PULSELESS ELECTRICAL ACTIVITY

TREATMENT DURING AND AFTER CARDIOPULMONARY RESUSCITATION AND PATIENT SURVIVAL

Sini Saarinen

ACADEMIC DISSERTATION

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<td>acute coronary syndrome</td>
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<td>AED</td>
<td>automated external defibrillator</td>
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<td>AHA</td>
<td>American Heart Association</td>
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<td>ALS</td>
<td>advanced life support</td>
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<td>ASY</td>
<td>asystole</td>
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<td>BLS</td>
<td>basic life support</td>
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<td>CA</td>
<td>cardiac arrest</td>
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<td>CAG</td>
<td>coronary angiography</td>
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<td>CPC</td>
<td>Cerebral Performance Category</td>
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<td>CPR</td>
<td>cardiopulmonary resuscitation</td>
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<td>DNAR</td>
<td>do not attempt resuscitation</td>
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<td>ECG</td>
<td>electrocardiogram</td>
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<td>ECLS</td>
<td>extracorporeal life support</td>
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<td>EEG</td>
<td>electroencephalogram</td>
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<td>EMS</td>
<td>emergency medical service</td>
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<td>EMT</td>
<td>emergency medical technician</td>
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<td>ERC</td>
<td>European Resuscitation Council</td>
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<td>FRU</td>
<td>first responding unit</td>
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<td>HEMS</td>
<td>helicopter emergency medical service</td>
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<td>ICU</td>
<td>intensive care unit</td>
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<td>IHCA</td>
<td>in-hospital cardiac arrest</td>
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<td>IQR</td>
<td>interquartile range</td>
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<td>NSE</td>
<td>neuron-specific enolase</td>
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<td>OHCA</td>
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<td>OR</td>
<td>odds ratio</td>
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<td>PEA</td>
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<td>return of spontaneous circulation</td>
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<td>targeted temperature management</td>
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<td>ventricular fibrillation</td>
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<td>VT</td>
<td>ventricular tachycardia</td>
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<td>WFSICCM</td>
<td>World Federation of Societies of Intensive and Critical Care Medicine</td>
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ABSTRACT

Aims:
The aim of this thesis was to investigate the treatment of cardiac arrest (CA) patients with pulseless electrical activity (PEA) during and after cardiopulmonary resuscitation (CPR). The methods, prevalence and effect on survival of treating the underlying cause of PEA during CPR were described (II). Patient selection to intensive care units (ICUs) and high dependency units for post-resuscitation treatment was evaluated (III, IV). Differences in post-resuscitation treatment between units with different levels of care, as well as between the Nordic countries were studied (III, IV). In addition, the long-term survival and quality of life after CA with PEA was assessed (I).

Material and Methods:
424 adult patients who had CA with PEA and were treated by emergency medical service systems, receiving hospitals and ICUs between 1999 and 2013 were studied for this thesis. Of these, 320 patients had out-of-hospital cardiac arrest (OHCA) and 104 had in-hospital cardiac arrest (IHCA).

IHCA patients were included in the study evaluating the treatment of possible reversible causes of CA during CPR (II). Patients receiving specific treatment for the cause of CA during CPR were compared to those treated with conventional CPR (II).

Factors determining the intensity of hospital care after OHCA with PEA was evaluated by comparing patients treated at units offering different levels of care (IV). Post-resuscitation care units were classified according to the World Federation of Societies of Intensive and Critical Care Medicine’s Level 1–3 ICUs, with Level 3 referring to most advanced care, and ordinary wards. Treatment methods and survival were also compared between patients with different levels of care (IV). In addition, differences between the Nordic ICUs in OHCA patients’ admission criteria and post-resuscitation care were evaluated with a two-phase online questionnaire (III).

Long-term survival 1 and 5 years after PEA was analyzed, as well as change in Cerebral Performance Category (CPC) class (I). Quality of life was estimated with a questionnaire of health-associated quality of life (I).

Results:
Among IHCA patients, 18% received specific treatment for their primary cause of PEA during CPR (II). Thrombolysis and rapid fluid loading were the most commonly used specific treatment methods (II).

Most (62.4%) OHCA patients with PEA were admitted to Level 2 ICUs for post-resuscitation care. The mean age of the Level 3 ICU group was significantly lower compared to other groups. Pre-arrest coronary artery disease, cardiac failure, performance class and CPC class were significantly different between the groups, with patients in the Level 3 ICU group having those diagnoses the least and having the best performance. Longer time to return of spontaneous circulation (ROSC) and advanced age decreased the admission rate to Level 2 or 3 post-resuscitation care, whereas good pre-arrest CPC increased the admission rate to Level 2 or 3 ICUs independently (IV). In the questionnaire study, over half of the Nordic ICUs reported having a predefined protocol according to which OHCA patients are admitted to the ICU (III). Most used age, delay to ROSC or initial rhythm as a criterion. Of responding ICUs, 16% stated that patients with initial PEA or asystole were not admitted to ICU treatment.
Among Finnish PEA patients, treatment with targeted temperature management (TTM) (4.1%) or early coronary angiography (CAG, 3.3%) was very rare (IV). Between the Nordic ICUs, usage rates of TTM for all actively treated OHCA patients varied between 20–69% and use of early CAG varied between 13–54% among counties. Norwegian ICUs provided these treatments most actively and Finnish ICUs most rarely (III). In 2014, 33% of ICUs had started to use TTM at 36°C (III). Prognostic decisions for comatose OHCA patients were made earlier in the lower treatment intensity groups (p<0.01) in Finnish post-resuscitation care units (IV).

Patients who received specific treatment for the primary cause of their IHCA had a favorable 30-day survival rate (32% vs 11%) compared to patients receiving standard CPR, but in multivariable analysis, age was the only individual prognostic factor (II). The 1-year survival rate for OHCA patients with PEA was 24.0%, and 17.1% survived with a good neurological outcome. The neurological outcome was better with more intensive care. However, the level of care was not an independent predictor for outcome: only time to ROSC, cardiac arrest cause and pre-arrest performance independently associated with 1-year survival, and age and ROSC with neurologic outcome. Long-term (1-year and 5-year) survival rates of OHCA PEA patients in the earlier study (I) were 7% and 6% respectively. Most patients (71%) had the same CPC classification after CA as before CA and 87% of factors related to quality of life were evaluated as normal or mildly impaired (I).

Conclusions:
In one-fifth of IHCA PEA patients, a specific reason, other than hypoxia, was found and treated during CPR. These patients were more likely to be alive 30 days after IHCA, although specific treatment was not an independent predictor for outcome (II). OHCA patients with PEA were usually admitted to Level 2 ICUs for post-resuscitation care in the capital area of Finland. Increasing age and ROSC decreased the probability of admission to higher levels of post-resuscitation care, whereas good pre-arrest CPC increased it (IV). In the Nordic countries, criteria for OHCA patients' ICU admission are highly variable (III). TTM (4.1%) and early CAG (3.3%) were rarely provided and only for Level 3 ICU patients resuscitated from OHCA with PEA (IV). Despite international guidelines promoting TTM and early CAG, the implementation seems to vary between the Nordic countries and hospitals, partly because of inconclusive evidence of these treatments among PEA patients.

Good neurologic survival was more common with more intensive levels of post-resuscitation care. However, the level of care was not an independent predictor for survival or neurologic outcome: only ROSC, cardiac arrest cause and pre-arrest performance predicted 1-year survival, and age and ROSC the neurologic outcome (IV). The documentation of moderately favorable chances for good outcomes among PEA patients might encourage treating physicians to attempt causal treatment options during CPR and motivate receiving hospitals to consider more intensive treatment options, such as TTM.
INTRODUCTION

Cardiac arrest (CA) is defined as an absence of signs of circulation (Perkins 2015). The initial rhythm is the first monitored rhythm in a CA patient and rhythms are divided into shockable and non-shockable rhythms, according to whether the rhythm potentially responds to defibrillation. The initial rhythm also reflects the cause of the CA: shockable rhythms are commonly associated with ischemic heart disease, whereas long treatment delays or non-coronary causes often result in a non-shockable rhythm. Pulseless electrical activity (PEA) is the most common non-shockable initial rhythm in in-hospital cardiac arrest (IHCA), and its proportion of out-of-hospital cardiac arrests (OHCA) has been increasing in recent decades: it accounts for almost half of IHCAs (Bergum 2015, Chan 2013, Girotra 2012, Nolan 2014) and approximately one-third of OHCAs (Jacobs 2011, Mader 2012, Kudenchuk 2012, Teodorescu 2012). In the adult population in Europe, approximately 41/100,000 persons per year suffer an OHCA and are treated by emergency medical service systems (Berdowski 2010). With the European population being 742 million, this equals ~100,000 annual OHCA patients with PEA. In addition, 1–10 hospital patients out of 1000 hospital admissions have been reported to experience IHCA (Adamski 2016, Buanes 2014, Morrison 2013, Nolan 2014, Sandroni 2007).

The objective of this study was to evaluate PEA patients’ treatment during and after cardiopulmonary resuscitation (CPR). CA leads to death unless rapidly and properly treated. Modern CPR methods date back to the 1960s (Aitchison 2013, Safar 1996). The first CPR guidelines were published in 1966 and have been updated regularly since then according to current scientific knowledge. The term “chain of survival” describes crucial phases in the treatment of a CA patient: early recognition of CA and the call for help, early bystander CPR, early defibrillation and early advanced life support by emergency medical service systems and standardized post-resuscitation care (Monsieurs 2015). Advances in all these phases have increased OHCA patients’ survival: 19–50% of patients with an initial rhythm of ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) survive to hospital discharge (Perkins 2015, Abrams 2013), whilst only 6–16% of PEA patients survive to hospital discharge (Andrew 2014, Bergum 2016, Bueh 2015, Hauck 2015, Kudenchuk 2012, Teodorescu 2012). This means approximately 6,000–16,000 patients survive OHCA with PEA on the European scale annually. Among IHCA patients with PEA, 11–13% have been reported to survive to hospital discharge (Bergum 2015, Nolan 2014).

Despite the uniform guidelines for PEA patients’ CPR and post-resuscitation care, differences in treatment during and after resuscitation have been reported (Blom 2014, Linder 2013, Strömsoe 2015, Worthington 2017). Guidelines recommend treatment of the underlying cause during CPR – especially with PEA patients – but how often causal treatment is attempted, remains unknown (Soar 2015). Some OHCA patients with PEA surviving to hospital admission are treated in units other than intensive care units (ICUs) due to anticipated poor prognosis. The latest advances in post-resuscitation care include targeted temperature management (maintaining a stable body temperature at 32–36°C after CA) and early coronary angiography (Geri 2015, Nolan 2015, Sideris 2014, Vyas 2015). Evidence on these treatment modalities from randomised controlled trials for non-shockable rhythm patients is lacking, which has led to varying implementation of these treatments in PEA patients (Bueh 2015, Blom 2014, Linder 2013, Strömsoe 2015). Additionally, survival rates differ between hospitals and countries (Andersen 2015, Berdowski 2010, Nolan 2013, Teodorescu 2012).

This thesis aims to describe the treatments and survival of both OHCA and IHCA patients.
with PEA. The prevalence of specific causal treatment attempts during resuscitation was investigated in IHCA patients (II). Studies on post-resuscitation care describe factors affecting admission to different levels of hospital care (IV) and the prevalence of special treatment methods provided, such as targeted temperature management and early coronary angiography (III, IV). In addition, differences in post-resuscitation care between the Nordic countries were assessed (III). PEA patients' survival rates and quality of life, as well as factors affecting survival were reported (I, II).
CARDIAC ARREST

Definitions

When cardiac activity and contractions cease, a person becomes unresponsive, is not breathing normally and no palpable pulse is detected. Cardiac arrest (CA) is defined as an absence of signs of circulation. CA leads to death or may, when treated properly, lead to a return of spontaneous circulation (ROSC), which is defined as clinically assessed signs of life, comprising a palpable pulse or generating a blood pressure (Perkins 2015).

The term CA patient may include all patients with an absence of signs of circulation, or only patients to whom resuscitation has been attempted (Berdowski 2010). In studies, CAs are commonly divided into out-of-hospital cardiac arrests (OHCAs) and in-hospital cardiac arrests (IHCAs), since they differ in epidemiology, process of care and treatment (Perkins 2015). IHCA is more likely to be witnessed and ROSC is achieved earlier, but patients are older, have more co-morbidities and their initial rhythm is more often non-shockable (Bergum 2015, Buanes 2014). OHCA is well studied, while fewer studies focus on IHCA. Commonly, patients with an obvious external reason for CA, such as trauma, hemorrhage, airway obstruction or drowning, are excluded from studies, since patients with a presumed cardiac cause form a more homogenous population for comparison and, for example, treatment of traumatic CA is different.

Incidence

In the adult population, the worldwide incidence of emergency medical service (EMS)-attended OHCA is estimated to be 96/100,000 persons a year and the incidence of EMS-treated OHCA 62/100,000 persons a year (Berdowski 2010). In Europe, the estimated incidence of OHCA with presumed cardiac cause is 35–37/100,000 persons a year (Atwood 2005, Berdowski 2010). In Finland, the incidence of EMS-treated OHCA has been reported to be 51/100,000 persons a year (Hiltunen 2012). A ten-fold variability in OHCA incidence is observed globally. The incidence of EMS-treated OHCA with presumed cardiac origin is higher in North America and in Australia compared to Europe and Asia. The percentage of EMS-treated OHCA of all OHCAs is higher in Asia (96%) than in Australia, Europe and North America (46–60%) (Berdowski 2010). Significant variability has also been reported in the frequency of OHCA by the hour of day, day of the week and month of the year, with the highest incidence occurring during the daytime, from Friday to Monday and in December (Bagai 2013).

The incidence of IHCA is less well documented and varies between countries and hospitals. Previously, 1–13 IHCAs per 1000 hospital admissions have been reported (Adamski 2016, Buanes 2014, Morrison 2013, Sandroni 2007). A large prospective study showed a median of 1.5 IHCAs per 1000 admissions across UK hospitals (Nolan 2014).
Initial rhythm

The first monitored rhythm in a CA patient is called the initial rhythm, which affects the choice of treatment methods and prognosis. Initial rhythms are divided into non-shockable and shockable rhythms according to the rhythm’s ability to respond to defibrillation. Pulseless electrical activity (PEA) and asystole (ASY) are non-shockable rhythms, while ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT) are shockable rhythms.

In Europe and North America, 23–52% of OHCA patients have VF as their initial rhythm (Abrams 2013, Avalli 2014, Berdowski 2010, Blom 2014, Bosson 2014, Stromsoe 2015, Teodorescu 2012). The proportion of VF has been reported to be as high as 76%, if the initial rhythm is recorded soon after collapse (Berdowski 2011, Weisfeldt 2010). Although VF has been the most common initial rhythm, its incidence has been consistently declining in recent decades (Atwood 2005, Berdowski 2010, Blom 2014, Cobb 2002, Kuisma 2001, Stromsoe 2015). Concomitantly, the proportion of PEA has increased, currently ranging between 19 to 35% in OHCA (Jacobs 2011, Kudenchuk 2012, Mader 2012, Teodorescu 2012). This decline in the incidence of VF/VT may be attributable to the decline in prevalence of ischemic heart disease due to lifestyle changes, smoking cessation and drug use, such as statins and anti-hypertensives (Hulleman 2015). The improved treatment of ischemic heart disease, such as beta blockers, primary percutaneous coronary intervention (PCI) and implantable defibrillators have been associated with VF decline (Hollenberg 2015, Myerburg 2013, Youngquist 2008). ASY is the initial rhythm in approximately 23–24% of OHCAs (Jacobs 2011, Teodorescu 2012).

The most common initial rhythm in IHCA is PEA, accounting for 46.5–48.8% of IHCAs (Bergum 2015, Chan 2013, Girotra 2012, Nolan 2014, Thompson 2018). Only 16.9–17.4% of IHCA patients have been reported to have a shockable initial rhythm (Nolan 2014, Thompson 2018). The proportion of non-shockable rhythms have increased in recent decades, since in the beginning of this century 30–37% of patients had PEA as their initial rhythm (Gwinnutt 2000, Parish 2000, Peberdy 2003). IHCA occurs most often in the departments of intensive care, internal medicine, cardiology and emergency medicine (Adamski 2016, Chan 2013).

PULSELESS ELECTRICAL ACTIVITY

Definition

In PEA, there is spontaneous organized electrical activity (other than VT) in electrocardiogram (ECG) monitoring, but no palpable pulse (Monsieurs 2015, Myerburg 2013). Formerly, PEA was called electromechanical dissociation. Cardiac contractility can be absent or insufficient to maintain consciousness, create a palpable pulse and to perfuse organs (Myerburg 2013). The definition of true-PEA refers to absent contractility and the term pseudo-PEA refers to insufficient contractility or circulation to produce a palpable pulse (Aufderheide 2007). Emergency ultrasound examination during PEA has shown coordinated ventricular wall motion in 58–78% of PEA patients (Breitkreutz 2010, Chardoli 2012). PEA can also present after defibrillation, where the term post-counter-shock, post-shock, post-defibrillation or secondary PEA is used. The absence of cardiac contractions is common in post-defibrillation PEA (Myerburg 2013).
QRS complexes in ECG, which present cardiac ventricular activity, are often widened and the heart rate is slow, but QRS complexes and heart rate can also be normal (Bergum 2016, Hauck 2015). Agonal rhythm at the end of prolonged CA with very wide and slow, usually irregular, QRS complexes is not included in the definition of PEA (Myerburg 2013).

Etiology and pathophysiology

Approximately 50% of CA with PEA are primary cardiac events (Myerburg 2013); 12.5–33% have acute coronary occlusion, suggesting that PEA is an event resulting from ischemia (Beun 2015, Dumas 2010). Acute coronary occlusion results in metabolic stress leading to the loss of contractile force (Myerburg 2013). Activation of the intrinsic immune system and production of cytokines and cardiokines may acutely depress cardiac contractility (Myerburg 2013). Non-cardiac causes include acute respiratory failure with combined hypoxia and hypercarbia in approximately every fourth PEA patient (Beun 2015). Hypoxic CA results in an initial rhythm of PEA, almost without exception (Truhlar 2015). In one of eight PEA patients, CA is a consequence of trauma (Beun 2015), which causes major bleeding, tension pneumothorax or cardiac tamponade. Hyperkalemia has been reported in up to 12% of PEA patients (Wang 2016). Pulmonary embolism, hypovolemia, intoxication and hypokalemia occur in fewer than 10% of PEA patients. Approximately 7% have intracranial hemorrhage as a cause of PEA (Beun 2015). In these non-cardiac PEA patients, cardiac contractility usually exists and may be normal or only mildly impaired (Myerburg 2013). Interestingly, PEA patients who underwent autopsy had more non-cardiac causes (such as aortic dissection or rupture and pulmonary embolism) and less cardiac causes than those whose cause of death was assessed clinically (Virkkunen 2008).

Risk factors

Risk factors for PEA include older age (Engdahl 2001), womanhood (Teodorescu 2010, Herlitz 2004), black race (Teodorescu 2010, Teodorescu 2012), pulmonary disease (Teodorescu 2010), clinical history of syncope (Teodorescu 2012), antipsychotic drug use (Teodorescu 2013) and beta blocker use in some studies (Youngquist 2008), but not in others (Teodorescu 2013).

Prevention

CA can develop suddenly, or it can occur as a continuum of slow physiological deterioration. A quarter to a third of OHCA patients have been reported to have typical chest pain, angina, before CA (Muller 2006). Up to 47–80% of all-rhythm CA patients have been reported to have abnormal vital signs before IHCA (Peberdy 2007, Skrifvars 2006). Since the early and effective recognition and treatment of a deteriorating patient could prevent some IHCAs and deaths, the European Resuscitation Council (ERC) has highlighted forming and documenting an individual plan for each patient on how to monitor their vital signs and suggests staff education in acute care (Soar 2015). Scoring systems for recognition of abnormal vital signs
have been developed together with rapid response teams or medical emergency teams, which have reduced IHCAs and mortality (Bellomo 2003, Bellomo 2004).

CARDIOPULMONARY RESUSCITATION

History of CPR

The history of modern CPR begins in the 1960s, when the first guidelines for closed-chest CPR were published in 1966 in Belfast (Aitchison 2013). Decades earlier, single reports on resuscitative maneuvers had been reported. The first reported closed-chest cardiac compressions were performed in the 1890s and the first successful open-chest compressions in 1901 (Safar 1996). Closed-chest compressions were forgotten for several decades until they were rediscovered in 1958 (Aitchison 2013). Defibrillation was also first carried out with open chest in 1947 by Beck, followed by closed chest defibrillation by Zoll in 1955 (Aitchison 2013). The first portable external defibrillator was developed in 1979 (Aitchison 2013). The modern mouth-to-mouth ventilation technique was described in 1958 (Aitchison 2013). In-hospital resuscitation teams started in the 1930s, and out-of-hospital physician-staffed units started in the 1960s (Aitchison 2013, Safar 1996). Education of bystander CPR and advanced cardiac life support courses started in the 1970s (Aitchison 2013). Twenty years later, in the 1990s, public access automated external defibrillators (AEDs) were implemented (Aitchison 2013).

Guidelines

Since the first CPR guidelines in 1966, regular updates have been published according to the latest scientific evidence in resuscitation medicine. The International Liaison Committee on Resuscitation, ERC, American Heart Association (AHA) and other resuscitation organizations worldwide publish updated guidelines every five years. The latest European guidelines were published in 2015 (ERC 2015), followed by an update in 2017 (Perkins 2018). Resuscitation guidelines are divided into basic life support (BLS) recommendations for bystanders and medical personnel without equipment to start CPR and advanced life support (ALS) recommendations for equipped medical personnel.

Basic life support

When CA is recognized, and an emergency call is made, CPR should be started immediately (Figure 1). Persons with CPR training should give chest compressions together with ventilations in a ratio of 30:2, other bystanders deliver only chest compressions as the dispatcher instructs. Effective CPR generates approximately 25% of prearrest carotid artery flow (Nolan 2014). CPR-trained bystanders should perform five initial ventilations after opening the patient’s airway if a CA victim is a child, drowned or choked, or if the EMS response time is long. AED should be used for early defibrillation if available. Effective bystander BLS, uninterrupted and high-quality chest compressions and early defibrillation for shockable rhythms improve CA patients’ survival rates (Monsieurs 2015).
Figure 1. Adult BLS and ALS algorithm. Modified from the ERC’s BLS and ALS guidelines for Resuscitation 2015 (ERC 2015).

**BLS**

- Not responding
- Open the airway
- Not breathing normally
- Call the dispatch center
- **CPR**
  - 30:2 compressions and rescue breaths if trained and able
  - otherwise, continuous compressions 100–120/min

**ALS**

- Attach the AED
- Attach the defibrillator
- Secure the airway
- Give adrenaline 1mg every 3–5 mins*
- Seek for and treat possible reversible cause
- **CPR 30:2 2-min**
- **PEA or ASY**
- **VF or pulseless VT**
  - Defibrillate
  - Start post-resuscitation care
- Pulse present ROSC

*= if VF/VT, give first adrenaline after 3 shocks together with amiodarone 300mg (+150mg)
Advanced life support

In addition to BLS, EMS personnel attach defibrillation electrodes and analyze the rhythm (Figure 1). Tracheal intubation provides the most reliable airway and should be used if a skilled person is available, otherwise supraglottic airway (SGA) devices or bag-mask ventilation techniques can be used (Soar 2015). Observational studies have reported increased survival to ROSC, hospital admission and neurologically intact survival with endotracheal intubation by EMS compared to SGA (Benoit 2015, Wang 2012). On the other hand, a large Japanese observational study showed that neurologically favorable survival was higher for those treated with bag-mask ventilation compared with those receiving neither an SGA or tracheal intubation (Hasegawa 2013). Recently, Wang et al. (2018) published that in EMS systems without physicians, insertion of a laryngeal tube was associated with increased survival and increased neurological survival compared to tracheal intubation.

Waveform capnography is recommended for every patient undergoing ALS, as it reveals esophageal intubation, monitors ventilation rate, helps in identifying ROSC and pulmonary embolism, indicates efficacy of CPR and aids in prognostication (Monsieurs 2015, Nolan 2014).

In non-shockable rhythms, standard CPR is continued and when intravenous or intraosseous access is obtained, 1mg of adrenaline is administered according to current guidelines (ERC 2015). Rhythm analysis is carried out every two minutes and adrenaline is administered every 3–5 minutes. No medication has unequivocally been shown to improve OHCA survival (Herlitz 1995, Holmberg 2002, Jacobs 2011, Olasveengen 2009, Perkins 2018). A recently published randomized, double-blind trial comparing adrenaline to placebo (saline) showed higher rates to ROSC and 30-day survival in the adrenaline group, but no difference was found in survival to hospital discharge or 3-month survival with good neurological outcome (Perkins 2018). Further, severe neurologic impairment was more common in the adrenaline group at hospital discharge (Perkins 2018). Earlier randomized controlled trials (RCTs) comparing adrenaline to placebo or no intravenous drug have not reported a difference in survival to hospital discharge or in neurological outcome, but increased survival to ROSC and hospital admission was reported (Jacobs 2011, Olasveengen 2009). Subgroup analysis showed increased rates of ROSC and hospital admission in the adrenaline group in both shockable and non-shockable rhythm patients (Jacobs 2011), whereas in another study, only non-shockable patients receiving adrenaline had increased rates of ROSC and hospital admission (Olasveengen 2009). High-dose adrenaline has been reported to improve survival to ROSC and to hospital admission compared to standard dose adrenaline, but no difference in survival to hospital discharge or in survival with good neurology has been found (Lin 2014). Some concern regarding the potential harmful effects of adrenaline on post-cardiac arrest myocardial function and cerebral microcirculation has been raised (Deakin 2016, Ristagno 2007, Tang 1995).

If the rhythm changes into a shockable rhythm, immediate defibrillation is performed. Pauses that defibrillation causes in chest compressions should be minimized to less than 5 seconds (Monsieurs 2015). Adrenaline and amiodarone are given after the third defibrillation. Amiodarone has been shown to increase VF patients’ survival to hospital admission, but not to hospital discharge (Donian 2002, Kudenchuck 1999). When an organized rhythm is noted in rhythm analysis, the pulse is palpated and if present, post-resuscitation care is started.
Treatment of reversible causes

Resuscitation guidelines recommend considering the possibility of the presence of reversible causes during CPR, since survival from PEA or ASY is unlikely unless a reversible cause is diagnosed and treated effectively (Soar 2015). Patient records and pre-arrest clinical symptoms are the information sources most frequently utilized by the emergency team to establish the causes of CA; other means are ECG, imaging and after admission coronary angiography (CAG) (Bergum 2015).

Ultrasound imaging during CA has the potential to detect some reversible causes of CA, but no study has yet been able to report an improved outcome with the use of ultrasound (Flato 2015, Monsieurs 2015). Imaging should be carried out during rhythm analysis to minimize pauses in chest compressions. With ultrasound, cardiac motion, ventricular function, right ventricular dilatation, pericardiac collection and diameter of inferior vena cava indicating volume status can be detected (Breitkreutz 2010, Chardoli 2012), thus, diagnoses of cardiac tamponade, pulmonary embolism, hypovolaemia and pneumothorax can be made. Chardoli et al. (2012) reported pericardiac effusion in up to 14% and hypovolemia in 22% of PEA patients. In those with wall motion, reduced left ventricular function was reported in 50% of patients, pericardiac effusion in 10%, dilated right ventricle in 8% and hypovolemia in 4% (Breitkreutz 2010). Ultrasound findings affected the choice of treatment in 78% of CA or shock state patients (Breitkreutz 2010).

Blood sampling and point-of-care analysis during CPR is recommended since it may reveal potentially reversible causes, such as electrolyte disorders or acidosis (Monsieurs 2015). Invasive arterial pressure monitoring helps detect low blood pressure values after ROSC (Monsieurs 2015).

4Hs and 4Ts

4Hs and 4Ts is a commonly used mnemonic for exclusion of reversible causes. This was first described by Kloeck in 1995 as a 10-step training mnemonic (5Hs & 5Ts), but it has since been simplified to 4Hs and 4Ts (Kloeck 1995). These letters stand for hypoxia, hypovolemia, hypo-/hyperkalemia/metabolic, hypo-/hyperthermia, thrombosis (pulmonary embolism, coronary artery thrombosis), tension pneumothorax, tamponade (cardiac) and toxins. Of these, the most common reversible etiologies seem to be myocardial ischemia and hypoxia (Bergum 2015, Beun 2015).

Hypoxia

Hypoxia is treated with standard ALS including adequate ventilation with supplemental oxygen after securing a patient’s airway.

Hypovolemia

Hypovolemia results from massive bleeding or severe vasodilatation, as in sepsis or anaphylactic shock. If hypovolemia is proven or suspected as the cause for CA, rapid infusion of warmed crystalloid solutions, blood products and tranexamic acid is recommended simultaneously with hemorrhage control with direct pressure, tourniquets, topical hemostatic agents, splints, surgery or radiological interventions if needed (Monsieurs 2015, Truhlar 2015). Skin and mucosal changes may help in diagnosing anaphylactic shock. Any drug
suspected to trigger anaphylaxis should be discontinued. Standard doses of adrenaline are recommended in CA caused by anaphylaxis, but large volumes of fluid can be needed (Truhlar 2015). Pre-arrest symptoms of infection or fever may help to identify sepsis.

**Hypo-/hyperkalemia/metabolic**

Of electrolyte disorders causing CA, hyperkalemia is the most common, while hypokalemia, calcium and magnesium disorders are relatively rare (Desbiens 2008, Truhlar 2015). Electrolyte disorders should be suspected in at-risk patients, such as patients with renal failure, diabetes mellitus or severe burns (Truhlar 2015). Treatment of hyperkalemia during CPR includes intravenous calcium chloride, glucose–insulin and sodium bicarbonate. Dialysis has also been used safely and effectively during CA in special centers (Alfonzo 2006). For patients in severe hypokalemia causing CA, intravenous potassium-infusion is indicated. Hypomagnesemia should be treated with intravenous magnesium sulphate, and hypermagnesemia with calcium chloride or saline with diuretics. Hypocalcemia can respond to intravenous calcium chloride, and hypercalcemia to fluid replacement and diuretics (Truhlar 2015).

**Hypo-/Hyperthermia**

Hypothermia reduces cellular oxygen consumption by 6% per 1°C, which induces a protective effect on brain tissue, and neurologically intact survival is possible after prolonged CPR (Truhlar 2015). If three defibrillation attempts are unsuccessful, defibrillation, as well as medication, should be postponed in severely hypothermic patients until the patient reaches a core temperature of 30°C. Transportation with ongoing CPR to the nearest extra-corporeal life support (ECLS) center should be considered (Truhlar 2015). In hyperthermic CA, active cooling is recommended, otherwise the standard ALS protocol should be followed (Truhlar 2015).

**Thrombosis (coronary or pulmonary)**

Coronary artery thrombosis can be suspected with ST elevation in ECG, but diagnosis is more difficult when the patient is already in CA. When VF is the initial rhythm, the most likely cause of CA is acute coronary syndrome (ACS). Transport with ongoing CPR to CAG with possible PCI may be considered if the patient has a reasonable chance of survival and the local EMS and cardiology department have the required experience and training (Monsieurs 2015). In addition to risk factors for deep vein thrombosis, low capnography readings and an enlarged right ventricle upon ultrasound support diagnosis of pulmonary embolism. Fibrinolytic therapy is recommended for proven or suspected acute pulmonary embolism. When a fibrinolytic drug is administered, CPR should be continued for 60–90 minutes (Monsieurs 2015). Fibrinolytic therapy seems to be safe, effective and might increase survival to ROSC, hospital discharge and long-term neurological function, but no RCTs designed to investigate the survival benefit have been done (Li 2006, Sharifi 2016). Surgical or percutaneous mechanical thrombectomy should also be considered when feasible (Monsieurs 2015).

**Tension pneumothorax, tamponade**

In traumatic CA, PEA is the most common (66%) initial rhythm (Kleber 2014). Traumatic
CA is due to hypovolemia (up to 48%), tension pneumothorax (13%), cardiac tamponade (10%) or hypoxia (13%) (Kleber 2014). Tension pneumothorax can be diagnosed clinically or by ultrasound and treated with needle chest decompression or, more reliably, with thoracostomy (Truhlar 2015). In addition to trauma, respiratory disease or repeated attempts of central venous catheterization can cause tension pneumothorax. Penetrating chest trauma may also cause cardiac tamponade, which can be suspected on the basis of the clinical signs (dilated neck veins, hypotension and tachycardia) and detected by ultrasound. Other reasons for pericardial effusion and tamponade include complications of invasive procedures, infections, malignancy and myocardial wall rupture. For cardiac tamponade, thoracotomy should be considered, if expertise and equipment are available and delay to start this procedure is reasonable. For IHCA with PEA following cardiac surgery, emergency re-sternotomy should be performed within 5 minutes of CA (Monsieurs 2015).

Toxins

For intoxications, appropriate antidotes should be used if available. Sodium bicarbonate is recommended for tricyclic overdose. Intravenous calcium chloride is indicated for calcium channel-blocker overdose. Alternative approaches, such as prolonged CPR, hemodialysis and ECLS may be beneficial (Truhlar 2015).

Mechanical chest compression devices

Mechanical chest compression devices should be considered for patients not responding to initial ALS when CPR is prolonged or to facilitate patient transfer and interventions, such as CAG or pulmonary thrombectomy (Monsieurs 2015). However, mechanical chest compression was not shown to improve patient outcome in three RCTs (Perkins 2015, Rubertsson 2014, Wik 2014). In a small study of IHCA patients with PEA using mechanical chest compression devices during transport, diagnostic procedures and in the catheter laboratory, high rates of survival to hospital discharge with good neurological function (46.4%) was achieved (Bonnemeier 2011). Interestingly, in patients with pulmonary embolism, computer tomography–identified thrombus fragmentation was noted after mechanical chest compression without fibrinolytic therapy (Bonnemeier 2011).

EMERGENCY MEDICAL SERVICE SYSTEMS

Emergency Medical Service (EMS) can be defined as “a comprehensive system which provides the arrangements of personnel, facilities and equipment for the effective, coordinated and timely delivery of health and safety services to victims of sudden illness or injury” (Moore 1999).

The EMS system consists of a dispatch center taking care of processing emergency calls, advising bystanders, alerting appropriate help based on dispatching criteria as well as further medical personnel examining, diagnosing, treating and if needed, transferring a patient to hospital and stabilizing at hospital emergency department (Kurola 2001).

EMS systems differ greatly from each other between the continents and countries. EMS systems can roughly be divided into Franco-German and Anglo-American models, albeit today’s systems can have features of both models. The Franco-German model, which is
commonly used in Europe, aims to bring care to the patient: this system is usually run by physicians with advanced equipment and medication. The Anglo-American model aims at the fast transfer of the patient to hospital. This model is used in North America, with trained paramedics and emergency medical technicians (EMTs) providing care in the field and developed emergency departments at hospitals continuing the treatment (Al-Shaqqi 2010).

EMS system providers may be classified by the level of care they provide to BLS and ALS units. The education of BLS and ALS providers differs, as well as the care provided (Roudsari 2007). Basically, in the treatment of an OHCA patient, BLS units provide basic CPR with defibrillation and bag-mask ventilation. ALS units use SGA or intubation to secure the airway, administer drugs and are able to decompress a tension pneumothorax with needle thoracocentesis if needed.

In the treatment chain of an OHCA patient in Finland, dispatch center personnel give instructions to bystanders to start chest compressions when CA is suspected. The first responding unit (FRU), the closest BLS or ALS unit and physician-staffed unit, when available, are also alerted. FRU personnel, who are usually skilled first-aid non-medical persons or firemen, are alerted to minimize the delay in starting patient care. First responders and BLS units are able to provide immediate life-support including defibrillation and bag-mask ventilation or SGA (according to local instructions). BLS units are usually staffed with EMTs and firemen. ALS units with paramedics, who usually have four years of education, secure the airway with SGA or intubation and administer drugs. Physicians, commonly specialized in anesthesiology and intensive care, are able to deliver advanced diagnostic and treatment methods, for example bedside blood tests, ultrasound, blood or plasma transfusion, thoracotomy or transfer a patient to hospital with ongoing CPR with a mechanical chest compression device.

POST-RESUSCITATION CARE

Post-cardiac arrest syndrome

Whole body ischemia during CA initially causes global tissue and organ injury and additional injury occurs during and after reperfusion (Nolan 2008). These complex pathophysiological processes are termed post-cardiac arrest syndrome (Nolan 2015). This syndrome consists of post-cardiac arrest brain injury, post-cardiac arrest myocardial dysfunction and systemic ischemia/reperfusion response and persistent precipitating pathology that caused the CA. The duration and cause of CA affects the severity of this syndrome, as well as the pre-arrest state of health (Nolan 2008, Nolan 2015).

Post-cardiac arrest brain injury

Brain tissue is exquisitely vulnerable to lack of oxygen. Two-thirds of OHCA patients and one-fourth of IHCA patients dying after admission to an intensive care unit (ICU) die because
of neurological injury (Nolan 2015). The pathophysiology of post-cardiac arrest brain injury is complex. In animal studies, immediately after ROSC there is a short multifocal cerebral no-reflow, which is followed by hyperemia lasting 15–30 minutes (Monsieurs 2015). This is followed by cerebral hypoperfusion up to 24 hours after ROSC (Monsieurs 2015). Histologically, brain cell anoxia leads to loss of membrane resting potentials, calcium influx to cells and release of excitatory neurotransmitters, which further exacerbates neuronal injury (Girotra 2015). When ROSC is achieved, the formation of oxygen-free radicals causes direct injury to membranes and promote inflammation (Girotra 2015). Microcirculatory thrombosis might cause microcirculatory failure, which is combined with macrocirculatory hyperemia because of elevated cerebral perfusion pressure and impaired cerebrovascular autoregulation (Nolan 2008). This hyperemia can exacerbate brain edema and reperfusion injury (Nolan 2008). After asphyxial CA, edema occurs transiently after ROSC and, rarely, might cause a significant increase in intracranial pressure and even lead to risk of herniation (Girotra 2015, Nolan 2015). In addition, secondary injury hours to days after CA can be caused by hypoxemia, hypotension, hyperglycemia, seizures, pyrexia, impaired autoregulation and edema (Nolan 2008). Clinical symptoms of post-cardiac arrest brain injury are reduced consciousness, seizures, myoclonus, neurocognitive dysfunction or even brain death (Nolan 2008).

Post-cardiac arrest myocardial dysfunction

Post-cardiac arrest myocardial dysfunction is common, but usually a transient condition that responds to treatment (Binks 2010). A decrease in myocardial contractility might lead to hypotension, low cardiac output and elevated filling pressures (Girotra 2015). Significant myocardial dysfunction after CA is common and recovery usually begins 2–3 days after CA. (Nolan 2015). Most deaths during the first three days after CA are due to cardiovascular failure. (Nolan 2015).

Systemic ischemia and reperfusion response

Whole body ischemia and reperfusion response induce activation of the immune and coagulation systems, which can lead to multiple organ failure and increase the risk of infections (Nolan 2015). Hyporesponsiveness of circulation leucocytes causes an increased risk of infections. Blood coagulation is activated without activation of endogenous fibrinolysis, which produces a risk of microthrombosis (Nolan 2008). Vasodilatation, intravascular volume depletion, endothelial dysfunction and abnormalities in microcirculation are common and might resemble sepsis (Nolan 2015).

Targeted temperature management

Targeted temperature management (TTM), or the previously used term mild therapeutic hypothermia, means maintaining CA patients’ body temperature stable at 32–36°C for at least 24 hours after ROSC (Nolan 2015). After TTM, patients should be rewarmed slowly, about 0.25–0.5°C per hour (Arrich 2007). Hypothermia is neuroprotective, as it decreases the cerebral metabolic rate for oxygen and this may reduce the release of excitatory neurotransmitters and free radicals. The inflammatory response is also reduced (Fröchlich
Other possible physiological effects include shivering, bradycardia, an increase in systemic vascular resistance, hyperglycemia, diuresis, electrolyte abnormalities (hypophosphatemia, hypokalemia, hypomagnesemia and hypocalcemia), impaired coagulation, an increase in infection rates and a slowdown of drug clearance (Nolan 2015).

**Efficacy of TTM**

In 2002, TTM was found to be beneficial in two RCTs on comatose OHCA patients with VF as the initial rhythm (Bernard 2002, HACA study group 2002). Patients were cooled to 32–34°C using external cooling blankets or ice packs for 12–24 h. The neurological outcome was improved in both studies, survival was improved in one study. Based on these results, TTM has been recommended by the AHA and European Society of Cardiology guidelines since 2005 (Girotra 2015). In 2013, a large RCT of unconscious OHCA patients showed that TTM at 33°C had no benefit over TTM at 36°C: no difference in in-hospital mortality or survival with a favorable neurological outcome at 6 months were noted (Nielsen 2013). Meta-analysis of RCTs has also revealed that TTM at 33°C did not improve survival compared to TTM at 36°C, and both TTM at 33 and 36°C improved survival compared to no TTM (Vargas 2015). Cognitive function and quality of life have also been reported to be similar in patients treated with TTM at 33°C or 36°C in another study (Cronberg 2015). A higher temperature target is probably associated with a lower risk of adverse effects and requires less sedatives and paralytics (Girotra 2015).

The effectiveness of TTM in OHCA patients with PEA or ASY has not been evaluated in large RCTs (Girotra 2015). In a recent meta-analysis (Schenone 2016) and in a large North American study (Callaway 2014), TTM was associated with reduced hospital mortality and an increased likelihood of good neurological outcome at hospital discharge when all OHCA patients, including those in a non-shockable initial rhythm, were included. In a meta-analysis of non-shockable rhythm patients, TTM was associated with reduced hospital mortality (Kim 2012). Promising results among non-shockable CA patients have also been reported in some observational studies: Sung et al. (2015) reported an increased odds (OR 2.9; 1.9–4.4) of survival with good neurological outcome after adjustment for confounders and Testori (2011) reported an odds ratio (OR) of 1.84 (1.08–3.13) for good neurological survival with TTM. On the other hand, an observational study reported conflicting results (Dumas 2011), and a recent review was inconclusive (Freund 2017). Current guidelines suggest TTM for unresponsive OHCA patients with non-shockable rhythms (Nolan 2015). An ongoing multicenter RCT called the HYPERION study might answer this question in the future (Lascarrou 2015).

The benefit of TTM is also unclear for IHCA patients. Two small observational studies did not find TTM to improve survival (Kory 2012, Nichol 2013) and one study even reported a lower likelihood of survival to hospital discharge and a lower likelihood of favorable neurological survival in IHCA patients treated with TTM (Chan 2016), but this study was criticized because of the 12–24 h delay in reaching the targeted temperature. Reasons why IHCA patients would not benefit from TTM have been speculated: the prevalence of VF/VT is lower, risk of neurological injury is lower due to short response times and IHCA patients typically have many comorbidities, which might influence their ability to benefit from TTM (Girotra 2015). However, the use of TTM for IHCA patients is still supported by guidelines (Nolan 2015).
Methods and timing of TTM

The optimal cooling method remains unclear (Fröchlich 2013, Walters 2011). External cooling methods include cold pads or blankets, cooling caps, ice packs and wet towels (Fröchlich 2013). Invasive cooling methods include cold intravenous saline, intranasal evaporative cooling device or intravascular cooling catheters (Fröchlich 2013). No specific cooling technique increases survival, when compared with other cooling techniques, but internal devices have more precise temperature control than external ones (Deye 2015, Gillies 2010, Hoedemaekers 2007). Initial cooling might also be slower with external devices (Gillies 2010). Cooling devices with continuous temperature feedback are preferred (Gillies 2010). If a targeted temperature of 36°C is chosen, the targeted temperature is usually reached naturally since the patient’s temperature normally decreases within the first hour after ROSC (Nielsen 2013). If the temperature target is 33°C, 30 mL/kg of intravenous 4°C saline or Hartmann’s solution can be used to decrease the temperature 1–1.5°C (Fröchlich 2013, Kim 2014), but this may increase the risk of hypoxia, pulmonary edema and re-arrest (Arrich 2016, Kim 2014).

The timing of initiation and the optimal duration of cooling are also unclear (Fröchlich 2013). Some EMS start pre-hospital cooling, but an RCT failed to show the benefit of pre-hospital cooling compared to cooling initiated after hospital admission (Bernard 2010). Rapid infusion of 1–2 liters intra-venous cold saline during CPR decreased the ROSC rates and produced no trend toward improved outcomes at hospital discharge (Bernard 2016).

Reperfusion strategies in acute coronary syndromes

Reperfusion strategies include fibrinolysis and CAG±PCI. The ERC recommends CAG±PCI as a primary choice after CA, but emergency CAG is not available in all healthcare settings and therefore fibrinolysis is also used after OHCA (Nikolaou 2015). In ST-segment elevation myocardial infarction (STEMI) -patients without CA, fibrinolysis should be considered if the delay to CAG±PCI exceeds 60–90 minutes (Nikolaou 2015).

Early CAG (usually defined as <24 hours after hospital admission) and possible PCI has been associated with improved CA patients’ survival in many studies (Callaway 2014, Geri 2015, Larsen 2012, Sideris 2014, Vyas 2015, Wilson 2017), but current evidence is inconclusive (Kagawa 2013) since no RCTs have been published. The association of CAG and good outcomes may be a result of selection bias. A large meta-analysis showed that among all OHCA patients, early CAG±PCI was associated with improved survival to hospital discharge (59 vs 31%) and increased survival with good neurological outcome (58 vs 36%) (Camuglia 2014). Improved survival and favorable neurological outcome have been reported in both shockable and non-shockable rhythms (Kim 2015, Vyas 2015), with even greater associations among patients in a non-shockable rhythm (Kim 2015). However, some studies have not found a benefit of early CAG±PCI in OHCA patients without ST-segment elevation (Kleissner 2015) or in all OHCA patients after adjustment for confounders (Weiser 2013).
**OHCA with STEMI**

The efficacy of early CAG±PCI among STEMI patients has been shown in RCTs (O’Gara 2013). Increased survival and better neurological outcomes have been reported in observational studies for OHCA patients with STEMI treated with early CAG and possible PCI, but no RCTs have been done (Nikolaou 2015). The European Association for Percutaneous Cardiovascular Interventions consensus statement recommends immediate CAG±PCI for OHCA patients with STEMI (Noc 2014).

**OHCA patients without STEMI**

It remains debatable whether early CAG ± PCI should also be performed to OHCA survivors without STEMI (Bro-Jeppesen 2012), but there are two RCTs concerning this patient group going on (Girotra 2015). In observational studies, the absence of ST-elevation could also be associated with ACS after OHCA (Dumas 2010, Radsel 2011, Zanuttini 2013) since ECG is a poor predictor of ACS after CA (Larsen 2012). Approximately every fourth patient without STEMI has been shown to have a culprit lesion and an indication for PCI after OHCA (Radsel 2011). Of patients resuscitated from a non-shockable rhythm of presumed cardiac origin without STEMI, PCI was done to 33% of those undergoing early CAG, compared to 41% of similar shockable rhythm patients (Wilson 2017). The incidence of significant coronary artery disease ranged from 59 to 71% in OHCA patients without an obvious non-cardiac etiology (Larsen 2012).

Reduced mortality has been reported in a meta-analysis of patients resuscitated from all-rhythm (Larsen 2012) and in a retrospective analysis of non-shockable rhythm CA patients who underwent early CAG (Wilson 2017), but CAG was not an independent predictor for outcome (Wilson 2017). The European Association for Percutaneous Cardiovascular Interventions recommends consideration of CAG±PCI within 2 hours to other OHCA patients without obvious non-coronary cause, particularly if the patient is unstable (Noc 2014).

**General supportive care**

In addition to TTM and CAG±PCI, CA patients require intensive monitoring and treatment. Supportive post-resuscitation care generally relies on strategies for general intensive care (Girotra 2015). Patients usually require airway protection with tracheal intubation, mechanical ventilator support and monitoring to ensure adequate oxygenation and ventilation (Girotra 2015, Nolan 2015). Both hypoxia and extreme hyperoxia are harmful, and the ERC recommends targeting oxygen saturation in the range of 94–98% (Kilgannon 2010, Nolan 2015). Lung protective normoventilation is recommended, since hypokapnia is associated with poor outcomes (Nolan 2015). Hemodynamic support with fluids, vasopressors, inotropes or mechanical circulatory support devices may be necessary because of post-cardiac arrest myocardial dysfunction (Girotra 2015). Early echocardiography should be performed on all CA patients (Nolan 2015) and an arterial line should be established for continuous blood pressure monitoring. Seizures may be difficult to diagnose and therefore electroencephalogram (EEG) monitoring is recommended, as well as aggressive treatment of seizures, but prophylaxis is not recommended (Girotra 2015, Nolan 2015). Blood glucose should be maintained <10mmol/l and hypoglycemia should be avoided (Nolan 2015). Blood gases, electrolytes, glucose and infection parameters should be monitored as well as...
appropriate testing or imaging should be carried out to identify and treat the underlying cause of arrest (Girotra 2015, Nolan 2015).

Cardiac arrest centers

Studies have shown a marked variation in CA survival between hospitals after adjusting for patient characteristics (Herlitz 2006, Merchant 2014, Soholm 2013, Stub 2011). In a Danish study, admission to tertiary hospitals was independently associated with lower mortality rates after OHCA compared to non-tertiary hospitals (Soholm 2013). Better survival rates in hospitals which treat a high volume of CA patients has been published (Carr 2009).

The AHA has recommended the regionalization of post-resuscitation care in specialized "cardiac arrest centers" to improve CA outcomes (Nichol 2010). Since multidisciplinary post-resuscitation care already begins on scene with OHCA patients, clear roles for each team should be defined (Fröchlich 2013). A specialized multidisciplinary team on call 24 hours a day specialized in comprehensive post-resuscitation care (including TTM, 24 hours a day access to CAG±PCI and the availability of neurological investigations) and standardized treatment protocols are essential, as well as continuous data collection and improvement of quality of care (Donnino 2011, Fröchlich 2013, Girotra 2015). Post-resuscitation care protocols and regionalization of post-resuscitation care to CA centers have led to increased survival rates (Bosson 2014, Hollenberg 2013, Tagami 2016).

Neuroprognostication

Approximately two-thirds of CA patients who die after ICU admission die from hypoxic-ischemic encephalopathy, and most of the deaths occur because of withdrawal of care after prognostication of a poor neurological outcome (Dragancea 2013, Lemiale 2013). For that reason, it is important to ensure that false pessimistic prognostication does not occur prematurely when patients may have a chance to recover (Girotra 2015, Nolan 2015). In 2014, the ERC and European Society of Intensive Care Medicine published an advisory statement of prognostication after CA (Sandroni 2014).

Since the brain recovers gradually from hypoxic injury (up to 72 hours), the suitable timing for prognostication of comatose patients is >72h after ROSC. If a patient has received sedatives <12h before prognostication, or even longer when TTM is used, prognostication may not be reliable. Other physiological confounding factors should also be excluded. Absent or extensor motor response to pain >72h after ROSC, bilaterally absent pupillary and corneal reflexes and bilaterally absent somatosensory evoked potential wave N20 strongly predict a poor outcome. When none of these signs are present, 24h should be waited before new prognostication. A poor outcome is very likely if at least two of the following less accurate signs are present: status myoclonus <48h after ROSC, high neuron-specific enolase (NSE) levels, unreactive burst suppression or status epilepticus on EEG or diffuse anoxic injury in brain computer tomography or in magnetic resonance imaging. If two or more of these signs are not present, observation and re-evaluation should be continued (Sandroni 2014).

NSE and S-100B are protein biomarkers released from injured neurons or glial cells, respectively (Sandroni 2014). Both of these have been shown to predict in-hospital death after
adjustment for clinical and CA factors (Grubb 2007) and are likely to correlate with the severity of neurological outcome (Sandroni 2014). The European Society of Intensive Care Medicine recommends using NSE, which is better documented than S-100B, at 48–72h after ROSC in combination with other predictors, since it is difficult to find a particular threshold to predict poor outcome reliably (Sandroni 2014).

Brain computer tomography is recommended to be considered upon hospital arrival if a cardiac cause for the CA is unlikely (Nolan 2015). In brain computer tomography, marked reduction in grey matter/white matter interface attenuation or reduction in cerebral sulci less than 24h after ROSC predict poor outcomes. In magnetic resonance imaging, presence of extensive reduction in diffusion 2 to 5 days after ROSC also predicts poor outcomes. However, the European Society of Intensive Care Medicine suggests using brain imaging only in combination with other predictors, and only in hospitals where specific experience is available. Evidence on prognostication after CA using imaging is of low quality, since most studies reported are small and retrospective (Sandroni 2014).

Prognostication should not be made on the basis of any single variable alone. On the contrary, a multimodal approach should be used, taking into account both the pre-arrest and resuscitation details, repeated clinical examination, neurophysiological studies, biomarkers and imagining (Sandroni 2014).

SURVIVAL AND QUALITY OF LIFE

OHCA survival

According to Utstein resuscitation reporting guidelines, time points of interest in survival after CA are ROSC (any), surviving event (alive at hospital admission), 30-day survival or survival to hospital discharge (Perkins 2015). 1-year survival should be reported when possible, but because of challenges in long-term follow-up is considered as supplemental information (Perkins 2015). The majority of resuscitation studies report survival to hospital discharge.

The survival rates to hospital discharge following OHCA with any initial rhythm are globally highly variable, ranging from 2 to 20% (Andersen 2015, Berdowski 2010, Hiltunen 2012, Nolan 2013, Teodorescu 2012). Globally, the average survival to hospital discharge is 7% and in Europe overall survival is 9%, in Australia 11%, in North America 6% and in Asia 3% (Berdowski 2010). Besides varying survival between continents and countries, regional differences have also been noticed nationally, suggesting regional differences in pre-hospital and post-resuscitation care (Hasegawa 2013).

Survival to ROSC varies between 26–44% (Abrams 2013, Andersen 2015, Avalli 2014, Hiltunen 2012, Soholm 2015, Teodorescu 2012). Abrams (2013) reported 37% survival to ROSC for witnessed (CA seen or heard by another individual) OHCA patients and 18% for unwitnessed patients. Witnessed OHCA patients with VF/VT have even reached 50% survival to ROSC (Abrams 2013).
Factors associated with survival

Location of OHCA

Approximately 64–79% of OHCA happens at home or at another residence (Abrams 2013, Bagai 2013, Teodorescu 2012). OHCA in public locations has a better prognosis than at home (Hasselqvist-Ax 2015); almost twice as many patients have been reported to survive to hospital admission or discharge (11 vs 20%) (Fake 2013, Soholm 2015). Women are more likely to have OHCA at home than men (Teodorescu 2012). In addition, patients in urban municipalities have been reported to survive to hospital admission more often than patients in semi-urban or rural areas (Hiltunen 2012).

Witnessed OHCA

41–71% of OHCA in which resuscitation is attempted are witnessed in western countries (Abrams 2013, Avalli 2014, Bagai 2013, Hasselqvist-Ax 2015, Teodorescu 2012). Witnessed OHCA has a significantly better prognosis than unwitnessed OHCA (Abrams 2013, Avalli 2014). In witnessed CA, ROSC was 3.5 times more likely to be achieved (Soholm 2015). Survival to hospital discharge for unwitnessed OHCA patients was only 4%, while 16% of bystander witnessed patients survived (Abrams 2013). EMS-witnessed OHCA has an even better prognosis (Soholm 2015).

Bystander CPR

Bystander CPR is performed before EMS arrival in 26–51% of cases (Abrams 2013, Avalli 2014, Bagai 2013, Hasselqvist-Ax 2015, Hiltunen 2012, Teodorescu 2012). Bystander CPR is independently associated with increased survival (Avalli 2014, Hasselqvist-Ax 2015, Soholm 2015). In a large study of US OHCA patients, increased survival was found only with witnessed cases (Abrams 2013). In a large Swedish study concerning OHCA patients treated between 1990–2011, bystander CPR was associated with a 30-day survival rate (11%) more than twice as high as without bystander CPR (4%) (Hasselqvist-Ax 2015). Bystander CPR increases survival more when performed outside a patient’s home, probably because bystanders are often younger and may have been trained in CPR (Hasselqvist-Ax 2015).

Response time

A short response time (time from collapse or emergency call to EMS arrival) is independently associated with improved survival to ROSC and hospital discharge (Lai 2015, Rajan 2016, Soholm 2015). Response times over 8 minutes reduce the chances of survival in both witnessed and unwitnessed OHCAs (Abrams 2013). In a Swedish study, a shorter time from collapse to initiation of CPR was associated with improved 30-day survival (Hasselqvist-Ax 2015).
**Initial rhythm**

PEA and ASY are associated with significantly decreased hospital discharge rates compared to VF/VT patients (Avalli 2014). OHCA patients in VF/VT are up to 3.9 times more likely to reach ROSC and hospital admission than patients in PEA or ASY (Soholm 2015). PEA is associated with a better prognosis than ASY: survival rates to hospital discharge are approximately 5.9–15.7% for PEA (Andrew 2014, Bergum 2016, Beun 2015, Hauck 2015, Kudenchuk 2013, Teodorescu 2012) and 1–2.1% for patients in ASY (Andrew 2014, Kudenchuk 2013). The better PEA prognosis compared to ASY could be partly explained by the fact that some patients with PEA have undetectable, but minimally perfusing circulation preserved. PEA patients with ventricular wall motion detected in ultrasound have increased survival rates to ROSC (23.5–43%) and to hospital admission compared to those with no motion (Breitkreutz 2010, Chardoli 2012, Flato 2015, Myerburg 2013). ROSC is unlikely (0–2.4%) in patients with true-PEA (Blyth 2012, Chardoli 2012, Cureton 2012).

VF or pulseless VT is known to have the best prognosis, with 23% survival in Europe and 19% global survival to hospital discharge (Perkins 2015).

In PEA patients, survival to hospital discharge in those who converted into a shockable rhythm was similar compared to those who maintained a non-shockable rhythm (Thomas 2013), but in recent meta-analysis, conversion to a shockable rhythm increased survival to ROSC and hospital discharge (Luo 2017). Women with PEA are more likely to regain ROSC and survive to hospital discharge compared to men (Teodorescu 2012).

**Time to defibrillation**

For patients in a shockable initial rhythm, each additional minute delay in the time to defibrillation by EMS personnel significantly decreases survival to hospital discharge and functional survival (Drennan 2014). Bystander AED use is also associated with increased survival to hospital discharge, but it is quite rare: in only approximately 2–4% of OHCAs does a bystander use AED (Abrams 2013, Bagai 2013, Lai 2015).

**Time to ROSC**

Short time to ROSC is independently associated with a favorable outcome (Reynolds 2013, Väyrynen 2008). Reynolds et al. (2013) reported that after 16.1 minutes of CPR, 90% of patients with good neurological outcome at hospital discharge had achieved ROSC, and after 15 minutes the probability of good functional recovery falls to ~2%.

**Cause of CA**

A presumed cardiac cause of OHCA is associated with increased survival to hospital admission and one-year survival (Hiltunen 2012, Soholm 2015). Patients with OHCA due to ACS had better survival rates to hospital discharge and at 5-year follow-up than patients with OHCA due to other causes (Sideris 2014). For traumatic CA, survival rates of 3.3–3.7% have been reported (Zwingmann 2012). Good neurological survival after asphyxial CA is rare (Truhlar 2015).
Time of OHCA

Survival to hospital discharge has been reported to be lowest for OHCA that occurs overnight (from 11 PM to 7 AM; 7%) versus daytime or evening (11%) (Bagai 2013, Soholm 2015) and during winter (9%) versus spring, summer (11%), or fall (10%). The worse prognosis for overnight OHCA might be explained by longer delays to the emergency call and EMS arrival and overnight OHCA happening more likely at home (Bagai 2013).

Age

Patient age over 65 years is associated with worse CA outcomes compared to younger patients (Andersen 2015, Deasy 2011, Soholm 2015). For example, in the North American population, patients <20 years of age had the highest proportion of survival (17%) and good neurological outcome (15%), whereas these numbers for patients at age 95–99 years were 2% and 1%, respectively (Andersen 2015). A systematic review comprising almost 45,000 patients reported 4.1% survival rates to hospital discharge for all-rhythm OHCA patients ≥70 years of age (van de Glind 2013). Of OHCA patients aged 65–79 years with PEA as their initial rhythm, 6% survived to hospital discharge, while 3% of older age groups survived (Deasy 2011). However, there is wide variability in the effect of age on outcomes, including studies showing no association (Ceder 2014, Grimaldi 2014). A common conclusion is that age alone is not a good predictor for outcome and specific cut-offs for withholding CPR cannot be determined (Andersen 2015). Nursing home residency is reported to associate independently with decreased survival rates, while scientific evidence on effect of comorbidities is scarce (van de Glind 2013).

Improvement in survival

In recent decades, improvement in survival rates and neurological outcomes of CA patients have been reported (Avalli 2014, Blom 2014, Chan 2014, Kudenchuk 2012, Lai 2015, Malta Hansen 2015, Strømsøe 2015, Wong 2014). Some studies have reported improvement only in patients with a shockable rhythm (Blom 2014, Fothergill 2013), while others also report improvement among patients in a non-shockable rhythm (Chan 2014, Kudenchuk 2012, Strømsøe 2015). Improvement has been noted both in pre-hospital survival (Chan 2014, Soholm 2015) and in-hospital survival (Chan 2014). Investigators have speculated that public campaigns and training to recognize CA (Fothergill 2013, Strømsøe 2015), increased availability of mobile phones (Strømsøe 2015), increased bystander CPR (Chan 2014, Fothergill 2013, Hansen 2015, Lai 2015, Strømsøe 2015, Wissenberg 2013), increased dispatcher-assisted CPR (Avalli 2014, Strømsøe 2015), increased use of AEDs (Avalli 2014, Blom 2014, Fothergill 2013, Malta Hansen 2015, Strømsøe 2015), equipping fire brigades and police forces with AEDs and alarming them by dispatch center (Hollenberg 2013, Strømsøe 2015), education programs for EMS personnel (Fothergill 2013), implementation of ROSC guidelines (Fothergill 2013), use of TTM (Avalli 2014) and use of ECLS for selected refractory CA patients (Avalli 2014) are the reasons for increased survival rates.
IHCA survival

All-rhythm IHCA survival rates have improved in recent decades from 10–20% to 18–26% (Adamski 2016, Bergum 2015, Chan 2013, Girotra 2012, Memar 2018, Nolan 2014, Paradis 2007, Sandroni 2007, Thompson 2018). Improvement in survival is due to improvement in both acute resuscitation survival and post-resuscitation survival (Girotra 2012). Hospital discharge rates for non-shockable IHCA improved from 9% to 15% between 2001 and 2011, while 1-year survival improved from 5% to 8% during the same period (Thompson 2018). Significant variability in IHCA survival exists between hospitals despite adjustment for patient factors: 0–52% survival rates have been reported (Merchant 2014). The highest survival rates to hospital discharge have been reported in VF/VT patients (37-53%), compared to patients in PEA (11–13%) or ASY (9–17%) (Bergum 2015, Meaney 2010, Nolan 2014). A recent Swedish study reported that over half of non-shockable rhythm IHCA patients who survived 30 days, were alive 3–10 years later (Memar 2018). Mortality has been reported to be lower than average at ICUs (Adamski 2016, Chan 2013). In a Finnish study, survival to hospital discharge was 44% among patients who suffered CA in an ICU (Efendijev 2014).

Quality of life

Measuring quality of life

The World Health Organization defines health as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”. Health-related quality of life consists of biological, psychological and social functioning (International Health Conference 1946), which are influenced by a large number of factors such as a person’s beliefs, experiences, perceptions and values (Elliott 2015). A certain deficit or impairment may be significant for one survivor but may not be significant for another (Elliott 2011). Therefore, measuring overall quality of life after CA is challenging.

The Utstein guidelines promote the reporting of neurological outcomes at hospital discharge by recording the Cerebral Performance Category (CPC) class (BRCT I Study Group 1986, Phelps 2013) or modified Rankin Scale (mRS) score and defining how it was measured (face to face, extracted from notes or a combination) (Perkins 2015). The mRS is a 7-point scale ranging from no symptoms (0) to dead (6). CPC classification (Table 1) is a 5-stage scale of neurological state (BRCT I Study Group 1986, Phelps 2013). Briefly, classes 1–2 correspond to sufficient cerebral function for independent activities for daily life, while classes 3–4 reflect dependency on others and class 5 means death. Neurological outcome is considered favorable with CPC scores 1 or 2 or mRS scores 0–3 or no change in CPC or mRS from the patient’s baseline status (Perkins 2015).
Table 1. Cerebral Performance Category (CPC) classification. Modified from the Brain Resuscitation Clinical Trial I Study Group (1986) and Phelps (2013).

<table>
<thead>
<tr>
<th>CPC category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Good cerebral performance: conscious and able to work, possibly mild neurologic or psychologic deficit.</td>
</tr>
<tr>
<td>2</td>
<td>Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment.</td>
</tr>
<tr>
<td>3</td>
<td>Severe cerebral disability: conscious, dependent on others for daily life because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis.</td>
</tr>
<tr>
<td>4</td>
<td>Coma or vegetative state: unconscious, unaware of the surroundings, no cognition without the presence of all brain death criteria. May have spontaneous eye opening and sleep/awake cycles.</td>
</tr>
<tr>
<td>5</td>
<td>Brain death or death by traditional criteria.</td>
</tr>
</tbody>
</table>

Overall quality of life

In a review focusing on quality of life after OHCA or IHCA, 46 out of 70 studies supported the hypothesis that CPR produces good quality of life, while 17 were neutral and 7 negative to the hypothesis (Elliott 2011). 73–90% of OHCA survivors are reported to return home, up to 95% when only VF patients treated with TTM are included (Cronberg 2015, Deasy 2013, Smith 2015, Tiainen 2015). 18–27% of OHCA survivors need help with daily activities, and 68–74% of those working before CA returned to work, approximately 50–62% to their previous state of employment (Aiyagari 2015, Cronberg 2015, Deasy 2013, Smith 2015).

Cerebral Performance Category

Good neurological outcome (CPC 1–2) has been reported in 83–95% of all-rhythm OHCA patients surviving to hospital discharge (Andersen 2015, Hasselqvist-Ax 2015, Phelps 2013, Strömsöe 2015). At hospital discharge, 56% of patients in a non-shockable initial rhythm and up to 74% of those in PEA have been reported to have good neurological outcomes (Holmgren 2010). Results are less encouraging in the study of Andersen et al. (2015): regarding all patients to whom resuscitation was attempted, 8% of all-rhythm and 3% of non-shockable rhythm patients survived with good neurological outcome.
85.1–97.5% of all-rhythm IHCA patients and 95.6% of IHCA patients with PEA surviving to hospital discharge have been reported to survive with good neurological outcome (CPC 1–2) (Nolan 2014, Sandroni 2007).

Cognitive deficits

Despite relatively good quality of life scores, 17–50% of OHCA survivors experience cognitive deficits for up to several years post-discharge (Boyce-van der Wal 2015, Green 2015, Nichol 2015). Deficits are mostly mild or moderate, though approximately 11–17% experience marked or severe cognitive problems or disability (Deasy 2013, Phelps 2013, Smith 2015, Tiainen 2015). The most commonly reported cognitive deficits among CA survivors include impairment in declarative and long-term memory, attention, executive dysfunction, visuospatial abilities and verbal fluency (Green 2015, Parnia 2007). The majority of patients have no problems with mobility, personal care, usual activities or pain/discomfort (Deasy 2013). Two-thirds of survivors reported having made a complete mental recovery, but relatives or close acquaintances reported cognitive decline in more than half of the survivors (Cronberg 2015).

Emotional problems

CA may be emotionally extremely stressful, and patients may also suffer from emotional impairments. 27% fulfilled the criteria of post-traumatic stress disorder, while 10–45% experienced depression (Green 2015, Lilja 2015, Nichol 2015, Parnia 2007). Deasy et al. (2013) reported moderate or severe anxiety up to 61% among young (18–39 years old) OHCA survivors, while Lilja (2015) reported 24% having symptoms of anxiety, which was almost equal to the STEMI control group. Fatigue appears to also be commonly reported (Green 2015). Usually patients with cognitive defects experience more anxiety and depression, as well as lower quality of life (Boyce-van der Wal 2015, Lilja 2015, Ørbo 2015).
AIMS OF THE STUDY

The main purpose of this thesis was to investigate peri- and post-arrest treatment of OHCA and IHCA patients presenting with PEA. Specific aims were:

1. To examine if treating the underlying cause of PEA during resuscitation improves patients' survival (II).
2. To evaluate which factors affect PEA patients selection to different levels of post-resuscitation care (IV).
3. To investigate differences in post-resuscitation care after OHCA between the Nordic countries and between units with different levels of post-resuscitation care (III, IV).
4. To assess PEA patients' long-term survival and quality of life after OHCA (I).
MATERIALS AND METHODS

Data for this thesis consists of 424 adult patients who had CA with PEA and were treated by EMS systems, receiving hospitals and ICUs between 1999–2013. 104 of these patients had IHCA and the rest (n=320) had OHCA. IHCA patients were included in the study evaluating the treatment of possible reversible causes of CA during CPR (II). Patient selection to ICUs and high dependency units after OHCA with PEA was investigated, as well as post-resuscitation treatment in units with different levels of care (III, IV). Long-term survival and quality of life after OHCA with PEA was also assessed (I).

EMERGENCY MEDICAL SERVICE SYSTEMS AND INVOLVED HOSPITALS

EMS systems

The OHCA patients in this study were treated by four EMSs in Southern Finland. The EMS of the city of Helsinki is a 3-tiered system consisting of BLS and ALS units and a physician-staffed mobile unit, serving the capital’s 600,000 inhabitants. The surrounding capital area is served by a physician-staffed helicopter EMS (HEMS) system, covering a population of some 850,000 inhabitants. A similar HEMS system operates in the Turku area in the southwest, with a population of 630,000. A physician, a pilot and a HEMS paramedic form the HEMS crews. The EMS system in the city of Tampere was, at the time of study I, a 2-tiered ground system with BLS and ALS crews only, without physician presence. The population served was around 200,000.

Hospitals

Three hospitals treated the IHCA patients studied in study II of this thesis (II). Hyvinkää Hospital is a regional hospital in southern Finland, serving 180,000 inhabitants in 5 municipalities. Oulu University Hospital in northern Finland treats a population of 730,000. Södersjukhuset in Stockholm, Sweden provides medical care to half a million Stockholmers. During the period of study II, Hyvinkää lacked CAG and PCI facilities, Oulu had them daily during office hours and Södersjukhuset had them 24h/day on weekdays.

For the study on levels of post-resuscitation care (IV), patients were treated either in Helsinki University Hospital in Helsinki or in several regional hospitals around the capital area in Southern Finland. Helsinki University hospital consists of several separate hospitals, but only Meilahti and Töölö hospitals treated patients included in study IV. In Meilahti, patients resuscitated from OHCA were treated either in the ICU, Internal Medicine High Dependency Unit (operated by internal medicine specialists with the opportunity for invasive ventilation and monitoring and intermittent renal replacement therapy), Emergency Department (with basic invasive ventilation and monitoring and anaesthesiologist available) or at ordinary wards. In Töölö trauma hospital, there were three ICUs: burn unit, trauma unit and neurosurgical unit. Jorvi Hospital in Espoo also has an ICU. Regional hospitals in the study area include Lohja, Hyvinkää, Pejas, Porvoo and Tammisaari, all of which have high dependency units.
PATIENT DATA AND STUDY PROTOCOLS

Treatment during CPR

IHCA patients with PEA were investigated to evaluate if treatment of potential reversible causes of CA during CPR improves survival (II). All adult IHCA patients with PEA were included, if CPR was attempted. Data were collected retrospectively in Hyvinkää Hospital from March 2003 to May 2009, in Oulu University Hospital from January 2008 to March 2010 and in Södersjukhuset from March 2004 to January 2009.

The data collection form was created and piloted in Sahlgrenska University Hospital in Göteborg, Sweden and proved to be functional (unpublished data, personal communication with Maaret Castrén). The form comprised patient demographics, earlier diagnoses, reason for admission, IHCA and CPR details, survival as well as clinical- or autopsy-determined cause of IHCA (Appendix 1). In addition, documented vital signs for the 24h preceding IHCA were collected. Hospital medical records, nurse’s notes and autopsy reports provided the data.

A physician (S.S. or T.T.) or a trained nurse (D.F.) estimated patient by patient if potentially reversible causes of PEA (hypovolemia, hypoxia, acidosis, hyperkalemia, hypokalemia, hypernatremia, hyponatremia, hypoglycemia, hypothermia, cardiac tamponade, tension pneumothorax, acute myocardial infarction, pulmonary embolism, intoxication by toxin that has an antidote, other) were confirmed (before, during or after CPR), treated, suspected, potential, excluded or could not be evaluated. This estimation was made retrospectively based on patients’ medical records, vital signs before IHCA, resuscitation details and autopsy reports if available. A treatment was considered specifically targeted for the cause of PEA if suspicion of a specific cause was raised and the patient received specific treatment for it as recommended in the ERC Guidelines for Resuscitation (Deakin 2010). For example, pericardiocentesis for cardiac tamponade was considered a specific treatment, while sodium bicarbonate in the absence of tricyclic antidepressant overdose, hyperkalemia or severe acidosis was considered a non-specific treatment. The appropriate treatment of hypoxia is a part of conventional CPR and therefore these patients were also included in the non-specific treatment group. According to the treatment patients received, they were divided into two groups: treatment of the primary cause group and non-specific treatment group, which received conventional CPR.

Patient selection to post-resuscitation care units and post-resuscitation care

Factors associated with PEA patients’ selection to different levels of post-resuscitation was assessed (IV) and post-resuscitation care was described (III, IV).

The patients studied for the post-resuscitation intensity study were resuscitated by Helsinki EMS and the Helsinki area HEMS (FinnHEMS 10) (IV). All adult OHCA patients with PEA who were resuscitated between March 2010 and December 2013 were included, if the patient survived to hospital admission with sustained ROSC. OHCA patients were identified from Helsinki EMS’s cardiac arrest registry or FinnHEMS10 pre-hospital database. Pre-hospital and hospital patient records provided the data.
These patients were divided into groups according to the level of care provided as categorized by the World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM) Task Force: patients treated in ordinary wards, Level 1, Level 2 or Level 3 ICUs (Table 2). Briefly, in WFSICCM classification only Level 2 and 3 ICUs provide invasive monitoring and mechanical ventilator support. Only Level 3 ICUs are usually called ICUs in Finland and Level 1–2 ICUs are called high dependency units. Categorization of the units providing post-resuscitation care in the study area is presented in Table 2.

Table 2. Classification of ICUs as purposed by the WFSICCM and classification of units providing post-resuscitation care in the study (IV) area. Modified from Marshall et al. 2017.

<table>
<thead>
<tr>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capacity</td>
<td>Short-term support of mild organ dysfunction</td>
<td>Basic support of organ dysfunction</td>
</tr>
<tr>
<td>Treatment</td>
<td>Non-invasive respiratory support</td>
<td>Mechanical ventilator support, pharmacologic hemodynamic support, intermittent RRT</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Non-invasive</td>
<td>Invasive</td>
</tr>
<tr>
<td>Personnel</td>
<td>Nurse patient ratio 1:4 or 1:3, Physicians with some experience in critical care available during day</td>
<td>Nurse patient ratio 1:3 or more, Physicians with some ICU training during day, available at night</td>
</tr>
<tr>
<td>Post-resuscitation care units</td>
<td>Helsinki City Hospital and Tammisaari High dependency units</td>
<td>Meilahti and Töölö (University Hospital) Emergency Departments</td>
</tr>
<tr>
<td></td>
<td>Peijas Coronary Care Unit</td>
<td>Meilahti Internal Medicine High Dependency Unit</td>
</tr>
<tr>
<td></td>
<td>Jorvi, Hyvinkää, Peijas, Tammisaari Emergency Departments</td>
<td>Porvoo, Hyvinkää, Lohja, Peijas High Dependency Units</td>
</tr>
</tbody>
</table>

ICU=intensive care unit, RRT= renal replacement therapy

Groups baseline characteristics, post-resuscitation care and survival were compared. In addition, two senior anesthesia and intensive care specialists (T.S. and I.V.), who were
blinded to information about the treatments, survival and neurological outcome, estimated whether in their opinion there was an indication for a more intensive post-resuscitation treatment for patients admitted to ordinary wards or Level 1 ICUs. This evaluation was based on the data available on hospital admission (patient characteristics and resuscitation details). Only those patients who both of the physicians independently thought would have benefited from Level 2 or 3 intensive care were considered as probably benefiting from more intensive care.

Regional differences in selection to ICU and in post-resuscitation treatment of OHCA patients between Nordic countries were evaluated with a questionnaire study to Nordic ICUs (III). An online questionnaire included questions concerning OHCA patient’s admission criteria to ICUs and post-resuscitation care in the ICU (Appendix 2). A link to this questionnaire was sent in November 2012 via email to 188 chief physicians of Nordic ICUs, of which 84 were in Sweden, 52 in Denmark, 28 in Norway, 22 in Finland and 2 in Iceland. The second questionnaire, which was not planned in the beginning of the study, was created to investigate whether clinical practices had changed as a consequence of new findings published in 2013 and in 2014: Nielsen et al. (2013) showed no benefit of TTM at 33°C over TTM at 36°C in the treatment of comatose survivors after CA and Kim et al. (2014) reported no benefit of pre-hospital induction of TTM with cold fluids and significantly more serious adverse events were seen in the group receiving cold fluids. This questionnaire was received by 184 ICUs in October 2014. Responses were collected using a web-based tool (https://fi.surveymonkey.com/).

Survival and quality of life

IHCA patients’ 30-day survival was compared between PEA patients who received specific treatment for the cause of CA during CPR and those who received standard CPR (II). OHCA patients’ survival to hospital discharge and neurological survival 1-year after PEA were described for patients treated in ICUs and those treated elsewhere (IV). Long-term survival and quality of life after OHCA with PEA was assessed retrospectively (I).

The study population for the long-term survival assessment consisted of OHCA patients with PEA resuscitated between August 2001 and March 2003 by Turku or Helsinki area HEMS and Tampere EMS systems. Patients over 16 years of age were included if resuscitation was attempted and CA was of presumed or possible cardiac origin. The cause of arrest was presumed to be cardiac if no obvious external cause for CA, such as trauma, intoxication, airway obstruction, drowning or hemorrhage, existed (Jacobs 2004). Originally, this data was collected for a prospective study focusing on regurgitation during CPR (Virkkunen 2006). Long-term survival was analyzed 1 and 5 years after OHCA with data obtained from The National Registry of Statistics Finland. Pre-arrest CPC and CPC one year after OHCA was evaluated retrospectively based on patient medical records. The 15-D questionnaire of health-associated quality of life was sent to the long-time survivors (Sintonen 2001). The questionnaire includes questions of self-assessed performance in activities of daily life (Appendix 3).
ETHICAL CONSIDERATIONS

Study I’s protocol was approved by the ethical review board of the Helsinki University Hospital. The Institutional Review Boards of Helsinki and Oulu University Hospitals and Ethics Committee of Stockholm approved study II’s protocol. Since study III was a questionnaire study to ICU physicians, no permission from an ethical review board was required. Permission to conduct study IV was granted by the Helsinki University Hospital Research and Development Division. Because this study used previously collected registry data, the researchers were not required to submit the study protocol for ethical board review.

STATISTICAL METHODS

Statistical analyses were performed using SPSS for Windows (SPSS Inc., Chicago, IL, USA) V16.0 for study I, 18.0 for study II and IBM SPSS Statistics 24.0 and 25.0 software for study IV. Statistical analysis was performed using basic statistical tests, which were selected based on measurement scale and the symmetry of the distribution of outcome, as appropriate: Chi-Square test (I, IV) or two-tailed Fisher’s exact test (II, III) was used to analyze categorical variables, Mann-Whitney U test for continuous data (II). Statistical significance was set at p <0.05. The data were presented as mean ± standard deviation (SD) (I, IV) or median (interquartile range, IQR) (II, IV). In study III, reported percentages are proportions of responses.

In study II, survival to ROSC and 30-day survival were compared between treatment of the primary cause group and non-specific treatment group. A univariate analysis was made to compare patients who survived 30 days to those who did not, and factors with p <0.2 were included in a multivariable logistic regression analysis to identify individual prognostic factors for 30-day survival.

In study IV, the baseline characteristics and CPR data of the four patient cohorts (Ward, Level 1 ICU, Level 2 ICU, Level 3 ICU) were compared. In addition to tests mentioned above, 1-way ANOVA tests were used to compare group means of age. Multiple comparisons between group mean ages were analyzed with the Tukey’s Honestly Significant Difference (HSD) test. The independent samples Kruskal–Wallis test was used for comparison of the groups’ response, ROSC and ventilator times. For all other variables of baseline characteristics and post-resuscitation data with ordinary scales, the Mantel–Haenszel test of trend was used for comparison. To evaluate independent factors determining the level of care, baseline factors were included in a logistic regression model for adjustment. For this model, patients fully awake on hospital admission were excluded. Ward and Level 1 ICU groups were combined, as well as Level 2 and 3 ICUs. P values in logistic regression were calculated using Wald’s test. For comparison of post-resuscitation care, Ward and Level 1 ICU groups were combined. To adjust factors determining good neurologic survival, another logistic regression model was made. For 1-year survival, a proportional hazards regression model was fitted. The post-resuscitation care and survival models included baseline characteristics, CPR details and level of care as independent factors. The reduction of factors in these models was made by backward stepwise selection, based on the probability of the likelihood-ratio statistic. The inter-rater agreement of the two senior doctors’ opinions on whether the patient should have been admitted to ICU or not was estimated by Cohen’s kappa.
RESULTS

TREATMENT DURING CPR

IHCA patients included (n=104) were 34 from Hyvinkää Hospital, 32 from Södersjukhuset, and 38 from Oulu University Hospital. Specific treatment targeted for the primary cause of PEA was given to 19 (18%) patients and non-specific treatment was administered to 85 (82%) patients. Rapid fluid loading, thrombolysis and PCI were the most common specific treatments of the primary cause (Table 3). None of the patients received bicarbonate as a specific treatment and patients receiving it for other indications (n=15) were included in the non-specific treatment group. Patients in treatment of the primary cause group more often had myocardial infarction, a cardiac cause for admission and were treated more often in ICUs and less often in internal wards (Table 4).

Table 3. Specific treatment methods during CPR for reversible causes of CA and number of patients treated accordingly.

<table>
<thead>
<tr>
<th>Primary cause</th>
<th>Specific treatment</th>
<th>Patients, n=104</th>
</tr>
</thead>
<tbody>
<tr>
<td>hypovolemia</td>
<td>rapid fluid loading, surgery</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>hypo-/hyperkalemia</td>
<td>potassium infusion/calcium chloride, sodium bicarbonate, glucose–insulin infusion, dialysis</td>
<td></td>
</tr>
<tr>
<td>hypo-/hypercalcemia</td>
<td>calcium chloride/fluid loading</td>
<td></td>
</tr>
<tr>
<td>hypo-/hypermagnesemia</td>
<td>magnesium sulphate/calcium chloride</td>
<td></td>
</tr>
<tr>
<td>hypoglycemia</td>
<td>glucose</td>
<td></td>
</tr>
<tr>
<td>acidosis</td>
<td>sodium bicarbonate</td>
<td></td>
</tr>
<tr>
<td>hypothermia</td>
<td>re-warming</td>
<td></td>
</tr>
<tr>
<td>pulmonary or coronary thrombosis</td>
<td>thrombolysis</td>
<td>6 (6%)</td>
</tr>
<tr>
<td></td>
<td>percutaneous coronary intervention</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>cardiac tamponade</td>
<td>pericardiocentesis, thoracotomy</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>toxins</td>
<td>non-standard drug therapies, prolonged CPR</td>
<td></td>
</tr>
<tr>
<td>tension pneumothorax</td>
<td>thoracocentesis, thoracotomy</td>
<td></td>
</tr>
</tbody>
</table>
Table 4. Comparison of non-specific treatment group (n=85) and treatment of the primary cause group (n=19), n (%). ns=non-significant.

<table>
<thead>
<tr>
<th></th>
<th>Non-specific treatment group</th>
<th>Treatment of the primary cause group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (IQR)</td>
<td>74 (67–83)</td>
<td>71 (63–76)</td>
<td>ns</td>
</tr>
<tr>
<td>Cardiac reason for admission</td>
<td>17 (20%)</td>
<td>12 (63%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Current myocardial infarction</td>
<td>14 (16%)</td>
<td>8 (42%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Internal ward</td>
<td>35 (41%)</td>
<td>2 (10.5%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Critical care unit</td>
<td>13 (15%)</td>
<td>7 (37%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Survival to ROSC</td>
<td>41 (48%)</td>
<td>12 (63%)</td>
<td>ns</td>
</tr>
<tr>
<td>30-day survival</td>
<td>9 (11%)</td>
<td>6 (32%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

IQR=interquartile range, ROSC= return of spontaneous circulation

Of the potentially reversible conditions preceding PEA, hypoxemia and myocardial infarction were retrospectively estimated to be possible in over half of the patients. Hypothermia, tension pneumothorax, toxins and hypokalemia were estimated to be absent as a cause of PEA in over 90% of the patients. Autopsy diagnosis was available for half of the non-survivors (n=44, 49%): the most common etiologies were acute myocardial infarction (21%), pulmonary edema or heart failure (19%), pulmonary embolism (17%), pneumonia (12%) and aortic rupture or dissection (12%).

Before IHCA, disturbances in vital signs 24h preceding IHCA were documented in 55 patients (53%, 95% CI 43–62%). Blood pressure and heart rate were measured in over 85% of patients, while respiratory rate, oxygen saturation (with and without additional oxygen) and Glasgow Coma Scale were not reported in over 40% of patients.
PATIENT SELECTION TO POST-RESUSCITATION CARE UNITS

During the study (IV) period, 224 adult OHCA patients with PEA were admitted to hospital with sustained ROSC. Patients taken directly to an operation room for surgical intervention (ruptured aortic aneurysm) were excluded (n=3), thus the study population included 221 patients. Most of the patients (n=138, 62.4%) were admitted to Level 2 ICUs for post-resuscitation care, followed by Level 3 ICUs (n=39, 17.6%), ordinary wards (n=28, 12.7%) and Level 1 ICUs (7.2%).

The mean age of the Level 3 ICU group (56.7±14.2 years) was significantly lower compared to other groups: ward patients’ mean age was 13.4 years higher (p<0.01), Level 1 ICU patients’ 18.9 years higher (p<0.01) and Level 2 ICU patients’ 6.8 years higher (p=0.049). In addition, Level 1 ICU patients were on average 12.0 years older than Level 2 ICU patients (p=0.01). Pre-arrest coronary artery disease and cardiac failure diagnoses, as well as pre-arrest performance and CPC class were significantly different between the groups, with patients in the Level 3 ICU group having the fewest pre-arrest diagnoses and best performance (Table 5). The cause of CA also differed between the groups, with Level 3 ICU patients having fewer hypoxic and neurological etiologies. No statistical difference was found between groups in gender distribution, prevalence of other pre-arrest diagnoses (hypertension, diabetes, renal failure, memory impairment/disorder or other brain disease) or resuscitation details (witnessed OHCA, bystander CPR, EMS response time and time to ROSC).

For logistic regression models assessing factors independently affecting the selection of post-resuscitation care unit, patients fully awake at hospital admission (n=10) were excluded. Ward and Level 1 ICUs were compared to Level 2 and 3 ICUs. After adjustment, longer time to ROSC (OR 0.95, 95% CI 0.91–0.996, p=0.03) and advanced age (OR 0.97, 95% CI 0.91–0.996, p=0.03) decreased the admission rate to Level 2 or 3 post-resuscitation care independently, whereas good pre-arrest CPC 1 and CPC 2 independently increased the admission rate to Level 2/3 ICUs (OR 2.69, 95% CI 1.07–6.78, p=0.04 and OR 4.50, 95% CI 1.41–14.35, p=0.01 respectively).

According to the blinded assessment, both physicians estimated that 16 patients (36.4%) admitted to Ward or Level 1 ICUs could have benefited from Level 2/3 intensive care. The two doctors’ opinions differed from each other in the case of 10 (22.7%) patients, which means that they were in moderate agreement (Cohen’s kappa = 0.548).
Table 5. Baseline characteristics with significant difference between the different levels of post-resuscitation care groups, n (%).

<table>
<thead>
<tr>
<th></th>
<th>Ward n=28</th>
<th>Level 1 ICU n=16</th>
<th>Level 2 ICU n=138</th>
<th>Level 3 ICU n=39</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), mean ± SD</td>
<td>70.1 ± 15.2</td>
<td>75.6 ± 7.8</td>
<td>63.5 ± 14.9</td>
<td>56.7 ± 14.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pre-arrest diagnoses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>8 (28.6)</td>
<td>5 (31.3)</td>
<td>29 (21.2)</td>
<td>2 (5.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Heart failure</td>
<td>7 (25.0)</td>
<td>3 (18.8)</td>
<td>16 (11.7)</td>
<td>2 (5.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Pre-arrest performance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>0</td>
<td>7 (25.0)</td>
<td>3 (18.8)</td>
<td>53 (39.0)</td>
<td>25 (64.1)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8 (28.6)</td>
<td>3 (18.8)</td>
<td>37 (27.2)</td>
<td>4 (10.3)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3 (10.7)</td>
<td>0 (0.0)</td>
<td>18 (13.2)</td>
<td>5 (12.8)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>10 (35.7)</td>
<td>10 (62.5)</td>
<td>28 (20.6)</td>
<td>5 (12.8)</td>
<td></td>
</tr>
<tr>
<td>Pre-arrest CPC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1</td>
<td>10 (35.7)</td>
<td>5 (31.3)</td>
<td>69 (50.7)</td>
<td>30 (76.9)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>8 (28.6)</td>
<td>1 (6.3)</td>
<td>41 (30.1)</td>
<td>7 (17.9)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>10 (35.7)</td>
<td>10 (62.5)</td>
<td>26 (19.1)</td>
<td>5 (12.8)</td>
<td></td>
</tr>
<tr>
<td>Cause of CA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.048</td>
</tr>
<tr>
<td>Cardiac</td>
<td>8 (28.6)</td>
<td>6 (37.5)</td>
<td>40 (29.6)</td>
<td>12 (30.8)</td>
<td></td>
</tr>
<tr>
<td>Hypoxia</td>
<td>10 (35.7)</td>
<td>6 (37.5)</td>
<td>36 (26.7)</td>
<td>9 (23.1)</td>
<td></td>
</tr>
<tr>
<td>Intoxication</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>11 (8.1)</td>
<td>5 (12.8)</td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td>4 (14.3)</td>
<td>4 (25.0)</td>
<td>12 (8.9)</td>
<td>1 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (7.1)</td>
<td>0 (0.0)</td>
<td>20 (14.8)</td>
<td>2 (5.1)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (14.3)</td>
<td>0 (0.0)</td>
<td>16 (11.9)</td>
<td>10 (25.6)</td>
<td></td>
</tr>
</tbody>
</table>
ICU=intensive care unit, SD= standard deviation, CPC= cerebral performance category, CA= cardiac arrest, ECOG=Eastern Cooperative Oncology Group (0=fully active, 1=physically strenuous activity restricted, able to do light work, 2=independent on self-care, unable to work, 3=limited self-care, in bed more than 50% of waking hours, 4=completely disabled, confined to bed, 5=dead) (Oken 1982).

Selection criteria in the Nordic ICUs

The questionnaire study to Nordic ICUs (III) revealed different admission criteria to ICUs between countries and hospitals. To the first questionnaire, 96 (51%) Nordic ICUs responded and 84 (46%) to the second one. Fifty-one (59%) ICUs had a predefined protocol, according to which OHCA patients are admitted to the ICU. In an additional analysis combining ICUs in the same hospital, 60.8% of hospitals had at least one ICU with a predefined protocol for OHCA patient admission. A predefined protocol was reported to exist more often in Norway (n=10, 77%) and Denmark (n=16, 76%) than in Sweden (n=17, 49%) or Finland (n=7, 47%), but there was no statistical difference.

Of those ICUs having predefined criteria, 25% stated that ROSC time is a criterion, with maximum acceptable ROSC time varying between 15 to 60 min. Of ICUs with predefined criteria, 27% included initial rhythm as a criterion and half of them accepted only patients with initial VF or VT to ICU treatment; in 13 ICUs (16%), patients with initial PEA or ASY were not admitted to the ICU. Of hospitals, 11 (15.3%) reported that only VF/VT patients are admitted to ICU, while in 61 (84.7%) hospitals at least one ICU also admitted non-shockable rhythm patients. Age was used as a predefined criterion in 16% of the ICUs, with maximum age enabling ICU admission ranging from 65 to 80 years. Patients requiring help in activities of daily life were accepted to the ICU in 70 (89%) responding hospitals.

POST-RESUSCITATION CARE

In Finnish post-resuscitation care units (IV), TTM (n=9, 4.1%) and early CAG (n=7, 3.2%) were very rarely provided and only for Level 3 ICU patients. Seven additional patients, 4 in the Level 2 ICU group and 3 in the Level 3 ICU group, underwent CAG later during their hospital stay. Level 3 ICU patients also had the longest median time on ventilator, 35h (18–67h). Ventilator treatment times differed between the Ward/Level 1 ICU (3h, 0–12h) and Level 2 (20, 6–46) and Level 3 ICU groups (p<0.001 for both), but no difference existed between Level 2 and Level 3 ICU groups (p=0.06).

Regional differences between the Nordic ICUs

In 2012, all OHCA patients were treated with TTM at 33°C in 29 (37%) ICUs and in 28 (40%) hospitals at least one ICU treated all OHCA patients with TTM. TTM was provided significantly more often in Norway compared to Finland and Sweden, p=0.02 and 0.014.
respectively (Table 6). Reasons not to treat a patient with TTM at 33°C included severe co-
morbidities, a non-cardiac cause of OHCA or return of consciousness after resuscitation.
TTM was induced in the pre-hospital setting of 28 (35%) ICUs, in Norway and Finland more
often than Sweden, p=0.001 and p=0.009 respectively (Table 6). In 2014, most ICUs (n=52,
63%) still used TTM at 33°C, but 27 (33%) used TTM at 36°C.

Early CAG with possible PCI was routinely provided for all survivors of OHCA in 34 (39%)
ICUs in 2012, significantly more frequently in Sweden and Norway compared to Finland,
p=0.014 and 0.042 respectively (Table 6). 29 (40%) hospitals provided early CAG in at least
one ICU. In 2014, 23 (28%) ICUs provided routine CAG to all actively treated victims of
OHCA. Most (n=75, 90%) ICUs reported that they had not changed policies regarding CAG
and PCI between 2012 and 2014.

Table 6. Number of hospitals providing pre-hospital induction of TTM, in-hospital TTM or
early CAG for all OHCA survivors in 2012.

<table>
<thead>
<tr>
<th>Country</th>
<th>Pre-hospital TTM</th>
<th>In-hospital TTM</th>
<th>Early CAG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark</td>
<td>6 (27%)</td>
<td>21 (43%)</td>
<td>6 (27%)</td>
</tr>
<tr>
<td>Finland</td>
<td>8 (53%)</td>
<td>3 (20%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Iceland</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>Norway</td>
<td>9 (69%)</td>
<td>9 (69%)</td>
<td>7 (54%)</td>
</tr>
<tr>
<td>Sweden</td>
<td>7 (25%)</td>
<td>4 (14%)</td>
<td>18 (51%)</td>
</tr>
</tbody>
</table>

TTM = targeted temperature management, CAG = coronary angiography, OHCA = out-of-
hospital cardiac arrest

Neuroprognostication

Among Finnish OHCA patients (IV), the decision whether to continue active post-
resuscitation care of a comatose patient was made earlier in the lower treatment intensity
groups (p<0.01); up to 93.5% of patients in Ward or Level 1 ICUs had a prognostic decision
<24h after OHCA (Table 7).
Table 7. Prognostication of comatose survivors of OHCA with PEA according to different levels of post-resuscitation care.

<table>
<thead>
<tr>
<th>Prognostication</th>
<th>All n=221</th>
<th>Ward/Level 1 ICU n=44</th>
<th>Level 2 ICU n=138</th>
<th>Level 3 ICU n=39</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24h</td>
<td>87 (61.7%)</td>
<td>29 (93.5%)</td>
<td>51 (54.8%)</td>
<td>7 (41.2%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>24–72h</td>
<td>36 (25.5%)</td>
<td>2 (6.5%)</td>
<td>26 (28.0%)</td>
<td>8 (47.1%)</td>
<td></td>
</tr>
<tr>
<td>&gt;72h</td>
<td>18 (12.8%)</td>
<td>0</td>
<td>16 (17.2%)</td>
<td>2 (11.8%)</td>
<td></td>
</tr>
</tbody>
</table>

ICU=intensive care unit

According to the questionnaire study, in the Nordic ICUs, prognostic evaluation was only rarely made during the first 24h following OHCA, but mostly (n=38, 49%) >72h after OHCA.

SURVIVAL AND QUALITY OF LIFE

IHCA patients with PEA who received treatment for the primary cause had increased 30-day survival rates compared to patients in the non-specific treatment group (Table 4). Patients who survived 30 days were younger, received appropriate treatment for the primary cause more often and were less frequently treated on general wards. These factors were included in a multivariable logistic regression analysis, in which only age was independently associated with survival: the adjusted odds for 30-day mortality increased 6% (95% CI 1–11%) per year of age. The odds of death within 30 days were 2.5 times higher for non-specifically treated patients and 3.1 times higher for patients treated in wards, but these results did not attain statistical significance.

Of Finnish OHCA patients with PEA, 72 (32.6%) survived to hospital discharge, 62 (28.1%) survived 90 days and 53 (24.0%) survived 1 year after OHCA (IV). No significant difference was found between the groups in 90-day and 1-year survival rates, however, good neurological survival was reported in 37 (17.1%) patients, significantly more often in PEA patients treated in units providing more intensive post-resuscitation care: 11 (28.2%) Level 3 ICU patients, 22 (16.1%) Level 2 ICU patients and 4 (9.8%) Ward/Level 1 ICU patients had CPC 1–2 one year after OHCA (p=0.02) (Table 8).
Table 8. Survival and neurological outcome according to the level of post-resuscitation care, n (%).

<table>
<thead>
<tr>
<th>Survival</th>
<th>All n=221</th>
<th>Ward/Level 1 ICU (n=44)</th>
<th>Level 2 ICU (n=138)</th>
<th>Level 3 ICU (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>62 (28.1)</td>
<td>11 (25.0)</td>
<td>39 (28.3)</td>
<td>12 (30.8)</td>
</tr>
<tr>
<td>1 year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>53 (24.0)</td>
<td>8 (18.2)</td>
<td>33 (23.9)</td>
<td>12 (30.8)</td>
</tr>
<tr>
<td>CPC at 1 year, n=217</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>37 (17.1)</td>
<td>4 (9.8)</td>
<td>22 (16.1)</td>
<td>11 (28.2)</td>
</tr>
<tr>
<td>3–4</td>
<td>12 (5.5)</td>
<td>1 (2.4)</td>
<td>10 (7.3)</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>5</td>
<td>168 (77.4)</td>
<td>36 (87.8)</td>
<td>105 (76.6)</td>
<td>27 (69.2)</td>
</tr>
</tbody>
</table>

ICU= intensive care unit, CPC= cerebral performance category

Level of care (Ward/Level 1 or Level 2 or Level 3) did not independently affect 1-year survival or neurological outcome after adjustment for baseline characteristics and CPR details. Independent predictors for 1-year mortality were long time to ROSC, neurological reason for OHCA (compared to cardiac reason) and poor pre-arrest performance. For poor neurological outcome or death, advanced age and long time to ROSC were independent predictors (Table 9).

Table 9. Independent predictors of 1-year mortality and poor CPC at 1-year (n=221).

<table>
<thead>
<tr>
<th>1-year mortality</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROSC (min)</td>
<td>1.04 (1.02–1.06)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cause of CA (neurologic vs cardiac)</td>
<td>1.92 (1.19–3.08)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Performance class (3–4 vs 1)</td>
<td>1.50 (1.04–2.20)</td>
<td>0.03</td>
</tr>
<tr>
<td>CPC 3–5 at 1 year</td>
<td>OR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Age (y)</td>
<td>1.05 (1.02–1.08)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ROSC (min)</td>
<td>1.17 (1.10–1.26)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

CPC= cerebral performance category, HR=hazard ratio, CI=confidence interval, ROSC= return of spontaneous circulation, CA= cardiac arrest, OR= odds ratio
Long-term survival and quality of life

For the long-term survival study (I), 99 OHCA patients with PEA were included. Their mean age was 69 years. Two-fifths of the patients (41%) achieved ROSC, 10% were discharged from hospital and alive after 30 days, and 7% were alive one year after OHCA. One year after resuscitation, five of the seven survivors had the same CPC class as before OHCA. Four patients were categorized into CPC classes 1–2 and three to CPC 3–4. Five of the six patients alive 5 years after OHCA responded to the 15-D questionnaire of health-associated quality of life. Patients assessed 65 of 75 (87%) estimated properties as normal or only mildly impaired. All patients reported normal or only mildly impaired function in seeing, hearing, sleeping, eating, speech and in urination or defecation. Levels of energy, distress and depression were also estimated to remain normal or only mildly worsened. Patients with pre-arrest CPC 2–3 reported moderate impairment in functional level, a need for help or total lack of capability to perform independently occupationally or in leisure activities, psychological functions, mobility and sexual life.
DISCUSSION

TREATMENT DURING CPR

Of IHCA patients studied for this thesis, in 18% a specific reason, other than hypoxia, was found and treated during CPR. To our knowledge, the prevalence of specific treatment attempts targeted for cause of CA during CPR has not been reported earlier. A recent North American study reported a 44% specific treatment rate for those PEA patients who had organized cardiac activity in ultrasound (Gaspari 2017).

Myocardial infarction and hypoxia were the most common reasons for IHCA with PEA in our study, similar to reports from other studies (Bergum 2015, Beun 2015). According to autopsy data in our study, over half of the non-surviving patients had a diagnosis for PEA which could possibly be reversible in some patients (for example, myocardial infarction), but based on this retrospective analysis, we cannot extrapolate which of the patients had a truly reversible cause.

The relatively low cause-specific treatment rate in our patient population is partly explained by the inclusion of hypoxia patients in the non-specific treatment group. In addition, none of the patients with possible hyperkalemia (13%) in our study received treatment for it and were included in the non-specific treatment group, but sodium bicarbonate was used in 15 patients with an indication that was unclearly marked in patient records. Some of the sodium bicarbonate could have been given with the assumption of hyperkalemia. This low rate of hyperkalemia treatment is in contrast with results from Wang et al. (2016), who reported that 21% of IHCA patients had biochemistry-proven hyperkalemia during CPR and 85% of them received specific treatment during CPR.

Other factors explaining the relatively low cause-specific treatment rate could be that the cause for CA may not have been identified or a treatment attempt during resuscitation could have been considered as futile. In a Norwegian study, the correct cause for IHCA was identified in two-thirds of patients, but how often patients received a specific treatment for the underlying cause was not reported (Bergum 2015). The utility of the 4Hs & 4Ts algorithm in identifying CA cause has also been questioned lately: Beun et al. (2015) reported that only 55% of PEA patients had a cause for CA that belong to these 4Hs or 4Ts. Alternative algorithms, such as 3Hs & 3Ts and 6Hs & 4Ts have been suggested (Beun 2015, Desbiens 2008).

Over half of the patients in this study had documented disturbances in vital signs 24h before IHCA. In addition, a notable deficiency appeared in registering vital functions. These findings are in line with previous studies: abnormal observations have been reported in 47–80% of all-rhythm IHCA patients (Peberdy 2007, Skrifvars 2006). These patients have reduced survival rates (Skrifvars 2006). Studies have indicated that disturbances in vital signs do not lead to any action in 48% of patients and that even 62% of IHCA could be avoidable (Hodgetts 2002). ERC guidelines recommend forming and documenting an individual plan for each patient on how to monitor their vital signs (Soar 2015). Additionally, educating staff to recognize and treat a deteriorating patient is emphasized (Soar 2015). Scoring systems for recognition of abnormal vital signs have been developed and rapid response teams or medical emergency teams have reduced IHCAs (Bellomo 2003, Bellomo 2004).
OHCA patients with PEA, who were selected for more intensive care, were younger, had a lower incidence of coronary artery disease and heart failure, had favorable pre-arrest CPC and performance categories and were more likely living at home independently. A favorable pre-arrest CPC category, shorter ROSC time and younger age were independent factors associated with Level 2 or 3 ICU admission in this study (IV). According to our questionnaire study, around 60% of the ICUs in the Nordic countries had pre-set criteria defining which OHCA patients are admitted to the ICU. The criteria were highly variable regarding the effect of the age of the patient, the initial rhythm, and the delay to ROSC.

To our knowledge, units providing post-resuscitation care for PEA patients or factors associated with admission to different levels of post-resuscitation care has not been described earlier. These results support the theory that patients considered likely to survive are more likely admitted to a higher level of intensive care, since all independent predictors have been reported to associate with increased survival (Deasy 2011, Reynolds 2013). Nursing home residents have been reported to have worse survival rates (Deasy 2011), which is in line with our findings on the effect of CPC class on Level 2 or 3 ICU admission. Worse outcomes have been reported in patients with pre-arrest diagnoses of myocardial infarction, congestive heart failure, hypertension and diabetes, (Fabbri 2006), but that data were not adjusted for CA factors. Advanced age is associated with worse outcomes in CA patients more than 65 years old (Deasy 2011), but there is a wide variation in the effect of age on outcomes, with some studies showing no association between the two (Grimaldi 2014). Resuscitation details other than short time to ROSC were not predictive of ICU admission in our Finnish study population, even though witnessed CA (Abrams 2013, Avalli 2014, Soholm 2015), bystander CPR (Avalli 2014, Soholm 2015) and short first response time (Soholm 2015) are known to associate with improved prognosis at the population level.

Also in the questionnaire study, time to ROSC was used as a criterion in whether to admit a patient to ICU after OHCA. 15% of hospitals defined a non-shockable initial rhythm as a criterion not to admit a patient to ICU. Even though a non-shockable initial rhythm is associated with worse survival than a shockable initial rhythm (Avalli 2014, Soholm 2015), it does not indicate complete futility, since 5.9–15.7% of PEA patients survive to hospital discharge (Andrew 2014, Bergum 2016, Béun 2015, Hauck 2015, Kudenchuk 2012, Teodorescu 2012). There is a risk that an assumed dismal outcome becomes a self-fulfilling prophecy when patients resuscitated from non-shockable rhythms are not admitted to ICUs because of their initial rhythm (Søreide 2016). However, as in our level of post-resuscitation study, large hospitals might have advanced high dependency units (which are not called ICUs) treating resuscitated patients with invasive methods and therefore not admitting a patient to ICU does not have to mean discontinuation of effective treatment.

The impact of the different ICU admission criteria on survival is unknown. According to the opinion of the blinded physicians in this study, more than one-third of the patients treated on Wards or Level 1 ICUs would possibly have benefited from more intensive care at Level 2–3 ICUs. Moderate agreement between the two physicians indicates that patient selection is an ambiguous process: information about the patient’s pre-arrest condition is often limited and predicting the futility of the treatment is very difficult at the time of hospital admission. In addition, limited Level 2–3 ICU resources may also influence this decision. Without predefined criteria, the decision to admit the patient to the ICU is likely to be physician-
dependent and made on a patient-by-patient basis. A patient-by-patient assessment allows evaluation of all factors associated with the OHCA, prediction of outcome and the indications for intensive care. However, individual variability in experience and opinions of the treating physician may lead to alternating patient selection. An evidence-based predefined criteria may prevent individual variability, but may also exclude those patients that could survive but do not fit these criteria. Scoring systems to predict OHCA patients’ outcome and therefore advocate for ICU treatment are not commonly used, although some prediction tools have been created (Abrams 2013, Aschauer 2014, Fridman 2007). Thus, implementing a reliable and tested scoring system could help clinicians in decision making.

POST-RESUSCITATION CARE

Use of TTM was very rare (4.1%) among OHCA patients with PEA (IV). None of the OHCA patients with PEA who were treated in Level 1 or 2 ICUs or at ordinary wards received this treatment. In the questionnaire study (III), utilization of TTM in Nordic ICUs on all OHCA patients varied between 30–69%; the lowest rate was reported in Finland and the highest in Norway. Low implementation rates and wide variation between countries is unexpected, since countries, in principle, follow the same ERC guidelines on post-resuscitation care (Nolan 2015). However, similar variation in the use of TTM has been reported: variation from 25% to 88% was reported in a Canadian study (Worthington 2017) and variation from 0% to 83% in a North American study (Callaway 2014). European studies have reported TTM rates of 41–76% (Blom 2014, Linder 2013, Strømsøe 2015), of which a Swedish study reported a TTM rate of 41% and a Norwegian study a rate of 70%. These are in line with our findings in the questionnaire study (III). The implementation rates have increased from the 2000s to 2010s (Blom 2014, Strømsøe 2015). Lower utilization of TTM has been reported with older age and female gender (Linder 2013). The initial rhythm seems to greatly affect the decision to start TTM: in a UK study, 87% of ICUs reported usually cooling patients resuscitated from VF/VT, but only 30% usually cool patients resuscitated from PEA or ASY (Binks 2010). In a North American study, 54% of VF/VT patients were treated with TTM, compared to 28% of PEA patients (Callaway 2014). Further, up to 39% of UK ICUs reported they never cool patients resuscitated from PEA or ASY (Binks 2010), which is in contrast with ERC guidelines promoting TTM also in cases of a non-shockable initial rhythm when active care is chosen (Nolan 2015). These results support our results, as PEA patients are less often treated with TTM, but still the TTM rate for PEA patients in our study was very low.

Only 3.2% of Level 3 ICU–treated PEA patients (and none of the patients who were treated elsewhere) underwent early CAG. However, CAG is a specific treatment for ACS and this study did not define which of the PEA patients had ACS and thereby had the potential to benefit from this treatment. Of Nordic ICUs, 13–54% reported providing CAG routinely for all survivors of OHCA. Rates of early CAG were lowest in Finland and highest in Norway. In other studies, variation in rates of early CAG have been reported. 10–40% of OHCA patients surviving to hospital admission have been reported to undergo early CAG with possible PCI in Europe (Beun 2015, Blom 2014, Strømsøe 2015) and 0–75% of patients in North America (Callaway 2014). 7–16% of PEA or non-shockable rhythm patients have been reported to undergo early CAG in North America, whereas 37–58% of VF/VT patients have been reported to receive early CAG (Callaway 2014, Wilson 2017).
According to these results, it seems that there is a lot of variation in Nordic post-resuscitation care and current guidelines are not always followed. Not admitting a patient to a Level 3 ICU has far-reaching consequences, since these patients are usually not treated with TTM or early CAG. Even when admitted to a Level 3 ICU, treatment modalities vary. The heterogeneity of provided post-resuscitation care partly reflects the patient population and inconclusive evidence regarding optimal post-resuscitation care. RCT-based evidence on the efficacy of TTM in non-shockable OHCA patients is still lacking (Girotra 2015), but up to 2.9 times increased odds for survival with good neurological outcome, associated with TTM, has been reported in observational studies (Sung 2015, Testori 2011). In the questionnaire study (III), most of the responding ICUs (63%) provided TTM at 33°C in 2014, reflecting the discussion on the evidence base of TTM at 36°C. In addition, data about the association of early CAG+PCI and better outcomes among OHCA patients comes from observational studies (Nikolaou 2015). Since the debate regarding the actual benefit of early CAG is ongoing (Bro-Jeppesen 2012), no significant changes to CAG policies were found in our follow-up survey.

However, international guidelines promote TTM and early CAG in post-resuscitation care (Noc 2014, Nolan 2015). It seems that treatment modalities are implemented more locally than according to existing international guidelines. Changing clinical practice and ensuring that guidelines are translated into high quality care is often demanding (Søreide 2013). Toma et al. (2010) reported lack of familiarity and availability of concrete therapeutic hypothermia protocols as the most frequent barriers for implementation. In addition, availability of equipment, costs, high workload demands for nurses, pessimistic outcome expectancy and choosing palliative care were reported to prevent the use of TTM (Blom 2014, Frochlich 2013, Toma 2010). In the future, special attention should be paid to truly extend the implementation of best practices throughout the complete chain of survival. One suggested solution is integrated cardiac arrest centers with the required expertise and equipment (Søreide 2016).

NEUROPROGNOSTICATION

Among the Finnish OHCA patients with PEA, the prognostic decision of a comatose patient was made earlier in the lower treatment intensity groups, <24h after OHCA in 93.5% of Ward or Level 1 ICU–treated patients (IV). In the questionnaire study (III), only 4% of the Nordic ICUs reported <24h prognostication, since prognosis was mostly reported to take place >72h after OHCA.

Prognostic decisions were made early, even though there are no indicators that reliably predict poor outcome <24 h after CA. Early prognostication practices have been reported in other studies as well: documentation of a poor prognosis occurred in 57% of OHCA patients during TTM or shortly after it, even if 64% of these patients were still receiving sedatives or paralytics (Perman 2012). 44% of intensivists reported that no precise timing for prognostication was used, and timing was decided based on individual patient data (Friberg 2015). Only 22% of ICUs had a protocol for prognostication (Friberg 2015). Elmer et al. (2016) reported that life-sustaining treatment was withheld from 22% of patients <72h after OHCA while adjusted analysis predicted that 26% of these patients could have survived, 16% with good neurological outcome.

However, before their CA, 28.1% of the study patients (IV) needed help in activities of daily life or lived in nursing homes and 5 had a do not attempt resuscitation (DNAR) order, of
which pre-hospital paramedics and physicians were not aware of. With attempted resuscitation, ROSC was achieved in patients with a severe medical history and high dependency on others, in whom a DNAR decision probably should have been made before OHCA. Still, for some patients, it is possible that the prognostic decision leading to withdrawal of life-sustaining treatment was made too early, based on unreliable indicators of poor outcome.

**SURVIVAL AND QUALITY OF LIFE**

Of IHCA patients with PEA studied for this thesis, patients who received treatment of the primary cause during CPR had increased 30-day survival rates, as well as young patients and patients whose CA occurred elsewhere than on general wards. It seems that younger patients are more often treated in critical care units, more often receive treatment of the primary cause and their 30-day survival rates are higher. However, age turned out to be the only individual prognostic factor after adjustment. Reported survival rates to hospital discharge for IHCA patients in PEA are 11.4–13% (Bergum 2015, Nolan 2014), indicating patients receiving treatment for the primary cause in our material had clearly preferable outcomes, with 32% surviving to 30 days. Our population was possibly too small to show statistically significant benefits of the appropriate treatment during CPR.

Recently, Norwegians have reported that if the cause of IHCA was recognized—regardless of whether the cause was treated or not—1-hour survival increased 29% and survival to hospital discharge increased 19% (Bergum 2015). The largest difference was found in patients with non-cardiac causes and non-shockable initial rhythms, whose 1-hour survival increased 49% and survival to hospital discharge increased 28% (Bergum 2015). In addition, case reports and studies focusing on treatment of a single reversible cause have been published frequently with promising results (Alfonzo 2006, Bonnemeier 2011, Gaspari 2016, Li 2006, Sharifi 2016, Wang 2016). In the REASON study, OHCA patients in PEA with organized cardiac activity were more likely to survive to ROSC if they received continuous adrenergic agents as special treatment (91% versus 55%), but only 4.5% of these specifically treated patients survived to hospital discharge (Gaspari 2017). Patients with pericardial fluid treated with pericardiosentesis have been reported to have increased survival rates to hospital discharge (Gaspari 2016).

Survival rates of OHCA patients in our study are encouraging: 32.6% of patients admitted to hospital survived to hospital discharge and 24% survived 1 year, 17.1% with good neurology. These figures are high compared to PEA patients reported survival of 5.9–15.7% to hospital discharge (Andrew 2014, Bergum 2016, Beun 2015, Hauck 2015, Kudenchuk 2012, Teodorescu 2012) and good neurological survival of 6.5% (Hauck 2015). Our material was collected from areas with physician-staffed EMS and pre-hospital DNAR protocols, which might partly explain the high survival rates. Survival with good neurology increased significantly with more intensive levels of care, but level of care was not independently associated with outcome. There is the possibility that the study population was too small to show association with the level of care and outcome. Some patients with a short time to ROSC could have been admitted to wards or Level 1 care because they had regained consciousness at hospital arrival, which could conflict the results. However, there were only 10 patients awake at hospital admission. On the other hand, the effect of intensive care on
survival has been questioned in the elderly general hospital patient population: a recently published multicenter, cluster-randomized clinical trial showed that among critically ill elderly patients (age over 75 years), promotion of ICU admission did not reduce 6-month mortality or improve functional status or physical quality of life 6 months after (Guidet 2017). In our population, the independent predictors of good outcome (young age, short time to ROSC, cardiac cause for CA and good pre-arrest performance) have also been reported to improve outcome in earlier studies (Deasy 2011, Reynolds 2013, Hiltunen 2012, Soholm 2015).

Long-term survival and quality of life

In our earlier material collected for long-time survival assessment, 10% of OHCA patients with PEA survived to hospital discharge, 6% survived 5 years and 1-year after resuscitation 4% had good neurological outcome. These results are in line with other studies: survival rates of 5.9–15.7% to hospital discharge have been reported for OHCA patients with PEA (Andrew 2014, Bergum 2016, Beun 2015, Hauck 2015, Kudenchuk 2012, Teodorescu 2012). In the Finnish FinnRESUSCI Prehospital study, 4.6% of OHCA patients with a non-shockable rhythm were alive 1-year after (Hiltunen 2010), compared to 7% of PEA patients in our study. The slightly higher survival rate in our earlier study could be explained by the fact that our material included only PEA patients (FinnRESUSCI also included ASY patients) and our material included patients with presumed cardiac cause from three urban areas. The percentage of good neurological survival is also in line with other studies: Holmgren et al. (2010) reported that 74% of OHCA PEA patients have good neurological outcome at hospital discharge, while in our study 71% of 1-year survivors had the same CPC as before OHCA. Regarding all patients to whom resuscitation was attempted, 3% of non-shockable rhythm patients have been reported to survive with good neurological outcome (Andersen 2015), while in our material 4% survived with good neurology.

According to the 15-D questionnaire, long-term survivors in our study also seem to have recovered quite well, have a good quality of life and some of them are even able to work. 87% of assessed properties were estimated to be normal or only mildly impaired. However, only five patients answered the questionnaire and therefore further conclusions cannot be drawn based on these results. Quality of life after CA is generally reported to be acceptable or good, even similar in comparison with age- and sex-adjusted population norms (Elliott 2011, Smith 2015, Tiainen 2015). In a Dutch study including 220 OHCA survivors, 93% gave their quality of life a value of 6/10 or more (Beesems 2014). Lack of a sensitive standardized tool to evaluate CA patients' quality of life in detail makes comparison between studies difficult since multiple different questionnaires and research methods are being used at the moment. Reporting CPC is recommended in Utstein guidelines and is probably the most commonly used parameter, but CPC is a rough scale and not designed to describe mild cognitive, emotional or behavioral defects, which might affect a patient's daily life markedly. Standardized quality of life measurements, such as the EQ-5D or SF-12 (12-Item Short Form Health Survey) and patient-reported outcome measures (outcomes selected by patients as being important) are recommended as supplemental information in Utstein guidelines (Perkins 2015). Further research is required to determine the optimal outcome assessment tool and the appropriate time to assess survivors of OHCA (Smith 2014).
LIMITATIONS

Data collection for studies included in this thesis was retrospective.

Treatment during CPR

The main limitation of the study focusing on treatment of the primary cause of IHCA was relatively small in sample size. Study data comes from medical record markings, which may lack some essential information and have led physicians estimating whether the primary cause was treated or not to false conclusions. Autopsy reports were also used for estimation of cause of IHCA, but only half of the non-survivors had autopsy reports available. Vital signs were considered to be measured only if those were documented in medical records and probably some measurements were left unrecorded. Hypoxia, which is a common reversible cause of PEA, does not have a specific treatment that differs from conventional CPR and these patients were included in the non-specific treatment group, which might reduce the percentage of patients receiving treatment for the primary cause.

Patient selection to post-resuscitation care units and post-resuscitation treatment

Patients in study IV were resuscitated and treated in Southern Finland in and around the capital area. Results cannot be generalized to all of Finland, despite hospitals following the same international guidelines; ICU and high dependency unit selection criteria might vary between different regions and hospitals due to regional policies and varying ICU capacity. Since data was collected retrospectively, researchers estimated patients' performance and CPC status according to patient records, which could lead to false evaluation. In addition, there were only a small number of patients in some groups.

The main limitation of the questionnaire study is the low response rates: 51% for the first questionnaire and 46% for the second one. In addition, to some questions the response rate was 61%, meaning only 31% of ICUs responded. It is possible that ICUs with a standardized post-resuscitation protocol for OHCA patients were more willing to respond than those without, which might affect study results. However, similar response rates are generally reported in online questionnaires. Furthermore, even if a response rate of 100% would have been achieved, the content of the responses would not have reduced the range of response variability and thus the differences in admission and treatment protocols. Opinions of the individual responder could also affect responses, but the questions of the survey had been directed at the general clinical conduct of ICUs - not at individual physicians. It is also possible that different respondents interpreted questions differently.

Long-term survival and quality of life

Study data was not collected according to the criteria set in the Utstein guidelines (Perkins 2015) and therefore the incidence of OHCA or PEA as the initial rhythm, survival per 100,000 per year cannot be accurately presented. Patients included represent a consecutive subgroup of OHCA patients treated by three distinct systems. Some patients may have been excluded from the study since EMS personnel may have forgotten to fill-in the documentation form after CPR or the documentation may have been lost during the tracking process. In
addition, EMS personnel may have been more willing to fill-in the study form after successful CPR, which could affect the outcome. The number of interviewed survivors was small, but the focus was not to compare but rather to assess the quality of life. CPC classification is commonly used to evaluate neurological survival after OHCA, but it is a rough scale and neuropsychological tests would provide more detailed information.
CONCLUSIONS

A specific reason, other than hypoxia, was found and treated during CPR in one-fifth of the in-hospital PEA patients. Patients receiving specific treatment of the primary cause were more likely to be alive 30 days after IHCA, but received specific causal treatment was not an independent predictor for the outcome (II).

OHCA patients with PEA were usually admitted to Level 2 ICUs for post-resuscitation care. Increasing age and ROSC decreased, whereas good pre-arrest CPC increased, the likelihood of admission to higher levels of post-resuscitation care (IV). Half of the Nordic ICUs had predefined criteria of which OHCA patients to admit to ICU. These criteria were highly variable between countries and hospitals (III).

OHCA patients with PEA who were not admitted to Level 3 ICUs did not receive TTM or early CAG and were less likely to survive with good neurological outcome (IV). Post-resuscitation care was not provided in a uniform fashion between the Nordic ICUs. Use of TTM for all actively treated OHCA victims varied between 20–69% and use of early CAG varied between 13–54% among countries. Norwegians provided these treatments most actively and Finnish most rarely. Despite international guidelines promoting TTM and early CAG, the implementation seems to vary locally, partly because of inconclusive evidence of post-resuscitation modalities. A more uniform approach to optimal post-resuscitation care should be sought in the Nordic countries, and special attention should be paid to truly translate guidelines into clinical practice.

Early prognostication of OHCA patients' outcomes and possible withdrawal of life-sustaining treatment is common, especially among comatose PEA patients treated at Wards or Level 1 ICUs. Since there are no reliable early predictors of outcome, early prognostication carries a risk that potential survivors' life-sustaining treatment is withheld too early.

Overall, the percentage of PEA as the initial rhythm is increasing, and prognosis of this patient group is not as dismal as generally considered. Of all IHCA patients included in this thesis, 14% survived 30 days. Of PEA patients whose OHCA occurred during this decade, up to 33% survived to hospital discharge. Even better survival rates were documented when the primary cause was treated or the patient was treated in Level 2–3 ICUs. The documentation of moderately favorable chances for good outcomes among PEA patients might encourage causal treatment attempts during CPR and receiving hospitals to use more intensive treatment options, such as Level 2–3 intensive care, TTM and early CAG.
FUTURE PERSPECTIVES

In previous decades, resuscitation science has mainly focused – with good results – on improving the shockable rhythm patients' chain of survival. However, since PEA is the most common initial rhythm in IHCA and its percentage in OHCA is increasing (Jacobs 2011, Kudenchuk 2012, Mader 2012, Teodorescu 2012), future focus in resuscitation studies may switch to non-shockable rhythms.

Survival rates of patients in initial PEA are often reported together with patients in ASY. Considering that ASY has markedly worse prognosis than PEA (Andrew 2014, Jacobs 2011, Kudenchuk 2012, Mader 2012, Teodorescu 2012), this gives the wrong assumption of PEA patients' dismal prognosis. In addition, PEA patients are a highly heterogeneous group of patients, in terms of etiology, ECG findings, hemodynamic state and survival. PEA comprises physiological states from deep shock (pseudo-PEA) to cardiac standstill with minor, end-stage electrical activity (true-PEA). These two hemodynamic groups also differ in survival rates, with true-PEA patients’ chances to survive clearly being lower (Blyth 2012, Chardoli 2012, Cureton 2012). This observed heterogeneity makes it difficult to draw conclusions on this patient group. Multicenter studies would be needed to obtain a study population large enough to divide patients into subgroups (according to etiology of CA, ECG findings or pseudo-/true-PEA) to obtain precise information on similar PEA patients’ treatment and prognosis.

Current guidelines promote utilization of the 4Hs and 4Ts algorithm, but in clinical practice, treatment attempts for reversible causes remain low. The functionality of the 4Hs and 4Ts algorithm to find reversible causes has been questioned and new mnemonics or treatment protocols have been suggested (Beun 2015, Desbiens 2008). Desbiens (2008) suggested the 3 and 3 rule, which divides PEA patients into three categories: severe hypovolemia, obstruction to circulation and pump failure. Obstruction to circulation is again divided into three sections: tension pneumothorax, cardiac tamponade and massive pulmonary embolus. Benefits of this rule are that it is logical and easier to remember. Beun (2015) suggested the 6Hs and 4Ts algorithm, which adds two Hs: hemorrhage-intracerebral and heart disease-other. This suggestion was based in their finding that 7% of PEA patients have intracranial hemorrhage and 8% other cardiac cause than thrombosis. In addition, Littmann et al. (2014) created an algorithm based on the width of the QRS complex. A narrow QRS is assumed to present because of mechanical obstruction (cardiac tamponade, tension pneumothorax, pulmonary embolism or mechanical hyperinflation), a wide QRS because of a metabolic problem (severe hyperkalemia or sodium-channel blocker toxicity) (Littmann 2014). However, these algorithms are not validated in clinical practice, but alternative approaches could be beneficial to improve identification and treatment of reversible causes.

New methods in post-resuscitation care might improve outcomes in the future. In an RCT, inhaled xenon combined with TTM at 33°C was shown to diminish white matter damage in OHCA patients compared to similar patients treated with TTM at 33°C only (Laitio 2016). Xenon may also provide a protective effect against myocardial injury, since patients receiving inhaled xenon had lower values of the myocardial damage marker troponin-T during TTM at 33°C (Arola 2013, 2017). However, no significant difference in neurological outcomes and mortality 6 months after OHCA has been reported in the xenon group (Laitio 2016).

Other suggested aspects to improve PEA patients’ chances to survive are identification of high-risk patients, increased public training of bystander CPR, for example in schools, and utilization of mobile technology to recruit nearby CPR-trained citizens (Hollenberg 2013).
New techniques, such as real-time monitoring of regional cerebral oxygen saturation with near-infrared spectroscopy might provide information on the effectiveness of chest compressions (Nolan 2014). ECLS could increase survival in carefully selected patients not responding to standard ALS or it may facilitate interventions, such as CAG±PCI or pulmonary thrombectomy. ECLS has been used for both OHCA and IHCA patients (Reynolds 2013). An association with increased survival has been reported in selected patients in an observational study (Tanno 2008), but data from RCTs is lacking (Randhawa 2015). Use of this treatment will likely increase in the future (Hollenberg 2013, Reynolds 2013). In post-resuscitation care, survival benefit could be obtained from determining which patients benefit from immediate CAG, improving cooling techniques and using a multimodal approach for prognostication (Hollenberg 2013, Nolan 2015). Special cardiac arrest centers have also been suggested to unify post-resuscitation treatment practices (Søreide 2015).
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REFERENCES


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Li X, Fu QL, Jing XL, Li YJ, Zhan H, Ma ZF, Liao XX. A meta-analysis of cardiopulmonary resuscitation with and without the administration of thrombolytic agents. Resuscitation 70: 31-6, 2006.


Nichol G, Aufferheide TP, Eigel B, Neumar RW, Lurie KG, Bufalino VJ, Callaway CW, Menon V, Bass RR, Abella BS, Sayre M, Dougherty CM, Racht EM, Kleinman ME,


APPENDIX 1. Study form for treatment of the primary cause study (II).

Patient identification number:

1. Demographic information
   Date of birth  dd/mm/yyyy  □ Not available
   Gender
     □ Male  □ Not available
     □ Female
   Date of admission  □ Not available
   Time of admission, if arrest within 24 hours hh:mm  □ Not available
   Underlying diseases/diagnoses
     Heart failure  □ Yes  □ No  □ Not available
     EF %  □ Not available
     Diabetes  □ Yes  □ No  □ Not available
     Previous MI  □ Yes  □ No  □ Not available
     Current MI  □ Yes  □ No  □ Not available
     Respiratory failure  □ Yes  □ No  □ Not available
     Previous stroke  □ Yes  □ No  □ Not available
     Current stroke  □ Yes  □ No  □ Not available
     Serum creatine mmol/l  □ Not available
     Cancer  □ Yes  □ No  □ Not available
     -> if yes, metastasis?  □ Yes  □ No  □ Not available
     Other diagnoses  □ Yes, specify  □ No  □ Not available
   Cause of admission  □ Not available
   Admission through emergency room  □ Yes  □ No  □ Not available
   DNAR-order
     □ Yes, dated (dd/mm/yyyy):  □ Not available
     □ No
### 2. Arrest and outcome variables

| **Date** | dd/mm/yyyy | □ Not available |
| **Time** | hh:mm | □ Not available |
| **Place** |  | □ Not available |
| □ Emergency room |  |  |
| □ CCU |  |  |
| □ Ward, internal medicine |  |  |
| □ Ward, neurology |  |  |
| □ Ward, surgical |  |  |
| □ Ward, orthopaedics |  |  |
| □ Ward, other, specify: |  |  |
| □ ICU |  |  |
| □ Operating / recovery room |  |  |
| □ Department of radiology |  |  |
| □ Public areas |  |  |
| □ Other, specify: |  |  |
| **Witnessed** |  | □ Not available |
| □ Yes |  |  |
| □ No -> seen alive (hh:mm): |  |  |
| **Cardiac arrest team response to the patient** |  | □ Not available |
| □ Yes -> time (hh:mm): |  |  |
| □ No |  |  |
| **VF as secondary rhythm** |  | □ Not available |
| □ Yes -> time (hh:mm): |  |  |
| □ No |  |  |
| **Number of defibrillation shocks** |  | □ Not available |
| **Total doses of drugs** |  | □ Not available |
| Adrenalin (mg): |  |  |
| Atropin (mg): |  |  |
| Amiodarone (mg): |  |  |
| Lidokaine (mg): |  |  |
| Sodium bicarbonate (mEq): |  |  |
| Other, specify: |  |  |
| **ROSC** |  | □ Not available |
| □ Yes -> time (hh:mm): |  |  |
| □ No -> time of ceasing a resuscitation attempt (hh:mm): |  |  |
| **Discharged alive** |  | □ Not available |
| □ Yes, to home -> date (dd/mm/yyyy): |  |  |
| □ Yes, to other hospital -> date (dd/mm/yyyy): |  |  |
| □ No |  |  |
| **Alive after 30 days** |  | □ Not available |
| □ Yes |  |  |
| □ No |  |  |
| **Autopsy** |  | □ Not available |
| □ Yes -> date (dd/mm/yyyy): cause of death: |  |  |
| □ No |  |  |
3. Latest vital signs before arrest

<table>
<thead>
<tr>
<th>Measurement</th>
<th>dd/mm/yyyy, leave empty if within 24 h</th>
<th>hh:mm</th>
<th>Not available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate</td>
<td></td>
<td></td>
<td>Not available</td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
<td></td>
<td>Not available</td>
</tr>
<tr>
<td>Systolic BP</td>
<td></td>
<td></td>
<td>Not available</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td></td>
<td></td>
<td>Not available</td>
</tr>
<tr>
<td>SpO2 (O2)</td>
<td></td>
<td></td>
<td>Not available</td>
</tr>
<tr>
<td>SpO2 (air)</td>
<td></td>
<td></td>
<td>Not available</td>
</tr>
<tr>
<td>GCS or AVPU</td>
<td></td>
<td></td>
<td>Not available</td>
</tr>
<tr>
<td>Temp</td>
<td></td>
<td></td>
<td>Not available</td>
</tr>
</tbody>
</table>

4. PEA when first recorded

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Not available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate</td>
<td>Not available</td>
</tr>
<tr>
<td>Complex width</td>
<td>Not available</td>
</tr>
<tr>
<td>Rhythm</td>
<td>Not available</td>
</tr>
<tr>
<td>Q-waves</td>
<td>Not available</td>
</tr>
<tr>
<td>ST-segment</td>
<td>Not available</td>
</tr>
</tbody>
</table>

- Supraventricular
- Ventricular
- Neutral
- Elevation: ____ mm
- Depression: ____ mm
- Cannot be determined
5. Potentially reversible cause of cardiac arrest

<table>
<thead>
<tr>
<th>Condition</th>
<th>Confirmation / exclusion</th>
<th>Aetiology, related diagnoses</th>
<th>Cause focused treatment given during resuscitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemia</td>
<td>□ Confirmed before, during or after resuscitation attempt</td>
<td>□ Treated during resuscitation attempt</td>
<td>□ Suspected based on the patient records</td>
</tr>
<tr>
<td></td>
<td>□ Excluded during resuscitation attempt or based patient records</td>
<td>□ Cannot be evaluated on base of patient records</td>
<td>□ Potential considering the clinical diagnosis of the patient</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>□ Confirmed before, during or after resuscitation attempt</td>
<td>□ Treated during resuscitation attempt</td>
<td>□ Suspected based on the patient records</td>
</tr>
<tr>
<td></td>
<td>□ Excluded during resuscitation attempt or based patient records</td>
<td>□ Cannot be evaluated on base of patient records</td>
<td>□ Potential considering the clinical diagnosis of the patient</td>
</tr>
<tr>
<td>Acidosis</td>
<td>□ Confirmed before, during or after resuscitation attempt</td>
<td>□ Treated during resuscitation attempt</td>
<td>□ Suspected based on the patient records</td>
</tr>
<tr>
<td></td>
<td>□ Excluded during resuscitation attempt or based patient records</td>
<td>□ Cannot be evaluated on base of patient records</td>
<td>□ Potential considering the clinical diagnosis of the patient</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>□ Confirmed before, during or after resuscitation attempt</td>
<td>□ Treated during resuscitation attempt</td>
<td>□ Suspected based on the patient records</td>
</tr>
<tr>
<td></td>
<td>□ Excluded during resuscitation attempt or based patient records</td>
<td>□ Cannot be evaluated on base of patient records</td>
<td>□ Potential considering the clinical diagnosis of the patient</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>□ Confirmed before, during or after resuscitation attempt</td>
<td>□ Treated during resuscitation attempt</td>
<td>□ Suspected based on the patient records</td>
</tr>
<tr>
<td></td>
<td>□ Excluded during resuscitation attempt or based patient records</td>
<td>□ Cannot be evaluated on base of patient records</td>
<td>□ Potential considering the clinical diagnosis of the patient</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>□ Confirmed before, during or after resuscitation attempt</td>
<td>□ Treated during resuscitation attempt</td>
<td>□ Suspected based on the patient records</td>
</tr>
<tr>
<td></td>
<td>□ Excluded during resuscitation attempt or based patient records</td>
<td>□ Cannot be evaluated on base of patient records</td>
<td>□ Potential considering the clinical diagnosis of the patient</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>□ Confirmed before, during or after resuscitation attempt</td>
<td>□ Treated during resuscitation attempt</td>
<td>□ Suspected based on the patient records</td>
</tr>
<tr>
<td></td>
<td>□ Excluded during resuscitation attempt or based patient records</td>
<td>□ Cannot be evaluated on base of patient records</td>
<td>□ Potential considering the clinical diagnosis of the patient</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>□ Confirmed before, during or after resuscitation attempt</td>
<td>□ Treated during resuscitation attempt</td>
<td>□ Suspected based on the patient records</td>
</tr>
<tr>
<td></td>
<td>□ Excluded during resuscitation attempt or based patient records</td>
<td>□ Cannot be evaluated on base of patient records</td>
<td>□ Potential considering the clinical diagnosis of the patient</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>□ Confirmed before, during or after resuscitation attempt</td>
<td>□ Treated during resuscitation attempt</td>
<td>□ Suspected based on the patient records</td>
</tr>
<tr>
<td></td>
<td>□ Excluded during resuscitation attempt or based patient records</td>
<td>□ Cannot be evaluated on base of patient records</td>
<td>□ Potential considering the clinical diagnosis of the patient</td>
</tr>
<tr>
<td>Cardiac tamponation</td>
<td>□ Confirmed before, during or after resuscitation attempt</td>
<td>□ Treated during resuscitation attempt</td>
<td>□ Suspected based on the patient records</td>
</tr>
<tr>
<td></td>
<td>□ Excluded during resuscitation attempt or based patient records</td>
<td>□ Cannot be evaluated on base of patient records</td>
<td>□ Potential considering the clinical diagnosis of the patient</td>
</tr>
</tbody>
</table>

- **SaO2 (%)**
- **pO2 (kPa)**
- **aB-pH**
- **S-K**
- **S-Na**
- **S-Gluk**
- **Tcore**
- **Autopsy**
- **Sonography**
- **Other**
<table>
<thead>
<tr>
<th>Potential considering the clinical diagnosis of the patient</th>
<th>Symmetry of lung sounds</th>
<th>X-ray</th>
<th>Other</th>
</tr>
</thead>
</table>

### Tension pneumothorax
- Confirmed before, during or after resuscitation attempt
- Treated during resuscitation attempt
- Suspected based on the patient records
- Excluded during resuscitation attempt or based patient records
- Cannot be evaluated on base of patient records
- Potential considering the clinical diagnosis of the patient

### Myocardial infarction
- ECG
- Biochemical marker
- Autopsy
- Other
- Potential considering the clinical diagnosis of the patient

### Pulmonary embolism
- Other
- Autopsy
- Potential considering the clinical diagnosis of the patient

### Intoxication by toxin that has an antidote
- Other, specify:
- Potential considering the clinical diagnosis of the patient

### 6. Classification of aetiology and clinical diagnosis (fill all that apply)
Modified from Schein R et al. Chest 1990

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>Autopsy diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td></td>
</tr>
</tbody>
</table>
Cardiopulmonary arrest in a patient with clinically significant underlying heart disease and no significant pulmonary, metabolic or neurologic disease.

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>Autopsy diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
</tbody>
</table>
Witnessed apnea or agonal respiration or the occurrence of cardiopulmonary arrest in a patient with acute pulmonary or upper airway disease and no evidence of significant cardiac, metabolic, or neurologic disease.

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>Autopsy diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic</td>
<td></td>
</tr>
</tbody>
</table>
Cardiac arrest associated with acute neurologic impairment as determined by clinical examination and no underlying significant cardiac, respiratory or metabolic disease.

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>Autopsy diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic</td>
<td></td>
</tr>
</tbody>
</table>
Progressive metabolic disturbance immediately preceding arrest in patient without significant cardiac, respiratory, or neurologic disease.
Abnormalities included:
- Sodium >155 or <125 mmol/l
- Potassium >5.5 or <3.0 mmol/l
- Serum osmolality >320mosm/kg
- Glucose >27.6 or <3.3 mmol/l
Arterial pH >7.55 or <7.25
Serum carbon dioxide >30 or <18 mmol/l
Serum phosphate level <0.3 mmol/l

- **Unclassified**

The absence of criteria listed above. Might reflect either no clinically apparent reasons for arrest or an insufficiently severe or progressive presentation of the processes described above.
**APPENDIX 2. Online questionnaire for study III.**

### Survey of intensive care treatment of out-of-hospital cardiac arrest patients in tertiary hospitals in Nordic countries

1. **Country**
   - Finland
   - Sweden
   - Norway
   - Denmark
   - Iceland

2. **City**

3. **Hospital**

4. **Position of the answerer**
   - Chief physician
   - Specialist doctor
   - Resident doctor
   - Other

5. **How many out-of-hospital cardiac arrest (OHCA) patients does Your hospital treat per year?**
   - >40
   - 21-40
   - 5-20
   - <5
   - 0

6. **Does Your hospital treat all OHCA patients treated by emergency medical service (EMS) system within the area of your hospital?**
   - Yes
   - No

7. **Number of hospitals receiving out-of-hospital cardiac arrest patients within Your area**

8. **Is percutaneous coronary intervention (PCI) provided routinely for all survivors of prehospital cardiac arrest?**
   - Yes
   - No

9. **Does Your intensive care unit have a predefined protocol according to which out-of-hospital cardiac arrest patients are admitted to ICU?**
   - Yes
10. If You have a predefined criteria which OHCA patients are admitted, please specify:

- age maximum
- initial rhythm
- ROSC maximum
- other

11. Are any out-of-hospital cardiac arrest patients admitted to ICU if they need help in activities of daily life?
- Yes
- No

12. Are out-of-hospital cardiac arrest patients admitted to ICU if their lifetime expectancy according to other illnesses is less than 5 years?
- Yes
- No

13. Are out-of-hospital cardiac arrest patients admitted to ICU only if they had VF/VT as initial rhythm?
- Yes
- No

14. Are out-of-hospital cardiac arrest patients with pulseless electrical activity (PEA) admitted to ICU if they are expected to recover?
- Yes
- No

15. Are out-of-hospital cardiac arrest patients with ASY admitted to ICU if they are expected to recover?
- Yes
- No

16. Are out-of-hospital cardiac arrest patients admitted to ICU if their ROSC time is >30 minutes?
- Yes
- No

17. Are all out-of-hospital cardiac arrest patients admitted to ICU treated with therapeutic hypothermia (expecting there are resources at the moment patient is admitted)?
- Yes
- No

18. If not, which patients are excluded?

19. Does EMS service in Your area use induction of hypothermia in the prehospital setting?
20. If yes, method of induction of hypothermia (cold iv-fluids, ice packs, other...)?
- [ ]
- [ ]
- [ ]

21. Would You feel comfortable treating out-of-hospital cardiac arrest patients without hypothermia?
- [ ] Yes
- [ ] No

22. After out-of-hospital cardiac arrest, what time is the prognostic evaluation performed?
- [ ] <24h
- [ ] 24-48h
- [ ] 48-72h
- [ ] >72h

23. Is the prognostic decision based on...
- [ ] NSE laboratory test
- [ ] S-100 laboratory test
- [ ] EEG
- [ ] SEP
- [ ] clinical signs
- [ ] all of the above

other
APPENDIX 3. Questionnaire on health-related quality of life (I).

TERVEYTEEN LIITTYVÄN ELÄMÄNLAADUN KYSELYLOMAKE (15D©)


KYSYMYS 1. Liikuntakyky

1 ( ) Pystyn kävelemään normaalisti (vaikeuksitta) sisällä, ulkona ja portaissa.
2 ( ) Pystyn kävelemään vaikeuksitta sisällä, mutta ulkona ja/tai portaissa on pieniä vaikeuksia.
3 ( ) Pystyn kävelemään ilman apua sisällä (apuvälinein tai ilman), mutta ulkona ja/tai portaissa melkoisina vaikeuksina.
4 ( ) Pystyn kävelemään sisässäkin vain toisen avustamana.
5 ( ) Olen täysin liikuntakyvytön ja vuoteenoma.

KYSYMYS 2. Näkö

1 ( ) Näen normaalisti eli näen lukea lehteä ja TV:n tekstejä vaikeuksitta (silmälaseilla tai ilman).
2 ( ) Näen lukea ja/tai TV:n tekstejä pienin vaikeuksin (silmälaseilla tai ilman).
3 ( ) Näen lukea ja/tai TV:n tekstejä huomattavina vaikeuksina (silmälaseilla tai ilman).
4 ( ) En näe lukea ja/tai TV:n tekstejä ilman silmalaseja tai niiden kanssa, mutta näen kulkea ilman opasta.
5 ( ) En näe kulkea oppaattia eli olen lähes tai täysin sokea.

KYSYMYS 3. Kuulo

1 ( ) Kuulen normaalisti eli kuulen hyvin normaalia puheääntä (kuulokojella tai ilman).
2 ( ) Kuulen normaalia puheääntä pienin vaikeuksin.
3 ( ) Minun on melko vaikea kuella normaalia puheääntä, keskustelussa on käytettävää normaalia kovempaa puheääntä.
4 ( ) Kuulen kovaakin puheääntä heikosti; olen melkein kuuro.
5 ( ) Olen täysin kuuro.

KYSYMYS 4. Hengitys

91
1 ( ) Pystyn hengittämään normaalisti eli minulla ei ole hengenahdistusta eikä muita hengitysvaikeuksia.
2 ( ) Minulla on hengenahdistusta raskaassa työssä tai urheillessa, reippaassa kävelyssä tasamaalla tai liévässä ylämäessä.
3 ( ) Minulla on hengenahdistusta, kun kävelen tasamaalla samaa vauhtia kuin muut ikäiseni.
4 ( ) Minulla on hengenahdistusta pienenkin rasituksen jälkeen, esim. peseryyessä tai pukeutuessa.
5 ( ) Minulla on hengenahdistusta lähes koko ajan, myös levossa.

**KYSYMYS 5. Nukkuminen**

1 ( ) Nukun normaalisti eli minulla ei ole mitään ongelmia unen suhteen.
2 ( ) Minulla on lieviä uniongelmia, esim. nukahtamisvaikeuksia tai satunnaista yöheräilyä.
3 ( ) Minulla on melkoisia uniongelmia, esim. nukun levottomasti tai uni ei tunnu riittävältä.
4 ( ) Minulla on suuria uniongelmia, esim. joudun käyttämään usein tai säännöllisesti unilääkeä, herään säännöllisesti yöllä ja/tai aamuisin liian varhain.
5 ( ) Kärsin vaikeasta unettomuudesta, esim. unilääkkeiden runsaasta käytöstä huolimatta nukkuminen on lähes mahdotonta, valvon suurimman osan yöstä.

**KYSYMYS 6. Syöminen**

1 ( ) Pystyn syömään normaalisti eli itse ilman mitään vaikeuksia.
2 ( ) Pystyn syömään itse pienin vaikeuksin (esim. hitaasti, kömpelösti, vavisten tai erityisapuneuvoin).
3 ( ) Tarvitsen hieman toisen apua syömisessä.
4 ( ) En pysty syömään itse lainkaan, vaan minua pitää syöttää.
5 ( ) En pysty syömään itse lainkaan, vaan minulle pitää antaa ravintoa letkun avulla tai suonensisäisesti.

**KYSYMYS 7. Puhuminen**

1 ( ) Pystyn puhumana normaalisti eli selvästi, kuuluvasti ja sujuvasti.
2 ( ) Puhuminen tuottaa minulle pieniä vaikeuksia, esim. sanoja on etsittävä tai ääni ei ole riittävän kuuluva tai se vaihtaa korkeutta.
3 ( ) Pystyn puhumana ymmärrettävästi, mutta katkonaisesti, ääni vavisten, sammaltaen tai änkyttäen.
4 ( ) Muilla on vaikeuksia ymmärtää puhettani.
5 ( ) Pystyn ilmaisemaan itseäni vain elein.
KYSYMYS 8. Eritystoiminta

1 ( ) Virtsarakkoni ja suolistoni toimivat normaalisti ja ongelmitta.
2 ( ) Virtsarakkoni ja/tai suolistoni toiminnasssa on lieviä ongelmia, esim. 
minulla on virtsaamisvaikeuksia tai loysä vatsa 
3 ( ) Virtsarakkoni ja/tai suolistoni toiminnassa on melkoisia ongelmia, esim. 
minulla on satunnaisia 
virtsanpidätysvaikeuksia tai vaikea ummetus tai ripuli. 
4 ( ) Virtsarakkoni ja/tai suolistoni toiminnassa on suuria ongelmia, esim. 
minulla on säännöllisesti 
"vahinkoa" tai peräruiskeiden tai katetroinnin tarvetta. 
5 ( ) En hallitse lainkaan virtsaamista ja/tai ulostamista.

KYSYMYS 9. Tavanomaiset toiminnot

1 ( ) Pystyn suoriutumaan normaalisti tavanomaisista toiminnoista (esim. 
anüotyo, opiskelu, kotityö, 
vapaa-ajan toiminnot).
2 ( ) Pystyn suoriutumaan tavanomaisista toiminnoista hieman alentuneella 
teholla tai pienin vaikeuksin. 
3 ( ) Pystyn suoriutumaan tavanomaisista toiminnoista huomattavasti 
alentuneella teholla tai 
huomattavin vaikeuksin tai vain osaksi. 
4 ( ) Pystyn suoriutumaan tavanomaisista toiminnoista vain pieneltä osin. 
5 ( ) En pysty suoriutumaan lainkaan tavanomaisista toiminnoista.

10. Henkinen toiminta

1 ( ) Pystyn ajattelemaan selkeästi ja johdonmukaisesti ja muistini toimii täysin 
moitteettomasti. 
2 ( ) Minulla on lieviä vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai 
muistini ei toimi täysin 
moitteettomasti 
3 ( ) Minulla on melkoisia vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai 
minulla on jonkin verran muistinmenetystä 
4 ( ) Minulla on suuria vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai 
minulla on huomattavaa 
muistinmenetystä 
5 ( ) Olen koko ajan sekaisin ja vailla ajan tai paikan tajua

KYSYMYS 11. Vaivat ja oireet

1 ( ) Minulla ei ole mitään vaivoja tai oireita, esim. kipua, särkyä, pahoinvointia, 
kutinaa jne. 
2 ( ) Minulla on lieviä vaivoja tai oireita, esim. lievää kipua, särkyä, 
pahoinvointia, kutinaa jne. 
3 ( ) Minulla on melkoisia vaivoja tai oireita, esim. melkoista kipua, särkyä, 
pahoinvointia, kutinaa jne.

<table>
<thead>
<tr>
<th>KYSYMYS 12. Masentuneisuus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ( ) En tunne itseäni lainkaan surulliseksi, alakuloiseksi tai masentuneeksi.</td>
</tr>
<tr>
<td>2 ( ) Tunnen itseni hieman surulliseksi, alakuloiseksi tai masentuneeksi.</td>
</tr>
<tr>
<td>3 ( ) Tunnen itseni melko surulliseksi, alakuloiseksi tai masentuneeksi.</td>
</tr>
<tr>
<td>4 ( ) Tunnen itseni erittäin surulliseksi, alakuloiseksi tai masentuneeksi.</td>
</tr>
<tr>
<td>5 ( ) Tunnen itseni äärimmäisen surulliseksi, alakuloiseksi tai masentuneeksi.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KYSYMYS 13. Ahdistuneisuus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ( ) En tunne itseäni lainkaan ahdistuneeksi, jännittyneeksi tai hermostuneeksi.</td>
</tr>
<tr>
<td>2 ( ) Tunnen itseni hieman ahdistuneeksi, jännittyneeksi tai hermostuneeksi.</td>
</tr>
<tr>
<td>3 ( ) Tunnen itseni melko ahdistuneeksi, jännittyneeksi tai hermostuneeksi.</td>
</tr>
<tr>
<td>4 ( ) Tunnen itseni erittäin ahdistuneeksi, jännittyneeksi tai hermostuneeksi.</td>
</tr>
<tr>
<td>5 ( ) Tunnen itseni äärimmäisen ahdistuneeksi, jännittyneeksi tai hermostuneeksi.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KYSYMYS 14. Energisyys</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ( ) Tunnen itseni terveeksi ja elinvoimaiseksi.</td>
</tr>
<tr>
<td>2 ( ) Tunnen itseni hieman uupuneeksi, väsyneeksi tai voimattomaksi.</td>
</tr>
<tr>
<td>3 ( ) Tunnen itseni melko uupuneeksi, väsyneeksi tai voimattomaksi.</td>
</tr>
<tr>
<td>4 ( ) Tunnen itseni erittäin uupuneeksi, väsyneeksi tai voimattomaksi, lähes &quot;loppuun palaneeksi&quot;.</td>
</tr>
<tr>
<td>5 ( ) Tunnen itseni äärimmäisen uupuneeksi, väsyneeksi tai voimattomaksi, täysin &quot;loppuun palaneeksi&quot;.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KYSYMYS 15. Sukupuolielämä</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ( ) Terveydentilani ei vaikuta mitenkään sukupuolielämääni.</td>
</tr>
<tr>
<td>2 ( ) Terveydentilani vaikeuttaa hieman sukupuolielämääni.</td>
</tr>
<tr>
<td>3 ( ) Terveydentilani vaikeuttaa huomattavasti sukupuolielämääni.</td>
</tr>
<tr>
<td>4 ( ) Terveydentilani tekee sukupuolielämäni lähes mahdottomaksi.</td>
</tr>
<tr>
<td>5 ( ) Terveydentilani tekee sukupuolielämäni mahdottomaksi.</td>
</tr>
</tbody>
</table>

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