden cardiac arrest

if the patient is not known to have a do not attempt resuscitation (DNAR)-order (ERC 2005; Pepe et al. 2001).

In hospital, the decision to withhold or abandon a resuscitation attempt is usually made by the doctor responsible for the treatment of the patient in question (Baskett et al. 2007). The same does not necessarily apply to the prehospital setting (Naess et al. 1997). Some EMS systems have no online medical direction and the decision whether to resuscitate or not is ultimately left to be made by paramedics or emergency medical technicians (Baskett et al. 2007; Weston et al. 1995). A physician may be consulted or a predefined protocol may exist, but, regarding the nature of a resuscitation attempt there is a need for immediate decision-making (Lockey 2002; Weston et al. 1995).

A particular aspect of prehospital emergency medicine is the lack of complete information concerning the patient, such as medical history or requests regarding resuscitation and life support, which further complicates the decision-making (Duchateau et al. 2008; ERC 2005; Ferrand et al. 2006; Iserson 1991). Two recent studies have evaluated end-of-life decisions in physician staffed prehospital EMS systems (Duchateau et al. 2008; Ferrand et al. 2006). In the prospective French study on 227 cardiac arrest victims, resuscitation was withheld by the physician in 113 cases. Withholding resuscitation was associated with lesser pre-existing functional independence and lower cognitive status, but how exactly this information was achieved in the prehospital setting was not described (Duchateau et al. 2008). Alike to the results by Duchateau and colleagues, in another French study approximately half of the decisions to withhold life-sustaining treatment were conducted by a single physician alone (ERC 2005; Ferrand et al. 2006; Francois-Xavier et al. 2008). In the majority of cases, the decision to withhold treatment was based on the subjective expectation of death in the short term (Ferrand et al. 2006).

Although prehospital physicians and paramedics have been observed to conduct end-of-life decision-making on similar bases (Naess et al. 1997), the general recommendation is that a physician should be consulted and among physicians consensus be sought when resuscitation is considered to be withheld (Baskett et al. 2007; ERC 2005; Ferrand et al. 2006). Optimally, the preferred course of treatment would be discussed with the patient prior to critical illness – 90 % of non-critically ill patients would prefer being asked their perception regarding a DNAR- order (Gorton et al. 2008). However, advance directives are not common in the prehospital setting with one study reporting a rate of 13 % among 724 non-hospitalized healthy respondents (Marco and Schears 2002). When possible, the perceptions of the close relatives of the patient should be taken into account when the decision whether to resuscitate is made (Baskett et al. 2007; Gorton et al. 2008).

From an economical standpoint, in a Norwegian study covering over 20 years and 1066 patients the cost per life year gained of out-of-hospital resuscitation from sudden cardiac arrest was 6632 € (Næss and Steen. 2004). Although the costs of resuscitation per life year gained are comparable to or less than most life saving or intensive medical interventions (Karlsson et al. 2009; Næss and Steen 2004; Tengs et al. 1995) it has been shown that these issues do not influence decision-making in the prehospital setting (Ferrand et al. 2006; Naess et al. 1997).

Even when resuscitation is initiated, the measures may prove futile during the attempt and a decision to withdraw these efforts needs to be made. This decision is equally demanding to the decision whether to initiate resuscitation in the first place (Baskett et al. 2007; Naess et al. 1997). However, certain rules for prehospital termination of resuscitation (TOR) have been developed based on criteria which have been prognostic of futility (Bonnin et al. 1993; Morrison et al. 2007). A recent retrospective analysis on 5505 prehospital cardiac arrest victims showed that if the arrest was not witnessed, layperson CPR and defibrillation were not applied and ROSC was not achieved, no patient survived to hospital discharge (Sasson et al. 2008). TOR rules have been criticized to possess the risk of becoming a self-fulfilling prophecy (Sanders and Kern 2008) and in the United Kingdom the adherence to TOR guidelines in the prehospital setting has been low (Lockey 2002). According to the current resuscitation guidelines, a resuscitation attempt may be considered futile in the absence of a reversible cause if asystole persists for more than 20 minutes with all ALS measures in place (ERC 2005). Otherwise the guidelines are indefinite of nature (ERC 2005) for within certain TOR scenarios unexpected cases of survival do occur (Sasson et al. 2008) and therefore each case should be assessed individually (Baskett et al. 2007; Naess et al. 1997).

Prehospital resuscitation

History and development of EMS systems

The birth of prehospital resuscitation saw place in Belfast, Northern Ireland on January 1, 1966 (Pantridge and Geddes 1967). Prior to this, the methods of defibrillation, external chest compressions and resuscitative ventilation techniques had been described (Kouwenhoven et al. 1960; Safar et al. 1958; Zoll et al. 1956). The first mobile intensive care unit in Belfast was physician staffed. Since then, the development of EMS systems has taken diverse directions internationally. In most countries, the systems are based on basic life support (BLS)-level responders such as fire-fighters and emergency medical technicians (EMTs). Commonly, these responders provide BLS and automated external defibrillation (AED) but do not administrate medications or initiate thrombolysis (Campbell et al. 2005; Ellis and Sorene 2008; Koichi and Keiichi 2006; Papaspyrou et al. 2004; Roessler and Zuzan 2006; Symons and Shuster 2004).

During the late 1970's and early 1980's, Eisenberg and colleagues extensively studied the performance of EMTs alone and in comparison to paramedic-treated cardiac arrest (Eisenberg, M et al. 1980; Eisenberg, M S et al. 1980). In one of their studies the final conclusion was that in comparison to EMT provided BLS, early ALS delivered by paramedics is associated with improved survival after prehospital cardiac arrest (Eisenberg, M et al. 1980). Thus, it is currently common that the BLS-level responders

are backed up by a second or even a third tier of paramedic and/or physician-staffed ALS units.

In Australia, Israel and most countries in Europe physician-staffed systems are common (Black and Davies 2005; Ellis and Sorene 2008; Langhelle et al. 2004; Papaspyrou et al. 2004; Roessler and Zuzan 2006; Trevithick et al. 2003) whereas in United States a paramedic-oriented approach is standard nowadays (Pozner et al. 2004). The repertoire of emergency interventions of a trained prehospital physician is more extensive than that of a paramedic, involving invasive procedures and advanced use of medications (Lossius et al. 2002). To which extent this difference is of benefit to the patient is a matter of debate (Dick 2003), although some studies suggest improved patient care and survival in physician-staffed EMS systems treating cardiac arrest victims (Lossius et al. 2002; Pepe et al. 1993; Väisänen et al. 2006).

In some countries, such as Iran and Mexico, there are EMTs providing BLS in the prehospital setting only (Roudsari et al. 2007). However, underlying the terms "BLS" and "ALS" as well as the titles EMT and paramedic is a great variety in education, skills, knowledge and performance between different EMS systems (Roudsari et al. 2007). These different bases need to be taken into account when comparing separate EMS systems. Furthermore, in 2004, the benefits of ALS were questioned in a large multicentre trial involving 5683 patients (Stiell et al. 2004). In the trial no survival benefit was observed with the implementation of ALS when compared to previously optimized BLS approach consisting rapid defibrillation (Stiell et al. 2004). Resuscitation interventions classified as BLS and ALS procedures according to current resuscitation guidelines are presented in Table 2.

Resuscitation guidelines

Following the development of the basic modern resuscitation techniques in the 1960's, the increasing scientific and empiric evidence was translated to resuscitation guidelines and treatment recommendations first in 1966 and since then updated guidelines have been published regularly (Anonymous 1966; Anonymous 1974; Anonymous 1980; Anonymous 1986; Anonymous 1992; Anonymous 2000). Current resuscitation guidelines were published in 2005 and an update to these guidelines is anticipated in 2010 (ERC 2005).

According to the current guidelines the initial assessment of a patient suspected to be suffering a sudden, unmonitored cardiac arrest is similar regardless of the location or level of care (ERC 2005). If the patient is found to be unresponsive and not breathing normally, CPR should be initiated. If the decision to attempt resuscitation is made at this moment, initial treatment is striving for provision of, albeit limited, circulation by chest compressions, improved oxygenation and ventilation by artificial ventilation and, if a defibrillatable pulseless arrhythmia is present restoration of normal cardiac rhythm by rapid defibrillation. Especially chest compressions of good quality and timely defibrillation are important factors in the attempt to regain spontaneous circulation

(Edelson et al. 2006; ERC 2005; Gallagher et al. 1995; Gundersen et al. 2009; Ko et al. 2005; Larsen et al. 1993; Valenzuela et al. 1997; Van Hoeyweghen et al. 1993; Wik et al. 1994). This is accentuated in the prehospital setting as the number of rescuers is often limited to two and therefore the number of treatment modalities needs to be reduced to the essentials (Brucke et al. 2007). Modern prehospital cardiac care generally includes the same resuscitative measures as are available in hospitals. Therefore, in most cases of out-of-hospital cardiac arrest resuscitation is performed at the location of arrest and transport to hospital is initiated only if resuscitation is successful (ERC 2005). CPR during transport to hospital is inefficient and although it is not completely futile (Olasveengen et al. 2008), this method is principally reserved for cases of hypothermic cardiac arrest.

Resuscitation procedure	BLS	ALS
Chest compressions	+	+
Bag-mask ventilation	+	+
Intubation / Alternative airway device	-	+
Defibrillation	+/-	+
Administration of intravenous drugs	-	+

Table 2. Resuscitation procedures according to the basic life support (BLS) and advanced life support (ALS) algorithm (ERC 2005).

Delays in prehospital resuscitation

An important characteristic of prehospital emergency medicine is the inevitable delay to treatment unless the patient suffering a sudden cardiac arrest collapses in the presence of emergency medical personnel. In the 2004 Utstein guidelines (Jacobs et al. 2004), recommended initial core time events to be recorded are the time of onset of a witnessed arrest, time of emergency call received, time of first CPR attempts and, in the case of shockable initial rhythm, the time of first defibrillation attempt. In the study by Herlitz at al in 1999 the median interval between call for ambulance and ambulance arrival was 5 to 7 minutes in a bystander witnessed cardiac arrest. In the same material from five regions in Europe, the median interval between collapse and first defibrillation was 7 to 11 minutes (Herlitz et al. 1999).

The purpose of time interval registration lies within the direct effect of delays on survival. For every minute of delay to CPR and, if necessitated, defibrillation, survival

models predict a 7-15% decrease in survival (Larsen et al. 1993; Waalewijn et al. 2001; Valenzuela et al. 1997; van Alem et al. 2003). Even if immediate CPR, defibrillation and ALS were available at the time of collapse, the initial calculated survival rate has already decreased to 67% (Larsen et al. 1993). Therefore, basic life support (BLS) provided by witnesses of cardiac arrest serves as a vital link in the chain of survival when immediate ALS by EMS personnel is not available. Bystander CPR attenuates the decline in survival to 3-4% per minute and almost triples the chance of survival from witnessed arrest (Holmberg et al. 2000b; Larsen et al. 1993; Waalewijn et al. 2001; Valenzuela et al. 1997). A further attempt to improve the immediate response to prehospital cardiac arrest is the installation of automated external defibrillators to public locations. This so-called public access defibrillation is intended to be available in locations of high risk of cardiac arrest with laypersons or employees trained in defibrillation such as airports or casinos. Promising results have been achieved, but it is yet to be determined whether public access defibrillation is cost-effective and where it should be available to best meet the demand (Colquhoun 2008; TPADTI 2004).

Even if immediate BLS is provided, CPR produces only up to approximately 40% of normal cerebral perfusion (Ristagno et al. 2008). As cerebral perfusion is compromised when mean arterial pressure decreases below 60 mmHg, the mean arterial pressure of generally less than 40 mmHg generated by chest compressions is inadequate in terms of cerebral metabolism (Paradis et al. 1989). CPR produces a small but significant blood flow to the brain and myocardium during cardiac arrest, but if ROSC and sufficient cerebral perfusion is not achieved, hypoxic-ischaemic cerebral injury ensues (ERC 2005). The negative impact that delays have on survival is reflected to some EMS system protocols with a suggestion to withhold resuscitation in patients with no resuscitation for ≥ 15 minutes after collapse that have no pulse or respiratory effort on arrival of the EMS personnel (Bailey et al. 2000; Lockey 2002).

Mechanisms of cerebral injury after cardiac arrest

Ischaemia

As the cardiac pump function ceases and complete haemodynamic collapse occurs, global hypoxia-ischaemia develops. Of all organs facing the ischaemia, the human brain is particularly vulnerable to suffer permanent damage. The evolving cerebral injury consists of immediate damage caused by ischaemia and of delayed mechanisms such as reperfusion injury (Greer 2006).

After the onset of cardiac arrest a minimal antegrade blood flow persists for approximately 5 minutes due to the pressure gradient between the compliant arterial vasculature and flaccid right heart (Andreka and Frenneaux 2006). Experimental studies have shown that this flow is detectable also in the microvasculature of the cerebral

cortex, although significantly reduced and continuing only for approximately 3 minutes (Ristagno et al. 2008). During the initial 2,5 minutes after the onset of ischaemia the depletion of cerebral glucose and high-energy substrates such as ATP is most pronounced and by 10 minutes of global ischaemia the depletion of ATP and phosphocreatine substrates exceeds 96% (Wagner and Lanier 1994). After complete cessation of cerebral perfusion, i.e. "no flow", anoxia develops and cerebral metabolism shifts from aerobic to anaerobic glycolysis with resultant formation of detrimental metabolites such as lactic acid and protons (Hoxworth et al. 1999; Rossi et al. 2007; Wagner and Lanier 1994). Acidosis is deleterious to cerebral tissue causing neuronal and glial cell death even after relatively brief exposure (Nedergaard et al. 1991). In addition to the loss of ATP and generation of tissue acidosis, lack of oxygen impairs the function of electron transport chain in the mitochondria leading to production of reactive oxygen species (ROS) that cause cellular damage via oxidative stress (Abramov et al. 2007).

The subsequent and simultaneous mechanisms of damage caused by cerebral ischaemia are numerous. Alongside the accumulation of lactic acid and hydrogen ion release to the extracellular space, changes in cellular membrane function occur. An increased efflux of potassium is observed, as well as an increase in cellular influx of calcium. Cell membrane disruption results in cellular oedema aggravated by increasing acidosis. Enzymatic activation of proteases, lipases and nucleases induce further neuronal damage (Greer 2006).

Apoptosis

A further mechanism of cellular damage after cerebral ischaemia is the activation of programmed cell death, i.e. apoptosis (Linnik et al. 1993). The process of apoptosis is not completely understood. The disruption of plasma membranes, energy depletion and impaired metabolism in combination of deranged protein synthesis and regulation might be the triggering factor of premature programmed cell death (Nedergaard et al. 1991). Current evidence shows that interneuronal gap junctions play a key role in inducing and mediating apoptosis to adjacent cells. Thus the initial ischaemic damage to a certain cell is conducted to neighbouring cells in a neurotoxin manner causing expansion of the injury (Talhouk et al. 2008). Important mediators of neuronal cell death are excitotoxic neurotransmitters such as glutamate, release of which is increased during cardiac arrest and after ROSC (Choi and Rothman 1990; Greer 2006; Keelan et al. 1999).

Reperfusion injury

After ROSC, cerebral microvascular blood flow similar to pre-arrest is restored within 3 minutes (Ristagno et al. 2008). The restoration of cerebral circulation is not solely beneficial to the cerebral tissue. Immediately after ROSC a period of 15 to 30 minutes of hyperaemia, i.e. "high flow" occurs (Angelos et al. 1994). This aggravates pre-existing

cerebral oedema and microhaemorrhages that develop due to ischaemic capillary lesions (Greer 2006).

Succeeding the brief period of hyperaemia, a prolonged period of cerebral hypoperfusion persists. The exact mechanisms of decreased cerebral blood flow after ROSC are unclear. A "no re-flow" phenomenon occurs in the cerebral microvasculature due to a combination of vasospasm and endothelial swelling, increased blood viscosity, DIC and leukocyte interactions with the endothelium (Ames et al. 1968; Chiang J et al. 1968; Fischer and Hossmann 1996; Popp and Bottiger 2006; Safar et al. 2002a). After cardiac arrest the autoregulation of cerebral blood flow is lost and an imbalance of vasoactive substances such as nitrous oxide, adenosine, endothelin and cyclic guanosine monophosphate causing vasoconstriction is observed (Buunk et al. 1997; Buunk et al. 1996; Safar et al. 2002a).

Concomitant to the no-reflow type of multifocal hypoperfusion, reperfusion syndrome wreaks additional havoc in the cerebrum. The reperfusion injury is associated to reoxygenation and accelerated production of oxygen radicals, continued glutamate mediated excitatory neurotoxicity and renewed calcium shifts further activating cytotoxic enzymes such as endonucleases, proteases, phospholipases and xanthine oxidase (Greer 2006; Rincon and Mayer 2006). This cascade leads to fragmentation of the DNA, mitochondrial lesions and disseminated cell death adding to the primary intra-arrest cerebral injury (Safar et al. 2002a).

Mitigating the cerebral injury – chain of survival

Numerous endeavours in terms of therapeutic interventions have been made to improve the neurological and overall outcome of cardiac arrest. These include a number of pharmacological and neuroprotective agents as well as procedural and mechanical aids (ERC 2005; Greer 2006). So far only a handful of treatment modalities have been consistently proven to improve long-term survival from cardiac arrest. The most important factors have been depicted as the chain of survival. The chain consists of four links. The first link is early recognition of symptoms preceding cardiac arrest and call for help to prevent cardiac arrest. The second link is early CPR to buy time and the third link is early defibrillation to restart the heart. The rationale of these factors has been discussed previously. The fourth link depicts post resuscitation care and the goal to restore quality of life (Nolan et al. 2006).

Post resuscitation treatment strives to maintain homeostasis and to counteract the multiple organ dysfunction of post resuscitation syndrome following global ischaemia (Nolan and Soar 2008). Recent evidence strongly suggests that the post resuscitation syndrome is characterised by sepsis-mimicking inflammatory changes such as elevated plasma cytokines, presence of circulating endotoxins, leukocyte dysregulation, and adrenal dysfunction (Adrie et al. 2002; Adrie et al. 2005; Hekimian et al. 2004). The key factors at this point are early coronary reperfusion and haemodynamic optimization,

control of ventilation, blood glucose control, temperature control and the treatment of seizures (Balan et al. 2006; Gaieski et al. 2009; Garot et al. 2007; Gorjup et al. 2007; Kilgannon et al. 2008; Krauss et al. 2001; Krumholz et al. 1988; Kuisma et al. 2006; Laurent et al. 2002; Losert et al. 2008; Nolan and Soar 2008; Oksanen et al. 2007b; Sunde et al. 2007; Sundgreen et al. 2001; van den Berghe et al. 2001; Zeiner et al. 2001).

Although ischaemic heart disease accounts for majority of sudden cardiac arrests (Chugh et al. 2004; Gorgels et al. 2003; Myerburg 1987), and early reperfusion as a definitive treatment improves survival (Garot et al. 2007; Spaulding et al. 1997), it is neurological injury that accounts for two thirds of deaths of the patients who eventually die prior to hospital discharge after successful prehospital resuscitation and ICU admission (Laver et al. 2004). Until recently, there was no clinically relevant therapy to specifically counteract neurological injury after cardiac arrest as interventions such as calcium-entry blockade (Roine et al. 1990) or barbiturates had failed to significantly improve neurological outcome (BRCT 1986a; BRCT 1991; Safar et al. 2002a). The use of xenon as a neuroprotective agent (Fries et al. 2008) and caspase inhibitors for suppression of apoptosis (Vogel et al. 2003) are promising areas of investigation, but conclusive clinical studies in human cardiac arrest victims have not been reported.

Mild therapeutic hypothermia

When core temperature in the human body decreases below 37° C, it is considered a state of hypothermia - mild classified as 32 to 36° C and moderate as 28 to 32° C (Rincon and Mayer 2006). The physiologic cerebral effects of mild hypothermia are numerous including decrease in metabolic rate, oxygen demand, blood flow and inhibition of glutamate release (Rincon and Mayer 2006; Royl et al. 2008; Wong 1983).

Mild hypothermia decreases cerebral metabolic rate by approximately 6 to 7 % per degree Celsius decrease in temperature (Alzaga et al. 2006; Rosomoff and Holaday 1954) resulting in improved tissue tolerance of hypoxia. Mild hypothermia also seems to reduce glutamate release (Takata et al. 2005). In addition to this, mild hypothermia inhibits apoptosis *in vitro* (Xu et al. 2002) and reduces reactive oxygen species formation in cerebral ischaemia (Kil et al. 1996). These are key factors in the cascade of evolving ischaemic cerebral injury and thus hypothermia seems to be an effective approach to counteract not only one, but several of these detrimental mechanisms of neurological insult after cardiac arrest. However, most of the data cited is obtained from experimental animal studies. Hence, a direct translation of this data to apply in human physiology can not be done and therefore the true mechanisms of action in the case of human cardiac arrest and post-resuscitation treatment are somewhat unknown.

Induced hypothermia in clinical practice

As hypothermia reduces cellular metabolism and oxygen consumption, it protects tissue during periods of hypoperfusion or complete ischaemia (Wong 1983). The first clinically relevant applications of hypothermia were introduced into cardiac and intracranial surgery in the 1950's and during the same decade a beneficial effect of induced hypothermia after cardiac arrest was reported (Bigelow et al. 1950; Williams and Spencer 1958). However, in further studies complications such as cardiac irritability, pneumonia and metabolic derangement were encountered and the treatment was abandoned for decades (Alzaga et al. 2006).

Research on therapeutic hypothermia was minimal until the 1990's. A group led by Peter Safar continued to study the effect of induced hypothermia in animal models of cardiac arrest (Leonov et al. 1990) and positive results attracted further investigation by the end of the millennium. After several laboratory and feasibility studies a significant change occurred in 2002 when two randomized controlled trials supporting the use of mild therapeutic hypothermia were published (Bernard et al. 2002; HACA 2002). In these two studies comatose survivors of out-of-hospital cardiac arrest with initial cardiac rhythm of ventricular fibrillation were treated with mild hypothermia of 32 to 34 °C for 12 to 24 hours. A beneficial effect in terms of overall survival and neurological outcome was found in favour of the groups treated with induced mild hypothermia. This improvement in outcome was of such magnitude that a strong recommendation to implement this treatment was given in the editorial of the same issue (Safar and Kochanek 2002b) and an international treatment recommendation was published the following year (Nolan et al. 2003). Currently, mild therapeutic hypothermia is recommended to be induced in comatose victims of out-of-hospital cardiac arrest with initial rhythm of VF and to be considered in cases of other initial rhythms also (ERC 2005). A recent report has shown this method to actually shorten the length of ICU stay in cardiac arrest survivors compared to historic samples (Storm et al. 2008).

Timing of hypothermia

Animal studies have shown that there exists a critical time window after cardiac arrest during which cooling should be initiated to achieve the beneficial effects of induced hypothermia (Kuboyama et al. 1993; Nozari et al. 2006). Although the mean delay to target temperature in the study by the Hypothermia After Cardiac Arrest Study group was up to eight hours and improved outcome was still observed (HACA 2002), current recommendation is that hypothermia should be induced as soon as possible (Castrén et al. 2009; ERC 2005). This applies, even though current scientific evidence is insufficient to determine the exact optimal timing for initiation, as well as the duration, discontinuation and optimal target temperature of mild hypothermia (Gazmuri et al. 2007).

To induce mild hypothermia effectively and fast, the method of induction should be simple and preferably available in the prehospital setting. In contrast to previous external

methods of cooling such as ice packs and cooling mattresses, Bernard et al reported their experience on cardiac arrest victims in whom cooling was achieved infusing a large volume (30 ml/kg) of ice-cold (4 °C) lactated Ringers solution (Bernard et al. 2003). This method proved to be safe, effective and furthermore it was inexpensive and associated with beneficial haemodynamic, renal and acid–base effects. This method has been found to be applicable also into the prehospital treatment of cardiac arrest victims soon after ROSC (Virkkunen et al. 2004). Recently, Kim et al published the first RCT investigating out-of-hospital cooling after ROSC using infusion of LVICF (Kim et al. 2007). Although not powered to assess effect on survival, in their study a trend towards improved survival was observed in the subgroup of patients resuscitated from ventricular fibrillation and treated with early induced hypothermia.

Therapeutic hypothermia is easily and rapidly inducible even in the prehospital setting using either infusion of LVICF (Kliegel et al. 2007) or external cooling methods (Bernard et al. 2002) and maintained in the ICU either externally (Haugk et al. 2007) or using special endovascular cooling systems (Pichon et al. 2007). There is however, a growing body of evidence suggesting that the protective effects of mild hypothermia should be pursued already during CPR and prior to the reperfusion injury occurring after ROSC (Abella et al. 2004; Nozari et al. 2004; Nozari et al. 2006).

Aims of the Study

The purpose of this thesis was to investigate out-of-hospital cardiac arrest and induction of mild hypothermia in the Tampere City Emergency Medical Service system and Helsinki Area Helicopter Emergency Medical Service system. Epidemiology and outcome according to the Utstein style and the feasibility of prehospital cooling were assessed with the following specific aims:

1. To investigate the epidemiology of out-of-hospital cardiac arrest in the city of Tampere according to the Utstein style with a focus on the reasons of the EMS personnel to withhold resuscitative efforts (I).

2. To compare temperature changes during standard post resuscitation care vs. induction of therapeutic hypothermia using ice-cold intravenous fluid after successful prehospital resuscitation (II).

3. To assess the feasibility, temperature effects and influence on haemodynamics of mild intra-arrest hypothermia induced by paramedics infusing ice-cold intravenous fluid during prehospital cardiopulmonary resuscitation (III, IV).

Material and Methods

Study setting and description of the EMS systems

Tampere EMS

Tampere is the third largest city in Finland with a population of approximately 203 000 of which 52 % are females and the population density is approximately 385/ km^2. According to the Tampere City annual statistical report in 2003, 15 % of the population was aged between 0 and 14 years, 15 % between 15 and 24 years, 30 % between 25 and 44 years, 25 % between 45 and 64 years, and 15 % 65 years or older. In the same year the life expectancy for men was 75,2 years and that for women 82,0 years. As in the general population of Finland, diseases of the cardiovascular system are the primary cause of death. In 2003, 1784 individuals died in Tampere, 717 (40 %) of them due to cardiovascular disease.

The emergency dispatch centre of Pirkanmaa covers the city of Tampere and 33 surrounding smaller communities, providing services for a population of approximately 460 000 inhabitants. The European emergency telephone number 112 is used for fire, rescue and medical emergencies as well as for police services. The centre receives 370 000 calls annually of which approximately 64 000 result in medical response. The dispatchers use criteria-based dispatch and provide telephone-assisted instructions for compressions-only cardiopulmonary resuscitation (CPR) when indicated. As the call rate per dispatcher influences dispatch delays and cardiac arrest survival indirectly (Kuisma et al. 2005), it is informative that above described dispatching system results annually in approximately 7000 calls per dispatcher, out of which 42 % are processed within 90 seconds.

The EMS system in Tampere city area is two-tiered with firemen - emergency medical technicians (EMTs) providing basic life support (BLS) as the first tier and paramedics providing advanced life support (ALS) as the second tier. The EMTs are authorised to use an automated external defibrillator (AED), perform endotracheal intubation of a lifeless adult patient and to establish an intravenous line. In the case of cardiac arrest, a single dose of intravenous adrenaline (epinephrine) is available for the EMTs to administrate prior to arrival of an ALS unit.

The nurse-paramedics have ALS training and administer intravenous drugs, provide sedation to facilitate endotracheal intubation in unconscious patients and initiate

thrombolytic treatment after consulting with a physician. The paramedics have standing treatment orders and perform under non- online medical supervision.

The city of Tampere is divided into four regions, each with its own rescue station. All stations have fire engines equipped with AEDs operating as first responding units (FRUs) when required, and BLS ambulances. In addition there are two ALS-equipped units covering the city. In total, there are six BLS ambulances and two ALS units operating on a 24- hour basis. During daytime there are five additional BLS ambulances, which can be staffed around the clock if necessary.

In medical emergencies, both the closest BLS and ALS units are simultaneously dispatched if the call is classified as a high-risk call, such as suspected cardiac arrest. If the risk is not evident, the nearest BLS unit is dispatched, supported by an ALS unit only if indicated later.

Cardiac arrest treatment is based on national guidelines (Castrén et al. 2006) adapted from and updated according to the ERC resuscitation guidelines (Anonymous 2000; ERC 2005). Resuscitation and post-ROSC stabilization is performed in the field. Only patients with a hypothermic cardiac arrest are transported to hospital with on-going CPR. In cases of no response to resuscitation the attempts are withdrawn in the field.

All successfully resuscitated prehospital cardiac arrest patients are admitted to a single tertiary-level university hospital providing mild therapeutic hypothermia and coronary reperfusion for eligible patients. During the study period, immediate coronary intervention was at the decision of the cardiology attending on call, and the use of therapeutic hypothermia was decided upon by the on-call intensivist. The emergency department (ED) physicians at this hospital act as consultants for the paramedics of the Tampere EMS regarding e.g. field thrombolysis and termination of resuscitation.

Helsinki Area HEMS

The Helsinki Area Helicopter Emergency Medical Service (HEMS) system operates in the capital area surrounding the city of Helsinki, covering a population of approximately 850,000 inhabitants and an area of 31 000 km2. Staffed with an anaesthesiologist experienced in emergency medicine, a pilot and a flight medic, the HEMS operates 24 h per day, responding to approximately 1900 missions annually.

Within the operational area the HEMS operates as a third tier to ~40 local paramedic staffed EMS units capable of BLS or ALS, depending on the unit. In high risk missions, such as cardiac arrest, a local EMS unit and the HEMS are dispatched simultaneously. Cardiac arrest victims with ROSC are transported to one of five receiving hospitals treating cardiac arrest victims. The hospitals have distinct policies regarding post resuscitation treatment and provision of therapeutic hypothermia.

Data collection

Data collection was performed between 1 August 2004 and 31 July 2005 (I), March 2005 and December 2008 (II), and October 2006 and December 2007 (III, IV). A total of 245 cases of out-of-hospital cardiac arrest were studied for this thesis. 191 of these were included in the epidemiological evaluation (I), 37 were assigned to a randomized controlled trial evaluating post-ROSC prehospital mild hypothermia (II) and the remaining 17 cases contributed to the intra-arrest interventional study (III, IV).

Epidemiology of out-of-hospital cardiac arrest in Tampere city

In this prospective observational study data from all sudden prehospital cardiac arrests attended by EMS personnel between August 1, 2004 and July 31, 2005 in the city of Tampere were investigated. The data were first collected on a separate data sheet and after completion analyzed according to the 1991 Utstein guidelines (Chamberlain et al. 1991). A subjective re-evaluation conforming to the 2004 Utstein guidelines (Jacobs et al. 2004) was performed to investigate the feasibility of the new guidelines

To ensure complete data to be recorded, the investigators contacted the paramedics of the Tampere EMS system on a daily basis. Furthermore, data on the post-resuscitation phase were obtained from patient records and interviews with staff involved in the treatment. Time intervals were analyzed from the registry of the emergency dispatch centre and EMS equipment.

As defined in the Utstein guidelines (Jacobs et al. 2004) epidemiological factors, patient characteristics and outcome were assessed. These include the definition of the time, location and characteristics of the arrest, patient demographics, resuscitation interventions and the delay to execute these interventions. Neurological outcome was evaluated at discharge using the Cerebral Performance Category described in Table 3 (BRCT 1986b).

The prospective epidemiological material was analysed in terms of withheld resuscitations. The characteristics of the cardiac arrest cases in which EMS crew did not initiate CPR were studied. The reasons to withhold resuscitation efforts in paramedic treated cardiac arrest were investigated in the light of national cardiac arrest guidelines (Castrén et al. 2006). Also a comparison between the patients with no resuscitation attempt and those with attempted resuscitation was performed (I).

Prehospital induction of mild hypothermia vs. standard post-resuscitation care

A randomized controlled trial evaluating prehospital induction of mild hypothermia using LVICF was undertaken. Study patients consisted of prehospital cardiac arrest survivors

treated by the physician staffed Helsinki Area Helicopter Emergency Medical Air Service (Helsinki Area, HEMS), with the prerequisite of fulfilment of inclusion criteria and a written informed consent from the next of kin. Patients aged ≥ 18 years were included if time to ROSC exceeded 9 minutes from the onset of arrest regardless of the initial cardiac rhythm. Exclusion criteria were: known pregnancy, cardiac arrest due to trauma or intoxication, or hypotension (systolic blood pressure < 100mmHg) not responding to treatment with fluid challenge and vasoactive support with dopamine or noradrenaline.

Resuscitation was conducted according to the ILCOR guidelines (Anonymous 2000; ERC 2005). When required, propofol or midazolam was used for sedation, fentanyl or alfentanil for analgesia and rocuronium as a paralytic in the post-resuscitation phase. After a written informed consent was received from the next of kin of the patient, a nasopharyngeal temperature probe was inserted (Zoll M-Series CCT; ZOLL Medical Corp., MA, USA) and the first temperature was recorded. Randomization was then performed by opening an unmarked envelope which stated the patient either to undergo induction of mild hypothermia or conventional treatment. Block randomization was not used. In the case of randomization to the hypothermia group, a rapid infusion of +4 °C Ringer's solution stored in a medical refrigeration transport box (Dometic MT4B, Dometic Group, Solna, Sweden) was initiated at a rate of approximately 100ml/min using a pressure bag. The target nasopharyngeal temperature was 33 °C. Alternatively to the target temperature a volume limitation of 30ml/kg of cold fluid was set. The infusion was stopped at the discretion of the treating physician or if the target temperature was reached. If a temperature decrease below 32 °C despite the cessation of the infusion was observed, slow external warming with blankets was initiated.

If the patient was allocated to the control group, only nasopharyngeal temperature monitoring was initiated besides otherwise standard post-resuscitation treatment. Passive cooling was not prevented nor was active warming initiated.

Data recording included monitoring of non-invasive blood pressure, pulse rate, end-tidal carbon dioxide, pulse oximetry and nasopharyngeal temperature every 5 minutes after ROSC until hospital admission. On arrival to the emergency department of one of the five hospitals in the Helsinki Area treating adult cardiac arrest patients, the nasopharyngeal temperature was recorded. This served as the primary endpoint of this study. Patient characteristics, resuscitation details and outcome data were recorded according to the Utstein guidelines (Jacobs et al. 2004). Neurologic outcome was evaluated using the Cerebral Performance Category (CPC) classification (BRCT 1986b). Due to focus on the prehospital treatment of the patient the in-hospital care such as continuation of hypothermia was left at the discretion of the hospitals' physicians.

Intra-arrest cooling

Induction of therapeutic hypothermia was further investigated in a paramedic-oriented EMS system using infusion of LVICF already during on-going cardiopulmonary resuscitation (III, IV). In the pilot study (III) the feasibility and temperature effects of

intra-arrest cooling were reported and the setting was continued with the effects on the rate of ROSC, rearrest and haemodynamics being observed (IV).

For induction of intra-arrest hypothermia, all prehospital patients aged ≥ 18 years with non-traumatic cardiac arrest not due to intoxication were considered for inclusion regardless of the initial cardiac rhythm. Exclusion criteria were known pregnancy, preceding clinical suspicion of accidental hypothermia, or ROSC within five minutes from the onset of resuscitation. The reason for the latter exclusion criteria was to prevent induction of therapeutic hypothermia in patients with potential to regain consciousness shortly after resuscitation.

According to the study protocol, priority of primary resuscitative measures of good quality was emphasized throughout the study. Cardiac arrest treatment followed the European Resuscitation Council guidelines (ERC 2005) and eligibility for inclusion was considered only after necessary resuscitative efforts were initiated.

The first EMS crew to arrive on the scene initiated primary resuscitative measures such as chest compressions, defibrillation and ventilation. Paramedics performed orotracheal intubation during continuous CPR and obtained intravenous access via the external jugular or antecubital veins. If no obvious exclusion criteria were present, infusion of cold (+4 °C) Ringer´s acetate was initiated at a rate of 33ml/min (III) and 50ml/min (IV) via the peripheral cannula, or if the antecubital cannula was not patent at this moment, via the external jugular vein. The reason for the protocol modification resulting in the slower initial rate was to avoid the overshoot of temperature decrease observed in the patients included in the pilot phase (III).

Intravenous medication such as adrenaline (epinephrine) or amiodarone was administrated when indicated. Blood glucose was measured and end-tidal CO_2 and pulse oximetry were monitored continuously. For temperature measurement a nasopharyngeal temperature probe was inserted and the temperature recorded using a separate portable device (YSI 4600 Precision Thermometer, YSI Corp., Dayton, OH, USA). Paramedics used anatomic landmarks to assess correct placement of the probe and similar site and depth of measurement between patients by advancing the probe the length of ipsilateral distance between the auricular lobule and nasal vestibule. A medical refrigeration transport box (Dometic MT4B, Dometic Group, Solna, Sweden) was used for storage of the cold fluids in the ambulance.

If the first recorded nasopharyngeal temperature was <33°C despite the lack of signs of preceding accidental hypothermia the infusion was either not initiated or discontinued. The nasopharyngeal temperature was continuously monitored and if a temperature reading of 33°C was reached the infusion was stopped. The infusion was later restarted if the temperature again began to increase above 34°C. If a temperature reduction below 32°C occurred, passive warming with blankets was initiated and the cold fluid was replaced with regular Ringer's solution.

When ROSC was achieved and the nasopharyngeal temperature was >33°C, a rapid infusion of the cold fluid was initiated via the antecubital vein at a rate of 100ml/min using an infusion pump (Power Infuser, Infusion Dynamics, Plymouth Meeting, PA,

USA). The target temperature for both the slow and the rapid infusion of cold fluid was set at 33°C.

In addition to the above mentioned monitoring, arterial blood pressure was monitored non-invasively every 5 minutes after ROSC. The patient was stabilised on scene prior to transport to a single tertiary-level university hospital. If indicated, vasoactive medication (dopamine) to treat hypotension (systolic blood pressure <100 mmHg despite fluid resuscitation) or thrombolytic treatment was initiated prior to transport or en route to the hospital. According to local policy, paramedics provided analgesia and sedation using intravenous alfentanil and diazepam when indicated. Intravenous paralytic agents were not used.

In the ED the nasopharyngeal temperature was recorded. Blood gas analysis and blood glucose were measured and registered on arrival. At this point the study intervention protocol ended. As the study protocol focused on prehospital treatment with intra-arrest hypothermia, further treatment such as whether to continue therapeutic hypothermia or not was at the discretion of the treating intensive care unit (ICU) physicians. Survival and outcome of the patients was assessed according to the Utstein guidelines (Jacobs et al. 2004) at the time of hospital discharge. In the pilot phase of intra-arrest cooling the causes of death of the patients was assessed (III).

Ethical considerations

In the epidemiological observation study, no clinical intervention was performed and therefore the approval of the institutional review board of the Tampere University Hospital was waived (I). The study protocol of study II was approved by the institutional review board of the Helsinki University Hospital and a written informed consent obtained from the next of kin of the patient was necessitated for inclusion. In the studies of intra-arrest mild hypothermia, the study protocol was approved by the institutional review board of the Tampere University Hospital, Finland. With the permission of the review board, written informed consent for inclusion in the study was obtained from relatives of the patients after completion of resuscitation (III, IV).

Statistical methods

Statistical analysis was performed using the SPSS for Windows V13.0 and V16.0 software (SPSS Inc., Chicago, IL, USA). Comparison between patient groups regarding whether resuscitation was initiated or not was performed (I). To compare categorical data the Chi-Square and Fisher's exact test were used. Statistical significance was set at $p < 0.05$. Two-tailed p-values are presented when significant (I).

In study II a power analysis with a power set at 80% and alpha at 0.05 was performed. With an assumption of 1.2 °C SD in core temperature of prehospital cardiac arrest survivors (Clifton et al. 2002; Virkkunen et al. 2004) it was calculated that a minimum of twelve patients per group would be required for the detection of a 1.5 °C difference in nasopharyngeal temperature between groups. The Kolmogorov-Smirnov test was used to test normality of the data. The Student's t test was used for continuous, the $\chi 2$ test for categorical variables and, in cases of non-normal distribution, the Wilcoxon rank and sum test was used for continuous variables to test differences between the groups. Significance was set at $p < 0.05$. The data presented are mean ± SD.

In the intra-arrest cooling studies, data are shown as mean ± 95% CI, unless otherwise indicated. Difference in core temperature prior to and after infusion of cold intravenous fluid was assessed. To measure statistical significance a two-tailed Student's t-test was used considering a p-value < 0.05 as significant (II, IV).

Cerebral Performance Category Scale	Definition
CPC 1	Good cerebral performance: conscious, alert, able to work, only mild neurologic deficit
CPC 2	Moderate cerebral disability: conscious, ability to perform independent activities of daily life
CPC 3	Severe cerebral disability: conscious, dependent on others due to impaired cerebral function
CPC 4	Coma or vegetative state: any degree of coma lacking criteria for brain death
CPC 5	Brain death

Table 3. The Cerebral Performance Category (CPC) scale. Modified from BRCT 1986b.

Results

An Utstein-style summary of the whole patient population included in this thesis is described in Figure 2.

Epidemiology

A total of 191 out-of-hospital cardiac arrests occurring during a one-year study period were analyzed. Patients were not excluded or lost from follow-up during the study. In 98 of the 191 patients (51 %), resuscitation was not attempted. The reasons to withhold resuscitation were estimated futility in 97 cases and a DNAR order in one case. The grounds to presume CPR to be futile were the presence of secondary signs of death in 60% of the patients with no resuscitation, 97% had asystole as the initial cardiac rhythm and 98% had suffered an unwitnessed cardiac arrest. The core data comparing the groups of attempted resuscitation vs. no resuscitation attempt are presented in Table 4.

Resuscitation was attempted in 93 patients, which yields an incidence of 46/100 000 inhabitants/year. Return of spontaneous circulation was achieved in 49 of the 93 patients (53%). ROSC was temporary in four patients. 45 (48%) patients were admitted to hospital where 33 (35%) died. Twelve patients were discharged alive from hospital (overall survival rate 13%), nine of them with a CPC score of 1 or 2. In 24 patients, the onset of cardiac arrest was bystander witnessed and the initial rhythm was ventricular fibrillation. In this Utstein style group of "golden standard" (witnessed arrest of presumed cardiac origin with VF as the initial rhythm) seven (28 %) patients survived to hospital discharge.

Prehospital induction of mild hypothermia after successful resuscitation

44 patients were screened for eligibility and 37 patients were enrolled to compare cooling with standard post-resuscitation treatment. The reason to exclude the seven patients was incomplete data in 2 patients, rearrest and death prior to randomization in 2, withdrawal of consent in 1, protocol violation in 1 and persistent hypotension preceding randomization in 1 patient. The remaining 37 patients were finally analyzed in the

hypothermia group (19 patients) and the normothermia group (18 patients). The baseline characteristics of the patients in these groups were comparable. None of the 37 patients were lost to follow-up or final analysis and all the patients received the allocated intervention.

The mean infused volume of cold fluid per patient in the intervention group was 2370 (± 500) ml producing a calculated mean dose of 27 ml/kg. Differences between the two groups regarding the rate of rearrest, pulmonary oedema or need for vasoactive medication were not observed (Table 5).

	No resuscitation attempt ***n* = 98 (100%)**	**Resuscitation** ***n* = 93 (100%)**	***p*-value***
Age			
Median (years)	57	67	
Gender			
Male	67 (68.4)	62 (66.7)	
Arrest witnessed	2 (2.0)	74 (79.6)	<0.001
Unwitnessed arrest	96 (98.0)	19 (20.4)	<0.001
Bystander CPR	3 (3.0)	29 (31.2)	<0.001
Location of arrest			
Home	81 (82.7)	54 (58.1)	<0.001
Aetiology of arrest			
Presumed cardiac	15 (15.3)	72 (77.4)	<0.001
Unknown	58 (59.2)	1 (1.1)	<0.001
Initial rhythm			
ASY	95 (96.9)	33 (35.5)	<0.001

Table 4. Core resuscitation and patient characteristics in attempted resuscitations vs. cases of withheld resuscitation efforts (I). CPR: cardiopulmonary resuscitation, ASY: asystole. * χ^2- and Fisher's Exact Test were used when appropriate. Statistical significance was set at $p < 0.05$, p-values are presented when found significant.

Increased rate of bystander CPR in the hypothermia group was observed; 11 (58 %) vs. 4 (22 %) cases, p=0.027. Otherwise the groups underwent similar periarrest care. The initial temperatures were similar in both groups; 35.5 (± 0.6) °C in the treatment group vs. 35.3 (± 0.6) °C in the control group. The temperature decrease in the hypothermia group (-1.5 ± 0.8 °C) was significant compared to that in the control group (-0.1 ± 0.6 °C), p <0.001) producing a lower admission temperature (34.1 ± 0.9 vs. 35.2 ±

0.8 °C, p<0.001). No difference in survival rate or neurological outcome was observed between the groups as 8 patients were discharged in both groups and all but 1 per group with a CPC level of 1. The main results are presented in Table 5.

	Hypothermia group n=19	Control group n=18	*p*
Age (years)	59 (± 15)	63 (± 11)	
Gender			
Male	18	17	
Weight (kg)	88 (± 13)	81 (± 9)	
Initial rhythm			
VF	14	14	
ASY	4	1	
PEA	1	3	
Aetiology of arrest			
Presumed cardiac	16	16	
Other noncardiac	3	2	
Layperson CPR	11 (58%)	4 (22%)	0.027
Time to ROSC (minutes)	23 (±7)	22 (±8)	
Nasopharyngeal *T* °C			
First measured	35.5 (± 0.6)	35.3 (± 0.6)	
In hospital	34.1 (± 0.9)	35.2 (± 0.8)	<0.001
Δ*T*	-1.5 (± 0.8)	-0.1 (± 0.6)	<0.001
Rearrest after onset of treatment	2	3	
Vasopressor after ROSC	11	6	
Pulmonary oedema after ROSC	0	0	
In-hospital data			
Survival to discharge	8 (42%)	8 (44%)	
CPC 1	7	7	
CPC 2	1	1	

Table 5. Patient and resuscitation characteristics (II). VF: ventricular fibrillation, ASY: Asystole, PEA: Pulseless electrical activity, CPR: cardiopulmonary resuscitation, ROSC: return of spontaneous circulation, *T*: temperature, Δ*T*: temperature change, CPC: Cerebral Performance Category. *p* is expressed when significant (<0.05), Student's t test and χ^2 test used when appropriate. Data are mean (± SD).

Intra-arrest cooling

During the complete study period 50 patients were screened for eligibility and 17 patients met inclusion criteria. Their mean age was 70 ± 6 years and 76% were males. The initial cardiac rhythms were ventricular fibrillation (VF) in 10 (59%), pulseless electrical activity (PEA) in 6 (35%) and asystole in one (6%) patient. Majority of the 33 excluded patients were excluded due to protocol violation as infusion of cold fluid was initiated after ROSC only.

Temperature and haemodynamics

In the initial set of five patients the mean volume of infused cold solution was 892 ml (220 - 2900 ml) during resuscitation at a mean infusion rate of 32 (9 - 50) ml/min. This resulted in a mean decrease in temperature of 1.9 °C during CPR. Based on this, the calculated mean rate of temperature decrease during CPR was 4.1°C per hour.
The total mean infused volume of cold solution during CPR and after ROSC was 1080 ml (14.0 ml/kg), which resulted in a mean decrease in nasopharyngeal temperature of 2.5 °C. In all of the five patients in the pilot study the infusion was paused because the temperature decreased to 33 °C. Despite this, the temperature continued to decrease in two patients, resulting in temperatures as low as 31.1 °C.

In the whole study population of 17 patients, nasopharyngeal temperature was measured during ongoing CPR in 15 patients. The mean first measured temperature was 34.73 ± 0.52 °C and within five minutes after ROSC it was 34.34 ± 0.55 °C ($p<0.01$). The calculated mean infusion rate during CPR was 57 ± 21ml/min and the mean total infused volume of cold fluid was 1571 ± 517 ml.

Return of spontaneous circulation was achieved in 13 patients (76 %). Their mean temperature at the time of ROSC was 34.76 ± 0.45 °C and a rapid infusion of cold fluid was initiated in 12 of them. In one patient ROSC was temporary and he rearrested before the rapid infusion was initiated.

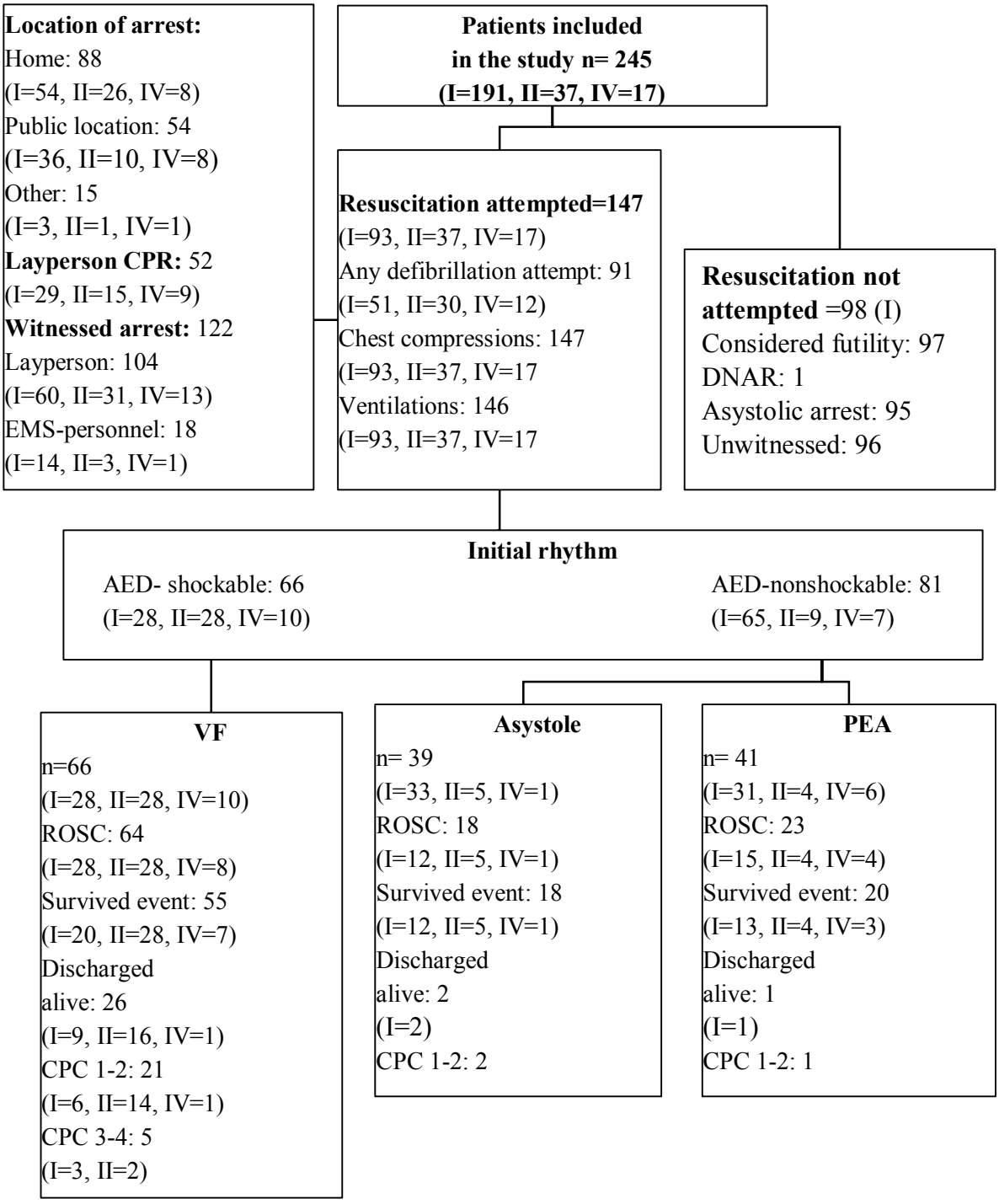
Hypotensive episodes (systolic blood pressure <100mmHg) were observed in five patients and haemodynamically stable bradycardia (pulse < 50 /min, lowest 32/min) in three patients during the rapid infusion after ROSC Five patients rearrested during the rapid infusion, one into asystole and four refibrillated. ROSC was re-achieved in four of them, whereas one of the patients who refibrillated was eventually declared dead on scene. Hence, 11 patients were admitted to hospital.

In-hospital data

11 patients survived the initial event and were admitted to hospital. In these patients the mean initial nasopharyngeal temperature at the early phase of resuscitation had been 35.17 ± 0.57 °C and on hospital admission it had lowered to 33.83 ± 0.77 °C (ΔT - 1.34 °C, $p < 0.001$). The mean initial temperature was higher among the patients who survived to hospital (35.17 °C) compared to those who did not (34.13 °C) ($p<0.03$). 3 patients were not considered to benefit of intensive care due to futility and therefore palliative care was commenced, whereas the remaining 8 patients were admitted to the ICU. Therapeutic hypothermia was continued for 24 hours in 6 of the patients admitted to ICU.

Seven of the patients admitted to the ICU died. Two of these died within 24 hours of admission and prior to further continuation of therapeutic hypothermia. The cause of death was acute myocardial infarction in 3 patients, hypo/hyperkalaemia in 2 patients, subdural haemorrhage and cerebral contusions in one patient without evident signs of trauma and primary arrhythmia in one patient. At the time of hospital discharge and six months after the cardiac arrest, the cerebral performance category (CPC) score of the single surviving patient was 1.

Figure 2. An Utstein-style flow diagram describing the patient population. CPR: cardiopulmonary resuscitation, DNAR: do not attempt resuscitation order, AED: automated external defibrillator, VF: ventricular fibrillation, PEA: Pulseless electrical activity, ROSC: return of spontaneous circulation, CPC: cerebral performance category.



Discussion

Epidemiological aspects

In this thesis, the incidence and outcome of prehospital cardiac arrest was evaluated according to the Utstein style in the city of Tampere, Finland (Jacobs et al. 2004). The observed annual incidence of attempted out-of-hospital resuscitation was 46 per 100 000. Initially this seems to be slightly less than in previous reports. From five regions in Europe Herlitz et al. reported this incidence to range from 50 to 66 per 100 000 per year (Herlitz et al. 1999). However, a six-fold variance of reported resuscitation incidence across individual communities in Europe has been reported (Atwood et al. 2005) with an overall incidence of prehospital resuscitation approximately to be 38 per 100 000 person years. Based on this, the incidence of prehospital cardiac arrest and attempted resuscitation in Study I is comparable to that in the report by Atwood et al. Focusing on Finnish prehospital incidence of attempted resuscitation, the incidence in this material is comparable to that reported from Helsinki in 1987 (53/100 000/year) (Silfvast 1990) but slightly less than in 1994 (67/100 000/year) (Kuisma and Määttä 1996).

When assessing the outcome of prehospital resuscitation it is crucial to bear in mind that results are dependent on numerous factors described as the chain of survival (Nolan et al. 2006). The chain is as strong as the weakest link - whether it were a delay in the activation of the EMS and delivery of emergency care (Calle et al. 1994) or lack of adherence to evidence based guidelines of post resuscitation care (Kirves et al. 2007). In this material, the overall and Utstein style 'golden standard' (witnessed arrests of presumed cardiac aetiology with VF as the initial rhythm) survival were comparable to those of previous reports (Atwood et al. 2005; Fischer et al. 1997; Herlitz et al. 1999; Waalewijn et al. 1998). Concerning this study, it is impossible to state whether the average survival of these patients reflects the function of the whole chain itself or could specific areas of development be found. Recently, Sunde et al reported that the implementation of a goal-directed treatment protocol for post resuscitation care improved the survival to hospital discharge after prehospital cardiac arrest from 26% to 56% (Sunde et al. 2007). The protocol of Sunde and colleagues included therapeutic hypothermia, percutaneous coronary intervention, control of haemodynamics, blood glucose, ventilation and seizures with a specific target for each treatment (Sunde et al. 2007). Reflecting the results of the Norwegian protocol implementation to the present material, a similar percentage of improved survival would annually result in ten

additional survivors with a favourable neurologic outcome. Therefore it seems tempting to scrutinise and develop the treatment of these patients in the Tampere EMS.

Withholding resuscitation

Although resuscitative measures have been practiced for thousands of years (Cooper et al. 2006), it was not until the late 19th and early 20th centuries that cardiopulmonary resuscitation became more common. In conjunction with the introduction of anaesthetic agents such as chloroform and ether the number of iatrogenic cardiac arrest mandating vigorous intervention increased. Thus the early focus of resuscitation was to counteract complications met in surgical procedures – to revive the living (Bains 1998). As resuscitative methods improved, cardiopulmonary resuscitation was applied to a variety of medical conditions and introduced to the lay public (Bains 1998; Cooper et al. 2006). Despite increased rate of lay-person CPR improving survival, a setback of this popularisation of resuscitation is the unrealistically optimistic expectation of the public regarding CPR outcome (Jones et al. 2000). Resuscitation may be expected even when survival is unlikely. In contrast to the early phases of resuscitation history, instead of providing CPR for the slightly dead but mostly alive, the opposite may apply.

In this material the proportion of patients in whom resuscitation was not attempted was surprisingly large - 98 out of 191 patients considered for resuscitation. In comparison, the percentage of attempted resuscitation in previous reports has ranged from 60 to as high as 96% (Hayashi et al. 2004; Weston et al. 1995). Although lower rates of resuscitation have been reported from physician staffed EMS in Copenhagen (34%) and in Estonia (48%) (Rewers et al. 2000; Sipria et al. 2006), the fact that resuscitation was not attempted in more than 50% of all cardiac arrest victims encountered by the EMS personnel requires closer attention to the underlying causes to withhold resuscitation.

Grounds of futility

Not attempting resuscitation in cardiac arrest victims presenting secondary signs of death, such as dependent lividity or rigor mortis (59 cases, 60%), is in line with current resuscitation guidelines. These cases represent the state of irreversible death with no reasonable outcome to be gained with resuscitative efforts (ERC 2005).

In association with a medical intervention, some authors have considered the treatment to be futile if survival or meaningful recovery has not occurred in preceding 100 similar cases (Schneiderman et al. 1990). However, a purely statistical approach is not completely agreed upon and therefore the American Medical Association Council on Ethical and Judicial Affairs has recommended a more process-based determination of futility (AMA 1999). Even when medical futility is considered as unachievable

meaningful recovery, the whole concept of meaningful recovery might be understood distinctly by physicians, patients and the relatives of the patients due to dissimilar values and expectations (AMA 1999; Schneiderman et al. 1990). Although protocol-based treatment does involve assets (Sunde et al. 2007) in the case of critical illness, the necessity and the goal of resuscitative measures need to be considered on a case-by-case basis, preferably in co-operation with the patient or the next of kin (Baskett et al. 2007).

There is a solid body of evidence to support the decision to withhold resuscitative efforts in cases of unwitnessed cardiac arrest with asystole as the initial cardiac rhythm or, rather, as the lack of cardiac rhythm (Engdahl et al. 2000; Engdahl et al. 2002; Kuisma and Jaara 1997b; Väyrynen et al. 2008a). In the presented material, nearly all of the patients in whom resuscitation was not attempted suffered an unwitnessed arrest (98%) with asystole as the initial rhythm (97%). Still, the survival percentage reported by Kuisma and Jaara on unwitnessed arrests of 4.9 % (Kuisma and Jaara 1997b) is higher than the proposed futility cut off point of 1% (Schneiderman et al. 1990), suggesting that complete futility does not apply to these cases. Can we afford to withhold resuscitative efforts categorically in certain cases of cardiac arrest at the expense of losing up to 5 patients per 100 resuscitation attempts? The question is debatable with a vast spectrum of medico-ethical as well as economical aspects. Recently, Väyrynen et al addressed this question in their multivariate analysis on prehospital cardiac arrest with a focus on asystolic arrest and medical futility (Väyrynen et al. 2008a). Their conclusion is clear and concise with a suggestion to withhold resuscitation in cases of unwitnessed asystole, excluding cases of hypothermia and/or near-drowning. Based on this evidence, the reasons of the paramedics of the Tampere EMS system to withhold resuscitation seem justified. Furthermore, the reasons of the paramedics to refrain from resuscitative efforts in our study patients are similar to those reported from prehospital cardiac arrests treated by a physician staffed EMS (Horsted et al. 2004).

An explanation to the diversity in reported rates of prehospital resuscitation lies within the non-uniform method of reporting. Although the Utstein guidelines provide a definition for the concept of confirmed cardiac arrest considered for resuscitation, it became obvious during Study I that this concept is not interpreted in a uniform manner across different EMS-systems and study centres. In some studies exclusion of patients with signs of irreversible death occurred despite EMS was dispatched and resuscitation considered (Lim et al. 2005; Rudner et al. 2004). In conclusion, prehospital cardiac arrests are not considered for resuscitation and reporting is not conducted in similar ways despite the availability of a defined template (Jacobs et al. 2004).

Current resuscitation guidelines recommend continuing resuscitation as long as the cardiac rhythm is ventricular fibrillation or ROSC is achieved. This recommendation reflects the perception that ventricular fibrillation is associated with a better outcome compared to other intra-arrest cardiac rhythms (ERC 2005). Some studies suggest indeed, that the conversion of initial PEA or asystole to VF during prehospital resuscitation is associated with improved outcome (Kajino et al. 2008; Olasveengen et al. 2009). However, there is also contradictory evidence regarding the presumed prognosis of a patient in whom conversion of a non-defibrillatable rhythm to defibrillatable one occurs

during resuscitation as Hallstrom and colleagues observed significantly lower survival in this subgroup of patients (Hallstrom et al. 2007).

As a conclusion, termination of resuscitation needs to be considered in a similar manner to the decision to withhold resuscitative efforts in the first place – on a case-by-case basis (Baskett et al. 2007).

Prehospital induction of mild hypothermia

Cooling after return of spontaneous circulation

A comparison of post ROSC induction of mild hypothermia to standard care was conducted in the prehospital setting (II). In this randomized controlled trial the infusion of +4 °C Ringer's solution after ROSC resulted in a significant decrease in nasopharyngeal temperature compared to the control group undergoing conventional fluid regimen. In this study the rate of spontaneous cooling was not observed to be of such a magnitude that the therapeutic level of core temperature (32 to 34 °C) (Bernard et al. 2002; HACA 2002) could be expected to develop without additional intervention. Based on prior evidence on healthy volunteers it seems that even the infusion of fluids kept at room temperature significantly colder than body temperature (23 °C) is insufficient to decrease core temperature to the therapeutic level (Moore et al. 2008).

It is well known that hypothermia predisposes to haemodynamic instability and cardiac arrhythmias of lethal potential. The risk of cardiac insufficiency and malignant arrhythmias increases gradually as the core temperature decreases below 33 °C with the risk being greatest at temperatures below 30 °C (Hervey 1973). On a hypothetical basis, the infusion of +4 °C intravenous fluid at a rapid rate does indeed carry a risk of iatrogenic cardiac complications. However, in this material no concerns were raised regarding the safety of this treatment as the rate of rearrest and the haemodynamic stability were comparable between the groups. Additionally, in an experimental setting mild hypothermia was found to improve defibrillation success and improve outcome from ventricular fibrillation (Boddicker et al. 2005). Still, the sample size in this study is inadequate to allow absolute conclusions regarding this approach and thus vigilance is necessitated when hypothermia is induced using LVICF to avoid temperature decrease below the therapeutic range and the increased risk for malignant arrhythmia.

The present results are similar to those in the first randomized controlled trial of prehospital induction of mild hypothermia by Kim et al (Kim et al. 2007). In the American trial paramedics infused up to 2 litres of cold saline after ROSC prior to hospital admission. The differences in study protocols might explain two observed disparities in our study and the one by Kim et al. First, in the American trial the patients in the intervention group were significantly more acidotic at the time of admission than the patients in the control group (pH 7.14 ± 0.18 vs. 7.23 ± 0.21, p=0.031). This occurred

despite similar partial pressures of CO_2 between the hypothermia group and the control group. In our study no differences regarding acid-base balance were observed between the two groups. This might be explained by the use of saline and increased chlorine load resulting in changes in strong ion difference and acid-base balance (Stewart 1978). It is debatable whether Ringer's solution might be superior to saline based on reduced chlorine concentration as the acid-base balance is influenced by numerous factors such as the degree of lactic acidosis. Secondly, comparison of the patients in the two hypothermia groups shows that the induced decrease in core temperature was more pronounced in our study (-1.5 ± 0.8 vs. -1.24±1 °C) (Kim et al. 2007). This may reflect dissimilar locations of temperature measurement (nasopharyngeal vs. oesophageal) or the restricted maximum volume of LVICF in the American trial. In the trial by Kim et al, the admission temperature of the patients was 34.7 ± 1.2 °C. As our patients were at the threshold of therapeutic range of mild hypothermia at the time of admission (34.1 ± 0.9°C) it may be more efficient in terms of cooling to adjust the volume of LVICF based on the weight of the patient rather than to use a preset volume as was in the American trial.

The survival rate and the neurological status of the survived patients were similar in both groups. However, no intent of this study was to assess the effect of prehospital cooling on outcome measured as survival or neurological status at hospital discharge

In the larger trial by Kim et al a non-significant improvement in outcome was observed in the subgroup of patients resuscitated from VF and treated with mild prehospital hypothermia. Our study was not powered nor intended to enable conclusions to be drawn regarding the potential therapeutic effects of induced prehospital hypothermia. Therefore further research is required to assess the long-term effects of this treatment.

A post hoc observation in this study was that none of the patients in whom therapeutic hypothermia was not continued in hospital survived. Current resuscitation guidelines advocate the use of therapeutic hypothermia in comatose survivors of prehospital cardiac arrest with an initial shockable rhythm and suggest the treatment to be considered in cases of other initial rhythm and in-hospital arrest also (ERC 2005). Due to the prehospital focus of our study, the decision whether to continue or initiate in-hospital cooling was left at the discretion of the treating physicians. It is not possible to state the exact reasons due to which hypothermia was not used in some of these patients. The reason might have been significant morbidity or predicted unavoidable death contraindicating the treatment. Currently it is not clear whether therapeutic hypothermia improves the outcome of patients resuscitated from non-VF arrests (Oddo et al. 2008) and in some institutions the protocol is to treat only the patients that fulfil the inclusion criteria in the HACA study (HACA 2002; Oksanen et al. 2007a). The specific inclusion criteria in the HACA trial were a witnessed cardiac arrest of presumed cardiac origin with a shockable initial rhythm, patient age between 18 to 75 years, an estimated interval of 5 to 15 minutes from the collapse to the first resuscitation attempt by EMS personnel, and an interval of no more than 60 minutes from collapse to ROSC (HACA 2002). In Study II, 23 out of the 37 patients fulfilled the HACA criteria. Hypothermia was continued in the hospital in 21 of these patients, whereas two patients not fulfilling the HACA criteria

were cooled in hospital. It is speculative whether the exclusion from the treatment serves as a self-fulfilling prophecy of presumed futility. Prehospital cooling alone is likely to be insufficient from the therapeutic viewpoint – the cold chain needs to be kept unbroken by maintaining hypothermia in the ICU (Kliegel et al. 2007) in order to provide optimal hypothermic cerebral protection. This mandates that indications to initiate prehospital cooling are similar to those of the receiving hospital for induction of therapeutic hypothermia.

Intra-arrest cooling

Therapeutic hypothermia is currently used in 95% of the intensive care units in Finland (Oksanen et al. 2007a). This method of post ischaemic neuroprotection is efficient as the number of patients needed to treat to prevent one unfavourable outcome is six (HACA 2002). In-hospital cooling with a delay of up to 8 hours is beneficial (HACA 2002) despite the fact that at this point several mechanisms of post-anoxic cerebral injury are activated (Rincon and Mayer 2006).

One of the relevant mechanisms of injury is the activation of programmed cell death, i.e. apoptosis (Rincon and Mayer 2006). Apoptosis is principally mediated through caspase-8 or caspase-9 activating pathway and DNA damage associated apoptosis requires activation of the p53 gene (Sakurai et al. 2005). *In vitro* studies have shown that hypothermia selectively protects cells from these mediators of cell death (Sakurai et al. 2005). Bearing this and the fact that hypothermia increases tissue tolerance to hypoxia (Alzaga et al. 2006; Rosomoff and Holaday 1954) in mind, it is tempting to pursue the beneficial effects of induced hypothermia already during the ischaemic insult, as currently done during cardiac and neurosurgery, in association with cardiac arrest.

The first laboratory study to investigate induction of therapeutic hypothermia during ongoing CPR using infusion of LVICF was reported by Nordmark and Rubertsson in 2005 (Nordmark and Rubertsson 2005). They found this method to be effective in piglets subjected to cardiac arrest with no evident injurious effects.

The feasibility, effects and safety of infusing cold (+4 °C) Ringer's solution during CPR and after ROSC were studied in the prehospital setting (III, IV). The primary observation was that a significant decrease in nasopharyngeal temperature was achieved with this method. Despite the recommendation to use nasopharyngeal temperature measurement as a surrogate for cerebral temperature during therapeutic hypothermia (Safar and Kochanek 2002b) it is debatable whether it reliably reflects changes in cerebral temperature especially in the case of circulatory arrest. Prior data from hypothermic surgical patients showed this method of temperature measurement to be superior compared to other non-invasive measurement sites in terms of correlation to brain temperature (Akata et al. 2007) but similar evidence in cardiac arrest victims is scarce. There is evidence that oesophageal measurement, not unlike to nasopharyngeal temperature measurement, is prone to misplacement (Deye et al. 2008) and that intermittent tympanic measurement is unreliable (Nolan et al. 2003). Yielding to the

limitations regarding nasopharyngeal temperature measurement in terms of correlation with brain temperature and susceptibility to artefacts, this method was chosen due to feasibility in the prehospital setting.

In the pilot phase (III), an overshoot decrease in nasopharyngeal temperature was observed as temperatures as low as 31.06 °C were recorded. Such low readings might be due to initial pronounced cooling of the core compartment described by Rajek et al in healthy volunteers (Rajek et al. 2000). Also a local influence of cold infusion flowing in the vicinity of the nasopharyngeal probe might be responsible for this effect. Due to safety aspects and adjustments in the study protocol, the resultant mean volume of cold fluid per patient in the final material was approximately 20 ml/kg and the rate of slow infusion was 57±21 ml/min (IV) which are significantly less than in previous studies utilizing infusion volumes of 30—40 ml/kg and rates of 100 to 150ml/min after ROSC (Bernard et al. 2003; Kim et al. 2005; Kim et al. 2007; Kliegel et al. 2005; Virkkunen et al. 2004). A more rapid rate of infusion and an increased volume of cold fluid already during CPR probably might have produced a more effective cooling than observed. Nevertheless, the protocol used in this study resulted in a consistent decrease in nasopharyngeal temperature. It is speculative whether the median delay to the onset of cold infusion of approximately 20 minutes is too long to consider beneficial effects of intra-arrest cooling to be gained (IV).

Comparing the results in the baseline epidemiological material (I) and patients undergoing intra-arrest cooling (IV), no decrease in the rate of ROSC was found, suggesting that the induction of mild hypothermia during CPR does not interfere with the chance of successful resuscitation. However, it needs to be acknowledged that comparison to historical data carries limitations. Still, recently a study similar to IV was reported by Bruel et al in which no decrease in the rate of ROSC was observed (Bruel et al. 2008).

In this material, 5 out of 12 patients (42 %) rearrested after ROSC during the rapid infusion of ice-cold Ringer's solution. This figure is higher than the percentage of overall rearrest rate (24%) reported in a recent study on prehospital post ROSC cooling (Kim et al. 2007). Refibrillation occurred in four patients, representing 40% of the patients in this study with VF as the initial rhythm. Refibrillation has previously been documented to occur in 54 to 68% of defibrillated patients (Callaham et al. 1993; Weaver et al. 1982; White and Russell 2002). Admitting the limitations of comparison to historical controls and the lack of a control group, it seems that an increase in the proportion of patients who refibrillated during the infusion of cold fluid did not occur.

Hypotension defined as systolic blood pressure <100 mmHg necessitating vasoactive medication after ROSC was observed in 5 of 11 (45%) patients. Proportionally this is more than in the trial by Kim et al. (11% in the intervention group and 14% in the control group) (Kim et al. 2007). It is unclear whether the administration of cold fluid during CPR and after ROSC results in increased susceptibility to hypotension. Prior evidence on post-ROSC infusion of large volume ice-cold fluid is contradictory to this assumption (Kim et al. 2005; Kim et al. 2007; Virkkunen et al. 2004). Actually, improved haemodynamic status after ROSC and infusion of cold fluid was observed in the study by

Bernard et al. and also in a recent experimental study on intra-arrest cooling (Bernard et al. 2003; Zhao et al. 2008).

According to local guidelines on post resuscitation care, one goal is to target systolic blood pressure to exceed 120 mmHg after ROSC and if necessary, vasoactive medication should be initiated after fluid resuscitation (Castrén et al. 2006; Mullner et al. 1996). In the Tampere EMS, the vasoactive agent in question is dopamine. In the five patients in whom hypotension was persistent, dopamine was not administrated in three cases. Even though reversible myocardial insufficiency and haemodynamic instability is common after out-of-hospital cardiac arrest (Laurent et al. 2002), it is of utmost importance to identify and treat this condition as cerebral perfusion is compromised after cardiac arrest (Buunk et al. 1997; Buunk et al. 1996; Sundgreen et al. 2001).

Although the rate of ROSC was not decreased and the rate of rearrest was not clearly increased in association with intra-arrest cooling, a poor overall survival was observed as only one (6%) patient was discharged from hospital. In (I), an overall survival of 13% from out-of-hospital cardiac arrest was reported in the same EMS system.

However, this study was designed merely to investigate the feasibility, safety and effects of intra-arrest cooling with no intention or power to study survival or neurological stage as an outcome end point. Based on previous and subsequent reports, this intervention is does not seem to account for the poor survival. Nordmark and Rubertsson found the use of cold fluid to be effective and safe already during CPR in an experimental study on piglets (Nordmark and Rubertsson 2005). Bernard and Rosalion recently described an encouraging case of prolonged CPR during which LVICF was administrated. Despite a pause in chest compressions for 10 minutes during the resuscitation, the patient was discharged with a satisfactory neurological outcome (Bernard and Rosalion 2008). Furthermore, Bruel et al. reported a ROSC rate of 60.6 % after prehospital intra-arrest cooling using LVICF. Overall survival in their material was 12 % (Bruel et al. 2008), which is comparable to most observational reports on prehospital cardiac arrest with no experimental intervention (Atwood et al. 2005).

As discussed earlier, the outcome of cardiac arrest victims is dependent on the performance of each component of patient care. Optimally, a goal directed therapy protocol such as the one by Sunde et al. described previously in this chapter would enable sufficient efforts to be carried out both in the prehospital setting and during post resuscitation care in the hospital (Nolan and Soar 2008; Sunde et al. 2007). Although factors related to the prehospital treatment of cardiac arrest victims significantly affect the outcome of these patients (Hollenberg et al. 2007), the impact of in-hospital care is inarguable (Langhelle et al. 2003). In the studies of this thesis, the post resuscitation care provided in the hospital was not evaluated according to the corresponding Utstein guidelines (Langhelle et al. 2005). 11 out of the 17 (65%) patients (IV) were transferred to hospital and therefore the influence of in-hospital factors associated with outcome should also be considered. Further analysis revealed that three of the admitted patients were not considered eligible for intensive care reasons being a pre-existing DNR-order in one case, presumed futility after prolonged resuscitation in one patient, and persistent myoclonus reflecting severe hypoxic-ischaemic injury in one elderly patient.

Additionally, of those patients admitted to the ICU, two patients died before therapeutic hypothermia could be initiated. The study protocol did not dictate the in-hospital care of these patients and further care was left at the discretion of the treating physicians.

In this material, prehospital induction of mild hypothermia using ice-cold intravenous fluids was found to be effective and, on a limited preliminary basis, safe. This method was feasible in the use of both prehospital physicians and paramedics. As applies to both prehospital and inhospital cooling, the scientific evidence regarding the optimal onset and duration of mild hypothermia is not known. Furthermore, the actual effects of mild induced hypothermia promoting better outcome after cardiac arrest are not complete understood. Several studies on prehospital and inhospital cooling are underway, aiming to shed light on the questions presented by the International Liaison Committee on Resuscitation (ILCOR) in the consensus report on scientific knowledge gaps and research priorities in resuscitation science (Gazmuri et al. 2007).

Limitations of the Study

In Study I, an important limitation regarding the recording of time intervals was observed as the lack of equipment time synchronization. As a psychological factor also known in some reports as the Hawthorne effect (Wickstrom and Bendix 2000), the possibility of improved performance by the EMS personnel related to the increased attention caused by this study can not be ruled out.

Although Study II was a randomized, controlled trial, the eventual study population was suggestive of selection bias. This was suspected due to overrepresentation of male patients and ventricular fibrillation as the initial rhythm. The inclusion rate was slow in this study and exclusions were unavoidable. It is possible that the trial on induction of prehospital hypothermia could have been more readily initiated (and remembered) by prehospital EMS physicians in cases of presumed better outcome, such as ventricular fibrillation. After inclusion in the study, the treating personnel could not be blinded to the allocated treatment.

In Studies III and IV there was no control group and the final sample size was small. Excluded number of patients was large due to protocol violation. Also, despite being technically feasible, the use of nasopharyngeal temperature measurement in studies II-IV was subject to misplacement and artefact. In the protocol of intra-arrest cooling, temperature measurement was initiated only after initiation of cold infusion. In cases of delayed temperature measurement, the assessment of actual intra-arrest cooling effect is not possible and this approach might also possess a safety issue. The correlation of nasopharyngeal temperature to cerebral temperature is not known especially in cases of cardiac arrest.

Summary and Conclusions

The purpose of this thesis was to study the epidemiology of prehospital cardiac arrest in Tampere, Finland and the induction of mild hypothermia in the prehospital setting. It was observed in these studies that in the city of Tampere the EMS personnel initiated resuscitation less frequently than reported from most other EMS systems. However, further analysis revealed that in a majority of the cases the decision not to resuscitate was based on generally known strong negative predictors of survival. In this material these were predominantly the presence of secondary signs of death and unwitnessed onset of cardiac arrest with asystole as the initial rhythm. These grounds to withhold resuscitative efforts conform to the best current scientific knowledge and resuscitation guidelines.

In the Tampere EMS system, the overall and Utstein style golden standard survival were average and comparable to results reported from international study centres. On a subjective basis, the revised Utstein style template for data recording published in 2004 proved to be more feasible than the previous detailed 1991 template.

The randomized controlled trial of prehospital induction of mild hypothermia suggested the infusion of cold Ringer's solution after ROSC to be an effective cooling method and compared to a small control group, also safe. The efficacy of this method was evident compared to standard treatment as a significant decrease in nasopharyngeal temperature was observed only in the intervention group. Spontaneous cooling alone did not decrease nasopharyngeal temperature to the level of therapeutic hypothermia prior to hospital admission.

In a small study on intra-arrest cooling, the infusion of cold fluid during resuscitation and after return of spontaneous circulation significantly reduced nasopharyngeal temperature. A slow infusion of cold fluid during resuscitation did not seem to impair the chance of achieving ROSC. Furthermore, a more rapid infusion of cold fluid after return of spontaneous circulation did not seem to cause haemodynamic instability. As a feasible method, paramedics could initiate cooling already in the prehospital phase of treatment.

In the light of current evidence and based on these results, it is suggested that induction of mild hypothermia should be implemented to the prehospital care of the comatose survivors of cardiac arrest to enable early effect of hypothermic cerebral protection. A preliminary result of these trials was that cooling can be initiated already during CPR and thus possibly providing hypothermic neuroprotection already during the initial ischaemic insult. However, the safety of intra-arrest cooling needs to be further assessed in a controlled setting with sufficient sample size.

Future Perspectives

For decades the prognosis of sudden cardiac arrest has been considered dismal. The encouraging study by Sunde et al described the effects of a goal directed protocol for the treatment of cardiac arrest victims which resulted in a significant increase in survival (Sunde et al. 2007). As observed in these studies, the outcome of prehospital cardiac arrest in Tampere is average compared to other cities. Based on the Norwegian experience, it is likely that similar optimization would be beneficial in Tampere also. As the majority of cardiac arrests occur due to cardiac aetiology (Engdahl et al. 2002), it is possible that the benefits of physician directed prehospital care observed in myocardial infarction and resuscitation patients would be influential in Tampere also (Väisänen et al. 2006). Although not a guarantee of improved adherence to post-resuscitation care guidelines, it has been shown that the presence of prehospital emergency physician improves the care of resuscitated patients (Kirves et al. 2007).

Another important objective is to further determine the optimal patients in whom resuscitation efforts can be considered worthwhile and in whom resuscitation should be withheld (Engdahl et al. 2000; Väyrynen et al. 2008a). It is of utmost importance to draft guidelines based on sufficient evidence to avoid denial of resuscitation from patients in whom efforts might be beneficial. And, vice versa, it is necessary to elaborate cases of absolute futility in which resuscitation should be withheld when restoration of circulation would produce nothing but burden and pain in the form of complete cerebral disability or prolonged unavoidable death.

Therapeutic hypothermia has proven to be beneficial after cardiac arrest. This perception is derived from studies conducted in patients of high selection (Bernard et al. 2002; HACA 2002). Another critical aspect is that in the HACA study, hypothermia was, in fact, not compared to normothermia as the patients in the control group showed a tendency towards mild hyperthermia. To which extent these results can be generalised to apply to all victims of cardiac arrest is unclear (Oddo et al. 2008). It is evident that not all patients benefit from intensive care even after a successful resuscitation attempt because of grave baseline morbidity or arrest of certain aetiology. However, if post-resuscitation care is carried on in the intensive care setting and until contradictory evidence is available it seems justifiable to strive for additional improvement in outcome in this group of patients with low overall survival, i.e. “just do it” (Alam 2008).

Currently the implementation rate of in-hospital therapeutic hypothermia in Finland is high (Oksanen et al. 2007a). The implementation rate of prehospital therapeutic hypothermia in European countries is not known, but a recent study in the United States showed that the use of this treatment modality is rare (Suffoletto et al. 2008). In the study

by Suffoletto et al, a significant factor restricting the use of prehospital hypothermia was the lack of specific guidelines.

Existing scientific evidence to support prehospital induction of hypothermia is scarce especially regarding the intra-arrest use of this treatment. Indications for prehospital cooling need to be similar to those applied for in-hospital cooling to enable continuation of the treatment. A sufficiently powered randomized controlled trial on prehospital induction of hypothermia with appropriately continued in-hospital treatment is necessitated to estimate the effects of this treatment and to lay basis for future guidelines. A further goal is to determine the optimal method of prehospital cooling (external vs. internal) and when to initiate the treatment (Uray and Malzer 2008; Virkkunen et al. 2004).

Errata

I. Page 238, Table 2, “PEA: pulse less electrical activity” should be “PEA: pulseless electrical activity”. Page 241, Discussion, Line 12, ”2005” should be ”2003”

III. Page 362, Discussion, Paragraph II, Line 24, “cooling can be achieved with simply” should be “cooling can be achieved with a simple method during CPR”

IV. Page 208, Table 2, Time intervals, Line 1, Range “0 to -4” should be “0 – 4”

IV. Page 208, Paragraph I, Line 2, “surviving patients was.[1]” should be “surviving patients was 1.”

IV. Page 209, Line 14, “Five of the 17 patients (29%)” should be “Five of the 12 patients (42 %)”.

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CLINICAL PAPER

Presumed futility in paramedic-treated out-of-hospital cardiac arrest: An Utstein style analysis in Tampere, Finland☆

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Summary
Aim: To report prospectively the outcome from prehospital cardiac arrest according to the Utstein template in the city of Tampere, Finland, with special reference to those patients in whom resuscitation was not attempted.
Materials and methods: In Tampere (population 203,000), a two-tiered emergency medical service (EMS) system provides first response and basic life support (BLS), supported by advanced life support (ALS) units staffed with nurse-paramedics. We analysed all out-of-hospital cardiac arrests considered for resuscitation during a 12-month period.
Results: Of 191 patients with prehospital cardiac arrest, resuscitation was not attempted in 98 patients (51%). Reasons to withhold from resuscitation were estimated futility (97 cases) and a do-not-attempt-resuscitation order (1). Sixty percent of the patients with no resuscitation had secondary signs of death, 97% had asystole as the initial cardiac rhythm and 98% had suffered an unwitnessed cardiac arrest. Resuscitation was successful in 45 of the remaining 93 patients with attempted resuscitation. Twelve patients were discharged (overall survival rate 13%), nine of them with a CPC score of 1 or 2. Fifteen patients were treated with therapeutic hypothermia. Of the bystander-witnessed cardiac arrests with VF as initial rhythm, 29% survived.
Conclusions: The Tampere EMS system initiated resuscitation less frequently than reported from other EMS systems, but the reasons to withhold resuscitation seemed

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justified. The overall and Utstein's 'golden standard' survival rates were comparable with previous reports.

Introduction

The Utstein templates for reporting on out-of-hospital cardiac arrest (OOHCA) were first published in 1991.[1] Due to the complexity of data to be reported and inconsistencies in terminology, the template was published in a revised and simplified form in 2004[2] to provide a better and more accurate tool for cardiac arrest and resuscitation attempt reporting.

The purpose of this study was to assess the usability of the template in prospective data collection with special reference to the subgroup of patients in whom the paramedics considered resuscitation to be futile. A secondary aim was for the first time to report survival from, and outcome of, out-of-hospital cardiac arrest according to the Utstein template in the city of Tampere in Southern Finland.

Materials and methods

Study design

Data were prospectively collected between August 1, 2004 and July 31, 2005. All consecutive OOHCA patients in whom resuscitation was considered in the city of Tampere were analysed. As no clinical intervention was performed, approval from the Local Ethics Committee was not required. The study was conducted according to the Ethical Standards of the Declaration of Helsinki.[3]

Study setting and population

Tampere is the third largest city in Finland with a population of 203,000. Fifty-two percent of the inhabitants are females. In 2003, 15% of the population was aged between 0 and 14 years, 15% between 15 and 24 years, 30% between 25 and 44 years, 25% between 45 and 64 years, and 15% 65 years or older. In the same year the life expectancy for men was 75.2 years and that for women 82.0 years. In 2003, 1784 individuals died in Tampere, 717 (40%) of them due to cardiovascular disease.[4]

The Tampere city area comprises a total of 688 km^2 with urban, suburban and rural areas. One hundred sixty-five square kilometers of the area is covered by water. The population density is approximately 385/km^2.

Description of the emergency medical service (EMS) system

The emergency dispatch centre serving the city also covers 33 surrounding smaller communities, providing services for a population of approximately 460,000 inhabitants. The European emergency telephone number 112 is used for fire, rescue and medical emergencies. Five months after the onset of this study, the police services were also included in the dispatch service. Currently, the centre receives 370,000 calls annually. The dispatchers use criteria-based dispatch and provide telephone-assisted instructions for compressions-only cardiopulmonary resuscitation (CPR) when indicated.

The EMS system is two-tiered with firemen—emergency medical technicians (EMTs) providing basic life support (BLS) as the first tier and nurse-paramedics providing advanced life support (ALS) as the second tier. The EMTs are authorised to use an automated external defibrillator (AED), perform tracheal intubation of a lifeless adult patient and to establish an intravenous line. The nurse-paramedics give intravenous drugs, provide sedation to facilitate tracheal intubation in unconscious patients, and initiate thrombolytic treatment after consulting with a physician.

The city of Tampere is divided into four regions, each with its own rescue station. All stations have fire engines equipped with AEDs operating as first responding units (FRUs) when required, and BLS ambulances. In addition there are two ALS-equipped units covering separate halves of the city. In total, there are six BLS ambulances and two ALS units operating on a 24-h basis. During daytime there are five additional BLS ambulances, which can be staffed around the clock if necessary.

In medical emergencies, both the closest BLS and an ALS unit are dispatched simultaneously if the call is classified as a high-risk call, such as suspected cardiac arrest. If the risk is not evident, the nearest BLS unit is dispatched, supported by an ALS unit only if indicated later.

Cardiac arrest treatment during the study period was based on national guidelines adapted from the ERC resuscitation guidelines 2000.[5] The antiarrhythmic drug in use was lidocaine. Chest compressions were performed manually. The guidelines support refraining from resuscitation

attempts in the following cardiac arrest situations; unwitnessed arrest with asystole as initial cardiac rhythm, patients with no CPR attempts for at least 15 min prior to EMS arrival and initial rhythm of asystole or pulseless electrical activity (PEA), asystolic traumatic cardiorespiratory arrest (TCRA), patients with end-stage malignant disease or a do-not-attempt-resuscitation (DNAR) order. Only patients with a hypothermic cardiac arrest are transported to hospital with on-going CPR. In all other circumstances the resuscitation attempt is terminated in the field if there is no response.

All prehospital cardiac arrest patients that were resuscitated successfully were admitted to a single tertiary-level university hospital providing mild therapeutic hypothermia for eligible patients. The emergency department (ED) physicians at this hospital act as consultants for the paramedics of the Tampere EMS.

Data collection and analysis

Data of all patients within the city limits of Tampere who suffered an out-of-hospital cardiac arrest and who were considered for resuscitation when the EMS was activated were collected prospectively on a separate data sheet according to the 1991 Utstein style recommendations.[1] During the study period the revised form of the Utstein template[2] was published and data were adapted to conform to this template after the study period. The researchers contacted the EMS personnel on a daily basis to ensure completeness of the data. Data on the post-resuscitation phase were obtained from patient records and interviews with staff involved in the treatment. Time intervals were analysed from the registry of the emergency dispatch centre and EMS equipment, but exact synchronisation of these systems could not be ensured during the study period.

Statistical analysis was performed using SPSS for Windows V13.0-software (SPSS Inc., Chicago, IL, USA).

Results

The EMS was dispatched to a total of 191 out-of-hospital cardiac arrests during the one-year study period. Core and supplementary data elements are reported according to the revised 2004 Utstein recommendations.[2] No patients were excluded or lost from follow-up during the study, and no rhythm analysis or defibrillation was performed in any patient prior to EMS arrival.

Table 1 Resuscitation attempts not initiated by the emergency medical service personnel $n = 98$

	n	(%)
Resuscitation attempts not initiated	98	100
Secondary signs of death	59	60.2
Delay to CPR over 15 min	16	16.3
Massive trauma	12	12.2
End-stage malignant disease	2	2.0
DNAR-order	1	1.0

CPR: cardiopulmonary resuscitation, DNAR: do-not-attempt resuscitation.

Cardiac arrests initially considered for resuscitation but resuscitation not attempted

In 98 of the 191 patients (51%), resuscitation was not attempted. The reasons to refrain from resuscitation and characteristics of these cases are presented in Tables 1 and 2.

In addition to these, the EMS was dispatched to two patients due to presumed cardiac arrest, but upon arrival of the EMS crew the patients had a spontaneous circulation after having received bystander CPR.

Resuscitation attempts initiated

Resuscitation was attempted in 93 patients, which yields an incidence of 46/100,000 inhabitants/year. The Utstein style core and supplementary data elements and characteristics of these 93 patients are presented in Figure 1 and Table 2.

Primary outcome and use of mild therapeutic hypothermia

Return of spontaneous circulation (ROSC), as defined in the Utstein definitions, was established in 49 of the 93 patients (53%). ROSC was temporary in four patients. Forty-five (48%) patients were admitted to hospital (survived event) where 33 (35% of all patients, 73% of those admitted) later died, 11 of them within the first 24 h.

Of the 45 patients admitted, mild therapeutic hypothermia (target core temperature approximately 33 °C for 24 h) was induced in 15 patients. Of these patients, the initial cardiac rhythm was VF in 11, asystole in two and PEA in two patients.

Table 2 Characteristics of patients considered for resuscitation at the time of dispatch

	No attempt $n = 98$ (100%)	CPR $n = 93$ (100%)	p-Value*
Age			
Median (years)	57	67	
Range	14—96 years	2 months—94years	
Gender			
Male	67 (68.4)	62 (66.7)	
Female	31 (31.6)	31 (33.3)	
Arrest witnessed	2 (2.0)	74 (79.6)	<0.001
Layperson witnessed arrest	2 (2.0)	60 (64.5)	
EMS-witnessed arrest	0 (0)	14 (15)	
Arrest not witnessed	96 (98.0)	19 (20.4)	<0.001
Bystander CPR	3 (3.0)	29 (31.2)	<0.001
Location of arrest			
Home	81 (82.7)	54 (58.1)	<0.001
Public location	12 (12.2)	31 (33.3)	
Nursing/shelter home	5 (5.1)	5 (5.4)	
Ambulance	0 (0)	3 (3.2)	
Aetiology of arrest			
Presumed cardiac	15 (15.3)	72 (77.4)	<0.001
Other non-cardiac	11 (11.2)	11 (11.8)	
Respiratory	2 (2.0)	5 (5.4)	
Submersion	0 (0)	4 (4.3)	
Unknown	58 (59.2)	1 (1.1)	<0.001
Trauma	12 (12.2)	0 (0)	
Initial rhythm			
VF	1 (1.0)	28 (30.1)	
ASY	95 (96.9)	33 (35.5)	<0.001
PEA	3 (3.1)	31 (33.3)	
Unidentified (AED-non-shockable)	0 (0)	1 (1.0)	

CPR: cardiopulmonary resuscitation, EMS: emergency medical service, VF: ventricular fibrillation, ASY: asystole, PEA: pulse less electrical activity, AED: automated external defibrillator.

* Chi-Square and Fisher's Exact Test were used when appropriate. Statistical significance was set at $p < 0.05$. p-Values are two-tailed and presented when found significant.

Secondary survival and neurological outcome

Twelve patients were discharged alive from hospital, yielding an overall survival of 13%. Survival in relation to the initial rhythm is presented in Figure 1. Of those treated with therapeutic hypothermia, nine patients (75% of the surviving patients) survived to hospital discharge, eight patients with VF and one with asystole.

Neurological outcome classified according to the cerebral performance category (CPC)[6] was CPC score 1—2 in nine and 3—4 in three of the discharged patients. None of the survivors were discharged in a permanent vegetative state.

Witnessed arrest with initial rhythm of ventricular fibrillation

In 24 patients, the onset of cardiac arrest was bystander witnessed and the initial rhythm was ventricular fibrillation. Seven (28%) of these patients survived to hospital discharge.

Arrests witnessed by EMS personnel

In 14 patients (15%), cardiac arrest occurred after EMS arrival. The initial rhythm was PEA in 11, asystole in two and VF in one patient. ROSC was achieved in 10 patients and they were admitted to hospital (survived event). Three patients were discharged, all with a CPC

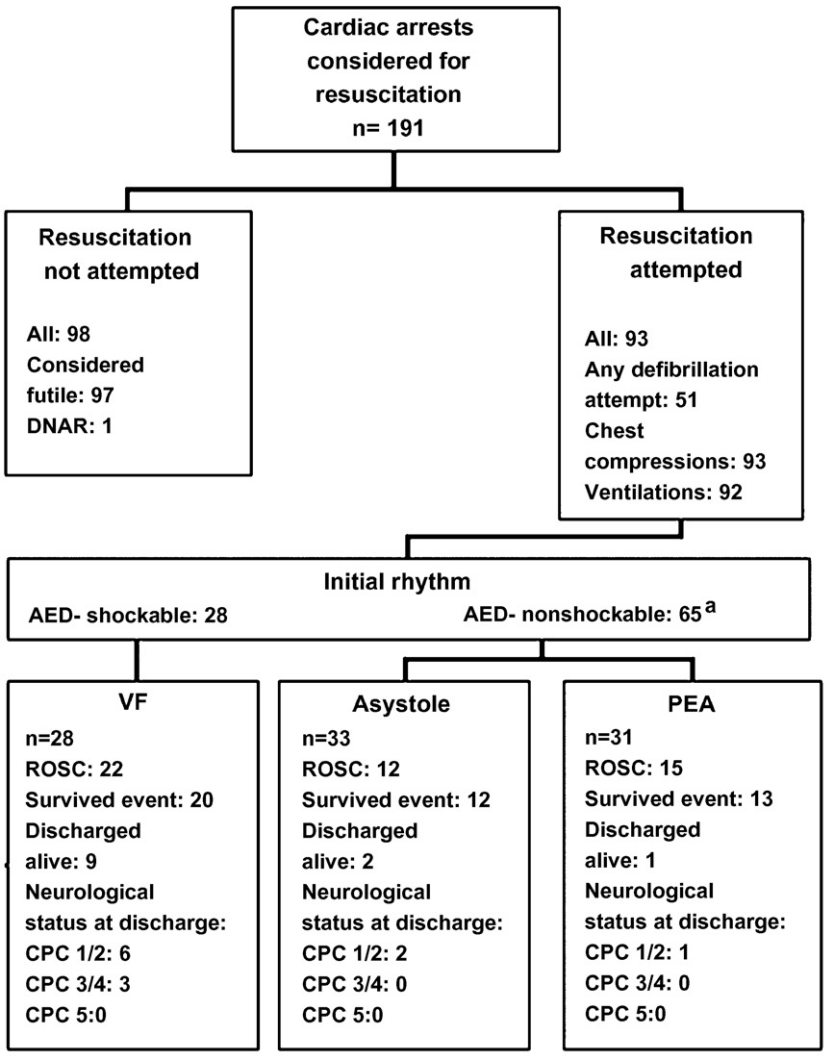

Figure 1 Cardiac arrests considered for resuscitation. DNAR: do not attempt resuscitation-order, AED: automated external defibrillator, VF: ventricular fibrillation, PEA: pulse less electrical activity, ROSC: return of spontaneous circulation, CPC: cerebral performance category. [a]One patient with an unknown AED-non-shockable rhythm expired in field.

score of 1—2 at the time of hospital discharge.

Time intervals

The core time elements of arrests not witnessed by the EMS ($n = 79$) are presented in Table 3. The interval between the onset of cardiac arrest and the receipt of the emergency call was identified reliably in 50 patients.

Supplementary time elements of the arrests not witnessed by the EMS are presented in Table 4 categorised according to the resuscitation attempt and success.

Table 3 Core time elements of arrests not witnessed by the EMS $n = 79$

Time interval (min)	Median	Range
Collapse to emergency call receipt ($n = 50$)	1	0—22
Call received, first rhythm analysis	10	2—33
Call received, CPR initiated	10	2—34
Call received, first defibrillation ($n = 27$)	9	3—17

CPR: cardiopulmonary resuscitation.

Table 4 Supplementary time elements of arrests not witnessed by the EMS

Time interval (presented in minutes, median and range)	Resuscitation not attempted ($n = 98$) median (min–max)	Expired in field ($n = 44$) median (min–max)	Survived event ($n = 35$) median (min–max)
Collapse, call received	NA	1 (0–22)[a] $n = 26$	1 (0–5) $n = 24$
Call received, dispatch	2 (0–13)	2 (0–10)[a]	2 (0–20)
Call received, on scene	7.5 (2–25)	8 (0–14)[a]	7 (2–23)
Call received, at patient's side	9 (3–30)	9.5 (4–33)	9 (2–24)
Call received, assessment of need for CPR	9 (3–30)	10 (4–33)	9 (2–24)
Call received, CPR	NA	10 (4–34)	10 (2–28)
Call received, first defibrillation[b]	NA	11 (6–17) $n = 8$	8 (3–12) $n = 19$
Call received, intubation	NA	16 (8–34)	14 (6–29)
Call received, IV-access	NA	17 (11–44)	15.5 (8–40) $n = 34$
Call received, ROSC	NA	30 (23–40) $n = 4$	26 (10–49)
Start of CPR (EMS), ROSC	NA	20 (15–26) $n = 4$	14 (1–29)
Duration of resuscitation	NA	29.5 (6–90)	NA

NA: not applicable, CPR: cardiopulmonary resuscitation, IV: intravenous, ROSC: return of spontaneous circulation, EMS: emergency medical service.

[a] In one case, collapse occurred when EMS was on scene, but not at patient's side.

[b] Defibrillation of initial AED-shockable rhythm.

Discussion

This is the first prospective study of out-of-hospital cardiac arrests according to the Utstein style in the city of Tampere, Finland. The principal difference between our results and earlier reports on OOHCA is the proportion of patients in whom resuscitation was not attempted. In our material, resuscitation was not attempted in a little more than 50% of all cardiac arrest patients encountered by the EMS. The reasons for this require closer attention.

The main documented reason for not attempting resuscitation was the presence of secondary signs of death (59 cases, 60%). The rapid risk analysis based on limited available information during the emergency phone call may result in overtriage of the response although the futility of resuscitation efforts may be evident from the beginning. Still, dispatch during the emergency phone call should not be delayed due to overtly thorough risk analysis.[7] Factors in common of the patients without attempted resuscitation were initial cardiac rhythm of asystole (97%) and unwitnessed arrest (98%)—both strong negative predictors of survival.[8,9] The futility of resuscitation attempts in unwitnessed cardiac arrest has been addressed by Kuisma et al. in 1997 who reported an overall survival rate of 4.9%.[10] Twelve patients had a primary traumatic cardiorespiratory arrest (TCRA) due to massive injuries, another condition associated with poor survival, only 2.2%.[11] In 16 patients the reason to withhold resuscitation was documented to be due to extended delays (15 min or more) without CPR. A further explanation for not attempting resuscitation in these patients may be due to the recognised importance of layperson CPR, a factor that has been consistently proven.[12,13]

The reasons to refrain from resuscitative efforts in these patients are similar to those reported by Horsted et al. from prehospital cardiac arrests treated by a physician staffed EMS.[14]

In 1995, Weston et al. assessed cardiac arrest patients in whom the paramedic staffed ambulance crew refrained from initiating CPR. In their study the rate of attempted resuscitation was 60%.[15] Higher percentages of attempted resuscitation have been reported from other paramedic staffed EMS in Geelong (66%), Alachua County (92%) and Osaka (96%), and also from physician staffed EMS in Heidelberg (68%), the Alps (92%), and Bodo (96%).[16–21] Lower rates of attempted resuscitation have been reported from physician staffed EMS in Copenhagen (34%) and in Estonia (48%).[22,23]

Although the concept of 'confirmed cardiac arrest considered for resuscitation' was defined

in the 1991 Utstein guidelines as 'all unresponsive, breathless and pulseless patients for whom the emergency personnel are called',[1] it seems that this concept is not interpreted in the same way across different EMS-systems and study centres. Patients with signs of irreversible death were excluded from some study settings even though the EMS had been dispatched.[24,25] This difference may partially explain the dispersion of the percentage of resuscitation attempts initiated in different EMS systems. Cardiac arrests are not considered for resuscitation in similar ways. In 2005, Fredriksson et al. stressed the importance of strict adherence to the Utstein guidelines to enable comparison between studies.[26]

It seems that the reasons for withholding resuscitation efforts in the prehospital setting need further investigation, and thorough documentation is encouraged. Future guidelines should further clarify whether to report all cardiac arrest patients met by the EMS, or should patients with secondary signs of death, for example, be excluded even though they might have been considered for resuscitation at the time of EMS dispatch.

During the study period, the incidence of attempted out-of-hospital resuscitation per 100,000 per year was 46, which seems slightly less than that reported by Herlitz et al. (50—66/100,000/year) in 1999 from five European regions.[27] However, in 2005 Atwood et al. reported the overall incidence from 37 European communities of all-rhythm cardiac arrests treated by the EMS to be 38 per 100,000 person years, with a six-fold variance across individual communities.[28]

Resuscitation attempts were not initiated in 98 of our 191 patients considered for resuscitation. With these included, there were 94 confirmed sudden out-of-hospital cardiac arrests per 100,000 inhabitants annually in the city of Tampere, a figure comparable to that reported from Helsinki in 1994[29] and Maastricht in 1997.[30]

The characteristics and results of resuscitations covered by the Tampere EMS are comparable to those reported earlier. The location of arrest, sex distribution and aetiology of arrest were similar to those in earlier studies.[7,31—34] The frequency of bystander CPR, the overall and Utstein 'golden standard' survival and the percentage of patients displaying signs of permanent neurological deficit at discharge did not differ markedly from previously reported data.[27,34,35]

It is reasonable to criticise the reported intervals in this study due to lack of equipment time synchronization. Castrén et al. have addressed this problem recently.[36] Similar difficulties concerning time documentation have been reported earlier from in-hospital resuscitations.[37] Differences in timing systems prevent accurate analysis of response times and delays that might affect patient treatment.

As the data were collected according to the 1991 Utstein recommendations[1] and analysed and presented according to the revised 2004 form[2] a comparison of these templates was possible retrospectively. Primarily, the simplified 2004 template proved superiority concerning evaluation of time intervals. In our material, some of the previously recommended time points occurred almost simultaneously when a patient was met by the EMS. Distinguishing the time of arrival at the patient's side and the time the arrest was confirmed from the time of determination of the need for CPR proved impractical.

We believe that difficulties in data collection will decrease by using the 2004 Utstein template.

Conclusions

We found that the personnel of the Tampere EMS initiated resuscitation less frequently than reported elsewhere, but further analysis revealed that in a majority of the cases the decision not to resuscitate was based on generally known strong negative predictors of survival. The overall and Utstein 'golden standard' survival in the city of Tampere were average and comparable to results reported previously.

The revised Utstein template proved more feasible than the previous detailed 1991 template.

Conflict of interest

None of the authors have conflicts of interest to declare.

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CLINICAL PAPER

Prehospital induction of therapeutic hypothermia during CPR: A pilot study☆

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Cardiac arrest;
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Temperature;
Prehospital

Summary
Aim of the study: We studied induction of therapeutic hypothermia during prehospital resuscitation from cardiac arrest using an infusion of ice-cold Ringer's solution in five adult patients.
Material and methods: Paramedics infused +4 °C Ringer's solution into the antecubital vein of the patients with a maximum rate of 33 ml/min to a target temperature of 33.0 °C.
Results: The mean infused volume of cold fluid was 14.0 ml/kg, which resulted in a mean decrease of 2.5 °C in nasopharyngeal temperature. The decrease in temperature continued after the cessation of infusion in two patients, causing suboptimal temperatures below 32 °C.
Conclusion: We conclude that the infusion of small volumes of ice-cold Ringer's solution during resuscitation results in an effective decrease in nasopharyngeal temperature. Caution should be taken to avoid temperatures below the range of mild therapeutic hypothermia.

Introduction

Mild therapeutic hypothermia improves survival and neurological outcome in comatose survivors of out-of-hospital cardiac arrest.[1,2] Current resuscitation guidelines recommend that therapeutic hypothermia should be induced as soon as possible,[3] and there is evidence that delays in the cooling process negates the beneficial effects of this treatment.[4,5] In experimental cardiac arrest studies, intra-arrest cooling significantly improved resuscitation outcomes.[6,7] Infusion of ice-cold intravenous fluids for induction of therapeutic hypothermia has been found to be feasible and safe after return of spontaneous circulation (ROSC) in humans,[8–11] and one experimental study has shown this method to also be effective during ongoing cardiopulmonary resuscitation (CPR).[12] We report our initial experience in the use of intravenous infusion of ice-cold Ringer's solution during ongoing CPR in prehospital patients treated by paramedics. The aim was to

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evaluate the feasibility of this approach and to study the cooling effects of this treatment during cardiac arrest.

Material and methods

We enrolled five consecutive patients treated by the paramedic-staffed Tampere Emergency Medical Service (EMS) system. This is a two-tiered EMS system with basic emergency medical technicians in the first tier, backed up by paramedics as a second tier. Patients, aged ≥18 years with cardiac arrest not due to trauma or intoxication, were included regardless of the initial cardiac rhythm. Exclusion criteria were pregnancy, return of spontaneous circulation within 5 min from the onset of resuscitative efforts, or clinical suspicion of accidental hypothermia. The reason to exclude patients with ROSC within 5 min from the onset of CPR was to prevent induction of mild hypothermia in patients who might regain consciousness shortly after ROSC.

The study protocol was approved by the institutional review board of the Tampere University Hospital, Finland. With the permission of the review board, written informed consent for inclusion in the study was obtained from relatives of the patients after completion of resuscitation.

Treatment of cardiac arrest followed the 2005 European Resuscitation Council guidelines.[13] On arrival of the first EMS crew, primary resuscitative measures such as chest compressions, ventilation and defibrillation as indicated were started immediately. CPR continued while paramedics performed orotracheal intubation and obtained venous access via the antecubital vein. In the absence of evident exclusion criteria, infusion of cold (+4 °C) Ringer's acetate was initiated via the peripheral cannula at a slow rate sufficient to keep the cannula patent. The cold fluids were stored in the ambulance in a medical refrigeration transport box (Dometic MT4B, Dometic Group, Solna, Sweden). A nasopharyngeal temperature probe was then inserted and the temperature recorded (YSI 4600 Precision Thermometer, YSI Corp., Dayton, OH, USA). Nasopharyngeal temperature measurement was chosen due to the clinical feasibility in the prehospital setting with easy placement and standardised site of measurement. If the first measured nasopharyngeal temperature was <33 °C the infusion of cold fluid was discontinued, otherwise the infusion rate was set at 33 ml/min using an infusion pump (Power Infuser, Infusion Dynamics, Plymouth Meeting, PA, USA). The target volume of cold fluids to be infused was 30 ml/kg. The nasopharyngeal temperature was monitored continuously and the infusion was stopped if a temperature reading of 33 °C was reached before the target volume had been infused. The infusion was later restarted if the temperature again began to increase above 34 °C. If a temperature reading below 32 °C was measured, passive external warming with blankets was initiated.

After ROSC, pulse oximetry and end-tidal CO_2 readings were monitored continuously. Arterial blood pressure was measured non-invasively every 5 min. If the target temperature had not been reached at the time of ROSC, the infusion was continued even if the target volume of 30 ml/kg had been infused. After stabilisation, the patients were transferred to a single tertiary-level university hospital. Further care in hospital was at the discretion of the treating physicians. As this study focused on the prehospital feasibility of inducing therapeutic hypothermia and the study protocol ended on arrival to the emergency department, treatment with therapeutic hypothermia was not continued systematically in the hospital. The reason for this was that patients were included regardless of the initial cardiac rhythm, and local hospital guidelines advocate therapeutic hypothermia primarily for patients with ventricular fibrillation as initial rhythm. Survival and outcome of the patients was assessed according to the Utstein guidelines.[14] If an autopsy was performed, the findings from this were also registered.

Results

The data of the study patients are shown in Table 1. There were four male and one female patient. Their mean age was 68 years and mean weight was 77 kg. All patients were resuscitated indoors. The initial cardiac rhythms were pulseless electrical activity in three patients, ventricular fibrillation in one and asystole in one patient. The mean delay from the onset of resuscitative efforts to infusion of cold fluids was 10 min.

During CPR, the mean volume of infused cold solution was 892 ml during a mean time of 28 min, yielding a mean infusion rate of 32 ml/min. This resulted in a mean decrease in temperature of 1.9 °C during CPR. Based on this, the calculated mean rate of temperature decrease during CPR was 4.1 °C/h.

Table 1 Patient characteristics and study variables

Patient	Sex	Age	Location of arrest	Initial rhythm	T_1	T lowest	ΔT	Infused volume (ml)	ROSC	Outcome	Cause of arrest
1	Male	86	Public	VF	33.42	31.06	−2.36	1050	No	Died in the field	AMI
2	Male	67	Home	PEA	34.50	32.74	−1.76	200	No	Died in the field	RAAA
3	Male	63	Care facility	PEA	33.06	32.00	−1.06	250	No	Died in the field	Asphyxia
4	Female	53	Home	ASY	34.80	31.60	−3.20	1000	Yes	Died in hospital	SDH
5	Male	71	Home	PEA	35.20	31.10	−4.10	2900	Yes	Died in the field	IHF

T_1: first measured nasopharyngeal temperature (°C), T lowest: lowest measured nasopharyngeal temperature during resuscitation (°C), ΔT: change of nasopharyngeal temperature (°C), ROSC: return of spontaneous circulation, VF: ventricular fibrillation, PEA: pulseless electrical activity, ASY: asystole, AMI: acute myocardial infarction, RAAA: ruptured abdominal aortic aneurysm, SDH: subdural haemorrhage, IHF: ischaemic heart failure.

The total mean volume of cold solution infused during CPR and after ROSC was 1080 ml (14.0 ml/kg), which resulted in a mean decrease in nasopharyngeal temperature of 2.5 °C. The mean time to infuse this volume was 39 min. The mean infusion rate was 28 ml/min due to pauses in infusion when the temperature fell below 33 °C. The mean temperature when ROSC was achieved in patients 4 and 5 was 34.0 °C. In all patients the infusion was paused because the temperature decreased to 33 °C. Despite this, the temperature continued to decrease during resuscitation and transiently even after ROSC in patients 4 and 5, resulting in temperatures as low as 31.1 °C. When the infusion was discontinued the temperature slowly tended to rise again in patients 1, 2 and 5. The infusion of small volumes (200—250 ml) resulted in a rapid decrease of temperature in patients 2 and 3.

Three patients who did not respond to resuscitation were declared dead on the scene. Of the two patients who regained ROSC, one died on the scene and the other was admitted to hospital where she died within 24 h of admission.

An autopsy was performed in three patients. The cause of death (COD) was acute myocardial infarction in one patient, haemorrhage due to ruptured abdominal aortic aneurysm in one patient, and subdural haemorrhage and cerebral contusions in one patient without evident signs of trauma on the scene. Patients 3 and 5 were not autopsied. The COD of patient 3 was considered to be asphyxia due to airway obstruction resulting from aspiration of food. Based on clinical judgement, the COD of patient 5 was cardiac failure due to ischaemia.

Discussion

In this pilot study, induction of therapeutic hypothermia by paramedics using cold fluids via a peripheral vessel was found to be feasible during CPR. We found that the infusion of moderate amounts of cold (+4 °C) Ringer's acetate during cardiopulmonary resuscitation resulted in a fall in nasopharyngeal temperature during ongoing CPR. The volumes needed were smaller than in our previous study.[9] It has been estimated that an infusion of 30 ml/kg of +4 °C saline decreases core temperature by 1.5 °C.[3] In our study, the average volume was 14.0 ml/kg with a mean decrease of 2.5 °C in nasopharyngeal temperature. In fact, the volumes used in our study caused the temperature to decrease below the target temperature even when the infusion was halted Rajek et al. previously reported the effects and mechanisms of cold intravenous fluids causing effective cooling of the core compartment during anaesthesia in nine healthy volunteers.[15] We hypothesize that the fall in nasopharyngeal temperature observed in our patients was due to the centralised circulation during CPR, which was cooled quickly by the infusion of cold fluid. The rapid changes in measured temperature using this method during resuscitation warrant caution as temperatures below mild hypothermia (32—34 °C) are to be avoided. If the target temperature of 33 °C can be achieved with smaller infusions before ROSC, the disadvantages of volume load feared by previous investigators might be avoided.[12]

In patients with an intact circulation, some studies suggest that nasopharyngeal temperature reflects core temperature reliably[16,17] although contradictory evidence regarding the relation to brain temperature exist.[18] According to Akata et al., it seems that nasopharyngeal temperature measurement is superior to other non-invasive temperature monitoring sites as an index of brain temperature.[19] Currently there is no evidence regarding the use or superiority of any temperature monitoring site in cardiac arrest patients. Although we found the nasopharyngeal temperature measurement to be clinically feasible by paramedics in the prehospital setting, it may be susceptible to errors during abnormal circulatory conditions. The proximity of the temperature probe to the internal jugular veins may expose it to venous reflux during CPR. If this occurs, the effect of infused cold fluid into the centralised circulation may result in an exaggeration of the temperature decrease. Also, a misplacement of the probe may result in false temperature readings.

As discussed above, we do not know whether the decrease of the nasopharyngeal temperature in these patients during CPR reflects brain temperature correctly as in previous studies on surgical patients.[20] If it does, it seems that cooling can be achieved with simply during CPR.

The temperatures of these patients measured initially were well beyond the normal range of human core temperature of approximately 37 °C. Thus, one may argue that infusion of cold fluids does not reduce core temperature alone significantly, but rather serves as a method to maintain and increase hypothermia to a therapeutic level. Currently there are no data on the rate of spontaneous reduction of core temperature during cardiac arrest.

It is debatable whether induction of mild hypothermia during CPR may cause suboptimal conditions for return of spontaneous circulation. Current evidence does not suggest this,[6,7,21] but further research is needed to evaluate the safety and feasibility of this treatment on a larger scale.

We believe that the null survival in our study group is explained by the generally fatal causes of cardiac arrest documented in these patients.[22,23] One may assume that the infusion of cold fluids did not contribute to the death of the patients.

It is reasonable to criticise the rationale of inducing therapeutic hypothermia in a patient with an initial core temperature of 33.06 °C (patient number 3). In this patient there were no initial clinical signs suggesting hypothermia, and venous access to enable medication was started using cold fluid.

The main limitations of this study are the lack of a control group and the fact that in patients in cardiac arrest, an established way of monitoring brain or core temperature has not been described.

Conclusions

We found that induction of therapeutic hypothermia using infusion of cold Ringer's solution by paramedics during cardiopulmonary resuscitation was feasible. This method warrants caution, however, as temperature is prone to decrease rapidly with small volumes of cold fluid and the decrease seems to continue even after the cessation of infu-

sion. To which degree nasopharyngeal temperature reflects brain temperature in this context has to be further investigated.

Conflict of interest

None of the authors have conflicts of interest to declare.

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CLINICAL PAPER

Induction of therapeutic hypothermia during prehospital CPR using ice-cold intravenous fluid☆

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KEYWORDS
Cardiac arrest;
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Fluid therapy;
Human experimentation;
Temperature;
Prehospital;
Return of spontaneous circulation

Summary
Aim of the study: Primarily, to investigate induction of therapeutic hypothermia during prehospital cardiopulmonary resuscitation (CPR) using ice-cold intravenous fluids. Effects on return of spontaneous circulation (ROSC), rate of rearrest, temperature and haemodynamics were assessed. Additionally, the outcome was followed until discharge from hospital.
Materials and methods: Seventeen adult prehospital patients without obvious external causes for cardiac arrest were included. During CPR and after ROSC, paramedics infused +4 °C Ringer's acetate aiming at a target temperature of 33 °C.
Results: ROSC was achieved in 13 patients, 11 of whom were admitted to hospital. Their mean initial nasopharyngeal temperature was 35.17 ± 0.57 °C (95% CI), and their temperature on hospital admission was 33.83 ± 0.77 °C (−1.34 °C, $p < 0.001$). The mean infused volume of cold fluid was 1571 ± 517 ml. The rate of rearrest after ROSC was not increased compared to previous reports. Hypotension was observed in five patients. Of the 17 patients, 1 survived to hospital discharge.
Conclusion: Induction of therapeutic hypothermia during prehospital CPR and after ROSC using ice-cold Ringer's solution effectively decreased nasopharyngeal temperature. The treatment was easily carried out and well tolerated.

Introduction

In the absence of adequate circulation during cardiac arrest, the development of ischaemic cerebral injury begins within minutes. Even after successful resuscitation and return of spontaneous circulation (ROSC), the generation of several metabolic mediators such as free radicals further aggravates

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this injury during the reperfusion phase.[1] This hypoxic-ischaemic neurological injury causes significant mortality and morbidity.[2] It has been shown that the induction of mild therapeutic hypothermia after cardiac arrest significantly improves the potential for survival and neurological outcome.[3,4] However, the optimal timing and duration of this treatment is still under investigation. There is evidence from experimental studies that early induction of mild hypothermia during cardiopulmonary resuscitation (CPR) promotes improved outcome[5,6] and some studies suggest that a delayed induction of mild hypothermia results in less favourable outcome.[7,8]

The infusion of ice-cold intravenous fluid has been found a feasible and safe method to induce therapeutic hypothermia after ROSC in the emergency department (ED).[9–11] In our recent pilot study, we found this method to be applicable also in the prehospital setting.[12] Another recent and randomized-controlled trial showed a non-significant trend towards improved outcome of prehospital patients receiving cold fluids after successful resuscitation from ventricular fibrillation.[13]

We have recently reported our initial experience of prehospital induction of therapeutic hypothermia during resuscitation in five adult cardiac arrest victims treated by paramedics.[14] Infusion of 4 °C Ringer's solution during CPR effectively decreased nasopharyngeal temperature. We wanted to further investigate the safety and effectiveness of this approach by increasing the number of patients from initial five of the pilot report. Thereby, with a larger group of patients we focused on the rate of ROSC and achieved temperature and description of haemodynamics after ROSC.

In this study, we present the results of using a slow infusion of 4 °C Ringer's solution during CPR followed by a rapid infusion (100 ml/min) after ROSC in the prehospital setting. The primary aim was to study the cooling effects of ice-cold infusion on the core temperature during resuscitation, the rate of ROSC and on temperature and haemodynamics after ROSC.

Patients and methods

This investigation was a continuation of the pilot study reported previously.[14] Thus, the patients enrolled to the pilot study are included in this report. The study was conducted in the city of Tampere, Finland (population 203 000). The city is served by a two-tiered emergency medical service (EMS) system with emergency medical technicians in the first tier backed up by two paramedic staffed advanced life support (ALS) units as a second tier. A detailed description of this system is reported in our prior observational outcome study.[15] All prehospital patients aged $\geq$18 years with cardiac arrest not due to trauma or intoxication were considered for inclusion regardless of the initial cardiac rhythm. Exclusion criteria were pregnancy, clinical suspicion of preceding hypothermia, or ROSC within 5 min from the onset of resuscitation. The reason for the latter exclusion criteria was to prevent induction of therapeutic hypothermia in patients with potential to regain consciousness shortly after resuscitation.

The study protocol was approved by the institutional review board of the Tampere University Hospital, Finland. With a permission of the review board, written informed consent for inclusion in the study could be obtained from relatives of the patients after completion of resuscitation.

According to the study protocol, quality and priority of primary resuscitative measures were emphasized throughout the study. Cardiac arrest treatment followed the European Resuscitation Council guidelines[16] and eligibility for inclusion was considered only after necessary resuscitative efforts were initiated.

The first EMS crew to arrive on the scene performed primary resuscitative measures such as chest compressions, defibrillation and ventilation. During continuous CPR, paramedics performed orotracheal intubation and obtained venous access via the external jugular or antecubital veins. If no exclusion criteria were present, infusion of cold (+4 °C) Ringer's acetate was initiated at an approximated rate of 50 ml/min via the peripheral cannula, or if the antecubital cannula was not patent at this moment, via the external jugular vein. The reason for this slow initial rate was to avoid the excessive temperature decrease observed in the patients of our pilot study.[14] Intravenous medication such as adrenaline (epinephrine) or amiodarone was administrated when indicated. Blood glucose was measured and end-tidal CO_2 and pulse oximetry were monitored continuously. For temperature measurement a nasopharyngeal temperature probe was inserted and the temperature recorded using a separate portable device (YSI 4600 Precision Thermometer, YSI Corp., Dayton, OH, USA). Nasopharyngeal temperature measurement was chosen due to its feasibility and convenience of use in the prehospital setting. Paramedics used anatomic landmarks to assess correct placement of the probe and similar site and depth of measurement between patients. A medical refrigeration transport box (Dometic MT4B, Dometic Group, Solna, Sweden) was used for storage of the cold fluids in the ambulance.

If the first recorded nasopharyngeal temperature was <33 °C despite the lack of signs of accidental hypothermia the infusion was either not initiated or discontinued. The nasopharyngeal temperature was continuously monitored and if a temperature reading of 33 °C was reached the infusion was stopped. The infusion was later restarted if the temperature again began to increase above 34 °C. If a temperature reduction below 32 °C occurred, passive warming with blankets was initiated and the cold fluid was replaced with regular Ringer's solution.

When ROSC was achieved and the nasopharyngeal temperature was >33 °C, a rapid infusion of the cold fluid was initiated via the antecubital vein at a rate of 100 ml/min using an infusion pump (Power Infuser, Infusion Dynamics, Plymouth Meeting, PA, USA). The target temperature for both the slow and the rapid infusion of cold fluid was set at 33 °C.

In addition to the above-mentioned monitoring, arterial blood pressure was monitored non-invasively every 5 min after ROSC. The patient was stabilised on scene prior to transport to a single tertiary-level university hospital. If indicated, vasoactive medication (dopamine) to treat hypotension (systolic blood pressure <100 mmHg despite fluid resuscitation) or thrombolytic treatment was initiated prior to transport or en route to the hospital. According to local policy, paramedics provided analgesia and sedation

using intravenous alfentanil and diazepam when indicated. Intravenous paralytic agents were not used.

In the ED the nasopharyngeal temperature was recorded. Blood gas analysis and blood glucose were measured and registered on arrival. At this point the study intervention protocol ended. As the study protocol focused on prehospital treatment with intra-arrest hypothermia, further treatment such as whether to continue therapeutic hypothermia or not was at the discretion of the treating intensive care unit (ICU) physicians. Furthermore, local guidelines advocate the use of therapeutic hypothermia to be used predominantly in cases of ventricular fibrillation. As patients were included regardless of the initial rhythm, a prehospital study protocol affecting in-hospital guidelines was not considered appropriate. Survival and outcome of the patients was assessed according to the Utstein guidelines.[17] However, this study was not intended or powered to effectively report survival. Thereby, it should be considered as a secondary outcome measure.

Statistical analysis was performed using the SPSS for Windows V13.0-software (SPSS Inc., Chicago, IL, USA). Data are shown as mean ± 95% CI, unless otherwise indicated. To measure statistical significance a two-tailed Student's *t*-test was used considering a p-value < 0.05 as significant.

Results

During the study period 50 patients were screened for eligibility and 17 patients were subsequently enrolled in this study. Their mean age was 70 ± 6 years and 76% were males. The initial cardiac rhythms were ventricular fibrillation (VF) in 10 (59%), pulseless electrical activity (PEA) in 6 (35%) and asystole in 1 (6%) patient. The reasons for exclusion of the 33 remaining patients are shown in Figure 1. Majority of these patients were excluded due to protocol violation as infusion of cold fluid was initiated after ROSC only.

Temperature and haemodynamics

Nasopharyngeal temperature was measured during ongoing CPR in 15 patients. In five of these patients, nasopharyngeal temperature was not measured prior to the initiation of cold infusion; the median delay to first measurement was 6 (range 5—16 min). The mean first measured temperature was 34.73 ± 0.52 °C and within 5 min after ROSC it was 34.34 ± 0.55 °C ($p < 0.01$). The calculated mean infusion rate during CPR was 57 ± 21 ml/min and the mean total infused volume of cold fluid was 1571 ± 517 ml. The mean of the lowest recorded temperature values after ROSC was 33.17 ± 0.65 °C.

Return of spontaneous circulation was achieved in 13 patients (76%). Their mean temperature at the time of ROSC was 34.76 ± 0.45 °C and a rapid infusion of cold fluid was initiated in 12 of them. In one patient ROSC was temporary and he rearrested before the rapid infusion was initiated.

Hypotensive episodes (systolic blood pressure <100 mmHg) were observed in five patients and haemodynamically stable bradycardia (pulse <50 min^{-1}, lowest 32 min^{-1}) in three patients during the rapid infusion after ROSC.

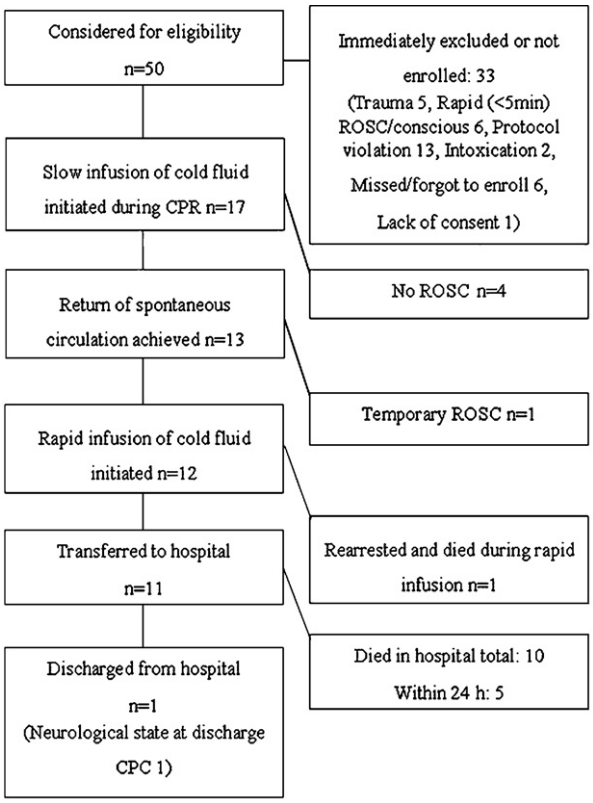

Figure 1 Inclusion and outcome flow diagram. ROSC: return of spontaneous circulation; CPC: cerebral performance category.

Five patients rearrested during the rapid infusion, one into asystole and four refibrillated. ROSC was re-achieved in four of them, whereas one of the patients who refibrillated was eventually declared dead on scene. Hence, 11 patients were admitted to hospital.

The mean measured temperatures and blood pressures are presented in Figure 2.

In-hospital results

Eleven patients were admitted to hospital. Their mean initial temperature on the scene had been 35.17 ± 0.57 °C, at the time of ROSC it was 34.84 ± 0.46 °C, and on hospital admission it was 33.83 ± 0.77 °C (−1.34 °C compared to initial temperature, $p < 0.001$). The mean initial nasopharyngeal temperature was higher among the patients who survived to hospital (35.17 °C) compared to those who died on the scene (34.13 °C) ($p < 0.03$). Of the 11 admitted patients, 3 who were not considered to have a potential for survival received palliative care, whereas the remaining 8 patients were admitted to the ICU. Therapeutic hypothermia was continued for 24 h in six of them. Two patients died in the ICU before therapeutic hypothermia could be further continued. Seven of the patients admitted to the ICU died, two of them within 24 h of admission. The cause of death was acute myocardial infarction in three patients, hypo/hyperkalaemia in two patients, subdural haemorrhage and cerebral contusions in one patient without signs of trauma and primary arrhythmia in one patient. At the time of hospital discharge and 6 months after the arrest, the

Table 1 Patient and resuscitation characteristics

	Mean (±95% CI)	Range
Age (years)	70 (±6)	52—88
Gender		
Male	13	
Female	4	
Weight (kg)	77 (±6)	50—100
Aetiology of arrest		
Presumed cardiac	9	
Other noncardiac	6	
Respiratory	2	
Volume of infused cold fluid		
Slow infusion (ml)	626 (±231)	50—1500
Rapid infusion (ml) ($n = 12$)	1338 (±536)	300—3000
Total volume (ml)	1571 (±517)	200—4000
Blood glucose (mmol/l)		
During CPR	10.9 (±2.9)	4.6—24.7
In the ED ($n = 10$)	14.7 (±3.1)	7.9—21.1
First arterial blood gas ($n = 10$)		
pH	7.19 (±0.14)	6.92—7.42
PaO_2 (kPa)	42.1 (±23.9)	6.3—75.6
$PaCO_2$ (kPa)	5.9 (±1.4)	2.4—9.1
BE	−10.2 (±6.96)	−21.7—9.1

CPR: cardiopulmonary resuscitation; ED: emergency department; BE: base excess.

cerebral performance category (CPC)[18] score of the single surviving patient was.[1] The Utstein-style patient characteristics, outcomes and time intervals are presented in Tables 1 and 2 and Figure 3.

Discussion

In this study we investigated the effects of infusing cold (+4 °C) Ringer's acetate during CPR and after ROSC in out-of-hospital cardiac arrest patients. The main finding was that a significant decrease in nasopharyngeal temperature was achieved. Nasopharyngeal temperature measurement has been suggested to be used as a proxy measurement for brain temperature during therapeutic hypothermia.[19] In hypothermic surgical patients this method was superior to other non-invasive measurement sites such as urinary bladder in terms of correlation to brain temperature.[20] However, it is debatable whether nasopharyngeal temperature reflects brain temperature reliably in the case of circulatory arrest. Current evidence does not suggest superiority of any other non-invasive method over nasopharyngeal temperature measurement in cardiac arrest victims. Oesophageal monitoring is subject to misplacement[21] and intermittent tympanic measurement has not been considered realiable.[22] Recognising the limitations regarding to correlation with brain temperature nasopharyngeal temperature measurement was chosen due to feasibility in the prehospital setting.

The mean infused volume of cold fluid was 1571 ± 517 ml. With a mean body weight of 77 ± 6 kg, this produced a mean volume per patient of approximately 20 ml/kg. This is significantly less than in previous studies in which volumes of 30—40 ml/kg have been used.[9–13] Also, the slow infusion rate of 57 ± 21 ml/min chosen due to safety aspects was less than reported in previous post-ROSC studies on cooling.[9–13] Although a more rapid rate of infusion and an

Table 2 Time intervals

Time interval (min)	Median (±95% CI)	Range
Collapse to emergency call receipt ($n = 12$)	1 (±0.93)	0 to −4
Call received—first rhythm analysis	8 (±1.94)	0—17
Call received—CPR initiated	8 (±1.94)	0—17
Call received—first defibrillation ($n = 10$)	11.5 (±3.76)	9—24
Call received—cold infusion initiated	20 (±2.96)	6—31
Call received—ROSC ($n = 13$)	29 (±3.85)	18—40
ROSC—admission to hospital ($n = 11$)	42.5 (±6.38)	29—61

CPR: cardiopulmonary resuscitation; ROSC: return of spontaneous circulation.

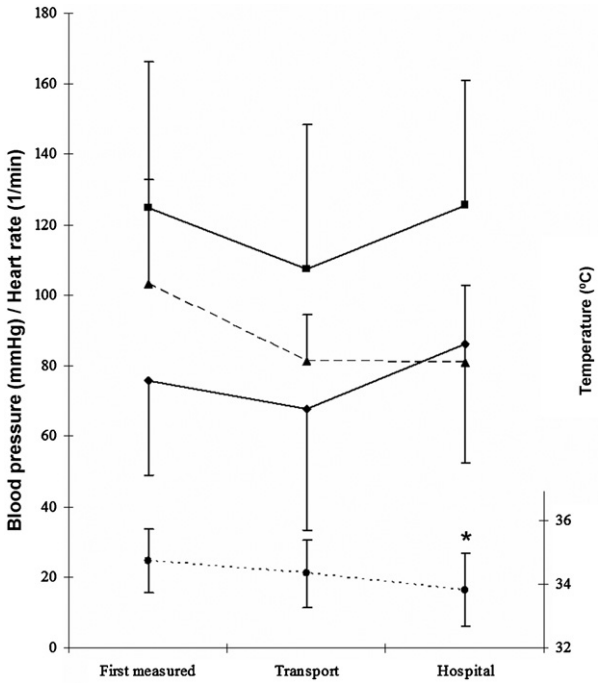

Figure 2 Haemodynamic variables (left axis) and temperature (right axis). (■) Systolic blood pressure (mmHg), (▲) heart rate/min, (♦) diastolic blood pressure (mmHg) and (●) temperature (°C). Values are mean, bars indicate S.D. *$p < 0.001$ compared to first measured temperature among patients admitted to hospital ($n = 11$).

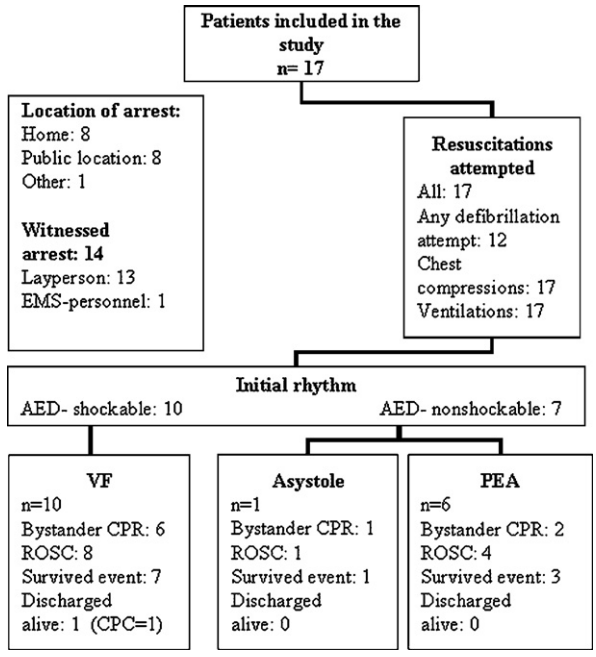

Figure 3 Resuscitation characteristics. EMS: emergency medical service; AED: automated external defibrillator; VF: ventricular fibrillation; PEA: pulseless electrical activity; CPR: cardiopulmonary resuscitation; ROSC: return of spontaneous circulation; CPC: cerebral performance category.

increased volume of cold fluid already during CPR probably would produce a more effective cooling than now observed, the regimen used in this study seemed to result in a consistent and steady decrease in temperature. On the other hand, one may argue that the median delay to the onset of cold infusion of 20 ± 2.96 min may be too long.

As a second main finding we found that of the 17 enrolled patients, ROSC was achieved in 13 (76%). We have previously observed that approximately 50% of all cardiac arrest patients treated by the Tampere EMS system regain spontaneous circulation.[15] Although comparison with historical data has limited reliability it seems that induction of therapeutic hypothermia during CPR did not interfere with the chances of ROSC.

Five of the 17 patients (29%) rearrested after ROSC during the rapid infusion of cold fluid. This figure is similar (24%) to the findings in a recent study on prehospital cooling.[13] Of the rearrested patients, four developed VF. They represent 40% of the patients in this study who had VF as initial cardiac rhythm. Refibrillation has previously been documented to occur in the same range (54—68%) among defibrillated patients.[23–25] Hence, the proportion of patients who refibrillated during the infusion of cold fluid did not seem to increase. Circulation was successfully again restored in four of the rearrested patients.

As a third main finding, we observed hypotension (systolic blood pressure <100 mmHg) necessitating vasopressive medication after ROSC in 5 of 11 patients with ROSC (45%). Proportionally this is more than the figure observed by Kim et al. (11% in the hypothermia group and 14% in the control group).[13] It is not known whether the administration of cold fluid during resuscitation and after ROSC results in susceptibility to hypotension, but previous studies regarding post-ROSC infusion of large volume ice-cold fluid do not suggest this.[10,12,13] On the contrary, improved haemodynamics related to the post-ROSC treatment were observed in the study by Bernard et al. and also in a recent experimental study on intra-arrest cooling.[9,26] Local guidelines recommend that systolic blood pressure should be targeted to exceed 120 mmHg after ROSC and if necessary, vasoactive medication should be initiated after fluid resuscitation. In these five patients, paramedics failed to administrate dopamine in three cases. Haemodynamic instability is known to be common after out-of-hospital cardiac arrest,[27] and the prompt treatment of this condition needs to be emphasized irrespective of other treatment modalities.

In addition to primary outcome measures of this trial, we here reported poor outcome of these patients. Although prehospital induction of therapeutic hypothermia was found feasible and did not seem to negatively affect the potential for ROSC, the poor overall survival is reflected by the fact that only one (6%) patient was discharged from hospital. We have previously reported an overall survival of 13% from out-of-hospital cardiac arrest in Tampere, Finland.[15] However, this study was neither designed nor powered to study survival or neurological stage as an outcome measure. Nordmark and Rubertsson found the use of cold fluid to be effective and safe already during CPR in an experimental study involving pigs.[28] An encouraging case report by Bernard and Rosalion recently described a case of prolonged resuscitation during which large volumes of ice-cold intravenous fluid were administrated. Despite the cessation

of chest compressions for 10 min during the resuscitation, the patient made a satisfactory neurological recovery.[29] Recently, Bruel et al. reported a ROSC rate of 60.6% after intra-arrest cooling and an overall survival of 12%—results that do not raise concerns regarding the safety of this intervention.[30] Of the 17 patients in our study, 11 (65%) were transferred to hospital and thus the influence of in-hospital factors associated with outcome should also be considered. Due to the prehospital focus of this study we did not systematically record data on the post-resuscitation phase as recommended by the Utstein guidelines.[31]

Three of the admitted patients were not considered eligible for intensive care. This decision was based on a pre-existing do not resuscitate (DNR)-order in one case, presumed futility after prolonged resuscitation (53 min) in one patient, and persistent myoclonus reflecting severe hypoxic-ischaemic injury in one elderly patient. Of those admitted to the ICU, two patients died before therapeutic hypothermia could be initiated.

Study limitations

This study carries a number of limitations. Several patients were excluded from the study mainly due to protocol violation. The most common reasons were induction of therapeutic hypothermia post-ROSC only or missed inclusion. Therefore, a selection bias cannot be ruled out. Indeed, this emphasizes the fact that investigations such as reported herein are demanding and carry a risk of protocol violation as an inherent part of the clinical scenario on the field. Secondly, and most importantly, due to the eventual small sample size and the lack of a control group, effect on survival or neurological outcome cannot be evaluated. Thirdly, as a technical note, measurement of the nasopharyngeal temperature is susceptible to error such as displacement of the probe. Although reported values are based on complete per patient data, some of the patients had missing data on temperature and blood pressure during transport. The infusion of cold fluid was started at a slow rate as soon as venous access was obtained if clinical signs of accidental hypothermia or other exclusion criteria were absent. Due to this, a temperature reading prior to onset of cold infusion was not available in five patients. On the other hand, the slow rate of infusion probably had a negligible effect on the temperature before the first reading was obtained.

Conclusions

In this small study, the infusion of cold fluid during resuscitation and after return of spontaneous circulation significantly reduced nasopharyngeal temperature. With this regimen, paramedics could initiate cooling already in the prehospital phase of treatment. A slow infusion of cold fluid during CPR did not seem to negatively affect the chance of achieving ROSC.

Conflict of interest statement

None of the authors have conflicts of interest to declare.

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