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Cardiac Arrest – mechanical chest compressions, gender differences and coronary angiography

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Abstract

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Cardiac arrest is a major health problem with over 6000 cases of out-of-hospital cardiac arrest (OHCA) and 2500 cases of in-hospital cardiac arrest (IHCA) per year in Sweden. Survival are low. Many factors affect the chances of survival, including effective cardiopulmonary resuscitation and optimal post resuscitation care. These thesis involve these areas. **Paper I +II** describe a randomized clinical trial (n=2589). We compared a novel CPR algorithm with defibrillations during ongoing chest compressions delivered with a mechanical chest compression device and manual CPR according to guidelines. We found no difference in 4-hour survival, 23.6% with mechanical CPR and 23.7% with manual CPR. The vast majority of survivors in both groups had good neurological outcomes by 6 months. **Paper III** is a registry study (n=1498). We investigated impact of gender in performance and findings of early coronary angiography (CAG) and percutaneous coronary intervention (PCI), comorbidity and outcome among OHCA victims with an initially shockable rhythm. We found no difference between men and women in rates of ST-elevation/left bundle branch block (LBBB), 40% vs. 38% or rates of CAG, 45% vs. 40%. Among patients without ST-elevation/LBBB more men than women had CAG followed by PCI, 59% vs. 42% (P=0.03) and more advanced coronary artery disease. We found no association between gender and use of early CAG. **Paper IV** is a retrospective observational single centre study (n=423) of ICU treated victims of cardiac arrest. OHCA and IHCA were compared regarding comorbidity, characteristics of the arrest, treatment including CAG and CAG findings and outcome. OHCA patients had less preexisting comorbidity, lower rates of bystander CPR 71% vs 100% (p<0.001) and longer time to return of spontaneous circulation, 20 vs 10 minutes (p<0.001). OHCA patients more often had a shockable first rhythm, 47% vs 13% (p<0.001) and CA without any obvious non-cardiac origin, 77% vs 50% (p<0.001). OHCA patients more often underwent early CAG, 52% vs 25% (p<0.001) but no difference in rates of subsequent PCI or angiogram with at least one significant stenosis was seen. OHCA and IHCA did not differ in 30-days survival, 42% vs 41% or 1-year survival, 39% vs 33%

Keywords: cardiac arrest, OHCA, IHCA, CPR, coronary angiography, percutaneous coronary intervention, PCI, mechanical chest compressions, lucas

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To Sara and Vera.

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I Rubertsson S, Silfverstolpe J, Rehn L, Nyman T, Lichtveld R, Boomars R, Bruins W, Ahlstedt B, Puggioli H, Lindgren E, Smekal D, Skoog G, Kastberg R, Lindblad A, Halliwell D, Box M, Arnwald F, Hardig BM, Chamberlain D, Herlitz J, Karlsten R. (2013). **The study protocol for the LINC (LUCAS in cardiac arrest) study: a study comparing conventional adult out-of-hospital cardiopulmonary resuscitation with a concept with mechanical chest compressions and simultaneous defibrillation.** *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine.* 25;21:5
- II Rubertsson S, Lindgren E, Smekal D, Östlund O, Silfverstolpe J, Lichtveld RA, Boomars R, Ahlstedt B, Skoog G, Kastberg R, Halliwell D, Box M, Herlitz J, Karlsten R. (2014). **Mechanical chest compressions and simultaneous defibrillation vs conventional cardiopulmonary resuscitation in out-of-hospital cardiac arrest: the LINC randomized trial.** *JAMA.* 311(1):53-61
- III Erik Lindgren, Lucian Covaciu, David Smekal, Rickard Lagedal, Per Nordberg, Ludvig Elfwén, Leif Svensson, Martin Jonsson, Stefan James, Sten Rubertsson. (2019). **Gender differences in utilization of coronary angiography and angiographic findings after out-of-hospital cardiac arrest: A registry study.** *Resuscitation.* 143:189-195
- IV Erik Lindgren, Vanessa Fernandez Stenman, Lucian Covaciu, David Smekal, Gabriel Arefalk, Ola Vedin, Sten Rubertsson. (2019). **A study comparing victims of out-of-hospital and in-hospital cardiac arrest admitted alive to the ICU.** *In Manuscript*

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Abbreviations

CPC	Cerebral Performance Category
CAD	Coronary Artery Disease
CAG	Coronary Angiography
CPP	Coronary Perfusion Pressure
CPR	Cardiopulmonary Resuscitation
ECG	Electrocardiogram
EMS	Emergency Medical Services
ICU	Intensive Care Unit
IHCA	In-Hospital Cardiac Arrest
ITT	Intention To Treat
LBBB	Left Bundle Branch Block
OHCA	Out-of-Hospital Cardiac Arrest
PCI	Percutaneous Coronary Intervention
PEA	Pulseless Electrical Activity
ROSC	Return of Spontaneous Circulation
TTM	Targeted Temperature Management
VF	Ventricular Fibrillation
VF	Ventricular Tachycardia

Introduction

The history of cardiopulmonary resuscitation (CPR)

Obviously, cardiac arrest is a major cause of death globally, and there has always been people occupied with thinking about how to possibly resuscitate a person back to life. We find what can be the first descriptions of CPR in the old testament, and history also tells us about the Egyptian goddess Isis resuscitating her husband Osiris. In the 18th century societies started to organize resuscitation efforts in Amsterdam, Paris and London. In the 19th century the modern CPR started to develop. 1827 Leroy d'Etiolles suggested a method where a person could be artificially ventilated, with or without moving the person's arms, and 1878 external chest compressions were described by Boehm in animal experiments. In the 1950s several steps towards today's CPR were taken, with Peter Safar's ventilation studies on sedated and paralyzed volunteers as one example¹. The development of general anaesthesia led to several cases of cardiac arrest, and standard care was open chest cardiac massage. 1960 Kouwenhoven and colleagues wrote a landmark paper describing the external chest compressions² which of course was a great progress, surgeons were no longer a prerequisite to perform CPR, and it could be performed by basically anyone with basic skills and knowledge.

The 21st century: Focus on chest compressions

Early this century reports of inefficient CPR³⁻⁶ were published, contributing to put focus on the importance of high-quality chest compressions. 2005 guidelines from European Resuscitation Council (ERC)⁷ and American Heart Association (AHA)⁸ emphasized the importance of chest compression. The AHA guidelines told rescuers to "push hard, push fast. The 2010 guidelines continued to stress high quality chest compressions with minimally interruptions. AHA launched a change from the well-known ABC, i.e. airway, breathing, circulation, to CAB, compressions, airway, breathing, a reorientation in order to minimize time to initiation of chest compression⁹. 2010 ERC removed the recommendation for Emergency Medical Services (EMS) personnel to give a period of about 2 minutes of CPR prior to defibrillation in patients with a prolonged collapse (>5minutes)¹⁰. The previous recommendations from 2005¹¹ were based on the thought that a brief period of compressions would provide oxygen and energy to the myocardium, increasing the likelihood of return of

spontaneous circulation (ROSC)^{12,13}. The AHA guidelines, however, kept their recommendation from 2005¹⁴ that 1.5 to 3 minutes of CPR before defibrillation could be considered in these specified cases¹⁵. In 2015 guidelines, both the ERC and AHA guidelines recommend defibrillation as soon as possible when a shockable rhythm, even if not witnessed by EMS personnel, but of course with immediate start of chest compressions until it is possible to defibrillate^{16,17}. The 2015 guidelines have kept their focus on high quality chest compression and minimizing pre- and post-shock pauses. The two organisations, AHA and ERC do not differ in reality. Conformity is now even reached regarding the depth and frequency when performing chest compressions, since AHAs change within the 2015 guidelines¹⁷, both organisations recommending 5-6 cm depth and a frequency of 100-120/min.

Cardiac arrest

Definitions

Cardiac arrest has been defined as “the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation”¹⁸. A cardiac arrest is often unexpected, and if not treated leading to death. Any cardiac arrest happening outside the hospital is defined as *out-of-hospital cardiac arrest (OHCA)* while *in-hospital cardiac arrest (IHCA)* is happening to a hospitalized patient.

Incidence and outcome

In Sweden, with a population just over 10 million people, there were 8663 reported cases of cardiopulmonary resuscitation (CPR) during 2018. Of these 71% were OHCA and 29% IHCA¹⁹. Both incidence and outcome vary greatly between studies, regarding both OHCA and IHCA, most likely due to differences in reporting coverage and inclusion criteria. In a review by Berdowski and colleagues²⁰, average incidence of EMS attended OHCA in Europe was 86 per 100,000 persons/year (range 19-108 in included studies) and average survival at hospital discharge of 9% (range 6-31% in included studies). Reported incidence of IHCA varies between 1.5% (Europe)^{21,22} to 4% (USA)²³ per 1000 admissions and survival to hospital discharge after IHCA varies between 15% and 19%.

Initial ECG rhythms

Ventricular Fibrillation (VF)

VF occurs when the coordinated contractions of the myocardium is replaced by disorganized high-frequency excitations, resulting in loss of pump function

and circulatory collapse²⁴. The mechanism behind this phenomenon is complex. Structural and electrical properties of the myocardium (tissue heterogeneity), together with dynamic factors such as action potential duration and conduction velocity, causes electrical wavebreaks which induces reentry and triggers a new cascade of wavebreaks, resulting in VF²⁵. Furthermore, several factors may interact with this process, making the myocardium more susceptible to VF (e.g. hypoxia, ischaemia, acidosis, electrolyte disturbances, drugs)²⁶.

VF may occur in several situations, but most often it is associated with coronary artery disease (CAD), either as an effect of acute myocardial infarction / ischaemia, or due to scarring from an old infarct. Cardiovascular disease has been shown being independently associated with VF/VT²⁷ and higher rates of VF/VT have been found in patients deemed having a cardiac origin of the arrest²⁸ and where coronary angiography (CAG) led to percutaneous coronary intervention (PCI) compared to CAG alone²⁹.

If not treated, a VF will deteriorate over time and end up in an asystole, why we can not tell the true incidence. In line with this, data collected from automatic external defibrillators in a highly monitored setting (a casino) where average response time was less than five minutes, tell us about an incidence of VF as high as 71%³⁰. This is in contrast to more recently published randomized controlled prehospital trials reporting VF/VT rates between 22-30%³¹⁻³³. Obviously the lower rates of VF/VT is affected by factors like the proportions of witnessed arrests and EMS response times, but it also illustrates the declining numbers of VF/VT seen worldwide^{19,34}. Data indicates that this is due to a decline in initial VF/VT rather than a more rapid transition from VF/VT into asystole³⁴. The reason for this decline in VF/VT is certain multifactorial. More effective treatment, e.g. implementations of implantable cardioverter defibrillators³⁵, use of beta-blockers³⁶ together with a decline in coronary heart disease mortality³⁷ are among possible reasons.

Asystole

There is a wide variation of the underlying causes of asystole in cardiac arrest, all of them leading to the failure of the electrical system generating any electrical depolarization. The term primary asystole refers to when the electrical system fails to generate a ventricular depolarization. This may be due to ischemia or degeneration of the sinoatrial node or atrioventricular conduction system. The term secondary asystole is sometimes used when specific situation causes severe tissue hypoxia or acidosis, leading to the electrical system failing to generate any electrical depolarization. Furthermore, reflex bradycardia/asystole may result from vagal reactions, e.g. pressure on the eye globe or ocular surgery. Any cause of cardiac arrest will eventually lead to asystole if not promptly treated. Survival after OHCA with asystole as first registered rhythm is poor, with 30-day survival just over one percent^{38,39}.

Pulseless electrical activity (PEA)

PEA is defined as an organized electrical rhythm without any palpable pulse. This can be due to electromechanical dissociation (organized rhythm but no pump function) or due to e.g. tamponade or pulmonary embolism causing mechanical obstruction. The incidence of PEA has increased over the last years and outcome is reported to be better than after asystole^{38,39}.

Ventricular tachycardia (VT)

VT is a wide complex tachycardia at a rate >100 beats per minute. The most common origin of VT is underlying ischemic heart disease. Even though VF is the most common tachyarrhythmia in CA, a VT proceeding to VF is thought to be the most common mechanism of sudden cardiac death in patients with ischemic heart disease⁴⁰.

Predictors of outcome

Chances of survival are certainly multifactorial, and factors affecting outcome after OHCA are well described. Age and comorbidity are two major predictors. The absolute youngest and oldest have worst outcome after cardiac arrest^{19,41}. VF as the initial rhythm has been found being the most important factor for ROSC and survival⁴². Other factors associated with increased survival are a short EMS response time, cardiac arrest outside home, witnessed cardiac arrest (at its best by the EMS crew) and bystander CPR⁴²⁻⁴⁵. Chronic obstructive pulmonary disease (COPD), neurological disease and diabetes are examples of co-existing disease associated with poor outcome⁴⁶. Female gender seems to be an independent predictor for early survival, but this effect is for some reason no longer seen in the long-time survival rates, i.e. from hospital discharge and forward¹⁴⁷⁻⁵⁰. This is discussed elsewhere in this thesis.

Physiological aspects of chest compressions and cardiac arrest

The physiology of cardiac arrest

One important link in the chain of survival after cardiac arrest is the delivery of high-quality chest compressions in order to buy enough time for correcting the underlying disorder, e.g. through defibrillation^{4,5,51,52}. During VF, blood is pooled in the venous circulation with a rise in right atrial pressure and a concomitant decrease in aortic pressure⁵. Besides from a diminished blood flow to the brain this also leads to a decrease in coronary perfusion pressure (CPP) which is defined as the difference between aortic diastolic pressure and right atrial pressure during the relaxation phase. Eventually, during VF the aortic pressure and right atrial pressure will reach equilibrium leading to CPP of

zero. Paradis and colleagues showed that a CPP of at least 15 mmHg seems like a threshold for where ROSC is possible⁵². Effective chest compressions are needed to avoid a drop in CPP to levels where chances of ROSC are minimal or even zero.

Blood flow during CPR

There have been two different competing theories proposed to explain how chest compressions produce forward blood flow during CPR. According to the initial hypothesis, *the cardiac pump theory*, compressions of the ventricles increase intraventricular pressure and thereby promotes flow. During decompression the intraventricular pressure falls, leading to passive refilling². In the early 1980s another theory was proposed, *the thoracic pump theory*⁵³. According to this theory chest compressions increase the intrathoracic pressure which forces blood from the thoracic vessels into the systemic circulation and thereby generating blood flow. During decompression intrathoracic pressure falls with return of venous blood. The authors did however consider both theories important, explaining different important mechanisms behind effective chest compressions.

It is plausible to believe the LUCAS™ device is working according to these two theories, with the piston delivering compressions over the sternum and the suction cup that may assist the chest back to neutral position⁵⁴. Another CPR device discussed within this thesis is the AUTOPULSE™. It is a load distributing based on the thoracic pump theory⁵⁵. Besides from chest compression it also increases the intrathoracic pressure and thereby generating blood flow.

However, you may assume that these two theories coexists during CPR, but their relationship and relative importance is certainly affected by several factors, e.g. duration of CPR, volume status, myocardial stunning, the patient's body size, comorbidity and type of CPR.

Manual CPR

The effectiveness of compressions are highly dependent on the skills and endurance of rescuers. Manual CPR provide only approximately 30% of normal cardiac output^{56,57}. Besides from correct depth and frequency, hands-off time must be minimized. In a study by Wik and colleagues⁶ the hands-off ratio (time without chest compressions divided by CPR time) after OHCA were 0.48, 0.38 after subtracting the time necessary for electrocardiogram (ECG) analysis and defibrillation and the majority of compressions were too shallow. Another study presented somewhat lower numbers, but importantly enough, hands-off ratio increased from 0.19 to 0.27 during transport⁵⁸. Also, the potential risks for the EMS personnel when performing CPR in a moving vehicle

are obvious, adding further to the potential benefits with a mechanical CPR device.

Mechanical chest compressions

Data from experimental and human studies with the mechanical chest compression device LUCAS™ have shown improved organ perfusion pressures, enhanced cerebral blood flow and higher end-tidal CO₂ compared to manual CPR^{54,59,60}. This device also sustains adequate circulation in the catheterization laboratory during PCI and has been used in cases of hypothermia /drowning with good outcome^{61,62}. For these reasons, mechanical chest compression devices have been developed in order to improve CPR.

Before the LINC trial, two randomized pilot studies compared mechanical chest compressions using the LUCAS™ and manual CPR after OHCA without finding any outcome differences. The first one, by Axelsson et al⁶³ (N=328) including witnessed OHCA of non-traumatic origin, showed no differences in ROSC or survival to hospital admission. Nor the second pilot study by Smekal et al⁶⁴ (N=149), including also non-witnessed OHCA, could show any difference in ROSC or survival at hospital discharge. This study was a safety- and feasibility study as well as providing data used for power calculation to the upcoming LINC trial.

The first randomized controlled study to compare manual and mechanical chest compressions after OHCA was the ASPIRE study⁶⁵, using the Autopulse™. This study was premature terminated following the first planned interim monitoring due to worse outcome in the mechanical CPR group. No difference in 4-hour survival existed, but the intervention arm showed lower survival and worse neurological outcome at hospital discharge. However, post hoc reanalysis revealed that the unsuspected outcome may be due to a change in protocol at one of the five sites during the study, with this site significantly interacting with the results, while the other four study sites were statistically homogenous and showed a positive learning curve favouring the intervention arm^{66,67}. The LINC trial³³, which is part of this thesis, was the first large randomized controlled trial comparing mechanical and manual chest compressions, considering the ASPIRE study was prematurely terminated.

Mechanical chest compression devices

Besides from the LUCAS™ device, which is described elsewhere in this thesis, several mechanical CPR devices have been developed. Most of them are no longer in use, but today's literature mention a few other devices:

- **LDB. Load-distributing Band.** Autopulse™. A circumferential chest compression device, consisting of a backboard and a band

applied and fitting around the chest. It delivers circumferential chest compressions and compresses 20% of the thoracic cavity.

- **ACD-CPR. Active compression-decompression CPR.** Ambu CardioPump™. A hand-held device with a suction cup that actively lifts the thorax during the decompression phase, leading to negative intrathoracic pressure and promoting venous return. ERC guidelines from 2015 do not recommend against the use of ACD-CPR⁶⁸, but it is used sparsely, most probably due to reports of injuries associated with the use of this device^{69,70}.
- **ITD. Impedance Threshold Device.** A pressure-sensitive valve attached to the endotracheal tube, supraglottic airway or facemask. This device limits the amount of air entering the lungs during the passive recoiling of the chest and is thus promoting venous return. A large RCT (n=8718) did not show any difference in survival with good neurologic function after OHCA when comparing CPR with ITD to those treated with CPR with a sham ITD device⁷¹. Better long-term outcome with good neurological outcome was seen when comparing a combination of ITD and ACD-CPR to manual CPR (n=27380)⁷², but the number needed to treat was high, and the use of ITD is not recommended, neither alone or in combination with ACD-CPR⁶⁸.
- **PTACD-CPR. Phased thoracic-abdominal compression-decompression CPR.** The Lifestick™. A handheld device that alternates chest compression and abdominal decompression. One small randomized study showed no difference in survival to hospital discharge⁷³.

Current recommendations regarding mechanical chest compressions in CPR

The ERC and AHA 2015 guidelines are consistent and both organisations recommend that mechanical chest compression devices should not be routinely used to replace manual chest compressions. They do state, however, that mechanical devices are a reasonable alternative in situations where it is hard to provide high quality chest compressions or the providers safety is compromised^{16,17}. Guidelines stress that when a mechanical CPR device is being used, it should be in a system with properly trained personnel.

CPR related injuries

Soon after Kouwenhoven described the external chest compressions the first report of CPR related injuries was published, and 1965 an editorial in *Circulation* described both the benefits and hazards of CPR⁷⁴. Perhaps the most

important in this editorial was that it stated that CPR was an emergency procedure that could be initiated by not only the doctors and that the possible injuries from CPR could be minimized if CPR was performed by CPR trained personnel. Several studies followed, confirming that CPR related injuries was a reality, and that skeletal injuries were most common with injuries to the ribs and sternum dominating.

Initial studies were somewhat conflicting regarding the safety of mechanical CPR^{70,75-77} and concerns were raised over its use in CPR^{78,79}. Regardless if any difference in injury burden was seen or not, in these studies multiple rib fractures, followed by sternal fractures were most common. Other, but far less often reported CPR injuries, with no difference in incidence between groups, was mediastinal bleeding, retrosternal bleeding, epicardial bleeding, hemopericardium, liver capsule rifts and rift in the spleen^{75,76}.

In order to further clarify the incidence of CPR-related injuries by mechanical chest compressions compared to manual chest compressions a larger multicentre autopsy study was conducted in conjunction with the LINC trial⁸⁰. In this study multiple rib fractures were more frequent after mechanical CPR, 79%, compared to after manual CPR, 65%. Like in previous studies, second most frequent injury was sternal fractures, 58% vs. 54% in the two groups, respectively. Among the less frequently found injuries epicardial bleeding was seen most often, 9% vs. 8%. However, no injury was deemed fatal by the pathologist.

Gender differences in OHCA

Approximately one third of all OHCA victims are women and they have several characteristics associated with poor outcome: they are older, have more comorbidities (although lower rates of previously known CAD and less often cardiac aetiology underlying the CA. They have more seldom a shockable first ECG rhythm and lower rates of witnessed cardiac arrest and bystander CPR^{46-48,50,81,82}.

Gender-specific data on survival after OHCA are conflicting. Despite several adverse female characteristics some studies have shown higher survival rates among women at hospital admission, a difference that no longer is seen at hospital discharge⁴⁸ or after one month⁸¹. Other studies report no survival difference between men and women or men having higher survival rates, both at hospital admission and hospital discharge^{47,50,82}. However, after adjusting for comorbidities and characteristics of the event, female gender seems to be independently associated with survival at hospital admission^{47,49,50}. This association was only seen after one month among patients with a shockable first rhythm^{49,82}.

Altogether, men and women differ in outcome after OHCA, but the reasons for this we do not know. Some researchers have suggested a possible

oestrogen effect among women resulting in better outcome during childbearing age^{83,84} even though these findings have been disputed⁵⁰. The possible mechanism behind this oestrogen effect is complex and poorly understood. Possible mechanisms might involve a protective effect against injury due to ischaemia and reperfusion, increased coronary flow due to actions of nitric oxide and an antiarrhythmic effect⁸⁵.

Revascularization after OHCA

Several studies have shown that CAG may improve outcome after OHCA⁸⁶⁻⁸⁸. The European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-Resuscitation Care 2015⁸⁹ stress the need for early revascularization, recommending CAG to be considered in all successfully resuscitated OHCA victims with no obvious non-cardiac cause of the arrest, even without an ECG indicating ischaemia. This recommendation has changed markedly just over the last ten years: 2005 guidelines recommended CAG to be considered only when evidence of coronary occlusion was present⁹⁰. However, with few exceptions^{91,92} data in support of early CAG are observational and from selected populations, i.e. patients already referred to the catheterization laboratory.

In order avoid unnecessary risks and minimize delays of targeted temperature management (TTM) and cardiovascular and respiratory optimization it is important to identify which patients to refer for early CAG after OHCA, i.e. to find those who will probably benefit from treatment with PCI. Furthermore, today's guidelines do not exclude patients without ST-elevation from early CAG, but evidence for immediate CAG are weaker in this group even if 58% of these patients have at least one significant coronary artery lesion⁹¹.

Gender differences in use of coronary angiography after OHCA

Similar to after acute coronary syndrome (ACS) women undergo CAG and PCI more seldom^{46,93-98} and female gender is independently associated with lower use of early CAG^{93,99,100} although men and women have similar rates of CAG leading to PCI after controlling for confounders^{93,99}. The lower rate of a shockable first rhythm among women might indicate a lower rate of cardiac aetiology, as discussed earlier. Among patients with a shockable first rhythm, female gender is even associated with good long-term outcome⁴⁹ which is not seen in studies of OHCA victims irrespective of first rhythm^{47,48,50}.

OHCA vs. IHCA

Despite one third of all cardiac arrest takes place inside the hospital, the absolute majority of research originates from OHCA. In a review from 2016 Sinha and colleagues¹⁰¹ identified a total of 92 randomized controlled trials from 1995 to 2014 focusing on treatment of non-traumatic cardiac arrest in adults. Of these only 4 trials (4.3%) involved exclusively IHCA and 7 (7.6%) involved both OHCA and IHCA. Evidence for how to treat cardiac arrest victims, regardless of the location of the arrest, are often extrapolated knowledge from OHCA research.

Since only few studies have compared OHCA and IHCA, there is a knowledge gap of the actual differences between the two groups. We do however know that the two groups differ in some important aspects. OHCA patients are younger, include fewer women, more often have a shockable first ECG rhythm but more seldom witnessed arrests and bystander CPR. OHCA patients also have longer time to ROSC but higher rates of both early CAG and TTM¹⁰²⁻¹⁰⁵. We also assume that IHCA patients have greater comorbidity, but this is not confirmed in any study.

Despite the limited evidence it appears that more patients undergo early CAG after OHCA than after IHCA¹⁰². One single study has investigated the role of early CAG after IHCA, demonstrating early CAG being associated with increased survival¹⁰⁶. Despite the known high incidence of significant occlusions after OHCA⁹¹, even in absence of ST-elevation, European guidelines do not address the role of early CAG after IHCA, probably reflecting the sparse evidence. Furthermore, we do not know anything about the possible difference in CAG findings between OHCA and IHCA.

Aims

Paper I and II

To investigate if administering mechanical chest compressions with defibrillation during ongoing compressions, compared with manual CPR according to guidelines would improve 4-hour survival (primary outcome).

Secondary outcomes were:

- ROSC
- Arrival at the emergency department with spontaneous palpable pulse
- Survival with good neurological outcome at ICU discharge, hospital discharge and at 1 and 6 months.

Paper III

To investigate the interaction of gender and utilization of early CAG and PCI, CAG findings, comorbidity and outcome.

Paper IV

To compare OHCA and IHCA in comorbidity, characteristics of the CA, post resuscitation care including utilizations of early CAG, CAG findings and outcome.

Material and methods

Paper I and II

Study enrolment and randomization

The LINC trial was a prospective multicentre, randomized trial, initiated by Uppsala University. The study was supported by institutional grants from Uppsala University and by Physio-Control/Jolife AB. Patients were enrolled from January 2008 to August 2012, from 6 participating EMS systems: Uppsala, Gävle, Västerås and Malmö in Sweden, Utrecht in the Netherlands and Dorset in the United Kingdom.

The device was supposed to be brought to all patients with dispatch codes for CA, loss of consciousness or other local guidelines suggesting OHCA. Enrolment took place when the paramedics recognised the situation as a cardiac arrest and all patients fulfilling the inclusions criteria without having any known exclusion criteria was randomized. This was done through opening a closed letter that was kept in the LUCAS™ back pack. A block randomisation with block size 6 was used.

Inclusion / exclusion criteria

Eligible patients for the study were adults with an unexpected OHCA where an attempt of resuscitation was considered appropriate.

Exclusion criteria were: 1. Traumatic cardiac arrest, including hanging 2. Age believed to be less than 18 years (no upper limit) 3. Known pregnancy 4. Defibrillated before LUCAS™ is brought to the scene 5. Patients body size not fitting the LUCAS™ System.

The algorithm

Patients randomized to the mechanical CPR algorithm were immediately treated with manual chest compressions until the device was deployed. Mechanical compressions were initiated and continued for 3 minutes; first defibrillation was delivered after 90 seconds into the first 3-minute cycle during ongoing compressions, without pausing to check the heart rhythm. Heart rhythm was checked after each 3-minute cycle; if a shockable rhythm was observed, a new 3-minute cycle was started, and the defibrillation was

delivered after 90 seconds of compressions without pausing. If no shockable rhythm was observed, a 3-minute cycle without interruption started. Patients randomized to receive manual CPR were treated in accordance with the 2005 European Resuscitation Council guidelines⁹⁰. In both groups, ventilation and drugs were given according to the same guidelines.

Before the start of the study all EMS personnel were trained in both study algorithms and were retrained every 6 months. Once a year randomly chosen EMS personnel were evaluated in training sessions using manikins regarding skill level and adherence to the algorithms. Feedback was given by the supervisors.

Patients suffering OHCA witnessed by the ambulance crew were treated according to a separate algorithm: Immediately when cardiac arrest is identified the ECG rhythm was analysed. If a non-shockable rhythm the patient was immediately randomized. When a shockable rhythm, one immediate defibrillation was performed followed by 2 minutes of manual compressions without any preceding analyse of ECG rhythm. After that patients not achieving ROSC was randomized.

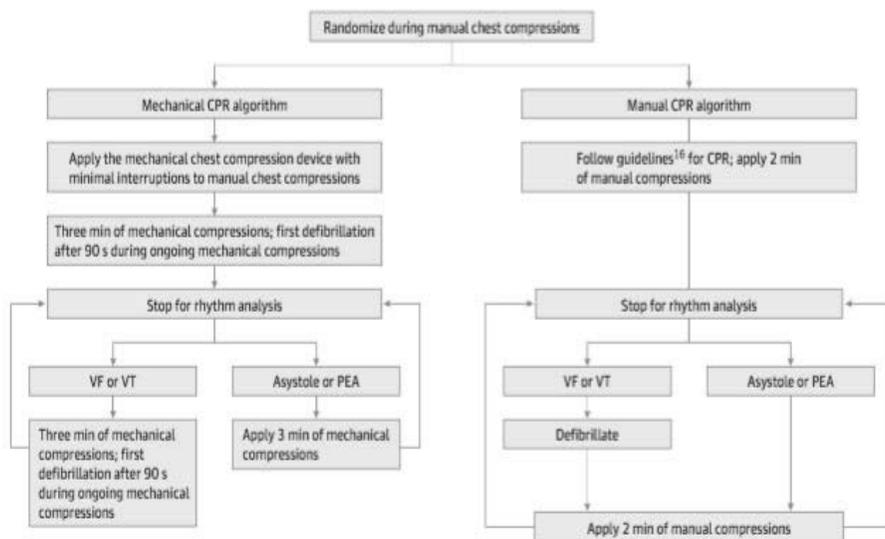


Figure 1. The study intervention algorithms.

The device

The Lund University Chest Compression Device. Jolife AB, Lund, Sweden, the manufacturer of the LUCASTM device, was the initial sponsor of the study, but since Jolife AB was acquired by Medtronic Inc., Minneapolis MN, USA (March 2011) and thereafter by Physio-Control, Redmond WA, USA the sponsorship was moved accordingly.

Two models of LUCAS™ was used during the study. The LUCAS™ 1 Chest Compression System was in use until early 2010. This was a pneumatic gas driven device. After that the LUCAS™ 2 Chest Compression System which is powered electrically was used. Both devices deliver compressions at a rate of 100/minute and to a fixed depth of 4-5 cm. The piston has a suction cup that may assist the chest back to neutral position.



Figure 2 The LUCAS™ device. © Physio-Control Inc.

Statistical analysis

All statistical analysis was coordinated by Uppsala Clinical Research Center, Uppsala, Sweden. Data was recorded in the Clinical Report Forms and entered into a web-based data capturing system.

Sample size and statistical methods

LINC was powered to detect superiority in 4-hour survival of the modified resuscitation algorithm, compared to manual CPR.

Sample size calculations were based upon data from the Uppsala-Gävle pilot study⁶⁴ together with data from the National Registry of Cardiac Arrest in Sweden¹⁰⁷. The proportion of 4-hour survival in the mechanical CPR group was assumed to be at least 31% and 25% in the manual treatment group.

To detect the anticipated difference of at least 6% with a power of 90% in the final analysis, the study required a total of 2500 patients, i.e. 1250 patients in each treatment group in the intention to treat (ITT) population. For the ITT and predefined populations the primary and all secondary endpoints was compared between treatment groups with frequency tables and two-sided Fisher's Exact Tests at the 4.8% and 5% level, respectively; 95% confidence intervals for difference in proportions was presented where applicable. The result for the primary endpoint in the ITT population was confirmative while the other results were regarded as supportive. Injuries after CPR was studied in detail⁸⁰.

Analysis population

Analysis populations were defined as:

- Safety population: all randomised patients except surviving patients without informed consent.
- Intention to treat population: all randomised patients except surviving patients without informed consent.
- Predefined population: all randomised patients, except surviving patients without informed consent, who have completed the study treatment without any protocol violations.

If a patient was randomized and thereafter given the wrong treatment, e.g. treated with manual CPR after being randomized to mechanical CPR the patient was included in the ITT population according to the randomization, but in the predefined population according to the given treatment.

Possible protocol violations were: violated inclusion or exclusion criteria; EMS response time exceeding 12 minutes; unwitnessed cardiac arrest or uncertainty thereof; the LUCAS™ device not brought to the patient at the first instance.

For missing data in the ITT population, the primary endpoint and all secondary endpoints, except survival to 1 and 6 months with CPC 1-2, was imputed as the worst outcome. Missing data, i.e. no record form filled in, was considered one of the possible protocol violations, thus no imputation of missing data was performed in the predefined population.

The confirmative analysis was performed in the ITT population. The predefined population analysis will be regarded as supportive.

Patient consent

All survivors with sufficient mental capacity were given both verbal and written information about the study, and opportunity to ask questions. If further participation was agreed on, written consent was obtained. If survivors did not have sufficient mental capacity, information was presented to family

members, who provided written consent if they decided to participate further. The ethics committees waived consent for included non-survivors

Post resuscitation care

If the patient achieved ROSC, he/she should be treated with TTM to 32–34 degrees Celsius for 24 h, regardless of initial ECG rhythm, unless contraindications existed. Acute CAG should be considered during the first 48 h of hospital admission.

Neurological outcome

Cerebral Performance Category (CPC) scale were used in survivors to define neurological outcome. CPC score 1 and 2 were indicating good neurological outcome¹⁰⁸. Neurological evaluation was done by the on-site responsible nurse or physician.

Safety Evaluation

Adverse device events and serious adverse events were recorded by both the EMS personnel and hospital personnel for each patient in order to record the clinical safety of the device.

The safety evaluation in the LINC trial comprised three main areas:

- Serious adverse events and serious adverse device events. This area cover events directly related CPR that occurs after randomization that severely affects the subject's health.
- The post mortem examination when subjects treated in the two different treatment arms was compared concerning CPR-related injuries⁸⁰.
- The third area relates to the criteria for termination stated in the study protocol¹⁰⁹.

According to protocol, after 1500 randomized patients an interim analysis of the primary end point of 4-hour survival in the ITT population was performed by an independent safety committee within the Scandinavian Society of Anaesthesiology and Intensive Care Medicine. The committee recommended to continue the study.

Paper III

The population and data sources

In this national descriptive study data was extracted from three different Swedish registers in order to identify our population, all patients 18 years or older, with an initially shockable first rhythm admitted alive and comatose after OHCA, see Figure 3:

- *The Swedish Register for Cardiopulmonary Resuscitation*¹⁹. All EMS organizations report to this register that covers almost all cases of OHCA in Sweden.
- *The Swedeheart Registry*¹¹⁰. This registry collects data on CAG and PCI from all patients investigated and treated at all centres in Sweden performing coronary interventions
- *The National Patient Register*. Comorbidity data were based on ICD codes from this register. All data were anonymized according to regulations.

Patients undergoing CAG on the same day as the OHCA were deemed to have early CAG. Missing registry data on ECG findings were completed from patients' electronic health records. ECGs were evaluated based on the 2017 European Society of Cardiology guidelines for the management of acute myocardial infarction in patients with ST-elevation¹¹¹. The presumed aetiology of the arrest was based on the paramedics' judgement and retrieved from the Swedeheart Registry.

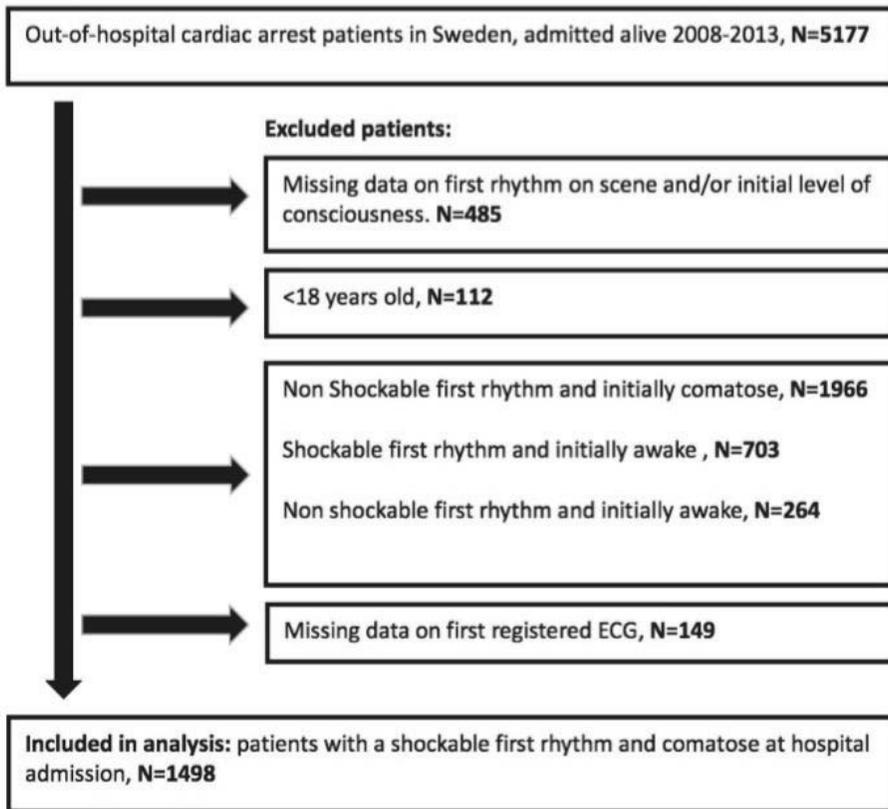


Figure 3. Participant flow

Statistics

Dichotomous variables were tested with the chi-square test. Continuous variables were compared across groups using the Mann-Whitney U Test. Logistic regression was performed, examining the impact of gender on utilization of early CAG while controlling for confounding variables. In this analysis all ST-elevations and Left Bundle Branch Blocks (LBBB) were analysed together in one group while patients with other ECG patterns were analysed in the other group. A p-value <0.05 was considered significant. In our multivariable analysis complete cases were analyzed. 5.9% of cases in the ST-elevation/LBBB group and 6.5% in the group without ST-elevation/LBBB had missing data, as shown in detail in Table 1. As a sensitivity analysis accounting for missing data, multiple imputation was performed under the assumption that data were missing at random. Multiple imputation was performed using all variables in our primary analysis model. Only minor dissimilarities regarding odds ratio estimates were seen after multiple imputation why we present the former.

Early CAG was defined as CAG performed during the same day as the OHCA. In the group receiving no early CAG, patients receiving no CAG at

all and those receiving CAG after that first day but no later than after 4 weeks were grouped together. Statistical analyses were performed using IBM SPSS Statistics for Mac OS, Version 23.0, Armonk, NY: IBM Corp.

Paper IV

The population

In this retrospective, observational, single-centre study, we included all successfully resuscitated comatose survivors of CA, treated at the general intensive care unit (ICU) of Uppsala University Hospital during 2006-2016.

Inclusion criteria:

- All cardiac arrest patients, comatose after successful sustained ROSC, admitted to the general ICU at Uppsala University Hospital during 2006 to 2016.

Exclusion criteria:

- <18 years old
- Treated at another ICU within the hospital
- ROSC but never treated within the ICU
- Awake after ROSC
- Immediate decision of palliative care after ROSC
- Initially treated (\geq day) at another hospital before transfer to the general ICU
- Awake and spontaneously breathing at arrival to the general ICU.

Data collection

Patients were identified through the hospitals electronic journal system, based on ICD codes for CA. Aetiology of the cardiac arrest was defined according to judgement of the treating physician at the time of the arrest. The first registered ECG following ROSC in cases with no obvious non-cardiac origin of the cardiac arrest were independently reviewed by two cardiologists to identify ECG indicating ischemia and thereby prompt investigation by CAG, according to guidelines¹¹¹. When the patients' actual ECG could not be found, the electronic journal system was searched for data on first registered ECG after ROSC (n=24). The electronic journal system was screened for all CAGs performed within 6 hours from the CA. Sustained ROSC was defined as 20 consecutive minutes with persisting circulation without the need for chest compressions¹⁸.

Settings

Study region

Uppsala University Hospital serves as the primary hospital for Uppsala County, with a population of 367,000 inhabitants. It also serves as a tertiary referral centre.

Pre-Hospital EMS system

Uppsala has a first-tier system. The dispatch centre simultaneously sends two ambulances to an expected OHCA. All ambulance crews are trained in advanced life support and consists of at least one registered nurse. Firefighters sometimes serve as first responders in remote areas.

Post Resuscitation care

During the study period, post resuscitation care was given according to a standard protocol including TTM, conventional supportive care and prognostication according to guidelines⁸⁹. At Uppsala University Hospital, the general ICU is the primary intensive care ward for post resuscitation care of OHCA and IHCA victims.

Neurological outcome was categorized according to the CPC scale¹⁰⁸, a 5-point scale where 1 or 2 is considered good neurologic outcome.

Statistics

Dichotomous variables were tested with the chi square test unless otherwise indicated. Continuous variables were compared across groups with Mann-Whitney U-test. Statistical analyses were performed using IBM SPSS Statistics for Mac OS, Version 22.0, Armonk, NY: IBM Corp.

Ethics

Ethical approvals

The studies included in this thesis were approved by the following regional boards of ethics:

Paper I and II

The regional ethics review board in Uppsala, Sweden (Reg. no. 2007/271), the research ethics committee in the United Kingdom (Reg. no. 08/H0201/33) and the United Human Subjects Research Committees in the Netherlands (Reg. no. NL 21034.10008. R-08.10E LINC).

Paper III

The regional ethics review board in Stockholm, Sweden (Reg. no. 2014/1139-31/2).

Paper IV

The regional ethics review board in Uppsala, Sweden (Reg.no 2017/278) All included studies were conducted in accordance with regulatory requirements, good clinical practices and the ethical principles of the declaration of Helsinki.

Ethical considerations

The question of consent and inclusion into studies is not only a question of protecting the patient from harm, it is also a question of autonomy and the patients free will. If a patient that cannot give consent would be denied inclusion, this would be based on an assumption that the patient values his or hers own privacy over the benefits for others.

Paper I and II

OHCA is a medical emergency and treatment must start instantly. All victims of cardiac arrest are at least temporarily incapacitated and most of them will die. The emergency of the situation in combination with an unconscious patient rules out the possibility to obtain informed consent prior to inclusion in a study. This is supported by paragraph 30 in the declaration of Helsinki¹² “if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group”, and instead the researcher must seek informed consent from “the legally authorized representative, i.e. a family member. This deferred consent is often sought later due to the often emotional and traumatic nature of the initial situation.

In the LINC trial, presented in this thesis, like other cardiac arrest studies, the regional boards of ethics waived consent from deceased patients. When the mortality numbers are high, like after cardiac arrest, this obviously preclude the option to demand a deferred consent from the patient since this would lead to inclusion bias. The argument against obtaining consent from a family member after their relative has passed away is the emotional stress this would lead to, raising concerns about the validity of this consent, or refusal thereof.

Besides from using the LUCAS™, the LINC trial tested a novel algorithm which included defibrillations during ongoing defibrillations without pausing to check the heart rhythm, i.e. without knowing if the rhythm was shockable or not. This decision from the study group was based on available knowledge in 2006-2007, and the rationale for this decision was the intention to minimize predefibrillation- and postdefibrillation pauses. Inappropriate shocks, i.e.

defibrillation of a non-shockable rhythm had previously been shown relatively common with little or no evidence that they were harmful¹¹³.

Paper III

In this register study data was extracted from the Swedeheart register system¹¹⁰. Patients included in this register are informed about inclusion into the registry and given the opportunity to decline participation. After obtaining data from the Swedish National Board of Health and Welfare data was anonymized according to regulations.

Paper IV

Data was retrieved from the hospitals electronic journal system. All patients were anonymized according to regulations. The ethics committee waived consent for included patients.

Results

Paper I and II (The LINC trial)

The aim of the LINC trial was to investigate if administering mechanical chest compressions with defibrillation during ongoing compressions, compared with manual CPR according to guidelines would improve 4-hour survival.

Main results

In this study 2589 victims of OHCA were included. After randomization 1300 patients were included in the mechanical CPR group and 1289 in the manual CPR group. There were two notable differences between the two groups in background variables: The mechanical group had longer time to defibrillation, 17.0 vs 15.5 minutes and a higher number of defibrillations were given in the mechanical CPR group (more patients received at least one defibrillation, and more patients received multiple shocks) This was possibly due to the different treatment algorithms.

Primary and secondary outcomes

There was no difference in primary outcome, i.e. 4-hour survival between the mechanical CPR group and the manual CPR group, 23.6% vs. 23.7%; risk difference -0.05; 95% C.I. -3.3 to 3.2. Neither were any differences between groups found in any of the secondary outcomes, see table 1.

No difference was seen between the groups in proportions of patients with CPC 1 or 2. After 6 months 99% of the surviving patients in the mechanical CPR group and 94% in the manual CPR group had CPC 1 or 2.

Serious adverse events

Seven cases of serious adverse events were reported in the mechanical CPR group:

- 1 possible airway bleeding
- 1 suspected rupture of the spleen (not confirmed during autopsy)
- 1 pneumothorax
- 1 fractured thoracic vertebrae (manual CPR performed in patient's bed before mechanical CPR)
- 1 flail chest (noted before start of mechanical CPR)

- 2 cases of where the device were removed due to problems attaching the device

Three cases of serious adverse events were reported in the manual CPR group:

- 1 flail chest
- 1 abdominal aortic aneurysm
- 1 pneumothorax

Table 1. *Primary and secondary outcome*

Outcomes	No. (%) of Participants		P Value	Treatment Difference, % (95% CI)
	Mechanical CPR (n = 1300)	Manual CPR (n = 1289)		
4-Hour survival ^a	307 (23.6)	305 (23.7)	>.99	-0.05 (-3.3 to 3.2)
ROSC ^b	460 (35.4)	446 (34.6)	.68	0.78 (-2.9 to 4.5)
Arrival at emergency department with palpable pulse	366 (28.2)	357 (27.7)	.83	0.46 (-3.0 to 3.9)
Survival to discharge from ICU with CPC 1-2 ^c	98 (7.5)	82 (6.4)	.25	1.18 (-0.8 to 3.1)
Survival to hospital discharge with CPC 1-2 ^c	108 (8.3)	100 (7.8)	.61	0.55 (-1.5 to 2.6)
1-Month survival with CPC 1-2 ^d	105 (8.1)	94 (7.3)	.46	0.78 (-1.3 to 2.8)
6-Month survival with CPC 1-2 ^d	110 (8.5)	98 (7.6)	.43	0.86 (-1.2 to 3.0)

Abbreviations: CPC, Cerebral Performance Category score; CPR, cardiopulmonary resuscitation; ICU, intensive care unit; ROSC, restoration of spontaneous circulation.

^a One patient in mechanical CPR group and 3 in manual CPR group with unknown 4-hour survival were imputed as nonsurvivors.

^b Two patients in mechanical CPR group and 1 in manual CPR group with unknown ROSC were imputed as having no ROSC.

^c 10 patients in mechanical CPR group and 8 in manual CPR group with unknown outcome were imputed as having a bad outcome.

^d 14 patients in mechanical CPR group and 15 in manual CPR group with unknown outcome were imputed as having a bad outcome.

Paper III

The aim of this registry study was to investigate the interaction of gender and utilization of early CAG and PCI, CAG findings, comorbidity and outcome.

Main results

We included 1498 resuscitated victims of OHCA with an initially shockable rhythm, comatose at hospital arrival, 78 % were men. 593 patients (40%) of the patients had ST-elevation or LBBB (79% men) and 905 patients (60%)

had other ECG findings (78% men). Men and women did not differ in respect to their first ECG findings, 30% vs 29% had ST-elevation, 10% vs. 9% had LBBB and 18% in both men and women had a normal ECG.

Among patients without ST-elevation more men had previously known ischaemic heart disease, 27% vs. 19% (P=0.02) and a presumed cardiac origin of the arrest, 86% vs. 72% (P<0.001), but shorter EMS response time, median 6 vs. 7 minutes (P<0.001) and lower incidence of crew-witnessed OHCA 7% vs. 15% (P=0.001). Regardless of gender, more women had OHCA at home.

No gender differences were seen in proportions of CAG in any of the groups but among patients without ST-elevation/LBBB more men had PCI following CAG, 59% vs. 42% (P=0.03) and more often at least one significant stenosis, 78% vs. 54% (P=0.001). In the same group more men had 3-, 2- and 1-vessel disease, see table 2

To investigate the impact of gender on use of early CAG while controlling for confounding variables, gender, age, comorbidity and circumstances of the arrest was entered in the model. Regardless of first registered ECG we found no association between female gender and the use of early CAG.

There was no difference between men and women in survival at 30 days, 6 months or 1 year regardless of first registered ECG, see table 3.

Table 2. ECG after ROSC, CAG findings and treatment^a. Data are presented as No. (%) of participants.

	Total population (n=1498)			ST-elevation or LBBB (n=593)			No ST-elevation or LBBB (n=905)		
	Men (n=1171)	Women (n=327)	P-value	Men (n=466)	Women (n=127)	P-value	Men (n=705)	Women (n=200)	P-value
First registered ECG			0.97			0.95			0.82
ST-elevation	346 (30)	96 (29)		346 (74)	96 (76)				
LBBB	116 (10)	30 (9)		116 (25)	30 (24)				
RBBB + ST-elevation	4 (0.3)	1 (0.3)		4 (0.9)	1 (0.8)				
Normal ECG	214 (18)	60 (18)					214 (30)	60 (30)	
ST-depression	163 (14)	51 (16)					163 (23)	51 (26)	
Pathologic T-wave	32 (3)	10 (3)					32 (5)	10 (5)	
Other	126 (11)	29 (9)					126 (18)	29 (15)	
Unknown	64 (6)	22 (7)					64 (9)	22 (11)	
RBBB + ST-depression	106 (9)	28 (9)					106 (15)	28 (14)	
Investigations and treatment									
Early CAG	529 (45)	130 (40)	0.08	320 (69)	82 (65)	0.38	209 (30)	48 (24)	0.12
PCI, % of patients treated with early CAG	364 (69)	82 (63)	0.21	241 (75)	62 (76)	P=0.96	123 (59)	20 (42)	0.03
	n=516	n=128	P-value	n=311	n=82	P-value	n=205	n=46	P-value
CAG findings			0.02			0.11			0.01
Normal findings or atheromatosis	84 (16)	32 (25)		38 (12)	11 (13)		46 (22)	21 (46)	
1-vessel disease	185 (36)	49 (38)		122 (39)	36 (44)		63 (31)	13 (28)	
2-vessel disease	107 (21)	29 (23)		66 (21)	24 (29)		41 (20)	5 (11)	
3-vessel disease	100 (19)	12 (9)		63 (20)	9 (11)		37 (18)	3 (7)	
LMCA stenosis ^b	40 (8)	6 (5)		22 (7)	2 (2)		18 (9)	4 (9)	
At least one significant lesion	432 (84)	96 (75)	0.02	273 (88)	71 (87)	0.77	159 (78)	25 (54)	0.001

Abbreviations: LBBB, left bundle branch block; RBBB, right bundle branch block; LMCA, left main coronary artery. ^a Statistics are calculated on all patients (n=1498) unless otherwise indicated. ^b LMCA stenosis plus 0, 1, 2 or 3 diseased vessels.

Table 3. Outcome data. Data are presented as No. (%) of participants.

	Total population (n=1498)			ST-elevation or LBBB (n=593)			No ST-elevation or LBBB (n=905)		
	Men	Women	P-value	Men	Women	P-value	Men	Women	P-value
30-days survival	644 (55.0)	177 (54)	0.78	277 (59)	69 (54)	0.30	367 (52)	108 (54)	0.63
6-months survival	612 (52)	169 (52)	0.85	265 (57)	65 (51)	0.25	347 (49)	104 (52)	0.49
1-year survival	597 (51)	164 (50)	0.79	260 (56)	63 (50)	0.22	337 (48)	101 (51)	0.50

Paper IV

The aim of this retrospective observational single-centre study was to compare OHCA and IHCA in comorbidity, characteristics of the CA, post resuscitation care including utilizations of early CAG, CAG findings and outcome.

Main results

We included 423 patients in this study, 213 OHCA patients (70% men) and 210 IHCA patients (61% men). When comparing OHCA and IHCA there was no difference in age, 66 vs. 69 years old, but fewer patients in the OHCA group had previously known hypertension, 47% vs. 58% ($P=0.02$), diabetes, 19% vs. 29% ($P=0.02$), cancer, 10% vs 20% ($p=0.008$) and kidney failure, 4% vs 24% ($P<0.001$).

More patients in the OHCA group had cardiac arrest without any obvious non-cardiac origin, 77% vs. 50% ($P<0.001$). There was no difference in proportions of patients with witnessed cardiac arrest but more OHCA patients had a shockable first rhythm, 47% vs. 13% ($P<0.001$). OHCA patients had longer time to both ROSC and sustained ROSC as well as lower rates of bystander CPR. See table 4.

OHCA patients more often had ST-elevation or LBBB, 30% vs. 12% ($P=0.001$). They also had higher rates of early CAG, 52% vs. 25% ($P<0.001$), but no difference in rates of PCI following CAG was seen. OHCA and IHCA did not differ in CAG findings of any significant stenosis, see table 5.

Regardless the location of the arrest, patients referred to early CAG more often had OHCA, witnessed arrest, a shockable first ECG rhythm and ST-elevation/LBBB on first ECG after ROSC. Patients not investigated with early CAG had higher rates of previous stroke, kidney failure, atrial fibrillation and more often had treatment withdrawal at ICU. Proportions of men and women did not differ between those investigated with early CAG or not.

A higher proportion of OHCA patients were treated with TTM, 82% vs. 45% ($P<0.001$). This difference was visible regardless of the presumed origin of the arrest. Among patients without any obvious non-cardiac origin of the arrest IHCA patients more often were treated with CRRT, 2% vs. 13% ($P<0.001$).

As seen in table 6, no survival difference between the groups was seen after 30 days, 6 months or 1 year.

Table 4. *Characteristics of the arrest. Data is presented as No. (%) of participants unless otherwise indicated.*

	OHCA n=213	IHCA n=210	p-value
Suspected origin of the arrest			
No obvious non-cardiac origin	164 (77)	104 (50)	<0.001
Non-cardiac origins of the arrest			
-Asfycytic origin	34 (16)	59 (28)	
-Circulatory failure, sepsis	1 (1)	16 (8)	
-Circulatory failure, bleeding	1 (1)	15 (7)	
-Circulatory failure, other ^a	1 (1)	4 (2)	
-Intoxication	4 (2)	1 (1)	
-Trauma	2 (1)	2 (1)	
-Drowning	4 (2)	0	
-Cerebral event	2 (1)	2 (1)	
-Anaphylaxis	0	6 (3)	
-Other non-cardiac origin ^b	0	1 (1)	
Circumstances of the arrest			
Witnessed ^c	185 (87)	177 (84)	0.45
Bystander CPR	150 (71) (n=211)	210 (100) (n=210)	<0.001
Shockable first rhythm	98 (47) (n=210)	26 (13) (n=204)	<0.001
Time to any ROSC ^d , minutes, median (range)	20 (2-80) (n=179)	10 (1-34) (n=161)	<0.001
Time to sustained ROSC ^d , minutes, median (range)	23 (2-120) (n=179)	10 (1-90) (n=161)	<0.001

Abbreviations: CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation. ^a 1 OHCA patient due to caval compression. 4 IHCA patients: 2 patients due to anaesthesia, no bleeding, 1 due to vagal reaction, 1 due to haemodialysis. ^b IHCA due to hypothermia and severe acidosis. ^c 22 of witnessed OHCA's were witnessed by EMS crew. ^d Only witnessed patients analysed.

Table 5. ECG findings and treatment data. Data is presented as No. (%) of participants.

	OHCA	IHCA	p-value
ECG findings, patients with no obvious non-cardiac origin of CA and ECG data.^a			
	n=162	n=84	
ECG indicating ischemia	49 (30)	10 (12)	0.001
-ST-elevation	18 (11)	3 (4)	
-LBBB	21 (13)	7 (8)	
-RBBB + ST elevation	10 (6.2)	0	
Other ECG rhythms, including normal ECG	113 (70)	74 (88)	
Revascularization data^{a,b}. Patients with no obvious non-cardiac origin of CA and ECG data. a,b			
	n=162	n=84	
Early CAG	84 (52)	21 (25)	<0.001
PCI, No (%) of early CAG	39 (46)	7 (33)	0.28
Early CAG when ECG indicating ischemia ^c	32 (65) n=49	5 (50) n=10	0.48
PCI, No (%) of early CAG when ECG indicating ischemia ^c	24 (75)	2 (40)	0.14
Time from CA to early CAG, minutes, median (range)	143 (68-334)	127 (51-243)	0.09
CAG findings. Patients with no obvious non-cardiac origin of CA and ECG data.^{a,b}			
	n=82	n=21	
Any significant stenosis (vs normal findings / atheromatosis)	55 (67)	10 (48)	0.10
-Main stem stenosis	6 (7)	0	
-3-vessel disease	6 (7)	0	
-2-vessel disease	28 (34)	6 (29)	
-1-vessel disease	15 (18)	4 (19)	
Normal findings/ Atheromatosis	27 (33)	11 (52)	

Abbreviations: CA, cardiac arrest; LBBB, left bundle branch block; RBBB, right bundle branch block; CAG, coronary angiography; PCI, percutaneous coronary intervention. ^a 6 patients with IHCA on the catheterization laboratory was already referred to CAG and thereby excluded from analysis. ^b 2 patients with OHCA and 1 patient with IHCA had early CAG but lack ECG data and was not included in the analysis. ^c Fishers Exact test

Table 6. Outcome. Data is presented as No. (%) of participants.

	OHCA	IHCA	p-value
Withdrawal of treatment at ICU	89 (42) (n=213)	85 (41) (n=209)	0.82
Time to withdrawal of treatment at ICU, hours, median (range)	57 (22-301) (n=85)	62 (3-1526) (n=84)	0.61
Survival to ICU discharge	111 (53) (n=210)	106 (52) (n=205)	0.82
Survival to hospital discharge	87 (42) (n=209)	75 (37) (n=205)	0.29
-with CPC 1-2	75 (36) (n=207)	50 (25) (n=202)	0.01
30-days survival ^a	88 (42) (n=209)	84 (41) (n=205)	0.82
6-months survival	83 (40) (n=208)	71 (35) (n=205)	0.27
1-year survival	82 (39) (n=208)	68 (33) (n=205)	0.19
Patients returning to home anytime	84 (40) (n=208)	64 (32) (n=203)	0.06

Abbreviations: ICU, intensive care unit; CPC, cerebral performance category.

^a 1 OHCA patient and 9 IHCA patients had 30-days survival but did not survive until hospital discharge.

Discussion

Main findings

The main findings in the papers included in this thesis were:

Paper I and II

A novel algorithm with mechanical chest compressions and defibrillation during ongoing CPR did not give any survival advantage compared to manual CPR according to guidelines. There was a good neurological outcome in the vast majority of survivors in both groups.

Paper III

In a population with an expected high incidence of cardiac aetiology underlying the OHCA, there was no gender differences in patients with ECG findings strongly indicating coronary ischaemia, i.e. ST-elevation or LBBB. Despite this men had more advanced CAD and women more often normal angiography findings.

Paper IV

In a population of consecutive successfully resuscitated ICU-treated cardiac arrest victims, despite OHCA patients had several factors associated with good outcome, IHCA patients had shorter time to ROSC and no difference in outcome was seen.

Paper I and II

We chose 4-hour survival as primary endpoint to study the two different algorithms as we believed it would minimize any influence of possible variations in post resuscitation care. However, post resuscitation care was similar between groups supporting the validity of our secondary endpoint findings of similar survival rates with good neurological up to six months after the arrest.

One important feature of the mechanical CPR algorithm was that defibrillations were given during ongoing compressions without assessment of

rhythm before defibrillation. The assumption was that the elimination of pre- and postshock pauses would potentially improve outcome. The design of the study was based on available knowledge from 2006-2007, where guidelines still recommended EMS personnel to give a period of compressions prior to defibrillation in cases with prolonged collapse before initiation of CPR¹¹. The blind shocks during ongoing compressions might today raise some concerns. Firstly, we can assume that many patients were defibrillated despite having a non-shockable rhythm. This however is shown to be relatively common and of little or no harm¹¹³. Secondly, when performing defibrillation during ongoing compressions we can assume defibrillations not to be given during the upstroke phase of the compression. This might sound potentially harmful but was based on earlier knowledge. Not until 2010 the first data was published showing that defibrillations given during the upstroke phase had the greatest chances of success¹¹⁴⁻¹¹⁶, possibly due to enhanced coronary blood flow and decreased volume of the heart with lower energy requirements.

We do not know if and to what extent our result was affected by the quality of manual CPR. Data from approximately 10% of the patients revealed a chest compression fraction (time with chest compressions divided by CPR time) of 0.78 in the manual CPR group which is reasonably good. The importance of minimizing time without compressions is previously discussed in this thesis. Also, we do not know what impact the 1.5 minutes delay to defibrillation in the mechanical CPR group had on the result. However, there is indications that quality of CPR deteriorated over time. Despite this reasonably good chest compression fraction, in a pre-planned secondary analysis of the VF/VT patients in the LINC trial, among patients with ROSC within 10 minutes from start of CPR, patients receiving manual CPR showed a significantly higher 6 months survival with CPC 1 or 2 compared to the mechanical CPR group, while the opposite was found when time to ROSC exceeded 10 minutes (no difference in 6 months survival in total was seen)¹¹⁷. A similar result was seen in a secondary analysis of the CIRC trial when duration of CPR exceeded 16.5 minutes¹¹⁸.

However, we can assume that our results were affected in some degree by our exclusion criteria. In order to optimize the evaluation of our mechanical CPR algorithm we excluded patients defibrillated before arrival of the EMS crew (n=377) and those with crew witnessed arrest achieving ROSC after first defibrillation. These excluded patients have an expected high survival, why our observed survival rates probably were affected in a negative way.

Notably, only 75% of the patients in the mechanical CPR group received at least one defibrillation, a number that obviously should have been 100% according to the ECG rhythm. Of those in the mechanical CPR group that did not receive at least one defibrillation 93% of the patients had a non-shockable rhythm why we suspect that some of the responders looked at the ECG before the shock.

The similar low rates of serious adverse events found in the two treatment arms, together with the previously discussed autopsy study performed in conjunction with the LINC trial⁸⁰ do not indicate that mechanical CPR using the LUCAS™ device shall be avoided. Still there is an ongoing debate concerning the possible harms of mechanical CPR. A recently published observational cohort study presented significantly higher rates of CPR related injuries after use of the LUCAS™ device compared to manual CPR¹¹⁹. On the other hand, in a randomized non-inferiority study¹²⁰ the LUCAS™ device did not cause significantly more serious or life-threatening damage than manual CPR but this risk could not be excluded for the other major device on the market, the AUTOPULSE™. This might reflect the differences in the way these two products work but this remains to be further studied in detail.

Following the LINC trial, two more large randomized trials, The CIRC trial³² (n=4231) and the PARAMEDIC trial³¹ (n=4471) could not show any evidence for improved outcome in patients treated with mechanical CPR compared to manual). The tested device was the Autopulse™ and LUCAS™ in the two trials, respectively. Different from the LINC trial, the two following studies did not test an entire new algorithm, instead the usual manual CPR was replaced by mechanical CPR. The absence^{5,121,122} of evidence supporting the routine use of mechanical CPR has been supported by reviews and meta-analyses^{123,124}.

So when to use mechanical CPR devices? What are these special circumstances when its use should be considered, according to guidelines^{16,17}, in what situations do potential benefits outweigh potential harm? We can assume there is a benefit of mechanical CPR in transport situations. The extrication process, i.e. the transport of patients from the scene of the OHCA to the ambulance was found significantly shortened from 270 to 39 seconds when using a mechanical device¹²⁵. Like discussed earlier we know that quality of manual CPR deteriorates during transportation and mechanical CPR has been reported being a feasible solution in ambulance and helicopter transports^{126,127}.

A CPR situation in a moving ambulance is also a matter of safety of the personnel. Unrestrained occupants riding in the patient compartment in an ambulance during emergency use, e.g. during ongoing manual CPR is at highest risk of injury and death if involved in a crash^{128,129}. Also, mechanical CPR is a plausible alternative during situations of hypothermia and drowning⁶².

What about mechanical CPR inside the hospital? Results from mechanical CPR in the emergency department show conflicting results^{130,131}, possibly due to different study designs and populations. However, mechanical CPR feels like a feasible alternative in situations with less rescuers available to perform CPR, e.g. in a smaller hospital during night time or in mass casualties. There is less debate whether mechanical CPR has a role in the cardiac catheterization laboratory. Mechanical CPR facilitates CAG and PCI and allow the initiation of circulatory support like intra-aortic balloon pump. It also serves well as a bridge to extracorporeal life support¹³²⁻¹³⁵.

A recent meta-analysis¹³⁶ found an association between mechanical CPR and survival after IHCA. The quality of evidence was however very low. Of the identified studies only three were randomized, all of them small^{121,122,137}. The same meta-analysis found an association between survival after IHCA and mechanical CPR, but this must be interpreted with caution, given the quality of the evidence. You might speculate if there is a role for mechanical CPR in-hospital, e.g. because of available trained teams opportunities and a decent opportunity to gain experience. However, there is an absolute need for further studies¹³⁸.

To summarize, we cannot with certainty tell to what degree the different components of the two compared algorithms affected the results. The question of whether this device shall replace manual chest compressions can still be debated. However, our studies support that this mechanical device, using the tested algorithm, can deliver CPR with similar outcome as manual CPR without major complications. Our findings were supported by a predefined subgroup analysis where patients without any protocol violations showed similar lack of outcome differences¹³⁹. Even if it was not investigated within this study, we believe it could be used according to what is now recommended in guidelines, i.e. in situations where manual high-quality CPR for any reason cannot be delivered. A prerequisite is that training must be performed as well as for manual as for mechanical CPR.

Paper III

To our best knowledge, this is the first study reporting gender specific findings after OHCA. Despite no gender differences in rates of ST-elevation or LBBB men had more advanced coronary artery disease and more often at least one significant stenosis. Men also more often had CAG followed by PCI, implicating that our data on CAG findings have clinical relevance. However, these differences were only seen among patients without ST-elevation/LBBB.

This gender difference in CAG findings might be a result of women more often having non-obstructive CAD^{140,141}, resulting in normal angiography findings. Furthermore, the investigated period was 2008-2013. The 2005 guidelines did not recommend immediate CAG in absence of ST-elevation or LBBB, in contrast to 2010 guidelines. Since women have lower rates of ST-elevation on post-resuscitation ECG there is a possibility that more women underwent early CAG after 2010, but to what extent, if any, this affected our result we do not know.

As previously discussed, we only included patients with an initially shockable rhythm. By this we intended to investigate a population with a high proportion of cardiac arrests with underlying cardiac aetiology. This might, at least partly, explain why we found no association between female gender and lower use of early CAG. This contrasts with previous studies^{99,100}.

In further support for the link between ST-elevation/LBBB and higher rates of cardiac aetiology we found that only among patients without ST-elevation/LBBB more men were deemed to have a cardiac origin of the arrest. However, this information is based on the paramedics' assumption why there always is a risk of them being influenced by first registered ECG, since this difference was not seen among patients with ST-elevation/LBBB.

We found no outcome differences between men and women, regardless of first ECG. In line with previous discussions, this is consistent with previous findings that women have increased odds of survival in cases with a presumed cardiac origin¹⁴².

In a recent study, Lemkes and colleagues¹⁴³ presented the first randomized clinical trial including victims of OHCA without ST-elevation and with an initial shockable rhythm, randomizing to either immediate CAG or CAG delayed until after neurologic recovery. They found no difference in 90-days mortality. Interestingly, only 5% of the patients had an acute thrombotic occlusion. Obviously this raises questions if OHCA victims without ST-elevation shall go directly to the cardiac catheterization laboratory or not, i.e. to the ICU for initial treatment and further evaluation. Comparisons between our selected material and this prospectively included population must however be done with caution and upcoming studies in this field is of greatest interest¹⁴⁴⁻¹⁴⁶.

Unfortunately, due to limitations in our register data we had to define early CAG as CAG during the same day as the cardiac arrest. By doing so we assume missing some CAGs performed during the first hours following the arrest. This could have biased our results.

Our study has several other limitations. The CAG and PCI data are from a selected population with patients already referred to the cardiac catheterization laboratory. We do not know if LBBBs on first ECG were previously known or not and we lack information of culprit lesions. We also lack information of performed TTM Finally, we cannot tell to what extent any "obvious non-cardiac causes" was present.

However, we have a solid number of patients with low numbers of missing data. Data was extracted from high-quality registers. Further studies are needed to identify those patients who will benefit most from early CAG after cardiac arrest, or alternatively to identify those patients where we should look for other reasons to the cardiac arrest.

Paper IV

To our best knowledge this is the first report comparing ICU treated victims of OHCA and IHCA regarding patients' characteristics, including data from early CAG. In line with the general perception, even though this has not been fully confirmed, IHCA patients had more extensive comorbidity. OHCA

patients more often had a shockable first ECG rhythm but lower rates of bystander CPR. Altogether OHCA patients had several factors associated with good outcome. Despite this IHCA patients had shorter time to ROSC and no difference in outcome between the groups were seen.

Except from the different rates of bystander CPR we can assume there is differences in quality of CPR between OHCA and IHCA affecting outcome. After OHCA in Sweden, there is a 30% chance that the layman providing CPR have education in basic life support, to compare with after IHCA where all hospital personnel regularly receive training in advanced life support. Furthermore, a resuscitation team is emergently called to all IHCAs.

Even though we could only categorize patients into having a cardiac arrest with or without any obvious non-cardiac origin, OHCA patients had higher rates of several characteristics pointing towards a possible cardiac origin. If there really is a true preponderance of arrests of cardiac origin in the OHCA group, this would differ from previous studies where similar rates of cardiac origin has been seen. This could however be due to different studied populations since this is the first study investigating an ICU population in this perspective.

One previous study has investigated the role of early CAG after IHCA, showing better survival after early revascularization¹⁰⁶. Probably reflecting the sparse evidence, European guidelines have never addressed the role of early CAG after IHCA. Unfortunately, our population was too small to perform a proper adjusted analysis investigating any associations between early CAG and outcome. We did however find OHCA patients more often being investigated with early CAG, although no difference in rates of subsequent PCI was seen. This probably reflects the different populations. You might suspect that patients with ST-elevation/LBBB were a more homogenous group, since no differences in rates in CAG or subsequent PCI was seen in that group.

Even though CAG findings might indicate a pattern of more multivessel disease in the OHCA group, we did not find any difference in rates of at least one significant stenosis.

Illustrating enough, we found that patients referred to early CAG, regardless the location of the arrest had several characteristics we associate with good outcome after cardiac arrest; they more often had experienced OHCA than IHCA and had higher rates of ST-elevation/LBBB, witnessed arrests and a shockable first rhythm. They also had lower rates of pre-existing comorbidities and withdrawal of ICU treatment.

The reason why more patients in the OHCA group were treated with TTM we do not know. Patients more often had an obvious non-cardiac aetiology underlying the arrest after IHCA, which might have affected decisions regarding TTM treatment. Despite this difference in post resuscitation care, together with previous discussed dissimilarities, survival did not differ between groups. The reason for this is certainly multifactorial.

This study has several limitations. We do admit that CAG after OHCA is recommended immediately in cases with ST-elevation and within 2 hours in absence of ST-elevation when cardiac aetiology is suspected. Due to logistical and organizational reasons we believed screening for CAGs performed within that time frame would have led to many investigations being missed. The results also showed that mean time for both OHCA and IHCA was over 2 hours. Based on previous data^{29,147,148} we therefore deemed CAG within two hours being early CAG. Similar to in paper III, we present CAG findings from a selected population and we lack information of culprit lesions. We were not able to classify cardiac cause or not underlying the arrest, making interpretation of revascularization data more difficult.

We do however report consecutive successfully resuscitated comatose ICU-treated cardiac arrest victims, comparing OHCA and IHCA with solid data from a population of a reasonable number of patients with a low number of missing data.

Summary/Conclusion

Paper I and II

In patients with OHCA, mechanical chest compressions in combination with defibrillation during ongoing compressions provided no improved 4-hour survival vs manual CPR according to guidelines. There was a good neurological outcome in the vast majority of survivors in both groups, and neurological outcomes improved over time.

Paper III

In a population with an expected high proportion of presumed cardiac aetiology, our results suggest that despite the fact that no gender differences in proportions of ECG findings indicating ischaemia were found, men seem to have more severe CAD while women more frequently have normal angiography findings. Despite this, no gender difference was seen in survival up to 1 year. Female gender was not associated with the utilization of early CAG.

Paper IV

Despite OHCA patients admitted to ICU after cardiac arrest have several factors associated with good outcome compared to IHCA patients, outcome do not differ between groups. A relatively larger proportion of all IHCA compared to OHCA patients are admitted to the ICU after successful resuscitation, stressing the need for more extensive research of IHCA patients.

Future Perspectives

This thesis underlines several knowledge gaps in the field of cardiac arrest and CPR.

Who will benefit from mechanical CPR? As previously discussed there are several convincing arguments for why mechanical CPR would improve outcome after OHCA. So why have three large randomized clinical trials not been able to show any difference?

The LINC trial tested a novel algorithm, not only a mechanical device, and we cannot tell to what extent the different unique components contributed to the absence of difference observed. Considering today's knowledge, it would be tempting to eliminate the 1.5 minutes delay of the first defibrillation. If the technique is available, it also sounds appropriate to defibrillate during the up-stroke phase of the compression. We also must continue to look for those sub-groups which you may suspect benefit the most from mechanical CPR. Maybe the OHCA populations tend to be "too heterogenous" in randomized larger trials, preventing us from detecting any outcome differences? It is reasonable to believe that some groups will benefit from mechanical CPR, e.g. like previously discussed, those with prolonged duration of CPR. But how do we identify those patients in advance in order to provide optimal treatment?

In the LINC trial we excluded those with ROSC after the first defibrillation and those defibrillated before arrival of the ambulance. No data was collected from these patients. For correct reasons they were not included in the original study, but this data would have been interesting to analyse in further analysis, e.g. in trying to identify those who with the greatest chance of early ROSC. Further gender analyses including also these patients is another attractive alternative.

In everyday practice we lean heavily on available guidelines and these depend on high quality evidence. For that reason, well-functioning cooperation between different centres and hospitals are needed. This is not only a question of funding, it may also speed up the inclusion rate, hopefully avoiding the results from a prehospital randomized trial to be depending on a study protocol written 8-10 years ago.

Just recently the COACT trial¹⁴³ showed no survival benefit for early CAG after OHCA. Further studies are on their way, much needed to bring clarity about this subject. For obvious reasons it is hard to include patients in shock in such a study, illustrating the great need for well-functioning

registries with thoroughly collected data, thereby facilitating studies of this category of patients.

After controlling for confounders female gender have been found associated with lower use of early CAG. We do not know the exact mechanisms behind this. Further studies are warranted. We also need prospectively collected data regarding CAG findings after OHCA to identify and confirm the assumed differences between men and women.

Studies are needed to investigate IHCA. Even though they constitute only one third of all cardiac arrests, they might constitute a larger part of all ICU treated patients. Very few studies have compared IHCA to OHCA, and we mainly treat IHCA based on extrapolated knowledge from OHCA patients. Only one single study has investigated the role of early CAG after IHCA and even though patients benefiting from this may be fewer than after OHCA, we must know better how to identify them.

Lastly, regardless of investigated intervention, when a large randomized trial is performed, even though it may come down to a question of resources, the follow-up shall involve studies of more thorough evaluation of neurologic outcome as well as of quality of life.

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