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Evaluation of various strategies
to improve outcome after out-of-hospital cardiac arrest
with particular focus on mechanical chest compressions

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To Åsa

Evaluation of various strategies to improve outcome after out-of-hospital cardiac arrest with particular focus on mechanical chest compressions

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ABSTRACT

Cardiopulmonary resuscitation (CPR) skills vary among health care professionals. A previous study revealed that chest compressions were only performed half the time in out-of-hospital cardiac arrest (OHCA). Field conditions and fatigue could be possible explanations. The aim of this thesis was to study the impact of the introduction of mechanical chest compression in OHCA according to survival and its usability and b) passive leg raising (PLR), to augment the artificial circulation, during CPR.

Methods: This thesis is based on a pilot study conducted in the Gothenburg/Mölndal and Södertälje Emergency Medical Service systems in 2003-2005. Witnessed OHCA (adult ≥ 18 years) received either mechanical (n=159) or manual (n=169) chest compressions. The pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) has been shown to correlate with cardiac output (CO) during CPR. To compare the effect of the different strategies, the $P_{ET}CO_2$ was measured, during CPR, with standardised ventilation.

Result: PLR during CPR increased the $P_{ET}CO_2$ value within 30 seconds. Mechanical active compression-decompression (ACD) CPR, compared with manual compressions, produced the highest mean of initial, minimum and average values of $P_{ET}CO_2$. However, mechanical chest compressions did not appear to result in improved survival. Clinical circumstances such as unidentified cardiac arrests (CAs) resulted in a large drop-out in the intervention group or a late start to the intervention in relation to CA. The late start meant that the intervention targeted a high-risk population with a low chance of survival.

The majority of identified CAs were coded by the Rescue Co-ordination Centre (RCC) according to symptoms (usually unconsciousness), while the minority were coded according to the diagnosis of CA. Patients coded according to the diagnosis of CA had an earlier start of CPR, a higher rate of bystander CPR and a tendency toward higher survival rates.

Conclusion: Since PLR during CPR appears to improve circulation after OHCA, larger studies are needed to evaluate its potential effects on survival. Compared with manual compressions, mechanical ACD CPR produces probably the most effective CPR. However, different clinical circumstances make the device difficult to study outside hospital. Coding a CA according to diagnosis rather than symptoms appears to improve the out-of-hospital care.

Key words: out-of-hospital cardiac arrest, mechanical chest compression, randomised clinical trial, dispatch code, end tidal carbon dioxide, passive leg raising

List of abbreviations

ACD-CPR   Active compression decompression-Cardiopulmonary resuscitation

AHA   American heart association

ALS   Advanced life support

BLS   Basic life support

CA   Cardiac arrest

CCU   Coronary care unit

CE   Conformité européenne

CO_2 Carbon dioxide

CPP   Coronary perfusion pressure

CPR   Cardiopulmonary resuscitation

DNAR   Do not attempt resuscitation

ECG   Electrocardiogram

EMDs   Emergency medical dispatchers

EMS   Emergency medical service

ERC   European resuscitation council

IHCA   In-hospital cardiac arrest

OHCA   Out-of-hospital cardiac arrest

PEA   Pulseless electric activity

PLR   Passive leg raising

$P_{ET}CO_2$ Pressure of end-tidal carbon dioxide

RCC   Rescue co-ordination centre

ROSC   Return of spontaneous circulation

VF   Ventricular fibrillation

List of original publications

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

I. Axelsson C, Nestin J, Svensson L, Axelsson ÅB, Herlitz J. Clinical consequences of the introduction of mechanical chest compression in the EMS system for treatment of out-of-hospital cardiac arrest- A pilot study. Resuscitation 2006;71:47-55.

II. Axelsson C, Axelsson ÅB, Svensson L, Herlitz J. Characteristics and outcome among patients suffering from out-of-hospital cardiac arrest with the emphasis on availability for intervention trials. Resuscitation 2007;75:460-468.

III. Axelsson C, Borgström J, Karlsson T, Axelsson ÅB, Herlitz J. Dispatch codes of out-of-hospital cardiac arrest should be diagnosis related rather than symptom related. Eur J Emerg Med. 2009 Dec 14 (E-pub ahead of print).

IV. Axelsson C, Karlsson T, Axelsson ÅB, Herlitz J. Mechanical active compression–decompression cardiopulmonary resuscitation (ACD-CPR) versus manual CPR according to pressure of end tidal carbon dioxide ($P_{ET}CO_2$) during CPR in out-of-hospital cardiac arrest (OHCA). Resuscitation 2009;80:1099-1103.

V. Axelsson C, Holmberg S, Axelsson ÅB, Herlitz J. Passive leg raising during cardiopulmonary resuscitation in out-of-hospital cardiac arrest – does it improve circulation and outcome? Accepted for publication in Resuscitation.

Contents

1.0 Introduction

The Gothenburg/Mölndal EMS responds to about 26,000 priority-one cases a year, of which 250-300 are cardiac arrest (CA) cases. On average, each ambulance crew responds, as the first unit, to a maximum of two CA cases a year. Two heads with two pairs of hands have to think, act and do exactly the right things during the first important minutes after arrival. In addition, insecurity in dispatch [1] often makes it impossible to predict a CA patient until the team arrives at the patient's side.

Recent emergency medical service (EMS) studies have shown poor cardiopulmonary resuscitation (CPR) quality with long pauses in chest compressions [2-4] and it has been suggested that CPR guidelines are too complex and result in patients not receiving known benefits such as chest compressions [5]. Furthermore, regardless of the etiology of CA and due to the difficulty in performing CPR during ambulance transport [6], most out-of-hospital cardiac arrest (OHCA) patients are traditionally treated at the scene until the return of spontaneous circulation (ROSC) or the termination of resuscitation. Since the introduction of early defibrillation, during the 1980s, survival rates in Gothenburg have remained unchanged [7]. To further improve survival in OHCA, the EMS link has to be strengthened by new strategies and methods.

2.0 Background

2.1 The Swedish national registry of out-of-hospital cardiac arrest (OHCA)

More than 4,000 resuscitations/year are attempted outside hospital in Sweden by either a bystander (helper on site) or the EMS personnel. During the last two decades, about 70% of all resuscitations attempted were registered by the EMS personnel at the Swedish registry for OHCA [8], which was started in 1990 by Stig Holmberg. Of all reported OHCAs, from 1991 to 2008, about 70% had a presumed cardiac aetiology, the median age was 72 years, one third were women and 55% were witnessed (seen or heard by a bystander). Further, 15% were witnessed by EMS personnel, so-called crew-witnessed cases. Crew witnessed cases have increased during the last two decades [8].

2.2 The chain of survival

In order to successfully resuscitate a person with an OHCA, various efforts, which are described as the four links in the chain of survival (early call, early CPR, early defibrillation and early advanced life support (ALS)), must be optimal [9]. According to the latest report from the national registry, people call the dispatch centre two minutes earlier today (three vs. five min in 1992) and initiate bystander CPR more often (56% vs. 33% in 1992) among witnessed CA. However, the time from calling for an ambulance to defibrillation (the third link) has increased by three minutes from eight to 11 minutes since 2004. We have also found an increase in ambulance delay from six to eight minutes during the last decade [8]. These changes are worrying, but the new guidelines introduced in 2005 [10], to initiate CPR for two minutes before defibrillation, could probably explain the increasing delay to defibrillation to some extent. During the last ten years, the use of epinephrine and tracheal intubation has been unchanged [8].

2.3 Survival rates in Sweden

The Swedish OHCA registry reports an increase in 30-day survival from 4.2 to 7.9% since 2000. Long-term survival from Sweden is less well reported, but a study from Gothenburg comparing two periods (1980-2002 and 2003-2006) shows an increase in one-year survival among patients found in VF from 37% to 57% [11]. However, the Swedish OHCA registry reports a reduction in the percentage of ventricular fibrillation (VF) from 47% to 39% since 1992. Possible explanations for the improvement in short-term survival could be the increasing number of educated rescuers trained to call earlier and start CPR more frequently. Today, between two and two and a half million lay persons in Sweden are educated in CPR [12, 13]. The increase in crew-witnessed cases might also indicate awareness in society of the need to call for an ambulance as soon as symptoms portending a CA are observed. That time is a critical component is clear when comparing survival rates from the national registry for in-hospital cardiac arrest (IHCA) [14], where survival to hospital discharge has been reported to be 30%. Among IHCA cases, 83% were witnessed. Of those, > 80% received CPR within two minutes from CA. Among all IHCA patients, 41% were found in VF and 81% of them were defibrillated within three minutes from CA. The IHCA population differs from OHCA according to structure, fewer trauma CA and more cases in which CPR (do not attempt resuscitation, DNAR) is not initiated. This produces a population with higher survival rates

than outside hospital, but a survival rate of 15% is probably a reasonable goal to reach in OHCA.

2.4 The EMS link

Berdowski et al. [15] found that not recognising a CA during an emergency call reduces survival. Compared with recognised calls (71%), the ambulance was dispatched later (0.94 minutes) and had a longer response time (1.4 minutes) among non-recognised calls. One reason for better survival among recognised calls could be the opportunity for the emergency medical dispatchers (EMDs) to offer instructions in CPR (telephone-initiated CPR, T-CPR). T-CPR appears to increase survival but is dependent on the accuracy of the EMDs in identifying patients with CA [16, 17]. A previous study from Gothenburg revealed that 47% of the CAs were recognised by the EMDs [1].

2.5 The importance of chest compressions in CPR

2.5.1 Chest compression before defibrillation

Most OHCAs have a presumed cardiac aetiology [18] and, according to the first recorded rhythm, patients with initial VF have the highest survival rates [7]. However, the time window for successfully defibrillating a VF is narrow and survival rates decrease dramatically during the first few minutes [19]. Studies have shown that this time window seems to be possible to expand. In 1999, Cobb et al. [20] published a report based on historical data in which they claimed that approximately 90 seconds of CPR prior to defibrillation was associated with increased survival when the EMS response intervals were four minutes or longer. Four years later a randomised, controlled trial from Norway [21] supporting Cobb et al. was published. Two hundred patients with out-of-hospital VF were randomised to early defibrillation according to guidelines (2000) or defibrillation subsequent to CPR for 180 seconds. Compared with early defibrillation, CPR prior to defibrillation did not improve outcome when all patients were included in the analysis. However, in a subgroup (81 patients) where the EMS response was longer than five minutes, survival to hospital discharge decreased among patients receiving early defibrillation but remained unchanged among patients receiving CPR prior to defibrillation [21]. Those findings lead to the initiation of CPR for two minutes before defibrillation in the guidelines introduced in 2005 [10]. Further, in an observational study, Bradley et al. [22] compared $\leq$ 45 seconds of CPR and CPR between 46-195 seconds prior to

defibrillation among OHCA patients with VF/VT. They found increased odds for survival in the latter group if the EMS delay was > 5 minutes.

2.5.2 The three-phase, time-sensitive model

A treatment model that describes when chest compressions before defibrillation should be applied was published by Weisfeldt et al. [23] in 2002. In a review report they suggested a three-phase model for CPR. This model reflected the time-sensitive progression of the pathophysiology during a CA, which in turn required time-sensitive interventions. They stated that the uniform treatment of VF (immediate defibrillation, according to guidelines) may be contraindicated in some patients, especially when the time from CA increases and with the simultaneous progress of myocardial ischemia.

The first phase in their model is the electrical phase and comprises the first four minutes after cardiac arrest. The treatment during this phase is rapid defibrillation. The circulatory phase comes second and lasts approximately from minute four to minute ten. The most important thing during this phase is to provide oxygen delivery and chest compressions in combination with defibrillation. The physiological mechanism behind this observation was not clear, but it was consistent with the notion that defibrillation of the ischemic heart beyond four minutes may be detrimental. The metabolic phase begins after approximately 10 minutes. During this phase, tissue injury from global ischemic events can result in circulating metabolic factors that cause additional injury beyond the effects of local or focal ischemia [23]. Resuscitation started during this phase is related to low survival rates [19]. Cooling before, or simultaneous to the start of chest compressions is discussed [23], but today there are still no practical solutions for performing this kind of intervention in the pre-hospital setting.

2.5.3 The pathophysiology behind the model

In 2003, Steen et al. [24] presented a possible explanation of the physiological mechanism behind the electrical and the circulatory phase. They found in animal studies that, during VF, the coronary perfusion pressure (CPP) decreased from 60 to 15 mmHg within 15 seconds and then gradually decreased to reach zero after four minutes. They explained the quick fall in CPP by the transport of arterial blood to the venous circulation, with the result that the left ventricle emptied and the right ventricle became more and more distended. The CPP fell to

zero when the pressure was equal on the venous and arterial side. This explanation was challenged by Sorrell et al. [25], who found that the quick fall in CPP was dependent on the fact that both the right and left ventricle increased in volume during the first five minutes of VF.

After 6.5 minutes of untreated VF, Steen et al. [24] found that chest compression for 3.5 minutes, before defibrillation, was necessary to achieve ROSC. Their result was explained by chest compression restoring the size and shape of the ventricles [26], priming the ischemic myocardium before defibrillation and, further, the restoration of the CPP to a level at which ROSC is possible. They found that 90 seconds of chest compression was enough to reach a CPP of at least 15 mmHg [24]. Moreover, in 1990, Paradis et al. [27] noted a correlation between the CPP and ROSC. Among 100 patients with CA, only patients with a CPP above 15 mmHg had ROSC.

2.5.4 Hands-off time, wave forms and CPP

Steen at al. [24] also found that the ROSC rate deteriorated dramatically during the "hands-off" interval, before the shock. The shock had to be performed immediately because the CPP level decreases to zero within 10 seconds. Efterstol et al. [28] found that ROSC could be predicted by a complex analysis of the electrocardiogram (ECG) wave forms during VF. When they studied "hands-off" time, before defibrillation and according to the ECG wave forms, they found that the success rate for ROSC rapidly decreased during the first 20 seconds [29]. Both fibrillatory wave forms and the CPP appear to be important predictors of ROSC, both can be maintained by chest compressions and both decrease rapidly during the "hands-off" time. Techniques to minimise the "hands-off" time before defibrillation are requested in the next European resuscitation council (ERC) guidelines [26].

2.6 The importance of chest compressions with high quality

2.6.1 Haemodynamics during CPR

In patients with OHCA, survival with good neurological outcome is dependent upon the generation of continuous blood flow, by chest compression, to the heart and brain during resuscitation [30]. The brain receives perfusion during the compression phase and the heart during the relaxation (decompression) phase. Incomplete chest wall recoil, as a result of leaning, during the relaxation phase is a common error during manual CPR and results in decreased venous return (preload), coronary blood flow and cardiac index [31].

2.6.2 The cardiac and the thorax pump theory

Fifty years after the introduction of CPR by Kouwenhoven et al. [32], the mechanism behind forward (antegrade) blood flow, during CPR, in humans, is mostly unknown. Kouwenhoven`s original hypothesis was that external compression squeezed the heart between the sternum and vertebrae. During the compression (systole), the atrioventricular valves would close, preventing retrograde blood flow, while the aortic and pulmonary valves opened, allowing antegrade flow. When the compression force was removed (diastole), the artrioventricular valves would open and allow ventricular filling. This theory, known as the "cardiac pump theory", was challenged by many investigators [33, 34] who observed that increased intrathoracic pressure alone can generate blood flow, the thorax pump theory. According to this theory, an increase in the intrathoracic pressure during chest compression generates a pressure gradient between the intrathoracic vascular compartment and the extrathoracic vascular compartment that causes blood to flow in the antegrade direction. According to this theory, the heart is presumed to be a passive conduit of blood flow during CPR.

In 1991, Kuhn et al. [35] performed transesophageal echocardiography during resuscitation, on one man with a CA, and found motion in valves and changes in ventricular size during CPR. The investigators attributed this observation to favour the cardiac pump theory as the predominant principle of blood flow during CPR. In a later published report, Kim et al. [36] found similar results using the same method. The direction of contrast flow was studied during CPR among ten non-traumatic CAs. Retrograde flow to the left atrium and forward blood flow to the aorta was found during the compression phase. These findings made the authors suggest that the left ventricle acts as a pump in generating blood flow during standard CPR in humans. However, they found an individual variation in retrograde flow suggesting that, in addition to the cardiac pump, another mechanism, such as the thoracic pump or the left atrium pump, might supplement the forward blood flow, although in this study the cardiac pump was found to be predominant. The intrathoracic pressure is a determinant of perfusion pressure. Low or negative intrathoracic pressure during the "diastolic" phase helps to augment venous return to the chest [37]. As a result, high intrathoracic pressure during the "diastolic" phase (e.g. to excessive ventilation) will reduce venous return to the thorax and decrease survival.

2.7 Passive leg raising (PLR) during CPR

The early guidelines for CPR [38-40] stated that the "elevation of the lower extremities may promote venous return and augment artificial circulation during external cardiac compression". In the guidelines from 1992 [41], this comment was deleted. Why it was deleted is not known, but it was probably because of too little clinical evidence. The use of the Trendelenburg position, head-down tilt, was used during World War One by Walter Cannon in the treatment of hypotension or shock. Studies of hypertensive patients revealed minor haemodynamic effects as a result of using the Trendelenburg position. Adverse effects, including respiratory compromise and increased cranial pressure, were also reported [42-45]. Zadini et al. [46] argue that the lack of clinical benefit among patients with hypotension is due to the vasoconstriction and increased arteriolar vascular tone which they believe are not present among patients with CA. They found (in animal studies) an increase of up to 1.4-fold in carotid blood flow during CPR in the Trendelenburg position. However, it is impossible to compare pigs in the Trendelenburg position with PLR among humans. Terai and colleagues [47] found that PLR increased left ventricular filling, stroke volume and cardiac output during ten minutes in eight healthy adult males. According to Préau et al. [48], the effect of PLR is reversible but is equivalent to a rapid intravenous volume expander by shifting blood from the lower extremities towards the intrathoracic compartment. PLR (45 degrees) for four minutes results in an increase in right and left ventricular preload [49] and, by definition, the stroke volume, if the heart is preload dependent [48]. This makes PLR predictive of fluid responsiveness among patients with circulatory failure [48-51] and has been recommended as a part of haemodynamic monitoring in recent international recommendations [52]. Two different strategies of PLR, $PLR_{SEMIREC}$ and PLR_{SUPINE}, have been tested by Jabot et al. [50].


$PLR_{SEMIREC}$ PLR_{SUPINE}
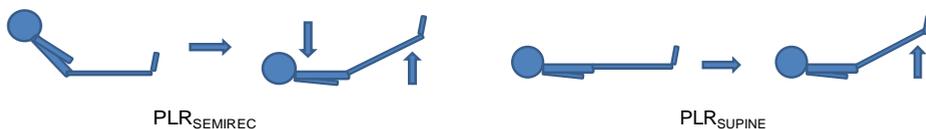
Figure 1. $PLR_{SEMIREC}$ = *elevation of legs simultaneously to transferring the trunk to the horizontal position.* PLR_{SUPINE} = *elevation of the legs from the horizontal position*

As a result of the larger increase in cardiac preload, $PLR_{SEMIREC}$ was recommended. Strategies for improving the venous return during CPR are vital for cardiac output [37]. To our knowledge, PLR during uninterrupted CPR has not previously been studied in humans.

2.8 End-tidal carbon dioxide, normal production and during CPR

Carbon dioxide (CO_2) is a by-product produced during cellular metabolism. At rest, the human body produces about 3 ml/kg a minute, but this may increase dramatically with heavy exercise. CO_2 is mostly transported, as a bicarbonate ion, by the bloodstream to the lungs, where it is normally exhaled. Changes in the body P_{CO2}, pH and P_{O2} result in alterations in alveolar ventilation designed to return these variables to their normal values. These changes are detected by the chemoreceptors and they supply the respiratory centre in the central nervous system with information to make the appropriate adjustment in alveolar ventilation [53, 54].

During CPR in OHCA, the efficacy of chest compressions, according to blood flow, is difficult to measure. The direct measurement of blood flow and CPP requires time-consuming invasive methods that are impossible to perform in the pre-hospital setting. In animal and human studies, measuring the pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) during CPR has been shown to be a practical non-invasive method for detecting pulmonary blood flow reflecting cardiac output (CO), as an almost immediate indicator of the return of spontaneous circulation (ROSC), and for presenting threshold values under which no resuscitation succeeded [55-68].

2.9 Mechanical chest compression devices, a historical review

In 1858, the Hungarian surgeon Janos Balassa reported a case in which he used the technique of closed chest compressions on a human being [69]. He was summoned to the home of an 18-year-old woman with asphyxia secondary to tuberculosis laryngitis. She had stopped breathing and was pulseless when Balassa performed a tracheotomy followed by anterior chest compressions for six minutes prior to her ultimate recovery. In 1908, "extra-thoracic massage" was performed on dogs by Pike et al. [70]. They found the method "exceedingly laborious" and developed a machine to massage the heart both internally and externally. However, they reported no benefit as compared with manual methods and, applied internally, it was less effective. During the next 50 years, open cardiac massage was the predominant

method that was used inside hospital and most frequently when CA occurred during surgery. In 1953, a series of 1,200 (1,068 during surgery) patients with IHCAs were reported [71] in whom resuscitation was attempted with open cardiac massage and the overall survival rate was 28%. After the introduction of closed chest CPR in 1960 by Kouwenhoven et al. [32], different manual or mechanical devices were introduced [72-74]. Many of these devices were used solely for experimental purposes, investigating the various mechanisms involved in CPR using a pre-programmed compression/ventilation sequence and without interruption or fatigue. Their use on humans was limited to a few centres and was restricted by cost and the need for experienced operators [75]. Taylor et al. [76] were one of the first to use a mechanical device in a randomised comparison with manual chest compressions. They used a pneumatic device (Thumper[TM] by Michigan Instruments) and randomised 50 patients to mechanical or manual CPR. The authors concluded that mechanical compression was comparable to manual when performed in ideal conditions and suggested that mechanical compressions should be employed when trained personnel were not available or when manual compression was difficult to perform. However, they also found an increase in sternal fractures.

2.9.1 Devices according to the thorax pump theory

During the 1980s and according to the thorax pump theory, a new mechanical device design, known as the CPR vest, was introduced [34]. This vest was designed to be placed around the thorax and inflated and deflated rapidly. At the time, this system was thought to be very promising for improved survival in humans. This principle has been developed into a more flexible version now known as the Auto-Pulse[TM] CPR load-distributing band [77]. Recently, two clinical studies compared the Auto-Pulse[TM] with manual CPR [78, 79]. The study conducted by Ong et al. [78] found increased survival to hospital discharge with the Auto-Pulse[TM] compared with manual CPR in an historic control group. However, survival to hospital discharge was very low (2.9%) in the historic control group. The study by Hallstrom et al. [79] was terminated early after interim analysis that revealed poorer survival to hospital discharge using the Auto-Pulse[TM]. Recent measurements made among 29 patients with OHCA and compared with manual chest compression revealed that the Auto-Pulse[TM] was associated with increases in systolic and diastolic mean pressure, but there was no significant increase in the $P_{ET}CO_2$ [80].

2.9.2 Devices based on the cardiac pump theory

Active decompression is a method based on the cardiac pump theory and is used by both manual and mechanical devices [72, 74]. The method was discovered by coincidence when a 65-year-old man was successfully resuscitated for the second time with a toilet plunger. The son, who was not trained in CPR, witnessed his father collapse in the living room. He did not know what to do but remembered what his mother did the first time his father had a CA (in the bathroom), so he ran for the plunger and started CPR [81]. The son, delighted by his mother's plunger technique, recommended that there should be a toilet plunger next to every bed at the CCU. This active decompression method resulted in two different manual devices called the ResQpump™ and the Cardio Pump™. This technique, which requires both tapping and dragging, was found to be more physically demanding for the rescuer than performing standard CPR [6,82]. Compared with standard CPR, no improvement in survival rates was found among patients receiving manual active compression decompression (ACD) CPR [83, 84]. The active decompression method was developed in a mechanical device called the LUCAS™. The LUCAS™ is a gas- or battery-driven CPR device providing mechanical ACD-CPR. In randomised studies of pigs, significantly better CPP and carotid/artery blood flow was found with mechanical ACD-CPR compared with manual CPR [85, 86].

2.9.3 Possible advantage of mechanical devices

As mentioned previously, the development of mechanical devices began back in the 1960s. Unfortunately, many of the early devices were not regarded as functional in the clinical setting. In 2000, automatic CPR devices began to receive approval for clinical use [72]. Lars Wik [74] advocated equivalence in chest compressions, optimised CPR performance, new optimised protocols and time for the rescuer to concentrate on the protocol as four main needs for mechanical chest compression during CPR.

2.10 Rationale for this thesis

Contemporary CPR research focuses on the importance of performing chest compressions of good quality and with limited interruptions. Outside hospital and subsequent to the arrival of the EMS, all patients with CA should have the same opportunity for equivalent treatment of the highest quality; mechanical chest compression could be a solution. However, before the implementation of different devices and in spite of approval for clinical use, pre-hospital factors relevant to survival, safety and usability have to be evaluated. This thesis aims to

identify some of these factors and, by measuring end-tidal CO_2 during CPR, evaluate other non-complex methods that might improve the artificial circulation after OHCA.

3.0 Aims of the study

The aims of this thesis were to a/ study the impact of mechanical chest compression in OHCA according to statistical and clinical factors relevant to its usability and the evaluation of survival and b/ evaluate simple strategies that might improve the artificial circulation during CPR. The specific aims of the papers were as follows.

I. To describe the outcome during a limited period in patients with a witnessed OHCA of presumed cardiac aetiology ($\geq$18 years) treated with standard CPR or standard CPR followed by mechanical ACD-CPR in the Municipalities of Gothenburg and Södertälje, Sweden

II. To describe a) the characteristics and outcome among all treated patients suffering from OHCA in a well-defined area according to the Utstein criteria and, in the same population of OHCA, describe the percentage who were ''theoretically'' and ''in reality'' available for early intervention trials and b) the characteristics and the outcome among patients who, for various reasons, are not available for intervention trials compared with those who are available

III. To describe the characteristics and outcome in OHCA in relation to early handling at a dispatch centre with regard to a) whether the dispatch code was a diagnosis (CA) or a symptom (mostly unconsciousness) and b) the delay from creating time to alerting the first ambulance unit

IV. To compare mechanical ACD-CPR with standard CPR according to $P_{ET}CO_2$, among patients with OHCA, during CPR and with standardised ventilation

V. To a/ detect whether PLR by 35 centimetres (about 20 degrees) during uninterrupted CPR would change the $P_{ET}CO_2$ value and b/ observe the alteration in $P_{ET}CO_2$ during CPR among patients who experienced a return of spontaneous circulation (ROSC) and those that did not.

4.0 Materials and methods

4.1 Organisation

4.1.1 Ambulance organisation

The EMS system in Gothenburg/Mölndal serves about 542,000 inhabitants in an area of 595 km^2. During the study period, the Gothenburg/Mölndal EMS ambulance fleet comprised 12 ambulances which were available around the clock, plus two daytime ambulances. In addition, three advanced life support (ALS) equipped ambulances were available around the clock. The ambulances were dispatched according to a two-tier system, i.e. the nearest basic life support (BLS) unit was simultaneously dispatched together with an ALS unit for each call judged to relate to a life-threatening state of health (priority-one cases). The BLS units were staffed by at least one nurse and the ALS units by a paramedic and a well-trained anaesthesia nurse. The city of Södertälje participated in the study for one year. The Södertälje EMS system serves about 344,000 inhabitants in an area of 580 km^2. Södertälje has a similar EMS system with one ALS-equipped ambulance available every day between 7 am and 7 pm. All OHCAs were treated according to American heart association (AHA) and ERC guidelines.

4.1.2 Gothenburg Rescue Co-ordination Centre (RCC)

The RCC in Gothenburg serves the whole region of Västra Götaland with a population of 1.5 million inhabitants. The RCC is the first response for calls to the national emergency number 112. During the study period, between four and seven EMDs responded to 1,100-1,200 calls around the clock. Only emergency calls relevant to ambulances (40%) or fire services (10%) were processed by the EMDs. Among the remaining emergency calls (50%), some were for the police or sea rescue and connected by the EMDs to the relevant departments, while the majority were false or made by mistake, by mobile phones dialing from people's pockets, for example.

When someone dials 112, the mean response time (2004-2005) ranges from eight to ten seconds. After 20 seconds, an automatic answering machine is activated, telling the caller to wait for an EMD to answer. When the emergency number 112 is answered, the caller describes the situation or request. If the receiving EMD identifies the need for an ambulance, he or she immediately creates a computerised ambulance protocol (creating time). Before

alerting the EMS system, the appropriate resources have to be defined. This definition is made according to an existing national medical index which was introduced in 1998. During the study period, a second edition introduced in 2001 was used. This index is based on 30 categories (symptoms or events) and guides the dispatcher through the call by questions to ask, medical advice, such as support in initiating T-CPR, to a priority and a categorisation code (dispatch code). The event or symptoms give priority at three levels.

Priority one = immediate dispatch (+ second tier when indicated)

Priority two = ambulance at patient's side within 30 minutes

Priority three = ambulance at patient's side within 90 minutes

4.2 Design and patients

This thesis is essentially based on a descriptive, controlled pilot trial studying mechanical chest compression in OHCA. All the data were collected prospectively according to a predesigned protocol during a limited period of two years (22/5/2003-25/5/2005) in Gothenburg/Mölndal and one year (1/10/2003-31/08/2004) in Södertälje. Patients included in this pilot study were selected by a cluster method to be treated with either mechanical ACD-CPR or manual chest compressions performed by the ambulance crew. In practice, this meant that two devices performing mechanical ACD-CPR were exchanged between four ALS units for approximate six-month periods.
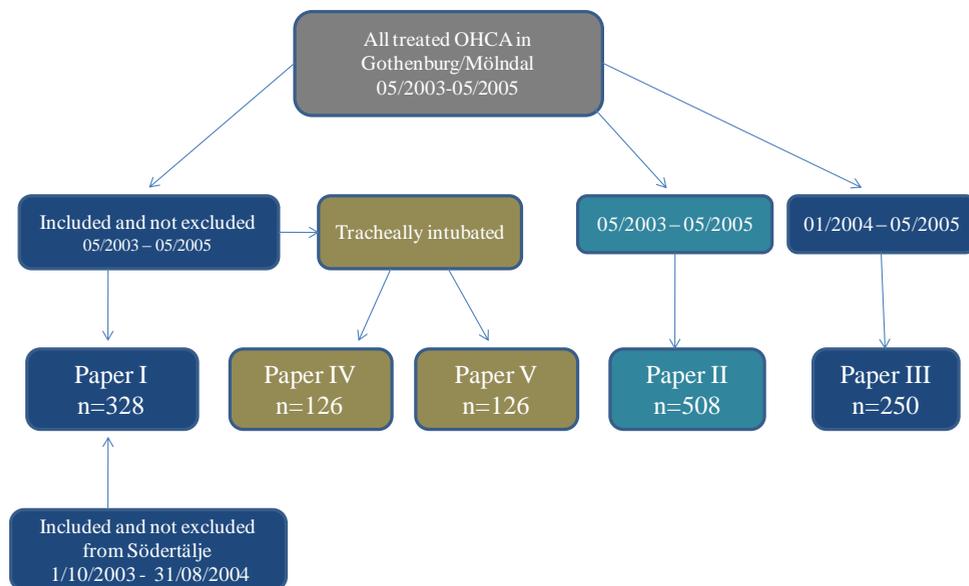
Figure 2. *Flow diagram for the recruitment of patients to Papers I to V.*

Paper I deals with patients, from Gothenburg/Mölndal and Södertälje, who were included in and not excluded from the present pilot study (Figure 2). Of these, Papers IV and V deal only with tracheally intubated patients included in Gothenburg/Mölndal, where the mean values of $P_{ET}CO_2$ were measured during CPR. In Paper IV, the mean values of $P_{ET}CO_2$ were related to the treatment with manual or mechanical chest compressions. The mean $P_{ET}CO_2$ values were categorised as the initial (first obtained value), maximum (highest value), minimum (lowest value) and average value. Paper V compares the mean $P_{ET}CO_2$ values, prior to and after the elevation of the lower extremities, in a small group of patients. This group was stratified by the study protocol according to differences in treatment (e.g. mechanical or manual chest compressions). Paper II describes the characteristics and outcome of all OHCA patients treated by Gothenburg/Mölndal EMS during this two-year period. Paper III describes characteristics and outcome in relation to dispatch time and dispatch codes among all treated OHCAs (judged to have had a CA at call) in Gothenburg/Mölndal during a 17-month period from January 2004. Only the analysis in Paper I deal with patients included by Södertälje EMS.

4.3 Inclusion and exclusion criteria

Only patients with a witnessed OHCA were enrolled in the present pilot trial. The exclusion criteria were age < 18 years, trauma, pregnancy, hypothermia, intoxication, hanging and drowning, as the judged aetiologies of OHCA, ROSC before the arrival of the second tier, and other reasons, such as terminal illness.

4.4 Equipment

1. The LUCAS^{TM} (Lunds University Cardiac Assist System) is a device performing mechanical ACD-CPR. It is gas or battery driven and performs 100 uninterrupted compressions a minute.

2. The Ambumatic^{TM} is a volume-controlled ventilator with a tidal volume that can be set from 2 to 12 l/minute.

3. The Medtronic "LIFEPAK 12" (LP 12) is a defibrillator with different opportunities to monitor and record vital signs and events during the treatment period. The LP 12 is equipped with Microstream®/sidestream capnography measured with infrared spectroscopy. The $P_{ET}CO_2$ is continuously monitored and the configuration curve plus two values of $P_{ET}CO_2$ /minute are automatically recorded.

4.5 Intervention

4.5.1 Education

Before starting the study, 50 EMS personnel (paramedics and anaesthesia nurses) were trained to perform mechanical ACD-CPR and re-trained in manual chest compressions. The instructor was an anaesthesia nurse (project manager) educated as a LUCAS instructor by Jolife AB. Each training session lasted three hours and ended with a practical and a theoretical test. The practical test was a scenario at which the EMS personnel worked in pairs. On arrival, the first EMS staff member immediately started manual chest compressions on a manikin, while the second prepared the LUCAS^{TM} for attachment to the manikin. To pass the test, they had to minimise the hands-off interval between manual and mechanical chest compressions to < 20 s. During training, they were informed about the importance of minimising hands-off situations and preparing for fatigue by rotating the rescuers during manual CPR. In the

intervention group, the EMS staffs were told to attach the LUCAS to the patient as soon as possible after arrival. Before every half-year period during which the device was used, the EMS personnel took part in a two-hour retraining session. During the study period, the ALS personnel were contacted regularly by the project manager and had the opportunity to call a special phone number to report aspects such as ethical and safety questions to the project manager.

4.5.2 Passive leg raising (PLR)

We decided to test elevation of the lower extremities above heart level. As PLR was performed during CPR, the supine method (p. 13) was the only one that was feasible. The angle was selected for practical reasons and to standardise the elevation. The angle of 20 degrees was measured on a tall (192 cm) and a short (157 cm) person lying flat on the floor. We found that a 35 cm elevation of the heels from the floor corresponded to a rough calculation of 20 degrees on a person of medium size (170-175 cm). Since the LP12 was found to be 35 cm high, it was adjudged to be ideal as the criterion for standardising the elevation

4.5.3 The study protocol and measurement of $P_{ET}CO_2$

$P_{ET}CO_2$ was measured during CPR, according to a pre-designed study protocol and after the patient was tracheally intubated. The study protocol included two different flow charts, one for treatment during PLR and one for the treatment of patients without PLR. Standardised ventilation (7 l/min, 100% O2) was used and, if $P_{ET}CO_2$ exceeded 6 kPa, the ALS personnel were instructed by the protocol to increase the ventilation to 8 l/min (this was not necessary in any case). $P_{ET}CO_2$ was continuously measured during 15 min of CPR or until ROSC was detected. One milligram of epinephrine was given every second minute up to five mg during the measurement period. If ROSC was detected, or when performing PLR, the ALS personnel had to note the exact time by pressing the "event button" on the LP 12. Using this button, the event was saved in the memory of the LP 12, synchronised according to time and the registration of $P_{ET}CO_2$.

4.6 Data collection

Data relating to the cardiac arrest cohort were obtained from the Södertälje and Gothenburg/Mölndal EMS medical record and computer printout ($P_{ET}CO_2$, ROSC and time of elevation). Data were also collected from the dispatch centre and National Registry for Out-of-Hospital Cardiac Arrest in Sweden. Further medical data relating to patients admitted alive to hospital were obtained from hospital records. The primary study end-point was ROSC at any time during the treatment and the secondary end-point was survival at hospital admission in witnessed cardiac arrest. Additional major clinical study end-points, analysed for all enrolled patients, were survival to hospital discharge and neurological recovery. Data were collected according to the Utstein criteria and the Glasgow-Pittsburgh CPC (Cerebral Performance Classification) [87, 88].

4.6.1 Unit

In previous reports, $P_{ET}CO_2$ was specified in either mm Hg (millimetre mercury) or kPa (kilo Pascal). This thesis deals with kPa; converted, 1 mmHg = 0.133 kPa [89].

4.7 Statistical methods

Descriptive statistics

The distribution of variables is given as means, medians and percentages.

Statistical analysis

Group comparisons were performed using Fisher's non-parametric permutation test (Papers I, II and III) and the Mann-Whitney U test (Papers IV and V) for continuous/ordered variables and Fisher's exact test (all papers) for dichotomous variables.

In Paper IV, Wilcoxon's signed rank test was used for paired comparisons.

All tests were two-tailed and p-values below 0.05 were considered statistically significant.

5.0 Ethical approval and considerations

This pilot study conducted in Gothenburg/Mölndal and Södertälje was approved by the Ethics Committee at Gothenburg and Stockholm Universities (S-696 02). Prior to the present study, the Swedish Food and Drug Administration was contacted according to the conformité européenne (CE) label on the study equipment. According to the patient data act in Sweden, a register (777) of patient data was established during the study period at Sahlgrenska University Hospital.

According to the Helsinki convention of informed consent, patients included in the present intervention and discharged alive were contacted by a study information letter, approved by the Ethics Committee at Gothenburg and Stockholm Universities, if they were still alive one year after hospital discharge.

6.0 Result

6.1 The pilot study (Paper I)

About 536 patients who suffered from an OHCA and in whom CPR was started were available for inclusion in the trial. Some 379 patients fulfilled the inclusion criteria and 51 of them met various exclusion criteria (Table 1). The most frequent exclusion criterion was a pulse-giving rhythm on the arrival of the ALS unit. As a result, 328 patients were evaluated in Paper I (159 in the mechanical chest compression group and 169 in the control group).

Table 1. Number of patients who fulfilled the inclusion and exclusion criteria

_____

Inclusion criteria	**n=379**
Bystander witnessed	288
Crew witnessed	91
Exclusion criteria	**n = 51***
Traumatic aetiology	8
Pregnancy	1
Hypothermia	1
Pulse-generating rhythm	10
Intoxication	3
Drowning	0
Hanging	0
Other	32

_____

* Patients could have more than one exclusion criterion

6.1.1 Characteristics, place of cardiac arrest and aetiology

The patients were relatively old (mean age 71 years in both groups) and more than one third were women. The majority of cardiac arrests (about two thirds) took place in the patient's home and had a cardiac aetiology. A cardiac aetiology was more frequent in the control group.

6.1.2 Status on the arrival of the BLS and ALS team

A high percentage of patients received bystander CPR (Table 2) prior to the arrival of the rescue team. Less than one third had ventricular fibrillation on the arrival of the BLS team. The largest percentage had asystole. On the arrival of the BLS/ALS team, the results appeared

to be fairly similar between the mechanical and manual chest compression groups, with the exception of pulseless electrical activity (PEA), which was more frequent in the mechanical chest compression group on the arrival of the ALS team (two minutes later).

Table 2. *Rhythm and treatment prior to and on the arrival of the basic life support unit and on the arrival of the advanced life support unit*

	Mechanical chest compression n=159 %	Manual chest compression n=169 %	p-value**
Bystander CPR (0/1)*	45	42	
Rhythm on arrival of BLS (2/7)*			
VF/VT	30	32	
Asystole and "other"	34	35	
PEA	18	12	0.17
Pulse-generating rhythm	18	21	
Treatment by BLS (0/1)*			
Defibrillation	18	13	
Rhythm on arrival of ALS (3/3)*			
VF/VT	24	30	0.19
Asystole and "other"	41	41	
PEA	24	15	0.03
Pulse-generating rhythm	11	14	

* Number of patients with missing information

** p-values denoted if < 0.20

6.1.3 Delay

The median delay from cardiac arrest to the arrival of the ALS unit was 12 minutes, which was a median of two minutes after the BLS unit (Table 3). Among the patients in the mechanical chest compression group, the median delay between cardiac arrest until the start

of mechanical chest compression was 18 minutes (i.e. a delay between the arrival of the ALS and the start of mechanical chest compression of six minutes).

Table 3. *Time intervals*

	Mechanical chest compression	Manual chest compression	p-value**
Time from cardiac arrest to: (median;min)			
Call for ambulance (n = 126/125)	3[1]	2[1]	0.051
Start of CPR (n = 154/160)	3	3	
First ECG recording (n = 142/147)	10	9	
Arrival of BLS (n = 125/123)	10[1]	10[1]	
Arrival of ALS (n = 125/126)	12[1]	12[1]	
First defibrillation (n = 58 / 65)	10[2]	11[2]	
Start of mechanical chest (n=77/0) compression	18		
Return of spontaneous circulation (n = 71/76)	24	22	

[1] Crew witnessed not included

[2] When VF/VT was first rhythm, crew witnessed included

** p-value denoted if < 0.20

6.1.4 ROSC, survival and CPC

As shown in Table 4a, when all the patients (n=159/169) were included in the analyses, there was no significant difference between the two groups with regard to ROSC or survival to hospital admission, survival to hospital discharge or CPC score (Fig. 3).

Among all the patients allocated to the mechanical chest compression group (n=159), the device was actually used in only 105 cases (66%). The reasons for this are given in Table 5. When patients in whom the device was used were compared with a matched control population, in Table 4b, according to age, initial rhythm, bystander-/crew-witnessed status, aetiology and delay to start of CPR, no difference was found between the two groups in any of the parameters evaluated. Survival to hospital discharge was 2-4% in this analysis.

Table 4. ROSC and survival

|	Mechanical chest compression %	Manual chest compression %	p-value**
4a, All patients	**n=159**	**n=169**	
ROSC	51	51	
Hospitalised alive	38	37	
Discharged alive	8	10	
4b, Patients in whom the device was used versus a matched control	**n=105**	**n=105**	
ROSC	50	49	
Hospitalised alive	36	35	
Discharged alive	2	4	

** p-value denoted if < 0.20
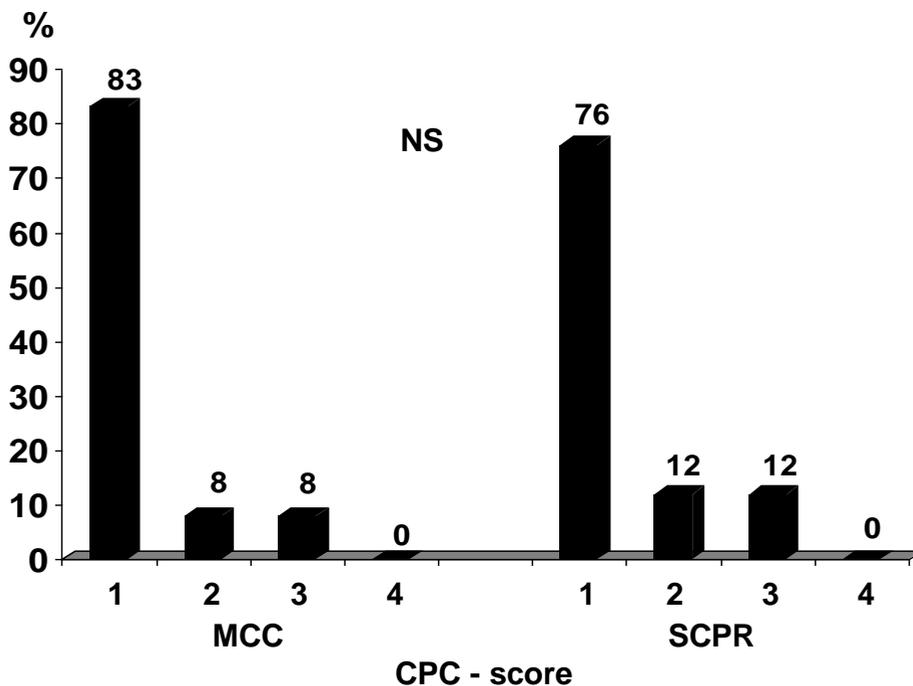
Figure 3. *CPC score at hospital discharge among survivors. In all, n = 29; MCC: mechanical chest compression (ACD-CPR); SCPR: standard cardiopulmonary resuscitation*

6.1.5 Safety

Only three technical problems were reported during this trial. Two technical problems were solved using a longer air pressure hose between the device and the double tubes containing compressed air and one was solved by replacing the gasket in the regulator with a low-temperature-resistant gasket. One resuscitative artefact reported in both groups was rib fractures. In the group receiving both manual and mechanical CPR, one case of suspected flail chest and several cases of skin injury from the suction cup were reported. The ALS personnel also noted that, during a long sequence of mechanical chest compressions, the device slid in an abdominal direction, especially when the patient was lying on a stretcher during the journey.

6.1.6 Drop-outs

As shown in Table 5, there were a variety of reasons for not using the device in 34% (n=54) of the cases. The two most common reasons were that:

a/ The dispatchers had not identified the CA at call (or the CA occurred after the call) and consequently the device was not brought to the patient

b/ The patients had such a short delay from the arrival of the ALS unit until ROSC that there was no time to adapt the device.

Table 5. Reasons for not using mechanical chest compression (n=54)

Reasons	n
Patients too small	1
Patients too large	2
Technical errors	3
Lack of experience, forgot device	7
Early ROSC	12
Cardiac arrest close to hospital	3
Cardiac arrest not identified at call or occurred after call (e.g. crew witnessed)	26
Codes related to breathing problems	9
Chest pain, cardiovascular disease	6
Diabetes, back and abdominal complaints	4
Unconsciousness	4
Missing	3

6.2 Measuring the $P_{ET}CO_2$ during CPR – a sub-analysis from the pilot study (Papers IV and V)

Of 291 patients (Fig. 4) included in and not excluded from the Gothenburg/Mölndal sample, $P_{ET}CO_2$ was not measured in 149 CA patients. The main reasons for drop-out were patients who were not tracheally intubated, early ROSC, severe field conditions and unfamiliarity with measuring $P_{ET}CO_2$. One hundred and forty-two patients were tracheally intubated and included in the sub-analysis to measure the $P_{ET}CO_2$ during CPR. In 16 cases, the measurement was interrupted for various reasons, such as mucus/aspiration (seven), technical errors (two) and unclear reasons (seven). As a result, 126 patients participated in this sub-analysis. Of these, Paper IV (Table 6 and Fig. 6) deals with 64 patients in the mechanical chest compression group versus 62 patients in the control group. Paper V deals with a/ 44 patients compared during ongoing CPR prior to and after PLR (Fig. 7 and Fig. 8) and compared according to patient characteristics (6.2.2) with those (n=82) without PLR and b/observations of the alteration in $P_{ET}CO_2$ during CPR in patients who experienced a ROSC (Fig. 9) and those that did not (Fig. 10).
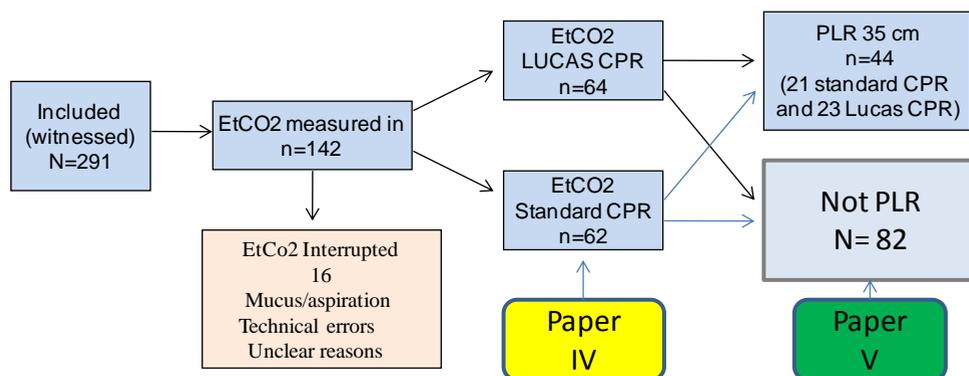

Figure 4. *Detailed flow chart of the recruitment of patients to the analysis of the $P_{ET}CO_2$ in Paper IV and Paper V.*
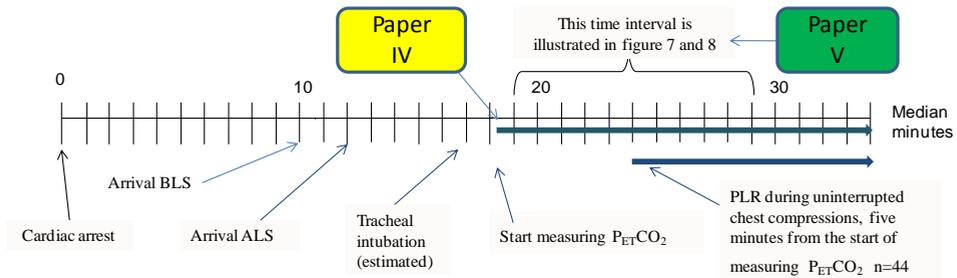
Figure 5. *Calculated time flow (median minutes) from witnessed CA to the start of measuring the $P_{ET}CO_2$ values (Paper IV) and to PLR during uninterrupted chest compressions (Paper V).*

6.2.1 Mechanical versus manual chest compressions (Paper IV)

The vast majority of the 126 CAs (Table 6) were witnessed and treated with epinephrine (1mg every second minute up to 5mg). About one third of the patients were found in VF/VT and a very low percentage of patients were discharged alive. There was a long time interval from CA to the start of CPR, ROSC and to start measuring the $P_{ET}CO_2$ (Fig. 5) in both groups. We found no differences between the two groups.

Table 6. *Baseline data and mean values of $P_{ET}CO_2$ (per cent, median and mean $\pm$ SD with 95% CI)*

Chest compressions		Manual n=62	Lucas n=64	p-value**
Age, years, mean $\pm$ SD		70 $\pm$ 13 (67-74) µ	71 $\pm$ 14 (68-75) µ	
Gender %				
Female		29 (19.1-41.3)	34 (24-46.6)	
Witnessed %		87 (76.3-93.6)	86 (75.2-92.6)	
Bystander CPR %		44 (31.9-55.9)	44 (32.3-55.9	
Treatment: epinephrine %		100 (93-100)	100 (93-100)	
VF/VT %		34 (23.3-46.3)	31 (21.2-43.4)	
Outcome %				
ROSC		52 (39.5-63.3)	44 (32.3-55.9)	
Admitted alive		32 (21.9-44.7)	31 (21.2-43.4)	
Discharged alive		3 (0.2-11.7)	3 (0.3-11.3)	
Time from CA to: median, minutes				
Start CPR	54/57*	6 (2-8)	7 (4-10)	
ROSC	28/25*	25 (23-30)	30 (23-35)	0.18
Start measuring $P_{ET}CO_2$	55/59*	19 (16-20)	20 (17-22)	
Mean values of $P_{ET}CO_2 \pm$ SD				
Average		2.69 $\pm$ 1.41 (2.33-3.05)	3.26 $\pm$ 1.68 (2.85-3.68)	0.04
Initial value		2.71 $\pm$ 1.81 (2.25-3.17)	3.38 $\pm$ 1.79 (2.93-3.82)	0.01
Maximum value		4.48 $\pm$ 2.39 (3.87-5.08)	4.88 $\pm$ 2.16 (4.34-5.41)	
Minimum value		1.69 $\pm$ 1.32 (1.35-2.03)	2.24 $\pm$ 1.73 (1.8-2.67)	0.01

µ = 1 missing   * Number of patients   ** p-value denoted if < 0.20

According to the average, initial and minimum values of $P_{ET}CO_2$, the values among patients receiving mechanical ACD-CPR were significantly higher. However, there was no significant difference according to the maximum value of $P_{ET}CO_2$. Since the Lucas device was applied before intubation, the initial value in the intervention group was recorded during mechanical chest compression. Mean values of $P_{ET}CO_2$, recorded at 30 s intervals for the LUCAS and standard CPR arms, are shown in Figure 6.
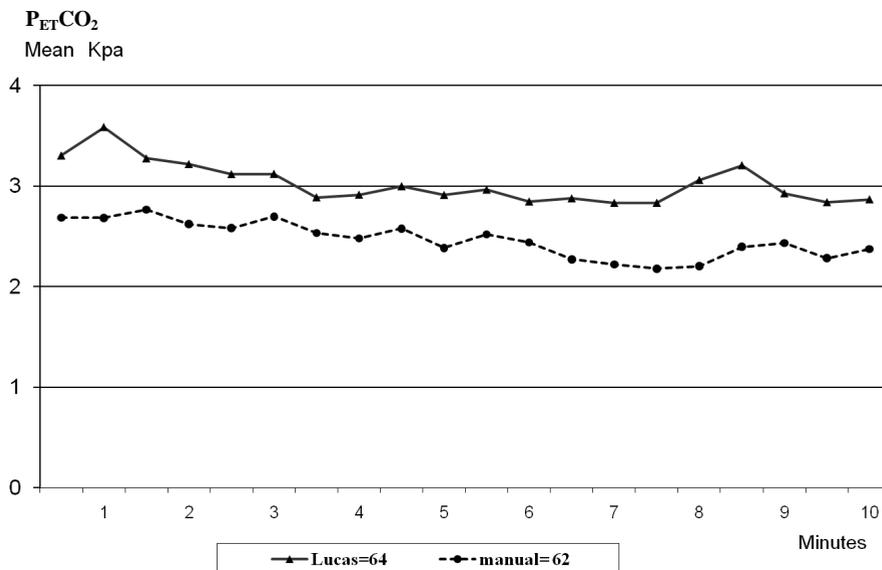
Figure 6. *Mean $P_{ET}CO_2$ values recorded at 30-second intervals for LUCAS and standard CPR arms. Note that the LUCAS device was applied prior to the first reading of $P_{ET}CO_2$.*

6.2.2 PLR during CPR (Paper V)

According to patient characteristics, we found no significant differences between patients when they were divided up according to PLR (n=44) or not PLR (n=82). However, there was a tendency towards a higher survival to hospital discharge (7% vs. 1%; p=0.12, NS), earlier start of CPR (5 vs. 7 minutes, NS) and fewer VF/VT (25% vs. 37%, NS) among the patients who had PLR.

34

Of patients selected by the study protocol to PLR, 21 were treated with manual chest compressions and 23 with mechanical chest compressions. Among all these patients (n=44), significant differences in the mean $P_{ET}CO_2$ values were found when comparing one, two and three values prior to and after PLR (Fig. 7). A similar result was found if patients received manual chest compressions (n=21) (Fig. 8). Among the patients receiving mechanical chest compressions (n=23) (Figure 8), the difference was only significant when comparing the mean of three values prior to and after PLR. However, the group who received mechanical chest compressions had significantly higher $P_{ET}CO_2$ immediately before PLR than the group who received manual chest compressions.

$P_{ET}CO_2$
Mean kPa

PLR

N=44

0.44 ± 0.9* p= 0.003, m= 4

0.45 ± 0.87** p=0.002, m=8

0.43 ± 0.63*** p=0.0001, m=16

Minutes
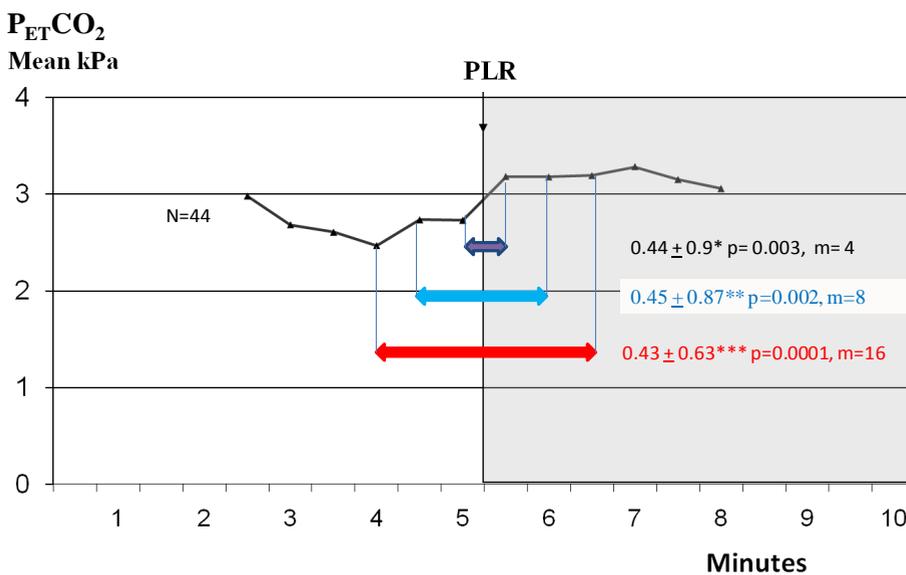
Figure 7. *Mean $P_{ET}CO_2$ values in kilo Pascal (kPa) prior to and after the PLR, during uninterrupted CPR, in 44 patients. Every spot represents a registered mean value. The range between the spots represents 30 seconds and all the mean values are synchronised from the time of elevation. The statistical evaluation for each patient refers to the mean difference in kPa $\pm$ SD between the last recorded value* and the mean of the two** and three*** last recorded values prior to elevation, compared (pairwise) with the same recorded values after elevation, m = missing. All the values were registered during uninterrupted CPR.*
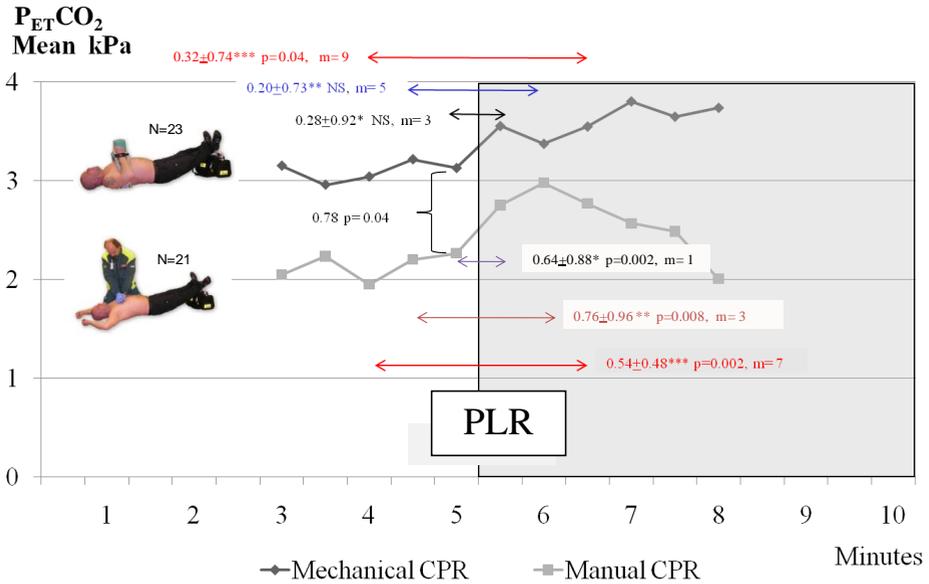
Figure 8. *The population described in Figure 7 (n=44) divided according to whether they received manual (n=21) or mechanical (n=23) chest compressions. The mean difference (0.78 kPa, p=0.04) between mechanical and manual chest compressions was evaluated in the last spot prior to elevation, m=missing.*

6.2.3 Observations of mean $P_{ET}CO_2$ in relation to ROSC

When analysing the last ten observed mean values ($\pm$SD) for patients who experienced ROSC (Figure 9, n=60), we observed a marked increase in $P_{ET}CO_2$ one minute before the detection of a palpable pulse. Among patients with no ROSC (Figure 10, n=66), the mean value tended to decrease with time. We observed a large spread in $P_{ET}CO_2$ between the patients in both groups.

P_ET CO₂
Mean kPa ± SD

The last recorded value before the detection of a palpable pulse

10 values / 5 minutes
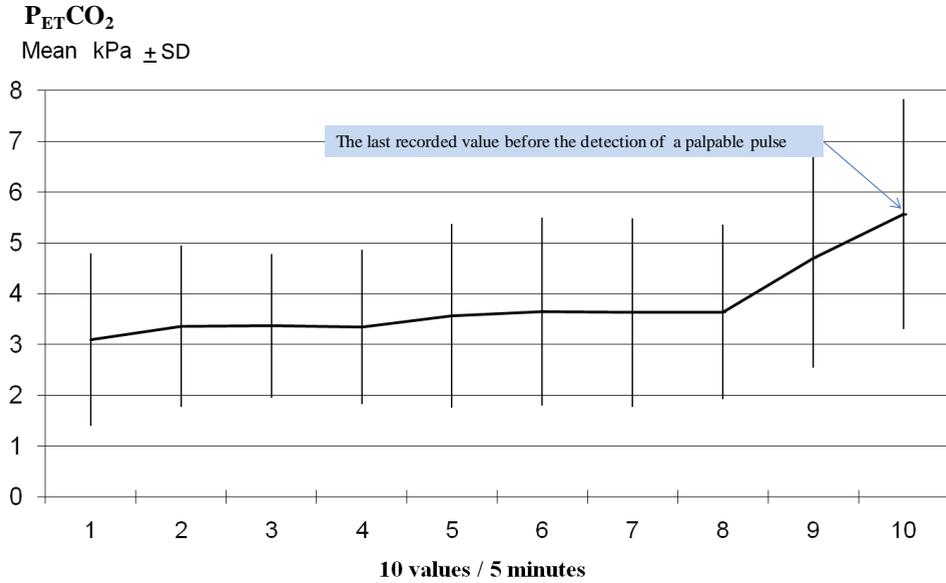
Figure 9. *The last 10 observed mean P_ET CO₂ (kPa ±SD) values during CPR for 60 patients who experienced ROSC. The values in the figure are synchronised from the last value (from the end of the line) prior to the detection of a palpable pulse (10 values = 5 minutes).*

P_{ET}CO₂

Mean kPa $\pm$ SD
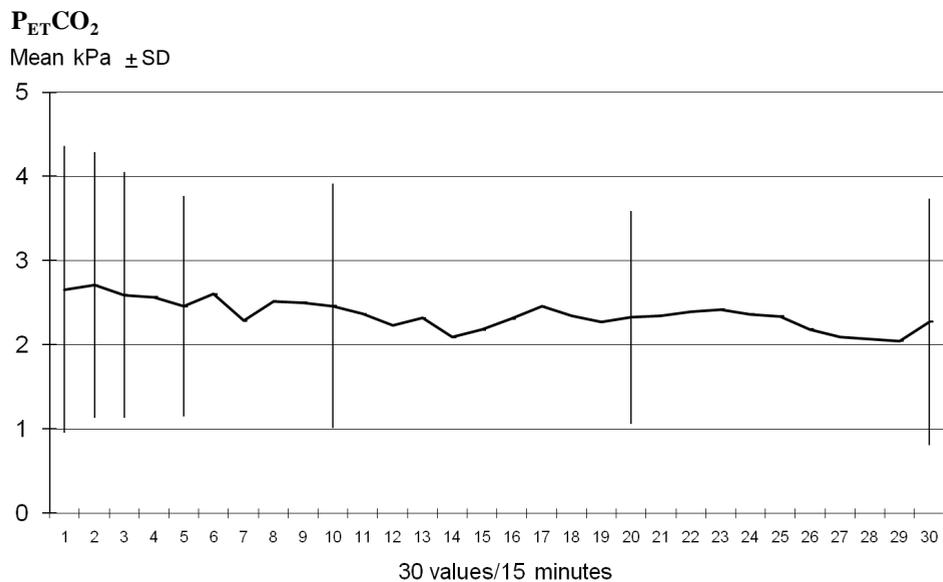
Figure 10. *Thirty mean values (15 minutes) of P_{ET}CO₂ (kPa $\pm$SD) during CPR among 66 patients with no ROSC.*

6.3 Characteristics and outcome among patients suffering from out-of-hospital cardiac arrest with the emphasis on availability for intervention trials (Paper II)

6.3.1 Utstein template, general results from Gothenburg/Mölndal (Figure 11)

The population in Gothenburg/Mölndal was 542,692 in 2005. During the study period of two years (2003–2005) 508 resuscitations were attempted. Of these cases, 307 (61%) were of cardiac aetiology (judged by the ALS crew) and 196 (39%) of non-cardiac aetiology. Information was missing in five cases.

6.3.1.1 Non-cardiac aetiology (Fig 11, plate 4)

Among the 196 patients with a non-cardiac aetiology, 10 patients (5.1%) were discharged alive and eight of these patients were still alive one year later. The CPC score for the 10 patients discharged alive was CPC 1 = five patients, CPC 2 = one patient and $\geq$ CPC 3 = four patients. The two patients who died during the first year were discharged with CPC 3.

6.3.1.2 Bystander-witnessed cardiac arrest (Fig 11, plate 3.1)

Of the bystander-witnessed cardiac arrests, VF/VT was the most common initial rhythm. Bystander CPR was reported in 58%. Patients found in VF/VT had received bystander CPR most frequently. The survival rate at discharge was 12.7% and one year later all the patients were still alive. The CPC score at discharge was CPC 1 = 20 patients, CPC 2 = three patients and $\geq$ CPC 3 = one patient.

6.3.1.3 Crew-witnessed cardiac arrest (Fig 11, plate 3.2)

Of the crew-witnessed cardiac arrests, 45% were defibrillated. Overall survival to discharge was 16.1%. All eight patients discharged alive had CPC 1 at discharge and, of those, seven patients were still alive one year later.

6.3.1.4 Non-witnessed cardiac arrest (Fig 11, plate 3.3)

Among the non-witnessed cardiac arrests, asystole was the most common initial rhythm. Bystander CPR had started in 36%. One patient (1.4%) was discharged alive with CPC 1 and was still alive one year later.

Utstein template

	1. Population served by Gothenburg/Mölndal EMS System n = 542 692			Dischrged alive n = 10
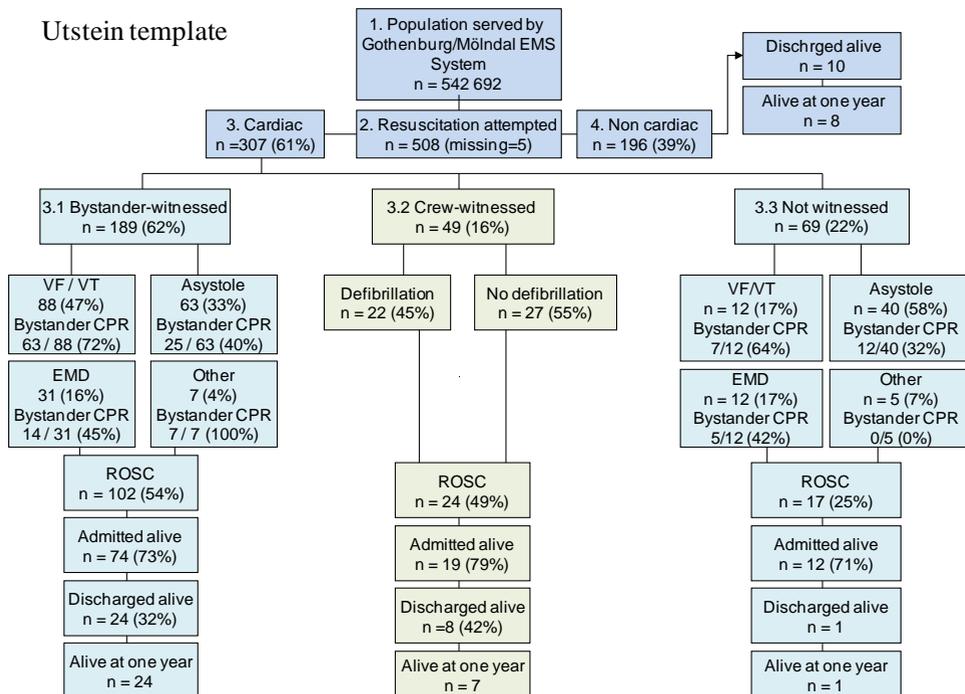
Figure 11. *Utstein template of all treated CAs in Gothenburg/Mölndal during May 03-05*

6.3.2 Characteristics and outcome in relation to criteria for inclusion in an interventional trial (Paper II)

Of all 508 patients treated in Gothenburg/Mölndal, 298 (59%) fulfilled the inclusion criteria and had no exclusion criteria; 49 patients (10%) fulfilled the inclusion criteria but had exclusion criteria and 161 patients (31%) did not fulfil the inclusion criteria (unwitnessed). According to Table 7a, b, the patients who were included were older and more frequently suffered a bystander-witnessed CA. They also had the highest percentage of CA of cardiac aetiology. Excluded patients more frequently had a previous history of "other disease", were more often crew witnessed and had the earliest start of CPR and time to ROSC. According to rhythm on the arrival of the ALS unit (start of intervention), excluded patients had the highest percentage of pulse-generating rhythm and the lowest percentage of VF, while patients not fulfilling the inclusion criteria had the highest percentage of asystole. Survival to hospital

discharge tended to be highest among excluded patients, while the group of patients not fulfilling the criteria had the lowest percentage of patients discharged alive.

Table 7 a, b *Characteristics and outcome among all treated OHCAs in Gothenburg/Mölndal with regard to availability for interventional trials. The statistical evaluation in Table 7a, b refers to a comparison of patients included versus patients excluded and not fulfilling the inclusion criteria respectively.*

7a		Included (n=298)	Excluded (n=49)	Not fulfilling inclusion criteria (n=161)
Age (years), mean		71	61 [##]	60 [###]
Previous history %				
Other disease	(m=161)	38	65[#]	55[#]
Cardiac aetiology %	(m=34)	73	40[###]	44[###]
Bystander witnessed %		79	55[##]	0
Bystander CPR %	(m=19)	55	48	35[##]
Crew witnessed %		21	45[##]	0
Rhythm on arrival of ALS %	(m=41)			
Pulse-generating rhythm		13	50[###]	0
VF		27	3[#]	12[##]
Asystole		39	34	71[###]
Survival to discharge		9.7	20.4	2.5[#]

(m)= missing

7b		Included	Excluded	Not fulfilling
Time from CA to (median, min)				
Start CPR	(n=368)	3	0	13[###]
ROSC	(n=165)	23	9[##]	32 [###]

(n) = number of patients

[#] p <0.01, [##] p<0.001, [###]p=0.0001

6.4 Dispatch codes in OHCA (Paper III)

This study includes only CA cases judged to have had a CA at the time when the RCC was approached. During the17 study months, starting in January 2004, 349 patients with OHCA were treated by the Gothenburg/Mölndal EMS (Figure 13). Excluded were 55 CAs (16%) that were crew witnessed and 33 CAs (9%) that occurred after calling for but before the arrival of the rescue team (survival to hospital discharge was 13.6% in this excluded group).

Information on possible exclusion was missing in 11 patients. This study deals with the remaining 250 cases. Of these 250 cases, the EMDs coded 50 (20%) as a diagnosis (CA). Of the remaining 200 cases, the EMDs coded the majority according to symptoms such as unconsciousness or unclear unconsciousness. In Paper III, the 50 patients who were coded as CA are compared with the 200 who were not.
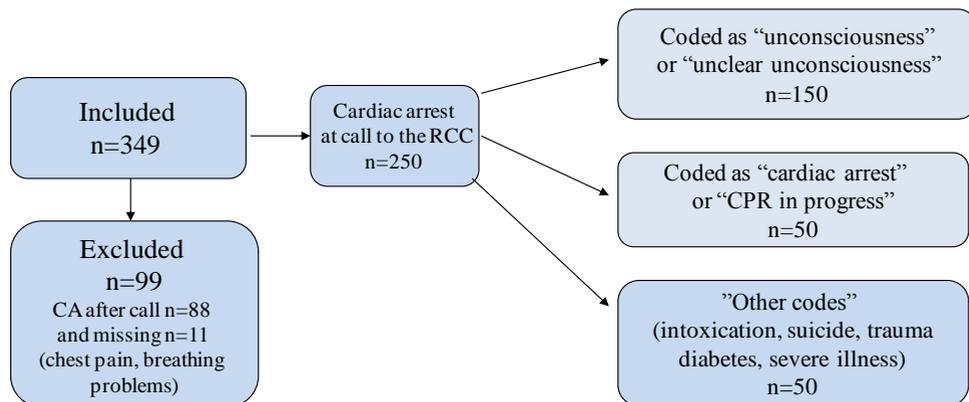

Figure 13. *Detailed flow chart for the recruitment of patients to the analysis in dispatch codes (Paper III).*

6.4.1 Bystander CPR, rhythm, outcome and delay

Bystander CPR was more than twice as common among patients who were coded according to diagnosis by the EMDs (86% vs. 42%, OR 8.5 CI (3.6-19.8) p<0.0001). These patients had a pulse-giving rhythm more frequently at the arrival of the first unit (6% vs. 1%, OR 12.3 CI (1.3-121.1) p=0.03). The percentage of patients surviving to hospital discharge was more than twice as high in this group (14% vs. 6.5%, OR 2.3 CI (0.9-6.2) NS). Time delay from creating time (= time at which the EMD identifies the need for an ambulance and creates the ambulance protocol) to alerting time (= time at which the EMD sends an alert to the ambulance unit) was a median of two minutes for the BLS unit and 2.5 minutes for the ALS unit. The time from creating time to alerting and the arrival of the two units did not differ between CA coded according to symptoms and diagnosis. However, the delay to alerting the first unit tended to be longer when the dispatcher coded the case according to diagnosis of

CA. The median time from CA to bystander CPR was eight minutes shorter (two minutes vs. 10 minutes, p<0.0001) among patients who were coded according to diagnosis by the EMDs.

6.5 Summary of main results

According to the Utstein template, the overall survival to hospital discharge in Gothenburg/Mölndal was 8.5% during the study period. Among patients that fulfilled the inclusion criteria for the trial and had no exclusion criteria, 9.7% survived to hospital discharge. The highest survival (20.4% NS) tended to be among patients fulfilling the inclusion criteria but who were excluded for various reasons. Of these, ten patients of 49 were excluded because of ROSC before the arrival of the ALS.

The primary end-point in this pilot study was pre-hospital ROSC and no difference was found between the groups receiving manual versus mechanical chest compressions.

The group receiving mechanical chest compressions always received manual compressions during the preparation of the mechanical device. The time to starting mechanical chest compressions was a median of 18 minutes from CA.

Only two thirds of the patients in the mechanical group (with intention-to-treat analysis) were actually treated with mechanical chest compressions. The two main reasons for not treating were early ROSC during the preparation of the mechanical device or that the device was not brought to the patient because of dispatch codes (CA not identified at call or occurred after call).

If a CA at the dispatcher centre was coded according to a diagnosis (cardiac arrest), the patients had an earlier start of CPR, received bystander CPR more frequently and tended to have higher survival rates compared with those CAs coded according to a symptom (unconsciousness).

Measurements of $P_{ET}CO_2$ during CPR showed higher mean values among patients receiving mechanical chest compressions compared with those who received manual compressions. Elevation of the lower extremities during CPR showed higher mean values of $P_{ET}CO_2$ directly

after elevation among 44 patients. These two observations were made subsequent to intubation and started > 20 minutes from CA in a late stage of resuscitation (Fig. 5).

7.0 Discussion

7.1 Method

7.1.1 Patient selection and limitations

The papers (I to V) are based on a pilot study with a limited sample size. The results can therefore only be considered as hypothesis generating. Papers II and III were designed during the study analysis and according to the findings made in the analysis of drop-outs. The study was conducted by the staff in the second tier (the ALS unit). The ALS units were chosen for two main reasons; they met all patients with a CA and were a small manageable group to train and rehearse in the implementation of the study protocol. During the study period, two devices performing mechanical chest compressions were exchanged between four ALS units for periods of six months. This exchange was made to create an intervention group and a control group according to a cluster method. The use of this method resulted in witnessed CAs being included in the intervention group when the device was included in the ambulance equipment and was therefore possible to use. The validity of the present study would have increased, and the large number of drop-outs would have decreased, if we had randomised by envelope in all cases in which the device was brought to the patient (considering inclusion and exclusion criteria).

The main reasons for the choice of the cluster selection were as follows.

1. The present study aimed to study when, if and how the device was used in clinical practice (envelope randomisation will always be an artificial situation).

2. Randomising a non-blinded treatment at the scene and by envelope could delay the intervention and increase the risk of a selected sample (selection bias among "promising cases" according to the treatment advocated by the crew) [90].

3. Extra equipment could adversely affect the treatment in the control group, since it had to be carried back to the ambulance while the personnel were performing manual chest compressions.

In Paper III, the study population was divided according to whether or not the call was coded according to the diagnosis of CA. This resulted in a small number of individuals in the group coded according to the diagnosis of CA. This distribution reduces the statistical power and larger studies are needed to confirm the tendencies found in this study.

In the sub-analysis in Paper V, the $P_{ET}CO_2$ was studied among 44 (of 126) tracheally intubated patients when performing PLR. According to dissimilarities in treatment, manual or mechanical compressions, we stratified the population at the scene and by the study protocol to PLR. The 44 patients were distributed in an acceptable way between manual and mechanical chest compressions. Unfortunately, the protocol was not numbered and, as a result, we are not able to present a proper analysis of drop-outs. However, according to personal communication with the ALS personnel, the main reasons for dropping out were either ROSC (about eight patients) before PLR or poor compliance with the protocol by the ALS crew (in eight to 10 cases).

7.1.2 Patient number and distribution

The limitation of the present pilot study was set by time and not by sample size. The study period was set at two years in Gothenburg/Mölndal. As a result of participating in another study, Södertälje EMS only took part for one year. Further, Södertälje EMS only included patients during the daytime between 7 am and 7 pm. During the study period, Gothenburg/Mölndal was divided according to three EMS districts. Each district was covered by one ALS unit and, when occupied, the closest ALS unit was alerted. We believe that the devices were divided evenly between the patients in the various districts during the two years in Gothenburg and one year in Södertälje.

7.2 Results

7.2.1 Epidemiology during the study period from Gothenburg/Mölndal

In a consecutive sample of patients suffering an OHCA in the Municipality of Gothenburg/Mölndal during the study period (May 2003 to May 2005), we found that as compared with previous experiences from the same district, the number of resuscitation attempts per 100,000 inhabitants and year had decreased from 61 to 47 [91], the survival rate was similar [7], except for 1991 and 1992 [92], but there was a higher level of estimated

cerebral function [7]. This was found despite an increase in ambulance response time [7], a lower occurrence of ventricular fibrillation [91] and a lower percentage of patients with a CA of cardiac aetiology (from more than 90% in the early 1980s to 60% today) [91]. Contributory factors to the unchanged survival, despite increasing ambulance response time and decrease in VF, could have been an increased percentage of patients receiving bystander CPR [91] and a higher percentage of patients suffering a crew-witnessed cardiac arrest [7].

7.2.1 Patient characteristics and ambulance delay

In the present study (Paper I) and according to patient characteristics, no differences were found between the intervention group and the control group. However, a cardiac aetiology was more frequent in the control group. According to delay and rhythm on arrival there was a higher percentage of PEA on the arrival of the second tier (the ALS unit) and a tendency towards a prolonged delay (one minute) from CA to calling for an ambulance in the intervention group. These findings might affect the results in the intervention group in a negative way. The ambulance delay, from CA to arrival, did not differ between the intervention and the control group. However, the ambulance delay, for the first and the second tier respectively, appeared to increase markedly from five and eight minutes in a previous report [7] to 10 and 12 minutes in the present one. One possible explanation for this huge increase in delay is that the previous report is based on delays estimated by the ambulance crew without knowing the time from call to alert at the RCC. However, in Paper III, it was shown that the delay from creating time to alerting time (at the RCC) was a median of two minutes for the BLS unit and 2.5 minutes for the ALS unit. Even when compensating by adding two and 2.5 minutes respectively to the previous delay, the present increase in ambulance delay was still more than two minutes during the study period. These findings are worrying and agree with national figures [8], so the availability of ambulances has to be evaluated and adapted to current needs.

7.2.2 Outcome

Our hypothesis that mechanical chest compression improves outcome was not confirmed. However, there are no clinical trials supporting the hypothesis that the widespread use of mechanical chest compression will increase overall survival in OHCA [78, 79]. When making a power analysis post hoc we found that, with the actual sample size, the effect in the intervention group had to exceed 30% (ROSC rate from 50% to 65%) to establish that mechanical chest compressions could increase the ROSC rate (80% power, p=0.05).

According to the drop-out analysis in Paper I, we found that only 105 of 159 patients in the intervention group were actually reached by the intervention and that the intervention started late (in relation to the collapse) among the 105 patients reached by the intervention. The large number of drop-outs, in combination with the late start of the intervention, probably makes an overall effect of 30 % impossible to achieve in the intervention group.

7.2.3 Sample size according to primary end-point

The primary end-point in the present pilot study was pre-hospital ROSC. However, ROSC or survival to hospital admission is not a good result if it is not followed by corresponding figures for survival to hospital discharge [93]. The choice of primary end-point has a great impact on the number of patients that need to be included in a study when the aim is to show a beneficial effect of an intervention. In the table below, figures from the present pilot study are used to show the differences in the number of included patients when ROSC, survival to hospital admission or survival to hospital discharge respectively are used as a primary end-point. We calculate the required sample size if we expect a positive effect of 30% from the intervention with a power level of 80% (type I error of 5%) [94].

Table 8. *Analysis of sample size according to the selection of primary end-point*

	Figures based on the present pilot study	30% calculated effect of the intervention	Specified power level with a type I error of 5% (p=0.05)	Number of patients needed to be included
ROSC	50%	65%	80%	180 x 2
Survival to hospital admission	35%	45.5%	80%	270 x 2
Survival to hospital discharge	9.7%	12.6%	80%	1950 x 2

As seen, the exponential increase in sample size implies that sizing the studied sample according to ROSC will most probably fail to show a positive effect on survival to hospital discharge.

Calculating with a higher anticipated effect of the intervention reduces the sample size. However, unreasonable faith in the efficacy of the intervention, especially if it is a late intervention, once again risks producing a result that is unable to say anything about survival to hospital discharge [95]. Sample sizes that are too small (based on ROSC as the primary end-point) or unreasonable faith in the efficacy of the intervention are probably reasons why most of the OHCA studies fail to show a beneficial effect on survival [95,96].

7.2.4 Sample size according to time from CA to start of intervention

In Paper II we reported that we found the shortest time from collapse to ROSC and a tendency towards the highest survival rates among the excluded patients. The time from collapse to ROSC appears to have a great impact on survival to hospital discharge [97]. Further, we found in the present study that the time from collapse to the start of the intervention appeared to have a great impact on the survival rate, which we want to influence with the intervention, and consequently the sample size. The present study started the inclusion of patients at a median of 12 minutes after collapse (arrival of the ALS unit). Survival to hospital discharge was 9.7% in the included population and, if the intervention had started immediately, we would have needed to include 1,950 x 2 patients to ensure an effect of at least 30% on survival to hospital discharge. However, the clinical reality meant that the device was actually started six minutes later, a median of 18 minutes from collapse. At that time, survival to discharge was about 4% (Table 4b) and consequently the present intervention would have needed to include more than 9,000 patients to show the same effect.

7.2.5 Why did the intervention start so late?

According to the previously mentioned median delay from call to the arrival of the EMS, the use of the second tier (the ALS unit), instead of the first (the BLS unit), to bring the device to the patients probably delayed the intervention by a median of two minutes. In the design, we estimated that, from the arrival of the ALS unit, less than three minutes would be enough for mechanical compressions to take over from manual compressions, but in reality six minutes were needed. According to personal communication with the ALS personnel, the reasons for the prolonged median delay to the start of mechanical compressions were related in several cases to an unexpected CA and the device was therefore brought to the patient afterwards.

In the present study the intervention started late among two thirds and was not used among one third of the patients in the intervention group. The analysis of drop-outs revealed early

ROSC, unfamiliarity with the extra equipment and unspecific dispatch codes as the main reasons for not using the device. The present pilot study clearly shows the problems associated with extra equipment that is only needed in a few cases and is too large (10+8 kilos) to be included in the standard equipment (24 kilos). In theory, this intervention could be started more than five minutes earlier if the device was brought directly and by the BLS unit to all patients with a suspected CA.

7.2.6 Dispatch codes in CA during the study period

It has previously been stated that survival will decrease if we do not recognise a CA during the emergency call [15]. The findings we made in the drop-out analysis from Paper I made us curious to analyse dispatch codes among the patients with a presumed CA at call. This analysis (Paper III) revealed that only a small percentage of all treated CAs were coded by the EMDs according to the diagnosis of CA. The majority of the CAs were coded according to symptoms (most often unconsciousness or unclear unconsciousness with the appropriate additions). The decision to start coding according to symptoms was made when the national medical index was introduced at the RCC in 1998. During the study period, a second edition of the index, introduced in 2001, was used. During the study period, a small group (50 patients) was still coded according to the diagnosis of CA and this could probably be due to old habits from some EMDs. In Paper III, we wanted to analyse how, and if, the recognition leading to a diagnosis code (CA) differs from the recognition that ends in a symptom in terms of early treatment and outcome. We found that a CA coded according to the diagnosis of CA was associated with an earlier start of CPR, a higher percentage of bystander CPR and a tendency towards a higher survival rate than if it was coded according to a symptom. Dispatching according to the diagnosis of CA therefore appeared to be beneficial to the patient. These results could reflect more optimal communication between the dispatcher and the caller, as well as the rescue team.

7.2.7 Dispatch codes in CA in 2009

In the above discussion, one of the reasons for the late start of the intervention was an unexpected CA and, as a result, the device was brought to the patient afterwards. It is possible to argue that an unconscious patient often has a serious disease and most often needs an

ambulance. However, the majority of patients who are unconscious do not have a CA. Using the resources incorrectly (e.g. alerting fire-fighters or the police force to perform early defibrillation and CPR) for all cases of unconsciousness could have ethical, financial and organisational implications [15].

According to Paper III, we found that the majority of all treated CA cases during the study period were found among cases in which the dispatch codes were the symptoms of breathing problems, chest pain and unconsciousness with the appropriate additions. To further extend this discussion, we made a new analysis of all treated CAs in Gothenburg/Mölndal in 2009 according to the above-mentioned symptoms index. In 2009, according to the ambulance journal system (Ambulink), a total of 247 CAs were treated. Of these, 196 (79%) were found among the symptoms of breathing problems (28), chest pain (17) and unconsciousness (151) with the appropriate additions. The 196 patients are analysed in the table below. We also report the distribution of CAs among the fixed additions (index 2) to the most common dispatch code: unconsciousness.

Table 9. *Dispatch codes among 79% (196/247) of all treated CAs in 2009*

Dispatch codes (index 1)	RCC data	Estimated from RCC data	AMBULINK data
	Cases*	Number of patients**	Treated patients with a CA (196/247)
Breathing problems	2 609	1305	28
Chest pain/cardiac disease	5 351	3290	17
Unconsciousness – adult	2 775	1389	151
Total	10735	5984	196
Unconsciousness – adult *** (index 2)			
CPR in progress	164	82	40
Does not respond when spoken to or shaken – breathing	1 724	864	24
Does not respond when spoken to or shaken – not breathing	475	238	34
Does not respond when spoken to or shaken – agonal breathing	251	126	13
Telephone CPR in progress	157	79	40
Total	2 771	1389[#]	151

* = Number of cases depends on number of units alerted (e.g. two tiers to one patient are two cases)

** = Number of patients estimated according to two-tier alerts. In 2009, the two-tier alerts were most common among the dispatch codes of unconsciousness and breathing problems

***= Appropriate additions to unconsciousness (e.g. unconsciousness – CPR in progress)

[#] = The figure 1,389 probably also contains the lion's share of patients judged to be dead at arrival (DAA)

To summarise, in 2009, the EMDs identified 151 of 247 CAs (61%) as unconscious with appropriate additions. However, the 151 identified CAs were identified as unconscious and were hidden among 1,389 patients also categorised as unconscious.

According to figures from the present pilot study, it can be presumed that mechanical chest compressions could probably be started five to six minutes earlier if the device was brought directly by the BLS unit to all patients with a CA. In practice, this means that, in 2009, the BLS unit had to include the device for 1,389 patients categorised as unconscious to reach 61% (n=151) of all treated CAs. If, as an alternative and according to Appendix 2, we instruct the BLS personnel to include the device for all cases categorised as unconscious, except for those with the appropriate addition "with normal breathing", the device should be included for 525 (1,389 -864) patients to reach 51% (151 -24=127) of the CAs. In this perspective, dispatching according to symptoms appears to be a blunt instrument.

In the literature, we found corresponding figures from three cities where dispatching according to the diagnosis of CA was used. In Amsterdam, during a period of eight months, the dispatch centre identified 203 of 285 CAs (71% sensitivity) [15]. In a further 64 cases, a CA was suspected but not present at ambulance arrival (64/203+64 = false CA in 24%). During the course of one year, the dispatcher centre in Helsinki identified 573 of 679 CAs (83% sensitivity) [98]. In a further 97 cases, a CA was suspected but not present at ambulance arrival (false CA in 15%). During a period of three months, the dispatch centre in Melbourne identified 566/738 CAs (76.6% sensitivity) [99]. In a further 403 cases, a CA was suspected but not present at ambulance arrival (false CA in 42%).

7.2.8 Mechanical chest compressions in OHCA – is it possible to show improved overall survival?

The present pilot study clearly shows that there is room for optimising the use of the device. However, even if we succeed in optimising the use, ambulance delay and clinical circumstances will probably mean that we do not reach more than 60-70% of the treated CAs, within 12 to 13 minutes from CA. According to our calculations, more than 3,000 patients fulfilling these criteria have to be included to power a study with survival to hospital

discharge as the primary end-point. These large studies call for co-operation between several centres and are probably difficult to implement for financial and quality reasons.

7.2.9 CAs occurring after ambulance dispatch

We have previously discussed the "late start of the device" according to dispatch codes and lack of identification of the CA at call. Ambulance delay is another reason. As previously mentioned (7.2.1), the ambulance delay among CAs has gradually increased by two to three minutes in Gothenburg since the 1990s (Paper II). The only way to eliminate the ambulance delay is to be close to or at the patient's side when the CA occurs and this is only possible among crew-witnessed cases. According to the Swedish national OHCA registry [8], crew-witnessed cases constitute about 15% of all OHCAs. The crew-witnessed cases in Sweden have increased from 9% to 15% during the last 14 years and have been reported to be strongly associated with the increase in survival (to one month) in Sweden [100]. During the study period in Gothenburg, we found, among patients with CA of non-traumatic origin, 16% crew-witnessed cases (Paper II) and a further 9% that occurred after calling for but before the arrival of the rescue team (Paper III). In Gothenburg, we estimate that these two groups comprise 35-40 patients each year. Among crew-witnessed cases, 49% experienced ROSC, 39% were admitted alive to hospital and 16% were discharged alive from hospital (Paper II).

7.2.10 Resuscitation during transport

In the present analysis, mechanical chest compressions were studied as a replacement for the ambulance crew in an existing concept. In Paper IV, we concluded that mechanical chest compressions, made by the Lucas device, appeared to perform more effective CPR than chest compressions performed by the ambulance crew (discussed later) also during transport. What happens if we change the old concept according to the new opportunity to perform resuscitation during transport? The following two cases (case reports in progress) were reported from the physician ambulance in Gothenburg in 2010.

1) One male patient, born in 1964, had a witnessed CA in public. High-quality CPR was started immediately by a bystander. When the ambulance arrived, the patient had asystole, immediate resuscitation failed, but the man was transported to hospital with mechanical chest compressions. One hour and five minutes after collapsing, the man experienced

ROSC in the hospital after repeated doses of epinephrine. He was discharged alive within 14 days, without any neurological deficit.

2) In February, a female born in 1960 had a crew-witnessed CA at work and the initial rhythm was VF that could not be defibrillated. The patient arrived at hospital 45 minutes later with ongoing mechanical chest compressions and PCI was performed during resuscitation. In all, CPR was performed for about two hours. Two months later, her only problem (according to her relatives) was a decrease in short-time memory.

According to the two ambulance physicians, neither of these two patients could have been resuscitated without mechanical compressions. Similar cases have been reported, both from the pre-hospital field and from the cath lab [101-105].

7.2.11 Causal thinking

These two cases in Gothenburg illustrate a new way of thinking. Unsuccessful OHCA treatment usually starts and ceases outside hospital. Transport during resuscitation has only been possible if the patient experiences ROSC. The reasons for this have been the difficulty in performing effective, safe CPR during transport on a stretcher and in a moving ambulance [6]. In these cases, mechanical compressions presents a new option to establish a bridge to hospital [106], according to a new causal way of thinking [107]. Causal thinking is based on cause and effect. When immediate resuscitation fails, we must learn to consider the new option of performing chest compressions during transport. An occluded coronary artery needs to be opened, even if the patient develops refractory VF in the ambulance [108]. A causal way of thinking requires good co-operation between the ambulance and the receiving hospital, quick decisions, new directions and plenty of information, both outside and inside hospital [109]. Old prejudices have to be changed. Recently noted and documented cases (published [103,104] and unpublished) show the need to identify OHCA patients who benefit from prolonged resuscitation with a need for mechanical chest compressions as a bridge to hospital. This group is probably to be found among non-ROSC patients receiving high-quality CPR within two minutes of collapsing. As mentioned previously, each year in Gothenburg, about 35-40 patients with OHCAs receive high-quality chest compressions within two minutes (crew witnessed + CA just before ambulance arrival), only 39% are admitted alive to hospital. For more than 20 years, the survival rates (overall to one year) outside hospital in

Gothenburg/Mölndal have remained stable, with few exceptions [92], at around 20 persons a year [7, 11]. Extending this exclusive group by five to ten more patients (from a group with no previous survival) would increase the survival rates in Gothenburg/Mölndal by more than 30%.

7.2.12 Injuries during mechanical compression

During the study period the ALS personnel noted that, during a long sequence of mechanical chest compressions, the device slid in an abdominal direction. Injuries confirming this observation were also found during autopsy by Englund et al. [110]. Our observation resulted in a stabilisation strap that is currently included when the device is delivered. This stabilisation strap was probably not used during the fatal complication, with a sliding device, reported from Amsterdam [111].

Internal injuries after mechanical compressions were investigated by Smekal et al. [112]. They investigated 85 patients, 47 of whom received manual CPR and 38 mechanical CPR. They concluded that mechanical compressions, made by the LUCAS^{TM} device, were associated with the same variety and incidence of injuries as manual compressions. The study made by Smekal et al. was commented on by Xanthos et al. [113] according to the combination of manual and mechanical chest compressions in the "mechanical group". Their position was that the combination may overestimate injuries made by mechanical compressions and hence limit the interpretation of the result [113]. We found that, according to field conditions, mechanical compressions always include a short period of manual compressions in the start-up period and so, to reflect reality, this concept probably has to be studied and compared with the purely manual concept. Larger studies of injuries during CPR are warranted, including interacting variables like age, gender and compression time.

7.2.13 The $P_{ET}CO_2$ as a predictor of the effect of chest compressions

In the present pilot study, we used the $P_{ET}CO_2$ as a predictor of the efficacy of external chest compressions during CA. For many years, the $P_{ET}CO_2$ has been thought to have a near linear correlation to pulmonary blood flow reflecting cardiac output during CPR [114-116]. In the present pilot study, we compared the effect between the groups by standardising the ventilation. Mechanical ACD-CPR resulted in the highest mean values according to the

initial, minimum and average value of $P_{ET}CO_2$, which suggests that mechanical ACD-CPR performs compressions with higher cardiac output than manual chest compressions performed by the ambulance crew. Our figures are in accordance with two earlier human studies which were both conducted in the late stage of resuscitation, one resulting in increased $P_{ET}CO_2$ [117] and the other [118] in higher mean arterial pressure for the benefit of patients treated with mechanical compressions. However, the present method has [119] been considered by one author to be a non-valid surrogate variable since the differences in the $P_{ET}CO_2$ were not related to the survival rates. The study that is requested is probably difficult to perform as the method of analysing the effect on the $P_{ET}CO_2$ forced us to start subsequent to intubation (a median of 19-20 minutes from collapse when survival rates were extremely low, less than three per cent).

The weakness when measuring the $P_{ET}CO_2$ is that we do not know anything about how much the increase in the $P_{ET}CO_2$ reflects the amount of cardiac output or how the time from collapse to the start of measurements reflects the cellular metabolism producing CO_2. However, direct measurements of blood flow during OHCA require time-consuming invasive procedures, which are impossible to perform outside hospital.

Further, we found that the $P_{ET}CO_2$ was helpful in predicting ROSC [61]. Figure 9 visualises the $P_{ET}CO_2$ graph before the detection of a palpable pulse. This knowledge indicates a way of improving CPR quality by minimising the pulse checks (hands-off situations). If the graph is still stable since the last pulse check, continue CPR. This method could be important when it comes to improving circulation when prolonged CPR is indicated.

It has been claimed by several authors that $P_{ET}CO_2$ could also be a tool for predicting non-survival during resuscitation [55, 59, 63]. The present result, which is shown in Figures 9 and 10, shows a large spread between the patients in both the ROSC and the non-ROSC group. Further, several error sources (mucus/aspiration, technical errors and unclear reasons) in measurements of $P_{ET}CO_2$ were reported during the present pilot study. Consequently, we do not support the claim that measurements of $P_{ET}CO_2$ could still be a predictor to cease resuscitation in the pre-hospital field.

7.2.14 Passive leg raising during CPR

To our knowledge, the effect of PLR during CPR in humans has not previously been studied. The Trendelenburg position (head-down tilt) has most frequently shown negative [42] or minor haemodynamic improvements [120]. However, Zadini et al. [46] suggest that the Trendelenburg position improves blood flow during CPR. When investigating the benefit of PLR during chest compressions the flow in our design was planned according to the haemodynamic explanation given by Steen et al. [24] in the circulatory phase [23]. Steen et al. [24] performed CPR for 3.5 minutes to restore the fibrillating heart before defibrillation in the circulatory phase and we could perhaps have performed the elevation after three minutes instead of five. However, we wanted to see if the elevation could potentially produce a bolus effect, a possible increase in CPP before defibrillation, and how long it would persist. Fichet et al. [51] accredit PLR with the transfer of approximately 200-300 ml blood from the limbs to the central venous compartment. The authors also presume that this transient increase in preload results in an increase in cardiac output. Jabot et al. [50] found the largest increase in cardiac preload when using the $PLR_{semirec}$ method (p. 13). However, the method for performing PLR during CPR only allows us to elevate the lower extremities from a horizontal position. The decision to standardise the elevation to 20 degrees was made according to the height of the standard equipment brought by the ambulance crew to all patients in priority-one cases.

The intervention with PLR started more than 20 minutes after collapse (Figure 5). According to patient characteristics described in the results, there were no significant differences between the patients who had PLR (n=44) versus those who did not (n=82), but, as mentioned previously in the limitations (7.1.1), the distribution between the groups was skewed and the results must therefore be interpreted with caution. However, we found some interesting tendencies. In spite of higher survival rates, the percentage of patients found in VF/VT was lower among the 44 patients with PLR. Does this indicate a beneficial effect from treatment even among patients found in PEA and asystole? The mechanism behind a possible effect of PLR during CA can only be speculated on. However, if PLR increases the venous return during CPR, it possibly also increases the cardiac preload. This effect might contribute to an increase in coronary blood flow that is predictive of ROSC [27]. When speculating on the negative effects, PLR during CPR might result in increased blood pressure in the right side of

the heart, resulting in a decrease in CPP or causing an additional injury by increasing circulating metabolic factors recruited from the large vessels in the legs [23].

8.0 Conclusion, future aspects and implications

8.1 Conclusion

In a consecutive sample of patients suffering from an OHCA in the Municipality of Gothenburg/Mölndal during the study period (May 2003 to May 2005), we found a similar survival rate but a higher level of estimated cerebral function compared with previous experience from the same district. This was found despite longer delays, a lower occurrence of ventricular fibrillation and a lower percentage of patients with OHCA of cardiac aetiology. Contributory factors could have been an increased percentage of patients receiving bystander CPR and a higher percentage of patients suffering a crew-witnessed cardiac arrest.

In the present study of patients with OHCA, our hypothesis that mechanical chest compression improves outcome was not confirmed. Contributory factors were the large number of drop-outs in combination with the fact that the intervention started late in relation to collapse. The late start of the intervention resulted in a high percentage of survivors escaping (being excluded from) the intervention because of an early ROSC. Intervention trials with either a device or medication therefore target a very high-risk population with a low chance of survival. The main reason for the large number of drop-outs was the combination of: 1) the size of the equipment and 2) CA not identified or coded as such by the RCC.

The effect of chest compressions was measured during standardised ventilation according to $P_{ET}CO_2$. Mechanical ACD-CPR resulted in the highest mean of initial, minimum and average $P_{ET}CO_2$ values, which suggests that mechanical ACD-CPR performs compressions with higher cardiac output than manual chest compressions. Moreover, passive leg raising during uninterrupted chest compressions appears to have a positive impact on the effect of chest compressions as estimated from the $P_{ET}CO_2$. Whether this increase in $P_{ET}CO_2$ is associated with an increase in survival has to be proved in larger randomised studies.

During the study period, the lion's share of the CAs were coded according to symptoms (usually unconsciousness) and a small number according to the diagnosis of CA. We found

that patients with OHCA who were not coded according to the diagnosis of CA had a longer delay to the start of CPR, a lower rate of bystander CPR and they finally tended to have lower survival rates.

8.2 Future aspects and implications

- In order to ensure a "good result" in an interventional OHCA study, the study probably has to be powered for survival to hospital discharge, at the very least. Simultaneously with the simulation test in the study protocol [121], time from collapse to the start of the intervention has to be estimated. Time from collapse to the start of the intervention appears to affect the outcome (survival) in the same way as time from collapse to ROSC affects survival after OHCA. If, for clinical reasons, the intervention starts too late or does not appear to have a fair chance of producing an effect for other reasons, the question of whether this intervention belongs to the pre-hospital setting should be considered.

- In the present study, we found that the LUCAS^{TM} device appeared to perform more effective chest compressions than those performed by the ambulance crew. In spite of this, mechanical chest compressions were found to be difficult to evaluate among the overall OHCA population. The present study revealed clinical circumstances that affect the calculated effect negatively, which recommends studies demanding larger patient populations. However, different reports and case studies encourage us to propose a study of mechanical chest compressions as a bridge to hospital when immediate resuscitation fails. The target group for such a study should be recruited among patients without immediate ROSC who have received high-quality CPR within the first two minutes after collapsing.

- The Swedish medical index used by the RCC is based on symptoms. This means that the RCC alerts different rescue resources according to dispatch codes based on symptoms. Our research proposes an improvement to the index by including a few critical diagnoses in the dispatch code system including CA. This would most probably help to use rescue resources more correctly and increase the preparedness of the rescue team when confronted with patients suffering from life-threatening conditions.

- Passive leg raising during uninterrupted chest compressions had a positive effect measured in $P_{ET}CO_2$. Whether or not this effect is relevant to increased survival has to be demonstrated in a larger randomised study. The design has to be simple and the intervention has to be started at an early stage during the first period of chest compressions just before defibrillation. To power such a study, national co-operation is needed.

9.0 Svensk sammanfattning

9.1 Bakgrund

Då någon drabbas av ett hjärtstopp kan kontinuerliga bröstkompressioner av hög kvalité vara avgörande för resultatet av behandlingen. Studier har visat att kvalitén på givna bröstkompressioner skiljer sig avsevärt mellan vårdpersonal. En studie som genomfördes på patienter med hjärtstopp utanför sjukhus visade att ambulanspersonal enbart behandlade patienten med bröstkompressioner under halva behandlingstiden och att de flesta kompressionerna inte var tillräckligt djupa. Möjliga orsaker kan vara fysisk trötthet samt fältmässiga förhållanden.

Syftet med denna avhandling var att a) studera betydelsen av mekaniska bröstkompressioner vid hjärtstopp utanför sjukhus utifrån statistiska och kliniska faktorer relevanta för dess användbarhet och patientöverlevnad samt b) studera enkla strategier som skulle kunna förbättra cirkulationen under hjärt-lungräddning (HLR).

9.2 Metod

Avhandlingen bygger i huvudsak på en pilotstudie som genomfördes av ambulanspersonal under behandling av patienter med hjärtstopp utanför sjukhus. Studien pågick under två år (maj 2003 – maj 2005) i Göteborg/Mölndal och ett år i Södertälje (aug 2003- aug 2004). I studien inkluderades patienter ≥18 år med bevittnade hjärtstopp. Exklusionskriterier var: trauma, hypotermi, graviditet, intoxikation, hängning, drunkning, terminalt sjuka patienter samt återkomst av egen cirkulation före studiestart. Patienterna behandlades antingen enligt gängse rutin med standard HLR, där manuella bröstkompressioner utfördes av ambulanspersonal, eller med mekaniska bröstkompressioner utförda av LUCAS[TM] (Lunds University Cardiac Assist System). LUCAS[TM] som utför mekanisk aktiv kompressions och

dekompressions (ACD) HLR drevs i denna pilotstudie med tryckluft. Patienturvalet genomfördes enligt en s.k. cluster metod. I praktiken innebar detta att två utrustningar, som utförde mekanisk ACD-HLR, flyttades halvårsvis mellan fyra ambulanser (tre Ola ambulanser och en akutbil) i Göteborg/Mölndal och Södertälje. Koldioxid i utandnings luft (s.k. end-tidalt koldioxid) uppmätt under HLR anses vara ett indirekt mått på patientens blodcirkulation. Vi valde därför att studera effekten av manuell jämfört med mekanisk ACD-HLR genom att mäta end-tidalt koldioxid ($P_{ET}CO_2$) på patienter som blivit trachealt intuberade. Mätningarna genomfördes under HLR med standardiserad ventilation med hjälp av ventilator. Enligt gängse rutiner behandlas patienterna normalt med HLR liggandes plant på hårt underlag. I ett försök att öka det venösa återflödet under HLR, och därmed öka effekten av bröstkompressionerna, valdes slumpvis en grupp till att få benen lyfta 35 cm under kontinuerliga bröstkompressioner. Patienterna var sin egen kontroll och $P_{ET}CO_2$-värden uppmätta under 75 sek före lyfta ben jämfördes med dito värden efter lyfta ben.

9.3 Resultat

Primärt jämfördes andelen patienter som någon gång under behandlingen återfick egen cirkulation men vi fann inga skillnader utifrån om patienterna fick mekaniska eller manuella bröstkompressioner under HLR. I bortfallsanalysen fann vi att enbart 2/3 av patienterna i försöksgruppen faktiskt behandlades med mekanisk ACD-HLR. Bland de 2/3 som behandlades startade behandlingen i median 18 minuter från hjärtstoppet. Gruppen som behandlades med mekanisk ACD HLR utgjordes därför av en högriskgrupp med låg chans till överlevnad.

Mätningarna av $P_{ET}CO_2$ visade signifikant högre medelvärde för gruppen som fick mekanisk ACD-HLR jämfört med dem som behandlades av ambulanspersonal med manuella bröstkompressioner. Likaså resulterade höjning av benen under pågående HLR i en signifikant ökning av $P_{ET}CO_2$-värdet efter att benen hade höjts. I jämförelse med gruppen som inte fick benen höjda fann vi en tendens till högre överlevnad i gruppen med höjda ben.

I vår bortfallsanalys fann vi att en stor andel av patienterna med hjärtstopp inte hade larmkodats som hjärtstopp av SOS. Vi undersökte därför larmkoderna för samtliga behandlade hjärtstopp under en period av 17 månader, där hjärtstoppet troligen hade inträffat

före samtalet togs emot av SOS. Vi fann att ca 80 % av fallen var kategoriserade utifrån symtom (oftast koden "medvetslös") och 20 % utifrån diagnos ("hjärtstopp"). Vi jämförde den mer allmänt symtombaserade kategorin (medvetslös) med den diagnosbaserade (hjärtstopp) och fann att i den diagnosbaserade kategorin startade HLR betydligt tidigare, samt att dessa patienter oftare fick tidig HLR av en livräddare på plats (s.k. bystander). Vi fann även en tendens till ökad överlevnad i den diagnosbaserade kategorin.

Under studieperioden (maj 2003 – maj 2005) registrerades alla hjärtstopp som behandlades utanför sjukhus i Göteborg/Mölndal. Då vi jämförde med historiska data från samma distrikt fann vi, under studieperioden, färre hjärtstopp av kardiell orsak, försämrad responstid (från larm till ankomst ambulans) samt lägre andel patienter med ventrikelflimmer som första arytmi. Trots försämrad responstid och färre ventrikel flimmer fann vi en oförändrad långtidsöverlevnad och att överlevarna hade en bättre bibehållen hjärnfunktion. Faktorer med positiv inverkan på överlevnad kan vara den ökade andelen patienter som under den studerade perioden fick tidig HLR av hjälpare på plats samt att andelen hjärtstopp som bevittnades av ambulanspersonal på plats (ambulansen var redan på plats p.g.a. tidiga symtom ex. bröstsmärtor) hade ökat.

9.4 Diskussion med slutsatser och implikationer

Mätningarna av $P_{ET}CO_2$ visade signifikant högre medelvärde för gruppen som behandlades med mekanisk ACD-HLR. Detta talar troligtvis för att mekanisk ACD-HLR är effektivare jämfört med manuella bröstkompressioner. Om denna skillnad i effekt är relevant för ökad överlevnad återstår fortfarande att visa. I vår studie fann vi att mekanisk ACD-HLR inte påverkade vår primära endpoint, som var återkomst av puls någon gång under behandlingen. Bidragande orsaker till detta resultat var troligen det stora bortfallet i försöksgruppen samt att interventionen startade sent i förhållande till tiden för det inträffade hjärtstoppet, vilket innebar dåliga förutsättningar för interventionen. Det stora bortfallet samt den sena starten berodde i huvudsak på den kliniska verkligheten, såsom att apparaten var för stor för att alltid tas med till alla patienter samt att flera patienter med hjärtstopp av olika anledningar inte identifierades av SOS alarm. Hur som helst, det bör ses som en möjlighet att LUCAS[TM] tycks ge effektivare bröstkompressioner än ambulanspersonal och att den kan användas även under

transport till sjukhus. Denna möjlighet gör att vi föreslår att nya behandlingsrutiner i syfte att öka den låga överlevnaden vid hjärtstopp utanför sjukhus studeras.

SOS alarm arbetar utifrån ett symtombaserat medicinskt index. Detta betyder att ambulansenheterna oftast larmas ut enligt symtombaserade larmkoder. Resultatet från vår studie visade att HLR startade oftare och tidigare då larmkoden var diagnosbaserad, även överlevnaden tenderade att vara högre. Orsaker till detta kan vi bara spekulera i, men en mer precis diagnos kan leda till bättre kommunikation mellan larmoperatör, inringare och ambulanspersonal, än en allmänt hållen symtombaserad larmkod som innehåller en stor grupp patienter med många olika diagnoser. Då den diagnosbaserade gruppen hjärtstopp i vår analys enbart utgjorde 20 % bör resultaten från vår analys tolkas med försiktighet. Vår studie visar dock på behovet av fler studier som säkrar kvalitén på svenskt medicinskt index.

Resultatet av $P_{ET}CO_2$ mätningarna kan tyda på att det venösa återflödet förbättras då benen på patienten höjs med 35 cm under pågående HLR. Metoden vi använde för att utvärdera effekten av att höja benen (mätning av $P_{ET}CO_2$) gjorde att interventionen genomfördes i median > 20 minuter från hjärtstoppet. Trots detta såg vi en liten tendens till ökad överlevnad i gruppen som fick benen höjda. Att höja benen under HLR är en enkel intervention som går att utföra tidigt. Resultaten från vår studie uppmuntrar till att genomföra större studier som dimensioneras för att utvärdera patientöverlevnad.

10.0 Acknowledgements

11.0 References

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