Cardiopulmonary resuscitation — guideline recommendations meet clinical practice

Thesis for the degree PhD

cand.med. Morten Pytte

Institute for Experimental Medical Research

&

Department of Anaesthesiology

Oslo University Hospital, Ullevål

University of Oslo, Faculty of Medicine

2009

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo
No. 851

ISBN 978-82-8072-486-1

Cover: Inger Sandved Anfinsen.
Printed in Norway: AiT e-dit AS, Oslo, 2009.

Produced in co-operation with Unipub AS.
The thesis is produced by Unipub AS merely in connection with the
thesis defence. Kindly direct all inquiries regarding the thesis to the copyright
holder or the unit which grants the doctorate.

Unipub AS is owned by
The University Foundation for Student Life (SiO)

Table of Contents

1. Acknowledgements

The work for this thesis was carried out at the Institute for Experimental Medical Research, at the Centre for Education and Skill Training, and in the Oslo EMS, Oslo University Hospital, Ullevål.

First I want to express my sincere gratitude to my principal supervisor Kjetil Sunde for introducing me to the research field of cardiopulmonary resuscitation. His extensive knowledge, contagious enthusiasm and relentless support are invaluable. I also want to thank my co-supervisor Petter Andreas Steen, whose shoulders this work stands on, who gave me the opportunity, both financially and as a part of his research group, to pursue my goals and to learn the skills of research.

This work has been made possible through the combined effort of many. I thank my co-authors Joar Eilevstjønn, Bjørn Bendz, Frank Brosstad, Anne Siri Rokvam, Jan Ottem, Kristin Godang and Tor Pettersen for their much appreciated collaboration.

I want to thank all the paramedics in the Oslo and Akershus EMS for their invaluable contribution to the studies and to Lærdal Medical for providing the Resusci Anne Simulator free of charge.

My gratitude also goes to Morten Eriksen for patiently teaching me surgical skills and for expert assistance, to Tævje A. Strømme and Jon Bach for the invaluable technical support, and to Bjørg Austbø and Unni Lie Henriksen for much appreciated laboratory assistance.

Furthermore, I also want to acknowledge Ole Sejersted, Lisbeth Winer and Jo-Ann Larsen for providing good working facilities.

I want to thank my skilful colleagues in the Cardiopulmonary Resuscitation group, in special Lars Wik, Elizabeth Dorph, Jo Kramer-Johansen, Theresa Olasveengen, Øystein Tømte, Trine Staff and Silje Ødegård for much appreciated company and discussions.

I want to express my gratitude to Terje Dybvik and Kristin Sem Thagaard for goodwill and financial support, ultimately providing me with excellent working conditions.

Finally, I want to thank my friends for showing interest in my work and to my family for always being there and for their unconditioned support. I am especially grateful to my partner Morten for his support and patients, and for reminding me of the joys of life.

Morten Pytte, June 2009

2. Abbreviations

AHA	American Heart Association
ALS	Advanced life support
AMI	Acute myocardial infarction
BLS	Basic life support
CCBF	Cerebral cortical blood flow
CPP	Coronary perfusion pressure
ECG	Electrocardiogram
EMS	Emergency Medical Services
ERC	European Resuscitation Council
FBF	Femoral blood flow
ILCOR	International Liaison Committee on Resuscitation
$PaCO_2$	Arterial carbon dioxide tension
PaO_2	Arterial oxygen tension
PCI	Percutaneous coronary intervention
ROSC	Return of spontaneous circulation
TAT	Thrombin anti-thrombin complex
VF	Ventricular fibrillation
VT	Ventricular tachycardia

3. List of papers

The thesis is based on the following papers, and is referred to in the text by their roman numerals.

Paper I:

Haemodynamic effects of adrenaline (epinephrine) depend on chest compression quality during cardiopulmonary resuscitation in pigs. Pytte M, Kramer-Johansen J, Eilevstjønn J, Eriksen M, Strømme TA, Godang K, Wik L, Steen PA, Sunde K. Resuscitation. 2006 Dec;71(3):369-78. Epub 2006 Oct 4.

Paper II:

Pre-arrest administration of low-molecular weight heparin in porcine cardiac arrest - hemodynamic effects and resuscitability. Pytte M, Bendz B, Kramer-Johansen J, Eriksen M, Strømme TA, Eilevstjønn J, Brosstad F, Sunde K. Critical Care Medicine. 2008 Mar;36(3):881-886.

Paper III:

Comparison of hands-off time during CPR with manual and semi-automatic defibrillation in a manikin model. Pytte M, Pedersen TE, Ottem J, Rokvam AS, Sunde K. Resuscitation. 2007 Apr;73(1):131-6. Epub 2007 Jan 30.

Paper IV:

Arterial blood gases during basic life support of human cardiac arrest victims. Pytte M, Dorph E, Sunde K, Kramer-Johansen J, Wik L, Steen PA. Resuscitation 2008 Apr; 77(1):35-8. Epub 2007 Nov 26.

4. Cardiac arrest introduction

"…a 28-year-old veteran marathon runner, collapsed 5 1/2 miles into the Olympic trials Saturday morning. It's likely he died before he hit the ground." USA today, November 2007.

Sudden cardiac arrest strikes individuals of all ages of both genders all over the world. It is recognised by an unexpected unresponsiveness and cessation of normal breathing and is inevitably fatal unless timely management is initiated within minutes. Although mortality after cardiac arrest is high, interventions performed by bystanders and health care professionals, comprising chest compressions, ventilation, and defibrillation of ventricular fibrillation (VF), may bring cardiac arrested victims back to life and normal living (Cummins, Ornato et al. 1991; Herlitz, Ekstrom et al. 1994).

4.1. Aetiology

Presumed cardiac disease accounts for more than 80 percent of cardiac arrests, among which ischemic heart disease is the prevailing underlying condition (Pell, Sirel et al. 2003). Hence, the major risk factors for sudden cardiac death are those often associated with coronary heart disease, e.g. hypertension, high serum cholesterol, glucose intolerance, and relative weight. Common non-cardiac aetiologies of cardiac arrest include among other acute lung disease, acute cerebrovascular disease, trauma, asphyxia, and drug overdose (Pell 2003).

Other causes of sudden cardiac death in the adult population include different heart conditions such as hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, cardiac ion channelopathies and congenital heart disease (Sinha, Moss et al. 2007), and are the most frequent cause of unexpected cardiac death in athletes younger than 35 years of age (Maron, Epstein et al. 1983).

4.2. Epidemiology

The epidemiology of cardiac arrest parallels largely that of coronary heart disease. The mean age of cardiac arrested patients was 62 years in a large European multi-centre study of cardiac arrest with 70 percent male victims (Gueugniaud, David et al. 2008). The morbidity and mortality from cardiac disease in high-income countries has declined over the last 30 years, following the targeting of risk factors for cardiac disease (Nichol and Baker 2007).

The overall annual incidence of out-of-hospital cardiac arrest is the number of cardiac arrests that occur in one year within a population, the number of which differs between communities. Atwood et al. reported the over all incidence of out-of-hospital cardiac arrest treated by EMS in 37 European communities with an all-rhythm incidence of 38 and a VF incidence of 17 per 100.000 person years (Atwood, Eisenberg et al. 2005). Similarly, Becker et al. reported an incidence between 36 and 128 per 100.000 population based on twenty North American and European studies of out-of-hospital cardiac arrest (Becker, Smith et al. 1993).

Although the incidence of out-of-hospital cardiac arrest has decreased over time, there has been little improvement in survival rates (Herlitz, Engdahl et al. 2005). The overall survival for out-of-hospital cardiac arrest is calculated by dividing the annual number of survivors to hospital discharge by the annual incidence, and varies greatly between communities in the range from 1 percent to 25 percent (Eisenberg, Horwood et al. 1990; Herlitz, Bahr et al. 1999; Atwood 2005; Nichol, Thomas et al. 2008). Similarly, in Norwegian communities survival ranged between 7 percent and 23 percent (Sunde, Eftestøl et al. 1999; Hanche-Olsen and Nielsen 2002; Langhelle, Tyvold et al. 2003; Olasveengen, Vik et al. 2009).

The striking range in survival rates may be attributed to actual differences in survival rates between communities and socio-economic consensus tracts (Reinier, Stecker et al. 2006; Nichol 2008) and to variation in the denominator ascribed to methodological features (Eisenberg, Cummins et al. 1991). Finally, the variation may also be

explained by changes in survival rates over time, exemplified by a change in overall survival in Oslo from 7 percent in the period 1996-1998 to 13 percent in 2005 following improvements in the local «chain of survival» (Sunde 1999; Olasveengen 2009).

4.3. Treatment

4.3.1. «Chain of survival»

Survival after cardiac arrest depends on timely interventions performed by bystanders and medical professionals. The «chain of survival» was introduced in 1991 as a concept comprising a series of interventions to restore life after cardiac arrest. It summarises the vital steps for successful resuscitation, embodying standard principles of management, including early recognition and prevention of cardiac arrest, call for help, early CPR, early defibrillation of VF, and optimal post resuscitation care, as illustrated in Figure 1 (Cummins 1991).

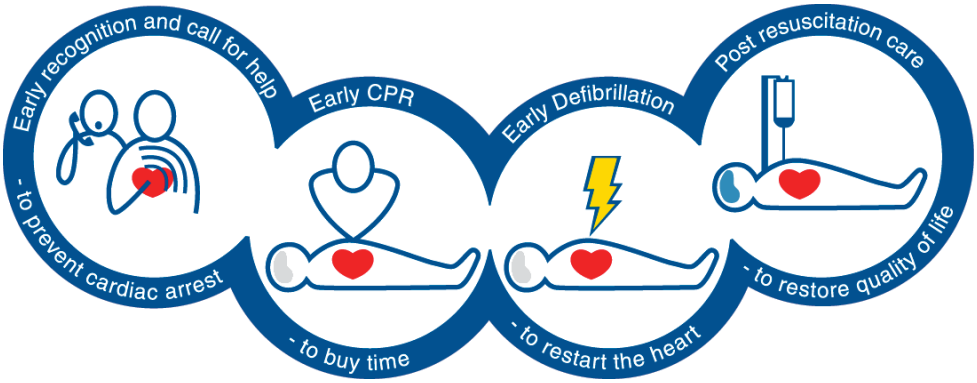

Figure 1

The «chain of survival» emphasises that there is no easy, single step approach to improving survival after cardiac arrest, but rather several interventions, when performed in sequence, may improve outcome from cardiac arrest.

The Ontario Pre-hospital Advanced Life Support (OPALS) study group reported the effect of the different interventions on overall survival after out-of-hospital cardiac arrest. Interventions associated with improved survival were presence of an

eyewitness, bystander CPR, and rapid defibrillation (Stiell, Wells et al. 2004) and standardised post resuscitation treatment, including percutaneous coronary intervention (PCI) and therapeutic hypothermia (Sunde, Pytte et al. 2007).

Although, not directly depicted in the «chain of survival», time from collapse to the different interventions has an impact on outcome. In a graphical model, Larsen et al. demonstrated that survival rate declined by 5.5 percent each minute CPR, attempted defibrillation, and advanced care were delayed (Larsen, Eisenberg et al. 1993). For each minute delay from collapse to initiation of CPR, survival rate declined by 2.3 percent. Similarly, survival rate declined 1.1 percent per minute delay until defibrillation. In the unlikely event that all interventions were initiated at the same time, survival rate was 67 percent. The model demonstrated that survival improved when each treatment intervention was placed earlier in the treatment protocol, illustrating the impact of elapsed time from collapse to the initiation of each «chain» element on survival.

4.3.2. International Guidelines

International guidelines for resuscitation of cardiac arrested patients are published periodically to ensure a uniform treatment of cardiac arrested patients based on up-to-date knowledge. The first guidelines that were published in 1966 encouraged practice of CPR with mannequins, although, out of concern for iatrogenic complications, it disapproved of teaching resuscitation to lay persons ("Cardiopulmonary resuscitation" 1966). In 1992 scientists representing the European Resuscitation Council (ERC), American Heart Association (AHA) and resuscitation councils from different parts of the world formed the International Liaison Committee on Resuscitation (ILCOR) (Chamberlain 2005). Considering the common understanding of the best treatment techniques, the different resuscitation organisations publish guidelines in accord with the ILCOR consensus document issued periodically every five years. Even though the guidelines issued are based on the same ILCOR statement, the ERC and the AHA have yet to agree on one common guideline for cardiopulmonary resuscitation (AHA 2005; ERC 2005).

Basic life support (BLS)

BLS is the term used to describe the level of medical care used for patients with a life threatening illness or injury until full medical care may be provided. BLS is commonly provided by lay persons who have received appropriate training, which often include first responder professionals such as police officers and fire-fighters, or by health care professionals while waiting for specialised medical equipment. BLS includes the identification of a medical emergency followed by rescue breathing and chest compressions in non-responsive individuals, the performance of which is associated with improved long term survival in some studies (Lund and Skulberg 1976; Holmberg, Holmberg et al. 2001). The introduction of automated external defibrillators (AED) facilitated early defibrillation by BLS providers, further improving outcome from cardiac arrest (Page, Joglar et al. 2000; Valenzuela, Roe et al. 2000; Caffrey, Willoughby et al. 2002; Myerburg, Fenster et al. 2002).

Advanced life support (ALS)

ALS is the term used for the highest level of medical care for cardiac arrested patients and is usually performed by specially trained ambulance personnel or nurses, and physicians. The initiation of ALS presumes ongoing BLS with the addition of advanced airway management (i.e endotracheal intubation or other means of securing the airways) and intravenous cannulation and drug administration. The impact of providing ALS on survival rate is not definite. Although a meta-analysis reported improved survival rate when ALS followed BLS (Nichol, Stiell et al. 1999), there was no improvement in survival with the addition of ALS in the more recent OPALS study (Stiell 2004).

4.4. Cardiopulmonary Resuscitation

Defibrillation of VF is the definite treatment of cardiac arrest, which together with chest compressions and ventilation constitute cardiopulmonary resuscitation (CPR). The window of opportunity for successful defibrillation is brief, albeit initiation of

CPR contribute to maintained VF (Wik, Steen et al. 1994) and «buys» time until definite treatment is available.

4.4.1. Chest compressions

Chest compression may be defined as a positive, externally applied, pressure to the centre of the chest of the cardiac arrested victim, sufficient to move the sternum four to five centimetres towards the thoracic spine, followed by a rapid release of force (decompression) and passive expansion of the thorax. The purpose of chest compressions is to provide blood flow to vital organs (i.e. heart and brain). During optimal conditions, chest compressions may provide 30-40 percent of normal cerebral blood flow and 10-30 percent of normal myocardial blood flow (Halperin, Tsitlik et al. 1986).

The first successful closed-chest compression of the heart was reported in the *Berliner Wochenshrift*, on March 21, 1892 by the German surgeon Friedrich Maass (Maass 1892; Taw 1991), who was also the first advocate of chest compressions as an effective means to assisting circulation. Until then, external pressure applied to the thorax in humans was believed to primarily support breathing (Robicsek and Littmann 1983). Nevertheless, the technique was forgotten for nearly 70 years and the far more difficult technique of internal compressions of the heart became the norm.

In 1901 open-chest «cardiac massage» was performed in Tromsø by Kristian Igelsrud after anaesthesia-induced cardiac arrest, during the time cardiac arrest was only survivable in an operating theatre where direct compression of the heart was possible, as reported by Keen (Keen 1904). External chest compressions were rediscovered by Guy Knickerbocker who by chance noticed a rise in arterial pressure when firmly compressing the electrode paddles to the thorax, and reintroduced clinically by William Kouwenhoven, James Jude and Knickerbocker, in 1958 (Kouwenhoven, Jude et al. 1960).

Mechanisms by which chest compressions generate forward blood flow

The exact mechanism by which chest compressions generate forward blood flow is elusive. The most applaudable theories are termed the «cardiac pump» and the «thoracic pump» theories.

The «cardiac pump» theory was initially described by Kouwenhoven in 1960, and include direct compression of the ventricles of the heart between the sternum and the thoracic spine ascribed to the force applied to the thorax, subsequently propelling blood forward through the systemic circulation (Kouwenhoven 1960). The theory was supported by echocardiographic findings of a closed mitral valve during the compression phase followed by an opening during the decompression phase, combined with the reduction in left and right ventricle cavity size during compressions (Redberg, Tucker et al. 1993).

According to the «thoracic pump» theory chest compressions cause forward blood flow through variations in intrathoracic pressure rather than the direct compression of the heart, rendering the heart as a conduit (Niemann, Rosborough et al. 1981; Werner, Greene et al. 1981). The theory implies that the force applied to the chest increases the intrathoracic pressure and thereby force the blood to exit the thorax through the thick walled arteries, while functional venous valves in the thoracic outlet prevent retrograde flow through the veins (Niemann 1981; Fisher, Vaghaiwalla et al. 1982). When the pressure to the thoracic wall is released, the negative pressure generated by the expansion of the thorax «draws» blood into the thorax from the venous system outside the thorax (Niemann 1981; Werner 1981). The theory was further supported by the fact that gasping and coughing generated cardiac output during cardiac arrest (Criley, Blaufuss et al. 1976; Xie, Weil et al. 2004).

It is, however, likely that both the «thoracic pump» and the «cardiac pump» theories apply to clinical chest compressions. A clinical study suggested that the mechanisms for blood flow vary between cardiac arrested victims. When transmitral and pulmonary flow were assessed, the mitral valve was closed during chest compression

in 5 of 17 cardiac arrested patients with forward mitral flow during the release of compressions, consistent with the «cardiac pump» theory. In the remaining patients the mitral valve was open with forward mitral flow during chest compressions, consistent with the «thoracic pump» theory (Ma, Hwang et al. 1995).

Coronary perfusion pressure

Coronary perfusion pressure (CPP) is defined as the pressure gradient between the ascending aorta and the right atrium during the decompression phase of chest compressions and is regarded as the driving force of blood flow to the myocardium (Ditchey, Winkler et al. 1982). CPP is one of the most reliable predictors of successful resuscitation and survival in experimental (Kern, Ewy et al. 1988) and clinical (Paradis, Martin et al. 1990) studies of cardiac arrest. In the normal range, blood flow to the heart is auto regulated based on myocardial demand (Mosher, Ross et al. 1964), while in the range of blood pressure produced by chest compressions the relationship between pressure and flow is linear (Mosher 1964). Therefore, CPP is commonly used as a surrogate for myocardial blood flow since direct measurements of blood flow are not readily available in the setting of CPR (Idris, Becker et al. 1996). Clinically cardiac arrested victims frequently suffer from coronary disease which may either partly or completely obliterate coronary blood flow and thus prevent myocardial blood flow at any CPP (Kern, Lancaster et al. 1990).

While chest compressions may rapidly restore carotid blood flow, there is a delay in the restoration of CPP. Steen et al. reported that while carotid blood flow was restored within seconds after the initiation of chest compressions, more than one minute of chest compressions was required to achieve CPP above the level known to prognosticate ROSC in pigs (Steen, Liao et al. 2003). The discrepancy in initial vital organ blood flow may be ascribed to the haemodynamic effect of chest compression on organs outside versus inside the thorax. While the perfusion pressure in organs outside the thorax (i.e. the brain) is positive during both chest compression and decompression (i.e. down-stroke and upstroke), the organ perfusion pressure is

positive in the decompression phase of chest compressions only in organs inside the thorax (Steen 2003).

Interruptions in chest compression

Interruptions in chest compressions are common (Sunde 1999; Valenzuela, Kern et al. 2005; Wik, Kramer-Johansen et al. 2005). Considering retrospective analysis of data collected by the defibrillator, studies report that intervals without chest compressions constitute more than half the time spent on resuscitation when ambulance personnel complied with the 2000 guidelines (Valenzuela 2005; Wik 2005). Common causes for interruptions in chest compressions are repeated reassessment of the patient, mouth-to-mouth ventilation and attempted defibrillation. Furthermore, endotracheal intubation, intravenous access, changing rescuer performing chest compressions and charging the defibrillator contribute to interruptions. Use of automated external defibrillators (AED) may particularly contribute to long intervals without chest compressions as the rescuer is prompted not to touch the patient during rhythm analysis and defibrillation. The adverse haemodynamic effects of interrupted chest compressions for ventilation were elucidated in experimental studies, including a sudden drop in blood pressure following interruptions with several chest compressions required to restore the blood pressure to levels before the interruption (Berg, Sanders et al. 2001; Steen 2003).

Guideline recommendations

Current recommendations for chest compressions include placement of the rescuer´s hands in the centre of the chest and compression of the chest at a rate of about 100 per minute. The compression should displace the victim´s sternum 4-5 centimetres towards the thoracic spine, allowing for the chest to fully recoil after each compression. Approximately the same time should be taken for compression and relaxation of the chest and interruptions in compressions should be minimised (ERC 2005).

4.4.2. Ventilation

Ventilation is the movement of air from the outside of the body into the lungs and alveoli in proximity to blood for efficient gas exchange. In 1946, during the middle of a polio outbreak, James Elam applied the principle of mouth-to-mouth ventilation on an older child in an emergency that led to his advocacy of mouth-to-mouth ventilation (Elam 1977). Later, Elam persuaded Peter Safar to join him in the effort to convince the world that expired air was sufficient for ventilation. Together they conducted compelling studies of mouth-to-mouth ventilation on paralysed voluntaries, demonstrating that the prone position did not allow a consistently patent airway for air exchange and that expired air provided sufficient oxygenation for effective artificial ventilation (Safar 1958). The technique of rescue breathing was soon endorsed by the American Medical Association (Dill 1958) and remained a separate life saving technique until 1960. Then Safar, Jude and Kouwenhoven introduced the formal connection between chest compressions and ventilation at the annual Maryland Medical Society meeting on September 16, 1960, creating CPR as we know it today.

Chest compressions to ventilation ratio

Recommendations for chest compression to ventilation ratio have changed gradually over time from the initial emphasis on ventilation with a ratio of 5:1 in the 1992 AHA guidelines (AHA 1992) to 15:2 in the previous AHA and ERC guidelines (AHA 2000; ERC 2000). In the 2005 revision of the guidelines, the compression to ventilation ratio was further increased to 30:2, based on animal studies (Sanders, Kern et al. 2002; Dorph, Wik et al. 2003; Dorph, Wik et al. 2004) since there is currently no evidence from human outcome studies to support any given compression to ventilation ratio during CPR.

The need for intermittent ventilation for out-of-hospital non-respiratory primary cardiac arrest is disputed (Ewy 2007). Alveolar ventilation is necessary for oxygenation of the haemoglobin and for removal of carbon dioxide (Dorph 2004) and is emphasised by the adverse effects of both hypoxia and hypercarbia on outcome (Idris, Wenzel et al. 1995). Furthermore, ventilation during low flow states may

improve mixed venous pH and PCO_2 thereby improve the acid-base condition of the tissue surroundings (Idris, Staples et al. 1994). On the other hand, cardiac output generated by chest compressions is only a fraction of normal cardiac output (Halperin 1986) and would require less ventilation to maintain ventilation to perfusion ratio, exemplified by the frequent finding of arterial alkalosis during cardiac arrest and CPR (Weil, Rackow et al. 1986). Moreover, ventilation during CPR demands interruptions in chest compression with prolonged reduction in CPP (Berg 2001), the effect of which is reinforced by frequent hyperventilation found in clinical studies (Aufderheide, Sigurdsson et al. 2004). Finally, ventilation requires the application of positive airway pressure, prohibiting the development of negative intrathoracic pressure during chest wall recoil, thereby inhibiting venous blood return to the heart decreasing the haemodynamic effectiveness of chest compressions (Lurie, Zielinski et al. 2002).

Studies omitting ventilation during CPR demonstrated similar or improved survival compared to CPR including ventilation, arguing for continuous chest compressions during early phase of cardiac arrest (Berg, Kern et al. 1993; Berg, Kern et al. 1997; Ewy, Zuercher et al. 2007). The experimental findings were further supported by clinical studies demonstrating equal or improved survival in patients with VF or ventricular tachycardia who received continuous bystander chest compressions without rescue breathing as compared to standard BLS (Bohm, Rosenqvist et al. 2007; SOS-KANTO 2007; Olasveengen, Wik et al. 2008).

Considering the aforementioned experimental and clinical findings of ventilation during BLS, the American Heart Association introduced the idea of «compression only CPR», omitting the recommendation for ventilation during BLS, thereby emphasising the importance of bystander CPR and continuous chest compressions (Sayre, Berg et al. 2008). The European Resuscitation Council did not find the evidence sufficient to change the current recommended ratio of chest compression to ventilation of 30:2 during BLS (Koster RW 2008). Therefore, rescue breathing

remains an essential component of BLS recommendation, however, the optimal tidal volume and compression to ventilation ratio remain elusive.

Guideline recommendations

Current recommendations for ventilation during BLS include mouth-to-mouth or mouth-to-mask ventilation with volumes sufficient to make the victim´s chest rise without inflating the stomach (AHA 2005; ERC 2005). The recommendations refer to animal studies on BLS and clinical studies on ALS suggesting that tidal volumes between 500 and 600 millilitres are adequate ventilation and oxygenation during BLS (Winkler, Mauritz et al. 1998; Dorph, Wik et al. 2004). However, there is to date no clinical evidence to support any given ventilation volume during BLS.

4.4.3. Defibrillation

Defibrillation is the passage of electrical current through the myocardium to terminate cardiac arrhythmia (e.g. VF and ventricular tachycardia, VT) and is the definitive and single most effective intervention in the «chain of survival» (Larsen 1993). The ability to deliver early defibrillation during VF cardiac arrest is one of the most important determining factors for survival. When defibrillation was delivered within a few minutes of collapse survival rates were as high as 70 percent in cases of out-of-hospital cardiac arrest (White, Asplin et al. 1996; Valenzuela 2000). The ROSC rate, declines rapidly over time and is virtually zero after ten minutes of untreated VF (Weaver, Cobb et al. 1986; Larsen 1993).

The method to treat VF was developed in the late nineteenth century. In 1899 Jean Louis Prevost demonstrated that electrical current could be used to restore normal rhythm to the canine heart, thereby inventing the defibrillator. Claude Beck performed the first human defibrillation, which took place in the operating theatre during open chest cardiac surgery in 1947 (Beck, Pritchard et al. 1947), while Paul Zoll achieved the first external defibrillation in 1956 (Zoll, Linenthal et al. 1956). The early defibrillators used the alternating current from a power socket and was difficult to

transport, the challenge of which was first solved in the 1960s when the first direct current defibrillator able to run on batteries was developed.

The initial defibrillators were available to professionally trained rescuers only, and were not readily available in the out-of-hospital setting. The importance of early defibrillation, however, lead to the rapid development of the lightweight, easy-to-use automated external defibrillator (AED).

Relationship between defibrillation and chest compressions

Weisfeldt and Becker proposed a framework for the treatment of VF comprising an electrical, a circulatory and a metabolic phase of VF (Weisfeldt and Becker 2002). The model implies that defibrillation is the most effective treatment if delivered during the initial four minutes of VF, while chest compressions before defibrillation improve survival rates in the interval from four to ten minutes of sustained VF, and the potential benefit of hypothermia and cardiopulmonary bypass in cases exceeding ten minutes of VF.

Clinical studies, in which AEDs were used to achieve rapid defibrillation in places where people congregate, demonstrated high rates of survival in different settings, including police rescuers trained in early defibrillation (White 1996; Myerburg 2002), casino security personnel trained with AEDs (Valenzuela 2000), airport personnel using AED (Caffrey 2002), and in-flight airline personnel (Page 2000). Albeit the deployment of AEDs facilitated early defibrillation with high survival rates in some studies, the overall survival rate remained unchanged (Stults, Brown et al. 1986; Weaver, Hill et al. 1988; Cobb, Fahrenbruch et al. 1999; van Alem, Vrenken et al. 2003).

An important determinant for survival after prolonged VF is the interval from collapse to attempted defibrillation (Larsen 1993). Clinical studies demonstrated that chest compressions delivered before attempted defibrillation improved survival rate in victims where time from collapse to initiation of CPR was delayed. In Seattle, Cobb and co-workers reported improved survival from out-of-hospital cardiac arrest when

defibrillation was preceded by approximately 90 seconds of chest compression, the benefit of which was predominant if the time from collapse to the arrival of emergency vehicle exceeded four minutes (Cobb 1999). Wik et al. later confirmed the findings in a randomised clinical study (Wik, Hansen et al. 2003).

Experimental studies demonstrated that increased duration of the interval between cessation of compressions and shock delivery was associated with poor outcome and post cardiac arrest myocardial dysfunction (Sato, Weil et al. 1997; Yu, Weil et al. 2002; Steen 2003). Similarly, in a review of ECGs obtained from cardiac arrested victims, Eftestøl et al. reported that segments of the ECG that were initially predictive for high success rate rapidly deteriorated during intervals without chest compressions (Eftestøl, Sunde et al. 2002). Finally, pre-shock pauses were associated with defibrillation failure in a prospective, multi-centre observational study of in-hospital and out-of-hospital cardiac arrests (Edelson, Abella et al. 2006).

Less extensive research has been performed on the impact of post-shock intervals without chest compressions. Previous studies reported that only a fraction of defibrillation attempts are followed by a perfusing rhythm (Sunde 1999). Thus, any delay in resuming chest compressions adds to the total time without blood flow to vital organs. In an experimental study, Berg and co-workers recently demonstrated that immediately resumed chest compressions after defibrillation attempts substantially improved outcome compared to simulated pre-hospital AED care (Berg, Hilwig et al. 2008).

Automatic external defibrillation versus manual defibrillation

AEDs are computerised devices that use voice prompts and visual prompts to guide first responders and health care professionals to safely attempt defibrillation in cardiac arrested patients. AEDs automatically provide automatic rhythm analysis and shock recommendation and thereby facilitate early defibrillation of VF. Most advanced defibrillators available to EMS also have the option of manual defibrillation. During

manual defibrillation, the rescuer performs the rhythm analysis and delivers the shock at his or her own discretion.

The advantage of AEDs is the minimal training required by the rescuer, thereby facilitating widespread deployment and early bystander defibrillation. The disadvantages include long intervals without chest compressions for rhythm analysis, shock delivery, and voice prompt instructions, the duration of which ranges from 8 to 28 seconds depending on the manufacturer (Sunde 1999; Snyder and Morgan 2004). The advantage of manual mode defibrillation is the shorter interruptions in chest compressions required, since chest compressions may be delivered during charging of the defibrillator and shorter time may be required for rhythm analysis depending on the rescuer. Manual defibrillation, however, requires a higher level of rescuer training and may be more prone to human errors compared to defibrillation in AED mode.

Guideline recommendations

Current guidelines for electrical treatment of VF state that one shock should be delivered immediately when the AED is available followed by promptly resumed chest compressions. In cases with prolonged collapses (i.e. more than five minutes) the guidelines state that it is «reasonable» to perform compressions for two minutes before defibrillation is attempted (AHA 2005; ERC 2005). Both AHA and ERC guidelines recommend that two minutes of chest compressions be delivered between each attempted defibrillation. The Norwegian guidelines, however, slightly modified the recommendation for chest compressions to include three minutes of compressions between each defibrillation attempt (Lexow and Sunde 2007).

While AEDs only are available to first responders, both AED and manual defibrillation are available to trained ambulance personnel. Current guidelines do not discriminate between defibrillation in AED mode and manual mode in the management of out-of-hospital cardiac arrests by trained personnel. Albeit it is assumed that defibrillation in manual mode may shorten the intervals without chest

compression, thus some communities, including the Oslo EMS, recommend that trained personnel operate the defibrillator in manual mode.

4.4.4. Quality of CPR

Quality is related to a degree or grade of excellence. In the context of CPR, good quality is related to how well treatment adhere to international guidelines for management of cardiac arrested patients. While the Utstein template facilitates uniform reporting of clinical (Cummins, Chamberlain et al. 1991) and experimental (Idris 1996) cardiac arrest management, there is no similar template for the recording and reporting of CPR quality. In a recent paper, Kramer-Johansen et al. suggested guidelines for the uniform reporting of CPR quality, including chest compression frequency, depth of chest compressions, ventilation frequency and the ratio between time spent on chest compression and the duration of the resuscitation attempt, based on international collaboration and a consensus building process (Kramer-Johansen, Edelson et al. 2007).

The impact of CPR quality on outcome from cardiac arrest has long been recognised. In 1976, Lund et al. reported that laypersons performed «efficient» resuscitation in 73 percent of cases, which was associated with improved survival compared to «not efficient» resuscitation (Lund 1976). How resuscitation «efficiency» was assessed, however, was not reported. The findings were later confirmed in studies reporting improved survival in patients who received good quality CPR measured by expansion of the chest during mouth-to-mouth ventilation and a palpable arterial pulse during chest compressions (Wik 1994; Gallagher, Lombardi et al. 1995).

Experimental and clinical studies imply that good quality CPR is a prerequisite for survival and complete neurological recovery. Factors such as pre-shock pauses, chest compression depth, and compression rate are all associated with improved short term survival (Eftestøl 2002; Abella, Sandbo et al. 2005; Edelson 2006; Kramer-Johansen, Myklebust et al. 2006). Furthermore, a clinical study reported improved survival after the implementation of the 2005 revision of the guidelines (Rea, Helbock et al. 2006).

The findings were contrasted by a study from the Oslo EMS, which reported no change in survival to hospital discharge when CPR quality was improved following the 2005 guideline implementation (Olasveengen 2009).

4.4.5. Measuring CPR performance

Technological advances have facilitated the shift from subjective evaluation of CPR performance (Wik 1994; Gallagher 1995) to objective measures of CPR quality. The advances include off-line reporting of hands-off intervals through analysis of thoracic impedance provided by the defibrillator (Sunde 1999; Valenzuela 2005), and online measurements of end tidal carbon dioxide (Ornato 1993; Kolar, Krizmaric et al. 2008), compression depth, force and duty cycle (Wik 2005), and VF waveform characteristics (Achleitner, Wenzel et al. 2001; Eftestøl, Wik et al. 2004; Li, Ristagno et al. 2008; Gundersen, Nysæther et al. 2009).

Conventional surface ECG obtained from the self-adhesive defibrillator pads convey information about myocardial blood flow and the probability of ROSC. VF may be described clinically as «coarse», recognised by a high ECG signal amplitude and high probability of ROSC, or as «fine» with low ECG signal amplitude and low probability of ROSC (Weaver, Cobb et al. 1985). The characteristics of VF waveform may further be described in mathematical models including features such as VF waveform amplitude and frequency. Previous animal studies demonstrated that VF waveform characteristics correlated positively with CPP and was a predictor of myocardial perfusion and the probability of ROSC (Noc, Weil et al. 1999). When the technology was implemented in commercially available AEDs it also served as a monitor of chest compression effectiveness (Achleitner 2001; Li 2008). Different predictors of ROSC have been proposed, all of which are negatively affected by interruptions in chest compression (Eftestøl 2002) and positively affected by sequences of chest compressions (Eftestøl 2004). The sensitivity and specificity for outcome prediction, however, vary between the predictors. When ten basic VF ECG features were tested retrospectively for outcome prediction in out-of-hospital and in-hospital cardiac arrest, sensitivity and specificity ranged from 95 percent - 100 percent and 0-53 percent,

respectively (Neurauter, Eftestol et al. 2007). The basic feature with best performance on outcome prediction was median slope, with a sensitivity of 95 percent and specificity of 53 percent. In other words, median slope was able to capture 95 percent of possibly successful defibrillation attempts and to detect 53 percent of shocks that would not achieve ROSC. Thus, avoiding interruption in chest compressions in 53 percent of shocks delivered. Also, 5 percent of possible successful defibrillation attempts would be omitted which might potentially be delivered later.

Noteworthy, recent experimental and clinical findings demonstrated that VF waveform characteristics were altered with concomitant acute myocardial infarction or chronic ischemic heart disease, questioning the feasibility of VF characteristics with concomitant underlying cardiac disease. (Indik, Donnerstein et al. 2006; Indik, Donnerstein et al. 2007; Olasveengen, Eftestol et al. 2009).

4.4.6. Pharmacological interventions

Drug therapy is a mainstay of ALS and is used during cardiac arrest and CPR to improve outcome. The recommended drug use is largely based on collective wisdom together with animal data since there is no placebo controlled clinical trial that shows that any drug administered during CPR improves survival to hospital discharge (ERC 2005). The most common drugs administered during out-of-hospital cardiac arrest are adrenaline (96 percent), atropine (50 percent), amiodarone (40 percent), sodium bicarbonate (40 percent), lidocaine (10 percent), vasopressin (10 percent), and heparin (6 percent) (Böttiger, Arntz et al. 2008). In the scope of this thesis, only adrenaline and unfractionated heparin for anticoagulation will be discussed.

Adrenaline

Adrenaline is a hormone mainly produced by the adrenal glands in response to stress and improve CPP and vital organ blood flow when administered during CPR in experimental studies (Michael, Guerci et al. 1984). Extracts from the adrenal gland was first used for the purpose of resuscitation in 1896 (Gottlieb 1896) and has been

the preferred adrenergic substance for management of cardiac arrest for more than 40 years.

The rationale for the use of adrenaline in the setting of cardiac arrest and resuscitation is the vasoconstrictive properties, ensuing that blood flow generated by chest compressions is directed to the heart and brain (Michael 1984). Numerous earlier studies reported improved cerebral blood flow when adrenaline was administered during CPR (Brown, Werman et al. 1986; Johansson, Gedeborg et al. 2003; Mortberg, Cumming et al. 2007). The main mediator of arteriolar vasoconstriction is the α_1 adrenoreceptor located in organs such as the kidneys, mucosa, skin and many veins (Hoffman 2001; Hoffman 2001). Other dose dependent circulatory effects of adrenaline include chronotropic and inotropic actions of β_1 adrenergic stimulation with subsequent increase in oxygen demand in the beating heart, and vasodilatation through activation of the β_2 receptor in skeletal muscle. Non-circulatory effects of adrenaline include blood glucose elevation, breakdown of lipids from fat cells, and platelet aggregation (Mills and Roberts 1967; Hoffman 2001; Hoffman 2001).

A merging body of evidence has drawn the attention to the lack of benefit and potentially harmful effects of adrenaline administered during cardiac arrest. The OPALS study found no benefit from adrenaline delivered during cardiac arrest (Stiell 2004). A retrospective cohort study of survival in cardiac arrested patients identified cumulative doses of epinephrine as an independent predictor of unfavourable neurological outcome (Behringer, Kittler et al. 1998). Similarly, more patients survived to hospital discharge among those who did not receive adrenaline, with adrenaline as an independent predictor for lower likelihood of survival in a retrospective study including 14 065 cardiac arrested victims (Holmberg, Holmberg et al. 2002). Finally, in a recent prospective and randomised clinical study from the Oslo EMS Olasveengen and co-workers reported no difference in survival between out-of-hospital cardiac arrested patients who received intravenous access along with adrenaline and those who did not receive intravenous access (Olasveengen, Sunde et al. 2008).

The potential harmful effects of adrenaline was further elucidated in animal studies, including increased myocardial oxygen consumption (Ditchey and Lindenfeld 1988), ventricular arrhythmia (Niemann, Haynes et al. 1986), ventilation-perfusion defects (Tang, Weil et al. 1991), and more severe post resuscitation myocardial dysfunction (Tang, Weil et al. 1995). Angelos et al. reported a paradoxical myocardial adrenaline response with increasing duration of cardiac arrest, in which adrenaline became increasingly more important to attain ROSC, at the same time increasingly associated with post-ROSC myocardial dysfunction (Angelos, Butke et al. 2008). Other potentially harmful effects of adrenaline include reduced microcirculatory cerebral blood flow after ROSC (Ristagno, Tang et al. 2009), implying that adrenaline cross the blood brain barrier during cardiac arrest and cause vasoconstriction through activation of α_1-receptors. Previous studies reported that the blood brain barrier was intact following cardiac arrest (Schleien, Koehler et al. 1990), and that adrenaline did not cross the blood-brain barrier, except to a small extent in the hypothalamus (Weil-Malherbe, Axelrod et al. 1959). Moreover, β-adrenergic blocking agents demonstrated improved resuscitability and reduction in post resuscitation myocardial dysfunction (Ditchey, Rubio-Perez et al. 1994; Tang 1995; Cammarata, Weil et al. 2004), suggesting that the potentially adverse effects of adrenaline in cardiac arrested victims were associated with beta-adrenergic activation.

Guidelines recommendations

Current guidelines recommend that adrenaline 1 mg is administered intravenously either in a central or peripheral vein (AHA 2005; ERC 2005). ERC recommend adrenaline before the third shock, while AHA recommends adrenaline after the first defibrillation attempt. Neither guidelines specify the optimal timing of drug delivery related to chest compressions and attempted defibrillation. The Norwegian guidelines differ from those of AHA and ERC concerning drug administration, emphasising that adrenaline should be delivered early or when intravenous access is available and two minutes before attempted defibrillation, allowing for the drug to be distributed to target organs before attempted defibrillation (Lexow 2007).

Anticoagulation

Blood coagulation is activated in clinical and experimental studies of cardiac arrest (Hartveit and Halleraker 1970; Böttiger, Motsch et al. 1995; Gando, Kameue et al. 1997; Johansson, Ridefelt et al. 2004; Adrie, Monchi et al. 2005). Cytokines released into the circulation during CPR trigger intravascular coagulation (Gando, Nanzaki et al. 1999). Furthermore, alpha-adrenergic stimulation contribute to the activation of coagulation factor XII (McKay, Latour et al. 1970) and to the activation of platelets (Mills 1967). The thrombin generated through these processes converts soluble fibrinogen into insoluble fibrin found in the micro circulation of cardiac arrested patients (Hartveit 1970; Davies and Thomas 1984), accompanied by a marked dysfunction in myocardial microcirculation (Kern, Hilwig et al. 2006)

Despite the overwhelming evidence of coagulation activation in cardiac arrested patients, there is no clinical evidence that anticoagulation has any impact on survival. Previous clinical studies reported improved short-term survival in cardiac arrested patients who were treated with unfractionated heparin in combination with thrombolysis during CPR compared to historic controls (Böttiger, Bode et al. 2001). However, there was no benefit of thrombolytic therapy when anticoagulation with heparin was omitted in a multi centre clinical trial compared to placebo controls (Böttiger 2008). Nevertheless, unfractionated heparin is frequently administered in experimental studies of CPR to avoid intravascular coagulation (Holmes, Babbs et al. 1980; Halperin 1986; Wenzel, Lindner et al. 1999; Loeckinger, Kleinsasser et al. 2002; Voelckel, Lurie et al. 2002; Yannopoulos, Aufderheide et al. 2006).

Guideline recommendations

There is no recommendation for anticoagulation in the management of cardiac arrest and resuscitation.

5. Aims of the thesis

The thesis comprises four studies related to the management of cardiac arrest. *Paper I* and *II* are experimental studies aiming at the discrepancy between clinical and

experimental management of cardiac arrest. *Paper III* aims at the hands-off intervals that are generated by the operational mode of the defibrillator (AED versus manual mode), while *Paper IV* aims at the efficacy of rescue breathing in cardiac arrested patients.

The following hypothesises were tested:

Paper I

The pharmacokinetics and pharmacodynamics of adrenaline administered during CPR depend on chest compression quality, the effect of which may be monitored with median slope (VF waveform characteristic).

Paper II

Pre-arrest anticoagulation (enoxaparin) improves haemodynamics (CPP, CCBF) during VF and immediately after ROSC. We further anticipated an improved effect of adrenaline administered during CPR.

Paper III

Intervals without chest compressions (i.e. hands-off time) are shorter when the defibrillator is operated in manual mode as opposed to AED mode.

Paper IV

Ventilation with exhaled air during BLS in cardiac arrested patients is sufficient to maintain adequate arterial oxygen and carbon dioxide tensions.

6. Materials and Methods

6.1. Papers I and II - animal studies

6.1.1. Animal preparation and anaesthesia

The experiments were performed in a well-established porcine model of cardiac arrest in accord with The Norwegian Animal Welfare Authority Act and approved by Norwegian Animal Research Authority. Healthy domestic pigs weighing 27 ± 2.6 kg were anaesthetised with an intramuscular injection of 30 mg kg^{-1} body weight of ketamine followed by a continuous infusion of propofol 1.5-2.0 mg kg^{-1} and fentanyl 30-50 μg kg^{-1} t^{-1} (*Paper I*) or inhalation of desflurane (*Paper II*) during the preparations and thereafter discontinued. The pigs were tracheotomised and ventilated with ambient air during preparation.

6.1.2. Instrumentation and measurements

Haemodynamic measurements

A 7-Fr micro tip pressure transducers was inserted through the right carotid artery and advanced to the proximal aorta for continuous pressure monitoring. Another similar catheter was introduced into the right atrium through the right external jugular vein. After ligation of extra cranial branches of the right common carotid artery, a transit-time ultrasound flowmetry probe was applied to the right internal carotid artery for measurement of carotid blood flow. A similar probe was applied to the left femoral artery.

A craniotomy was performed approximately 10 mm anterior of the coronal suture and 15 mm lateral to the sagittal suture of the skull and the surface of the left hemisphere was exposed. A laser-Doppler flowmetry probe was place on the brain surface for continuous measurement of cerebral cortical blood flow (CCBF). Laser-Doppler flowmetry is an optical technique based on the Doppler effect measuring the total local micro circulatory blood perfusion in capillaries, arterioles, venules and shunting vessels utilised in numerous studies of cerebral cortical blood flow during experimental cardiac arrest (Johansson 2003; Dorph 2004). The helium-neon laser light emitted by the probe (780 nm) is scattered and reflected by moving blood cells.

The shift in frequency of the reflected light - Doppler shift - is proportional to the number and the velocity of blood cells moving through the illuminated area within 0.5-1.5 mm of the cortex of the brain. Photodetectors convert reflected light into electrical signals measured in millivolts that represents a relative value of the blood flow. Laser-Doppler flowmetry has been used in the study of blood flow regulation in the brain elucidating the dynamic aspects of autoregulation (Florence and Seylaz 1992), and to study the haemodynamic response to pharmacological interventions (Kumano, Shimomura et al. 1993). The technique gives an accurate real time measurement of changes in blood flow that correlates linearly with blood flow measured with the microspheres technique (Kirkeby, Rise et al. 1995), however, it is unsuitable for quantification of absolute blood flow levels.

Pressure and flow signals were sampled at a frequency of 200 Hz using PC-based real time data acquisition hardware supported by DASYLab software and printed on an eight-channel thermal array recorder.

VF analysis

Standard lead II of the surface ECG was monitored and recorded by the HeartStart 4000SP defibrillator at a sampling rate of 500 Hz and 16 bit resolution. VF analysis was performed off-line in MATLAB with the ECG down sampled to 200 Hz and filtered to remove 50 Hz noise and compression artefacts. Median slope was used as feature for VF analysis defined as:

$$\text{Median slope (mV/s)} = \text{median}(|ECG_i - ECG_{i-1}|)f_s$$

where ECG_i is an ECG sample in mV in a block of L samples and f_s is the sampling frequency in Hz (Neurauter 2007).

Blood sampling and analysis

A 7.5 Fr pulmonary artery flotation catheter was inserted into the right atrium through the right femoral vein for central venous blood sampling. Another fluid filled catheter was inserted into the aorta through the right femoral artery for arterial blood sampling.

Blood gas specimens were obtained from the liquid-filled femoral artery catheter and the right atrium and placed into containers treated with unfractionated heparin.

Arterial specimens for analysis of adrenalin (*Paper I*) was obtained from the right femoral artery catheter at baseline and 7, 9, 10, 11, 12, 13, and 14 minutes after VF and collected in containers pre-treated with glutathione. The samples were placed on ice before plasma was separated by centrifugation and stored at -80 ^{o}C until assayed. The samples were analysed for plasma noradrenaline and adrenaline by high performance liquid chromatography (HPLC) with a reverse phase column and glassy carbon electrochemical detector using a commercially available kit.

Activation of blood coagulation was determined by the generation of thrombin and measured by the levels of thrombin-antithrombin (TAT) complex (*Paper II*). TAT was analysed with commercially available human polyclonal antibodies that display cross-reactivity with porcine thrombin-antithrombin (Ravanat, Freund et al. 1995). Anti-factor Xa activity was measured to monitor the effect of enoxaparin. Since low-molecular-weight heparins are more specific for inhibiting factor Xa, anti-factor Xa is traditionally considered the laboratory monitoring parameter that best correlates with drug plasma levels (Smith and Gandhi 2001). Arterial specimens for analysis of TAT and anti-factor Xa were obtained at baseline, 12 and 14 minutes after the induction of VF, and ten minutes after ROSC. The samples were collected in citrate containing tubes, placed on ice before separation of plasma by centrifugation and stored at -80 ^{o}C until assayed.

6.1.3. Chest compressions

Mechanical chest compressions (Papers I and II)

In *Paper I*, an automatic hydraulic electrically driven device delivered consistent mechanical chest compressions of 45 mm depth at a fixed rate of 100 min^{-1} with equal compression-relaxation phases, in accord with previous methods (Sunde, Wik et al. 1998; Dorph 2003; Dorph 2004).

In *Paper II*, a custom-made, software-controlled, electrical compression unit (Laerdal Medical, Stavanger, Norway) delivered chest compressions of similar quality. The integrated servo unit with piston was mounted on a rack securely fastened to the operating table above the pig´s chest. The movement of the piston was controlled by PC-run, custom-made software displaying a control unit for compression depth, frequency, and duration of chest compressions.

Manual chest compression (Paper I)

A sternal chest pad was mounted on the lower part of the sternum which provided acceleration and force signals enabling accurate measurements of compression depth, rate, compression and decompression duty cycle which were all displayed and recorded by a modified HeartStart 4000SP defibrillator. The method was validated in a mannequin model (Aase and Myklebust 2002), and was also used in clinical studies of cardiac arrest (Wik 2005).

Clinical quality CPR was achieved with manually performed chest compressions with target depth of 30-38 mm and a frequency of 100 min^{-1} interrupted by manual ventilation (nine seconds) with 100 percent oxygen every 15 compressions (hands-off ratio 0.5), similar to clinical findings (Wik 2005).

6.1.4. Experimental protocol

Paper I

Baseline measurements were obtained for all variables after the instrumentation, and iv infusions and heating were discontinued. VF was induced by a direct current applied transthoracically for three seconds and confirmed by ECG changes and an abrupt fall in arterial blood pressure. After four minutes of untreated VF, BLS including mechanical chest compression and intermittent ventilation with ambient air was initiated. Eight minutes after induction of VF, the animals were randomised to receive either continuous mechanical chest compressions as described (LabCPR) or manual chest compressions (ClinicalCPR) for 6 minutes. Interposed ventilation (FiO_2=1.0) was delivered with a self-inflating bag operated single handedly in the LabCPR group and during the interruptions in chest compressions in the ClinicalCPR

group. Adrenalin (*Paper I*) was delivered intravenously in an ear vein after the onset of ALS followed by a 10 ml flush and continuous infusion of saline (Figure 2). Defibrillation was not attempted and chest compressions were stopped at the end of the experiment. Necropsy was performed to verify catheter placement and to exclude iatrogenic organ injury.

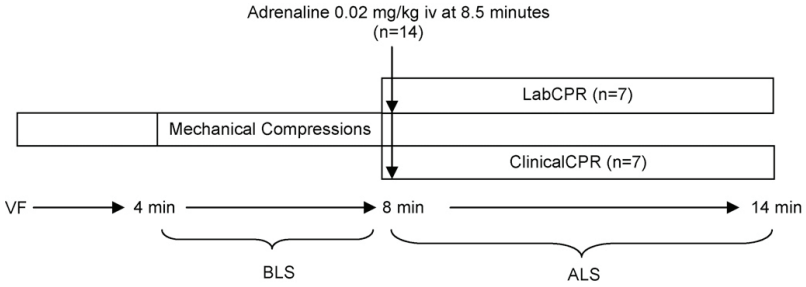

Figure 2.

Paper II

Baseline measurements were obtained for all variables after instrumentation. The pigs were randomly assigned to receive either enoxaparin in saline or saline placebo. The study drug was prepared by an engineer not part of the study, blinded to the investigators, and delivered in the ear vein 3 minutes before onset of VF. Mechanical ventilation was discontinued and followed by VF induction by a direct current delivered to the heart through a small incision in the thoracic wall close to the heart. Cardiac arrest was verified by an abrupt fall in blood pressure combined with VF on the ECG. After ten minutes of untreated VF, ALS was started for four minutes interposed by ventilation delivered with a self-inflating bag operated single handedly (FiO_2=1.0), followed by attempted defibrillation and two more minutes of chest compression. Adrenaline was administered two minutes before attempted defibrillation (Figure 3).

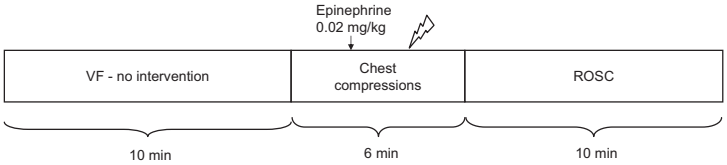

Figure 3.

The protocol was ended if ROSC was not achieved after 10 minutes of ALS, defined as a stable circulation for more than five minutes with mean arterial blood pressure above 60 mmHg. The animals that achieved ROSC were monitored for additionally 10 minutes followed by euthanasia. Necropsy was then performed to verify catheter placement and to exclude iatrogenic organ injury.

6.1.5. Calculations

All haemodynamic data were sampled with a frequency of 200 Hz and analysed by a custom-made procedure in MATLAB. CPP was calculated as the difference between the time coinciding aortic and right atrial pressures in the decompression phase. Cortical cerebral blood flow was reported as percentage of baseline values.

Paper I; Femoral blood flow was calculated as the mean flow signal obtained during 18 seconds periods. Normalised values were calculated by subtracting the mean of the sample form the value divided by the sample standard deviation. Plasma adrenaline concentrations were plotted on a semi-logarithmic scale. The slope of the straight line formed by the plotted data determined the elimination coefficient (K). Half life of adrenaline was calculated from the equation $t_{1/2}=0.693K^{-1}$.

Paper II; Haemodynamic data was calculated for each chest compression and reported as the mean of 50 compressions. The haemodynamic effect of adrenaline was determined as the difference between the haemodynamic values immediately before administration of adrenaline and the following peak plasma concentration.

6.2. Paper III - simulation study

Sixteen pair of ambulance personnel without previous knowledge of the study were recruited at random from the Oslo EMS amongst those available on the days of the study. All pairs were certified to perform ALS with the defibrillator in manual and AED mode.

The study participants were briefed and instructed to perform ALS according to the international guidelines from 2000 with focus on chest compressions and operation of the defibrillator only and to follow the voice prompts made by the defibrillator in AED mode. In brief, rhythm should be analysed after each shock, and up to three «stacked» shocks should be delivered in sequence in the case of persistent VF. The pulse should be examined after a series of one to three shocks. Chest compressions should be initiated for one minute if no pulse was detected and for three minutes in the case of asystole or PEA. CPR was executed with the defibrillator in manual and AED mode in a randomised, crossover study on a mannequin able to display rhythm scenarios and carotid pulsation.

Two rhythm scenarios were created in advance to prevent any learning effect from the first experiment, comprising initial VF followed by asystole or PEA (Figure 4). The total number of predefined shocks and the duration of the different rhythms were equal in both scenarios, each lasting approximately ten minutes.

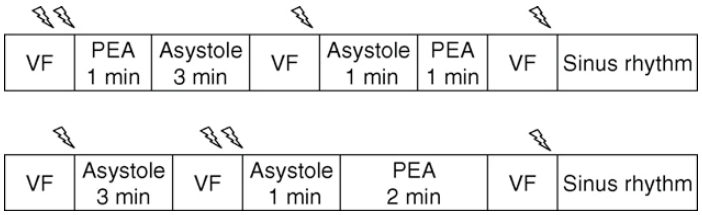

Figure 4.

Each pair simulated CPR with rhythm scenario one and two. The mode of the defibrillator was randomised to either manual or AED. The same individual operated the defibrillator in both scenarios. The screen of the defibrillator was concealed during

chest compressions to prevent rhythm analysis during chest compressions, and displayed when chest compressions were stopped.

6.2.1. Measurements

The performance was videotaped for later analysis. A custom-made computer programme was developed by one of the co-workers (EP) with the aid of JavaScript for registration of events. In brief, the recordings were digitalised and loaded to a computer together with the rhythm scenarios. Events were registered by hitting predefined keys during playback of the video recording. The computer program would subsequently report the duration and total number of predefined events.

Total time spent on each scenario, and total time with and without chest compressions were recorded. Hands-off ratio was defined as the time spent on chest compressions divided by the total duration of the scenario. Time from cessation of chest compressions until shock delivery and from shock delivery to resumed chest compressions was recorded together with shocks delivered on rhythms other than VF.

6.3. Paper IV - clinical study

Patients who were not successfully resuscitated by a physician-staffed ambulance were included in the study over a five year period. The Regional Committee on Research Ethics approved the study before the study was started. It was considered unethical to perform BLS on patients when personnel able to perform ALS were available. Thus, the study was performed on patients in whom the attending physician deemed the resuscitation attempt futile. The patients were treated in accord with the 2000 revision of international guidelines (AHA 2000).

After tracheal intubation, each patient was connected to a portable ventilator with tidal volumes adjusted to 700 ml with 100 percent oxygen at a frequency of 12 ventilations per minute based on previous studies on adequate ventilation volumes during ALS (Dorph 2004). Arterial blood was drawn at the end of the resuscitation attempt and analysed on scene with the aid of a portable blood gas analyser.

After the resuscitation attempt was considered futile and the patient declared dead, the tracheal tube was removed and BLS was initiated including chest compression and mouth-to-mask breathing with ratio 15:2. To enable recording of tidal volume, the BLS ventilation strategy was changed after four cases of mouth-to-mask breathing to include mouth-to-tracheal tube breathing utilising the endotracheal tube left in place from the resuscitation attempt, equipped with an impedance valve to prevent passive breathing during chest compression. Adequate rescuer breathing was verified by perceived chest rise in accord with guidelines recommendations. Percutaneous blood samples were drawn from the femoral artery after 7-8 minutes of BLS and analysed on scene.

6.4. Statistical analysis

Data were analysed with the aid of SPSS for Windows. Data are presented as median with quartiles when skewed and as mean with standard deviation when normally distributed. A p-value below 0.05 was regarded as significant.

Paper I

Mann-Whitney U test was used to determine differences between the groups. Paired t-test and Wilcoxon´s matched pairs signed rank test were used when the data were normally distributed or skewed, respectively. Pearson correlation coefficient was used to describe the degree of association between CPP and median slope, based on independent, normalised values of CPP and median slope.

Paper II

Student´s t-test or Wilcoxon´s signed ranks test was used to determine differences between the groups, as appropriate. Paired Student´s t-test with Bonferroni correction was used to detect time-dependent difference within the groups. Group size was determined by power calculation, based on CPP values from *Paper I*.

Paper III

Data are presented as median with quartiles. Differences are presented as mean with 95 percent confidence intervals when normally distributed, otherwise as median

difference. Student paired t-test and Wilcoxon´s signed ranks test was performed to determine differences between the operational modes. Chi-squared test with Yate´s correction was used for comparison of categorical data. The study was designed to detect a mean difference of 5 percent in hands-off intervals with alpha 0.05 and power 85 percent.

Paper IV

Data within subjects were compared with paired Student t-test.

7. Summary of results

Paper I

Pharmacokinetics and pharmacodynamics of adrenaline differed significantly between the groups with hands-off ratios of 51 percent and 8 percent in the ClinicalCPR and LabCPR groups, respectively. Median time from drug delivery to peak plasma concentration was 150 (90, 270) seconds in the ClinicalCPR group versus 90 (30, 150) seconds in the LabCPR group. While no significant drug effect was observed in the ClinicalCPR group, the expected increase in CPP and CCBF with concomitant decrease in FBF was observed in the LabCPR group. Median time to maximal CPP was 89 (53, 83) seconds in the LabCPR group. Furthermore, median slope was significantly higher at the time of peak adrenaline concentration in the LabCPR compared to before adrenaline administration. Finally, median slope correlated with CPP.

Paper II

Blood coagulation was activated in both groups after prolonged cardiac arrest, evidenced by a significant increase in TAT levels measured after started CPR. TAT levels were significantly higher in the saline placebo group compared to the enoxaparin group at 12, 14 and 24 minutes after onset of VF. There were no differences between the groups regarding CPP, FBF or CCBF during CPR or after ROSC. Intravenous adrenaline caused a significant decrease in FBF and increase in CCBF with no difference between the groups. Resuscitability did not differ between the groups.

Paper III

There was no difference in median time to delivery of first shock between the manual and AED mode. Median time from cessation of chest compression to shock delivery and the time from shock delivery to resumed chest compressions were significantly longer in the AED compared to the manual mode, also reflected in a higher median hands-off ratio in the AED mode. Sensitivity and specificity for shock delivery was 100 percent in AED mode, while 100 percent and 89 percent in manual mode,

respectively. In other words, all incidents of VF were detected and shocks were delivered appropriately in AED and manual mode. In manual mode, however, 12 percent of shocks were delivered on rhythms other than VF.

Paper IV

Eight patients were included in the study. Rescuer breathing with mouth-to-mask or mouth-to-endotracheal tube during BLS resulted in a slight arterial hypercarbia and hypoxia. Tidal volumes during BLS were measured in two cases with mouth-to-endotracheal tube ventilation with individual mean (SD) tidal volumes of 864 (176) and 1054 (165) millilitres.

8. Discussion

Paper I - Effect of CPR quality on pharmacodynamics and pharmacokinetics of adrenaline

As expected and in accord with previous studies (Babbs, Voorhees et al. 1983; Sunde, Wik et al. 1998; Berg 2001), CPR quality significantly influenced blood flow during cardiac arrest, evidenced by a delay in peak plasma concentration of exogenous adrenaline in animals that received ClinicalCPR compared to LabCPR. Furthermore, the blood flow generated by ClinicalCPR was insufficient for adrenaline to significantly increase systemic blood pressure and CCBF. This was contrasted by the blood flow generated by LabCPR, during which adrenaline significantly increased the systemic blood pressure and CCBF.

Adrenaline is recommended during cardiac arrest and CPR to elevate CPP and thereby increase the probability of achieving ROSC (AHA 2005; ERC 2005). It is therefore logical that chest compressions should be continued after adrenaline is delivered until peak drug effect occurs, before defibrillation is attempted. The guidelines recognise that 1-2 minutes of chest compressions may be required for the drug to reach the central circulation, however, there is no recommendation for the optimal timing of drug delivery (AHA 2005; ERC 2005). The median time from drug delivery to peak plasma adrenaline concentration and drug effect was within two minutes in the LabCPR group, suggesting that two minutes of chest compressions from the time of drug delivery to attempted defibrillation may be adequate in cases with optimal CPR quality. In contrast, the median time to peak plasma concentration in the ClinicalCPR group exceeded the two minutes of chest compressions recommended between defibrillation attempts (AHA 2005; ERC 2005). The findings suggest that the recommended two minutes of chest compressions between attempted defibrillation is insufficient for distribution of adrenaline during clinical cardiac arrest and CPR.

Guideline recommendations are published to ensure unified and good quality management of cardiac arrested patients. Most shocks delivered during clinical resuscitation, however, failed to achieve a perfusing rhythm in previous studies

(Sunde 1999), suggesting that the «one size fits all» approach in the management of cardiac arrested patients may not benefit all patients. Recent revisions of the guidelines have opened up for individual treatment based on assessment of the patients. It is acknowledged that chest compressions before initial defibrillation is beneficial in patients where time from collapse to treatment exceeds five minutes, while patients with short time from collapse to treatment may receive a defibrillation attempt first. However, recommendations for drug administration, the duration of chest compression between defibrillation attempts, and the timing of defibrillation apply to all patients.

Previous experimental and clinical studies suggested that a few minutes of chest compressions were beneficial for defibrillation outcome (Berg, Hilwig et al. 2002; Steen 2003; Wik 2003; Eftestøl 2004), the optimal duration of which was three minutes in a clinical study of VF characteristics (Eftestøl 2004). Considering these studies, the Norwegian guidelines recommend that three minutes of chest compressions should be delivered between each defibrillation attempt. The outcome of the initial defibrillation attempt should be evaluated after one minute of chest compressions. If ROSC is not achieved, adrenaline should be administered followed by two more minutes of chest compression and attempted defibrillation when appropriate.

The modification of the international guidelines is in accord with our findings when good quality CPR was performed. A previous clinical study on CPR quality reported a hands-off ratio of 10 percent with chest compression frequency and depth within guideline recommendations (Olasveengen, Wik et al. 2007), supporting the presumption that CPR quality similar to LabCPR is achievable in clinical cardiac arrest and resuscitation. However, there is to date no clinical evidence to support neither two nor three minutes of chest compressions between attempted defibrillation.

In accord with previous findings (Achleitner 2001; Li 2008), we demonstrated that VF waveform characteristics correlated with CPP and may be used as a surrogate to

monitor the impact of chest compressions and the effect of adrenaline administered during CPR and thereby facilitate «custom fit» management of cardiac arrest. If implemented into clinical practice, our findings argue that the technology may aid the rescuer to identify the optimal timing of attempted defibrillation, thereby avoiding unnecessary shocks and interruptions in chest compressions. Until such technology is available to the rescuer, two to three minutes of chest compressions between defibrillation attempts seem appropriate when good quality CPR is performed.

Multi-centre clinical trials comparing pharmaceutical approaches in the management of cardiac arrested victims have failed to confirm promising experimental findings. Experimental studies of vasopressin administered during resuscitation have demonstrated CPP levels similar to (Klouche, Weil et al. 2003) or higher (Lindner, Prengel et al. 1995) than for adrenaline followed by similar (Klouche 2003) or higher frequency of ROSC (Wenzel 1999). Vasopressin was further associated with better blood flow to vital organs (Lindner 1995; Wenzel, Lindner et al. 1999), delivery of cerebral oxygen (Prengel, Lindner et al. 1996), and neurological outcome (Wenzel, Lindner et al. 2000) compared to adrenaline. In two multi-centre clinical trials, however, survival to hospital discharge did not differ among the patients who received vasopressin compared to adrenaline (Wenzel, Krismer et al. 2004; Gueugniaud 2008). Similarly, a multi-centre study (Böttiger 2008) failed to confirm improved survival rate to hospital discharge and neurological function after thrombolytic treatment during resuscitation, as suggested in a meta-analysis (Li, Fu et al. 2006). Our findings suggest that one explanation why clinical studies failed to confirm promising experimental findings may be related to discrepancies between experimental and clinical management of cardiac arrest, including different quality of chest compression along with different sites for drug administration.

The algorithm for ClinicalCPR was based on the 2000 revision of the guidelines. Subsequent revisions of the guidelines included several changes in treatment recommendation to eliminate interruptions in chest compressions to improve haemodynamics during cardiac arrest and CPR (AHA 2005; ERC 2005). The changes

included increased focus on chest compressions with a recommended compression to ventilation ratio of 30:2 when accompanied by unprotected airways. Stacked shocks were no longer advised, and shock delivery was not warranted if in doubt about asystole or VF. Finally, two minutes of chest compression should be started immediately after a shock without prior rhythm analysis or pulse check eliminating inter and post-shock pauses. It is likely that the implementation of the current guidelines would reduce the hands-off-time during ClinicalCPR and thereby improve the haemodynamic effects of adrenaline, attenuating the observed differences between ClinicalCPR and LabCPR.

Paper II - prearrest administration of low-molecular-weight heparin

Coagulation was activated after cardiac arrest in accord with previous reports (Hartveit 1970; Böttiger 1995; Gando 1997; Johansson 2004; Adrie 2005). The amount of TAT reflected the amount of thrombin generated and was used as a measure of the degree of coagulation activation. Although, the TAT level was significantly lower in the enoxaparin group compared to placebo control, the elevation of TAT in the enoxaparin group was unexpected. The effect of enoxaparin was monitored through the activation of factor Xa and was within the level known to be therapeutic in humans; however, no information on the therapeutic level in pigs was available. One proposed mechanism for the reversed effect of enoxaparin on coagulation activity may be through asphyxia. In a previous study, the effect of unfractionated heparin on bleeding time in dogs was reversed following asphyxia induced cardiac arrest (Crowell, Sharpe et al. 1955). Although, the pharmacokinetic of enoxaparin differ from that of unfractionated heparin, the report may indicate that the tissue hypoxia that occurred during cardiac arrest and CPR may explain why enoxaparin administered in a clinically relevant dose did not completely abolish coagulation activation.

Conventional unfractionated heparin has been the preferred drug for anticoagulation in experimental studies of cardiac arrest. Clinically, however, low-molecular-weight heparins have gained acceptance as antithrombotic compounds. Both unfractionated

heparin and low-molecular-weight heparins exert their antithrombotic action through antithrombin. While unfractionated heparin has equivalent activity towards factor Xa and thrombin, low-molecular-weight heparins have greater activity against factor Xa. The advantages of low-molecular-weight heparins include a more predictive anticoagulation response, reflecting a better bioavailability, longer half-life, dose-independent clearance, and less bleeding compared to unfractionated heparin (Weitz 1997). Hence, enoxaparin in a clinically relevant dosage was used for anticoagulation.

The lack of haemodynamic effect of enoxaparin with a similar frequency of ROSC between the groups may have several aetiologies. Besides the formation of fibrin, the cessation of blood flow may cause red blood cells to aggregate within a few minutes after onset of cardiac arrest, leading to the formation of micro emboli and impairment of cerebral blood flow (Hekmatpanah 1973). Oedema development in endothelial cells may also impair blood flow. The fact that increased perfusion pressure and haemodilution improved microcirculation after cerebral ischemia (Fischer and Ames 1972), as opposed to anticoagulation alone, supports the assumption that factors not affected by anticoagulation are essential to blood flow in vital organs during cardiac arrest and CPR. It may be speculated that to detect effects of anticoagulation after cardiac arrest, the perfusion pressure must overcome the hindrance caused by blood cell aggregation and endothelial oedema.

Previous studies reported the effect of anticoagulation on survival after cardiac arrest. In 1955, Crowell et al. demonstrated that heparin 10 minutes before cardiac arrest dramatically improved recovery in dogs (Crowell 1955). Safar et al. reported better neurological outcome in dogs that received post-arrest treatment comprising heparin, normovolemic haemodilution, and hypertensive reperfusion (Safar 1976). However, when heparin, haemodilution, and hypertensive reperfusion were studied separately, there was no effect of heparin on survival. Finally, consistent with our findings, Johansson et al. reported that antithrombin administered during CPR had no haemodynamic effects in pigs (Johansson 2004).

Our study focuses on the prevention of blood clot formation to improve blood flow to vital organs. Heparins may, however, hold additional properties. A recent study on cerebral infarction suggested that ultra-low-molecular weight heparins may exercise their role during reperfusion through the scavenging of free radicals and modulation of intracellular calcium homeostasis (Zhang, Zhang et al. 2007). Although, the duration of the ischemic insult in cerebral infarction models differ from that of cardiac arrest, anticoagulation may also benefit cardiac arrested patients.

Anticoagulation is currently not recommended in the management of cardiac arrested patients (AHA 2005; ERC 2005). In contrast, experimental studies frequently administer unfractionated heparin to avoid coagulation. However, an increasing number of patients undergo percutaneous coronary intervention (PCI) following ROSC including unfractionated heparin for anticoagulation (Sunde 2007). We did not find short-term benefits of anticoagulation during cardiac arrest and resuscitation, however, there may be potential long term benefits which may be potentiated when combined with potent platelet antagonists (Kern, Cragan et al. 2007).

Paper III: manual versus semiautomatic defibrillation

We demonstrated that peri-shock intervals without chest compressions were significantly shorter when trained ambulance personnel operated the defibrillator in manual mode as compared to AED when complying with the 2000 revision of the guidelines (AHA 2000; ERC 2000). Our findings of median pre-shock pause of 17 and 11 seconds and post-shock pauses of 25 and 8 seconds in the AED and manual modes, respectively, were shorter than the pauses reported by others. Subsequent studies by Olasveengen and co-workers reported median pre-shock pauses of 17 seconds when ambulance personnel in the same EMS operated the defibrillator in manual mode in a clinical setting (Olasveengen 2009). In a retrospective analysis of prospectively collected data, Kramer-Johansen et al. reported median pre-shock pauses of 22 seconds when the defibrillator was operated in AED mode and 15 seconds when operated in manual mode by either ambulance personnel when out-of-hospital or resident physicians when in-hospital (Kramer-Johansen, Edelson et al.

2007). Others have studied clinical peri-shock intervals when AEDs only were used. Sunde et al. found pre-shock pauses of median 20 seconds (Sunde 1999). Similarly, other investigators reported median post-shock pauses ranging from 29 to 38 seconds (Berg, Clark et al. 2005; Rea, Shah et al. 2005).

Inappropriate shocks may have adverse effects on outcome. In our study, 12 percent of shocks given in manual mode were delivered on rhythms other than VF, while no unwarranted shocks were delivered in AED mode. Similarly, 26 percent of all manual shocks and 6 percent of shocks in AED mode were delivered on organised rhythm in the clinical study referred to (Kramer-Johansen 2007). The adverse effect of inappropriate shocks may be ascribed to the combination of extra energy delivered to the myocardium (Xie, Weil et al. 1997) and to increased peri-shock intervals without chest compressions (Sato 1997; Eftestøl 2002; Yu 2002; Edelson 2006; Berg 2008). Nevertheless, all inappropriate shocks were delivered in manual mode in our study, the total hands-off time in manual mode was favourable compared to AED mode.

As other sources of interruptions in chest compression are eliminated, faulty shocks may constitute an increasing and considerable part of the total hands-off time. In our study the typical time required for rhythm analysis in AED mode was 20 seconds, the time of which varies between different AED manufacturers in the range from 5 to 28 seconds (Snyder 2004). Eilevstjønn et al. reported that hands-off time may theoretically be reduced from 51 percent to 34 percent if the AED would allow for rhythm analysis during chest compressions and charging of the defibrillator during rhythm analysis in combination with immediate chest compression after attempted defibrillation (Eilevstjonn, Kramer-Johansen et al. 2005).

The 2005 revision of the international guidelines may further attenuate the observed differences between AED and manual mode defibrillation. Besides immediately resumed chest compressions after attempted defibrillation, omitting pulse check, the eliminated stacked shocks should reduce peri-shock intervals without chest compressions. The greatest effect of algorithm change should be seen in the AED

mode since most of the hands-off time generated in our study was related to pulse check between stacked shocks. Thus, either future modifications of the AED or implementation of the 2005 guidelines or the combination of both should reduce the hand-off time and argue for defibrillation in AED mode by trained personnel as well. Recommendation for preferred defibrillation mode should, however, be made within the local EMS depending on available resources and level of training among the rescuers.

Paper IV; rescuer ventilation during BLS

International guidelines recommend lower than normal minute ventilation during BLS with tidal volumes sufficient to make the victim´s chest rise (AHA 2005; ERC 2005). The $PaCO_2$ levels observed in our study suggest that ventilation volumes required for normal $PaCO_2$ may be as high as among patients with spontaneous circulation and in agreement with previous findings during clinical ALS (Dorph 2004). This does not, however, imply that normocapnia should be targeted during BLS, as high ventilation rate and volume may be detrimental to myocardial blood flow and survival (Aufderheide 2004).

The mean $PaCO_2$ of 9.6 kPa in our study was higher than 7.1 kPa previously reported in pigs ventilated with 4 percent carbon dioxide, compression to ventilation ratio 15:2 and mean minute ventilation of 200 ml kg^{-1} (Dorph 2003). Others have reported $PaCO_2$ levels below 4.0 kPa in pigs treated with compression to ventilation ratio 15:2 (Berg 1997; Kern, Hilwig et al. 2002). The discrepancy in $PaCO_2$ levels may be explained by passive ventilation with ambient air bypassing the active ventilation with 3-4 percent carbon dioxide caused by chest compressions when airways were open. In our study, an impedance valve connected to the endotracheal tube prevented passive ventilation. The recorded levels of $PaCO_2$ in the patients who received mouth-to-mask ventilation suggest that chest compressions did not cause passive ventilation when the airways were unprotected.

The mean PaO_2 8.5 kPa agrees with experimental findings of mean PaO_2 8.9 kPa in pigs ventilated with 17 percent oxygen at the ratio 15:2 (Dorph 2003). Although, the level of PaO_2 may be adequate in patients with normal acid-base condition, the adequate level during cardiac arrest and CPR is not known. The concomitant acidosis leads to a rightward shift in the oxyhaemoglobin dissociation curve, thereby reducing the arterial haemoglobin oxygen saturation and blood oxygen content at the same level of PaO_2, while facilitating unloading of oxygen in the tissues (Refsum, Opdahl et al. 1997), suggesting that a higher level of PaO_2 may be required for adequate oxygenation of the tissues in states of low blood pH.

Does arterial hypercarbia and hypoxia influence outcome? In a previous clinical study, only 8 of 15 patients with PaO_2 less than 5.3 kPa underwent successful defibrillation, compared with 21 of 22 patients with PaO_2 above 5.3 kPa (Kerber and Sarnat 1979). Also in pigs, hypoxia at PaO_2 5.7 kPa was associated with resuscitation failure, compared with controls with PaO_2 30.4 kPa. In the same study, hypercarbia at the level of 6.3 kPa was associated with resuscitation failure compared with 4.5 kPa (Idris 1995). The findings suggest that the mean PaO_2 of 8.5 kPa in our study was acceptable in the circumstances while the hypercarbia may be unfavourable, although, there is to date no clinical report on the influence of hypercarbia on resuscitation outcome.

The 2005 revision of the guidelines include increased focus on chest compressions, downplaying the importance of ventilation as evidenced by the increase in chest compression to ventilation ratio to 30:2 (AHA 2005; ERC 2005). The impact of the revised guidelines on acid-base condition was demonstrated in a previous experimental study, in which significantly higher $PaCO_2$ and numerically lower arterial pH were reported in pigs that received chest compression and ventilation at the ratio of 30:2 compared to 15:2, while PaO_2 was comparable between the groups (Yannopoulos 2006). The findings in this study were strengthened by an impedance device prohibiting passive ventilation ascribed to chest compression, however, limited by the us of 100 percent oxygen for ventilation. Thus, it is reasonable to assume that

the implementation of current guidelines will improve haemodynamics during BLS and reduce ventilation, the combination of which should aggravate metabolic acidosis accompanied by increased $PaCO_2$ and lowered PaO_2.

8.1. Limitations

Papers I and II

The studies were performed on healthy animals. In contrast, cardiac arrested patients are often multi morbid, thus the results should be interpreted with caution. The sample sizes were small, which may have prevented us from detecting differences that were present (Type II error). Survival data in *Paper I* was not available as the study was designed to closely observe the haemodynamic effects of adrenaline over a defined period. Limitations to the brain cortex micro circulatory measurements included the ability to measure only changes in blood flow, rather than absolute blood flow, to a small part of the cortex only. Additional limitations to *Paper II* include the timing of the intervention, since prearrest drug administration is not clinically relevant. However, the purpose of the study was to evaluate the effect of anticoagulation as provided in experimental studies. Furthermore, the study was concluded after 10 minutes of ROSC, thus precluding us from studying the long-term effects of anticoagulation following ROSC.

Paper III

The study was performed with the aid of a mannequin, focusing on chest compression and operation of the defibrillator only. Thus the study lacks the complexity of a real life setting. The reported intervals without chest compressions do not reflect hands-off generated by ventilation pre-intubation, endotracheal intubation, and establishment of intravenous access. However, the absolute difference between manual mode and AED mode should be valid also in the clinical setting. Furthermore, the results only reflect the skills and training of the volunteer ambulance personnel recruited, and may not be generalised. Finally, the study was performed before the implementation of new guidelines, and do not apply to the 2005 revision of the guidelines.

Paper IV

The study population comprised newly deceased patients as it was considered unethical to perform BLS in patients with cardiac arrest when health care professionals able to perform ALS were available. The number of subjects studied was few and tidal volumes were collected in two patients only, reflecting the difficulty of applying advanced measuring equipment during out-of-hospital cardiac arrest. The prolonged resuscitation effort may have influenced the compliance of the chest and thereby the passive ventilation potentially caused by chest compressions. Although good quality chest compression was pursued, constant blood flow was not achieved, complicating the interpretation of the arterial acid-base condition. Finally, trained health care professionals performed BLS and the quality of treatment is likely to differ from bystander BLS.

9. Conclusion

Paper I

Pharmacodynamics and pharmacokinetics of adrenaline administered during cardiac arrest depend on the quality of CPR performed. The haemodynamic effects of adrenaline may be monitored through alterations in VF waveform characteristics.

Paper II

Prearrest anticoagulation did not influence variables known to prognosticate survival from cardiac arrest, nor did it influence the haemodynamic effects of adrenaline and the ability to achieve ROSC.

Paper III

Peri-shock intervals without chest compression during CPR may be reduced when the defibrillator is operated in manual mode in contrast to AED mode, thereby potentially improve quality of CPR.

Paper IV

Ventilation during BLS performed according to the 2000 revision of international guidelines resulted in arterial hypercapnia and hypoxia.

10. Errata

Paper II

Page 2, third column, line 31: Epinephrine (0.02 mg kg^{-1} intravenously) was administered in a peripheral vein two minutes after commenced ALS, and two minutes before attempted defibrillation. CPR was resumed immediately for two more minutes.

Paper IV

Page 3, third paragraph, line 15: «...values of 8.5 kPa[17] and 10 kPa.[5]» should be «...value of mean 8.9 kPa[18]»

11. References

Aase S. O. and Myklebust H. (2002). "Compression depth estimation for CPR quality assessment using DSP on accelerometer signals." IEEE Trans.Biomed.Eng **49**(3): 263-268.

Abella B. S., Sandbo N., Vassilatos P., Alvarado J. P., O'Hearn N., Wigder H. N., Hoffman P., Tynus K., Vanden Hoek T. L. and Becker L. B. (2005). "Chest compression rates during cardiopulmonary resuscitation are suboptimal: a prospective study during in-hospital cardiac arrest." Circulation **111**(4): 428-34.

Achleitner U., Wenzel V., Strohmenger H. U., Lindner K. H., Baubin M. A., Krismer A. C., Mayr V. D. and Amann A. (2001). "The beneficial effect of basic life support on ventricular fibrillation mean frequency and coronary perfusion pressure." Resuscitation **51**(2): 151-8.

Adrie C., Monchi M., Laurent I., Um S., Yan S. B., Thuong M., Cariou A., Charpentier J. and Dhainaut J. F. (2005). "Coagulopathy After Successful Cardiopulmonary Resuscitation Following Cardiac Arrest: Implication of the Protein C Anticoagulant Pathway." Journal of the American College of Cardiology **46**(1): 21-28.

AHA (1992). "Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part II. Adult basic life support." JAMA **268**(16): 2184-98.

AHA (2000). "American Heart Association in collaboration with International Liason Committee in Resuscitation. guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cerdiovascular Care." Circulation **102(suppl)**: I-1-I-403.

AHA (2005). "2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care." Circulation **112**(24 suppl): IV58-66.

Angelos M. G., Butke R. L., Panchal A. R., Torres C. A., Blumberg A., Schneider J. E. and Aune S. E. (2008). "Cardiovascular response to epinephrine varies with increasing duration of cardiac arrest." Resuscitation **77**(1): 101-10.

Atwood C., Eisenberg M. S., Herlitz J. and Rea T. D. (2005). "Incidence of EMS-treated out-of-hospital cardiac arrest in Europe." Resuscitation **67**(1): 75-80.

Aufderheide T. P., Sigurdsson G., Pirrallo R. G., Yannopoulos D., McKnite S., von Briesen C., Sparks C. W., Conrad C. J., Provo T. A. and Lurie K. G. (2004). "Hyperventilation-

Induced Hypotension During Cardiopulmonary Resuscitation." Circulation **109**(16): 1960-1965.

Babbs C. F., Voorhees W. D., Fitzgerald K. R., Holmes H. R. and Geddes L. A. (1983). "Relationship of blood pressure and flow during CPR to chest compression amplitude: evidence for an effective compression threshold." Annals of emergency medicine **12**(9): 527-32.

Beck C. S., Pritchard W. H. and Feil H. S. (1947). "Ventricular fibrillation of long duration abolished by electric shock." Journal of American Medical Association **135**: 985-986.

Becker L. B., Smith D. W. and Rhodes K. V. (1993). "Incidence of cardiac arrest: a neglected factor in evaluating survival rates." Annals of emergency medicine **22**(1): 86-91.

Behringer W., Kittler H., Sterz F., Domanovits H., Schoerkhuber W., Holzer M., Mullner M. and Laggner A. N. (1998). "Cumulative Epinephrine Dose during Cardiopulmonary Resuscitation and Neurologic Outcome." Annals of Internal Medicine **129**(6): 450-456.

Berg M. D., Clark L. L., Valenzuela T. D., Kern K. B. and Berg R. A. (2005). "Post-shock chest compression delays with automated external defibrillator use." Resuscitation **64**(3): 287-291.

Berg R. A., Hilwig R., Berg M. D., Berg D. D., Samson R. A., Indik J. H. and Kern K. B. (2008). "Immediate post-shock chest compressions improve outcome from prolonged ventricular fibrillation." Resuscitation **78**(1): 71-76.

Berg R. A., Hilwig R. W., Kern K. B. and Ewy G. A. (2002). "Precountershock cardiopulmonary resuscitation improves ventricular fibrillation median frequency and myocardial readiness for successful defibrillation from prolonged ventricular fibrillation: a randomized, controlled swine study." Ann Emerg.Med **40**(6): 563-570.

Berg R. A., Kern K. B., Hilwig R. W. and Ewy G. A. (1997). "Assisted ventilation during 'bystander' CPR in a swine acute myocardial infarction model does not improve outcome." Circulation **96**(12): 4364-71.

Berg R. A., Kern K. B., Sanders A. B., Otto C. W., Hilwig R. W. and Ewy G. A. (1993). "Bystander cardiopulmonary resuscitation. Is ventilation necessary?" Circulation **88**(4 Pt 1): 1907-15.

Berg R. A., Sanders A. B., Kern K. B., Hilwig R. W., Heidenreich J. W., Porter M. E. and Ewy G. A. (2001). "Adverse Hemodynamic Effects of Interrupting Chest Compressions

for Rescue Breathing During Cardiopulmonary Resuscitation for Ventricular Fibrillation Cardiac Arrest." Circulation **104**(20): 2465-2470.

Bohm K., Rosenqvist M., Herlitz J., Hollenberg J. and Svensson L. (2007). "Survival is similar after standard treatment and chest compression only in out-of-hospital bystander cardiopulmonary resuscitation." Circulation **116**(25): 2908-12.

Brown C. G., Werman H. A. and Davis E. A. (1986). "Comparative effect of graded doses of epinephrine on regional brain blood flow during CPR in a swine model." Annals of Emergency Medicine **15**(10): 1138-44.

Böttiger B. W., Arntz H., Chamberlain D. A., Bluhmki E., Belmans A., Danays T., Carli P. A., Adgey J. A., Bode C., Wenzel V., Investigators T. T. and Group E. R. C. S. (2008). "Thrombolysis during resuscitation for out-of-hospital cardiac arrest." N Engl J Med **359** (25): 2651-62.

Böttiger B. W., Bode C., Kern S., Gries A., Gust R., Glatzer R., Bauer H., Motsch J. and Martin E. (2001). "Efficacy and safety of thrombolytic therapy after initially unsuccessful cardiopulmonary resuscitation: a prospective clinical trial." The Lancet **357**(9268): 1583-1585.

Böttiger B. W., Motsch J., Böhrer H., Böker T., Aulmann M., Nawroth P. P. and Martin E. (1995). "Activation of blood coagulation after cardiac arrest is not balanced adequately by activation of endogenous fibrinolysis." Circulation **92**(9): 2572-8.

Caffrey S. L., Willoughby P. J., Pepe P. E. and Becker L. B. (2002). "Public use of automated external defibrillators." N Engl J Med **347**(16): 1242-7.

Cammarata G., Weil M. H., Sun S., Tang W., Wang J. and Huang L. (2004). "Beta1-adrenergic blockade during cardiopulmonary resuscitation improves survival." Crit Care Med. **32**(9 Suppl): S440-S443.

"Cardiopulmonary resuscitation." (1966). JAMA **198**(4): 372-9.

Chamberlain D. (2005). "The International Liaison Committee on Resuscitation (ILCOR)-past and present: compiled by the Founding Members of the International Liaison Committee on Resuscitation." Resuscitation **67**(2-3): 157-61.

Cobb L. A., Fahrenbruch C. E., Walsh T. R., Copass M. K., Olsufka M., Breskin M. and Hallstrom A. P. (1999). "Influence of Cardiopulmonary Resuscitation Prior to Defibrillation in Patients With Out-of-Hospital Ventricular Fibrillation." JAMA: The Journal of the American Medical Association **281**(13): 1182-1188.

Criley J. M., Blaufuss A. H. and Kissel G. L. (1976). "Cough-induced cardiac compression. Self-administered from of cardiopulmonary resuscitation." JAMA **236**(11): 1246-50.

Crowell J. W., Sharpe G. P., Lambright R. L. and Read W. L. (1955). "The mechanism of death after resuscitation following acute circulatory failure." Surgery **38**(4): 696-702.

Cummins R. O., Chamberlain D. A., Abramson N. S., Allen M., Baskett P. J., Becker L., Bossaert L., Delooz H. H., Dick W. F., Eisenberg M. S. and et al. (1991). "Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein Style. A statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council." Circulation **84**(2): 960-75.

Cummins R. O., Ornato J. P., Thies W. H. and Pepe P. E. (1991). "Improving survival from sudden cardiac arrest: the "chain of survival" concept. A statement for health professionals from the Advanced Cardiac Life Support Subcommittee and the Emergency Cardiac Care Committee, American Heart Association." Circulation **83**(5): 1832-47.

Davies M. J. and Thomas A. (1984). "Thrombosis and acute coronary-artery lesions in sudden cardiac ischemic death." The New England Journal of Medicine **310**(18): 1137-1140.

Dill D. B. (1958). "Symposium on mouth-to-mouth resuscitation (expired air inflation)." JAMA **167**(3): 317-319.

Ditchey R. V. and Lindenfeld J. (1988). "Failure of epinephrine to improve the balance between myocardial oxygen supply and demand during closed-chest resuscitation in dogs." Circulation **78**(2): 382-9.

Ditchey R. V., Rubio-Perez A. and Slinker B. K. (1994). "Beta-adrenergic blockade reduces myocardial injury during experimental cardiopulmonary resuscitation." J Am Coll Cardiol **24**(3): 804-12.

Ditchey R. V., Winkler J. V. and Rhodes C. A. (1982). "Relative lack of coronary blood flow during closed-chest resuscitation in dogs." Circulation **66**(2): 297-302.

Dorph E., Wik L. and Steen P. A. (2004). "Arterial blood gases with 700 ml tidal volumes during out-of-hospital CPR." Resuscitation **61**(1): 23-27.

Dorph E., Wik L., Stromme T. A., Eriksen M. and Steen P. A. (2003). "Quality of CPR with three different ventilation:compression ratios." Resuscitation **58**(2): 193-201.

Dorph E., Wik L., Stromme T. A., Eriksen M. and Steen P. A. (2004). "Oxygen delivery and return of spontaneous circulation with ventilation:compression ratio 2:30 versus chest compressions only CPR in pigs." Resuscitation **60**(3): 309-318.

Edelson D. P., Abella B. S., Kramer-Johansen J., Wik L., Myklebust H., Barry A. M., Merchant R. M., Hoek T. L., Steen P. A. and Becker L. B. (2006). "Effects of compression depth and pre-shock pauses predict defibrillation failure during cardiac arrest." Resuscitation **71**(2): 137-45.

Eftestøl T., Sunde K. and Steen P. A. (2002). "Effects of interrupting precordial compressions on the calculated probability of defibrillation success during out-of-hospital cardiac arrest." Circulation **105**(19): 2270-3.

Eftestøl T., Wik L., Sunde K. and Steen P. A. (2004). "Effects of cardiopulmonary resuscitation on predictors of ventricular fibrillation defibrillation success during out-of-hospital cardiac arrest." Circulation **110**(1): 10-5.

Eilevstjonn J., Kramer-Johansen J., Eftestol T., Stavland M., Myklebust H. and Steen P. A. (2005). "Reducing no flow times during automated external defibrillation." Resuscitation **67**(1): 95-101.

Eisenberg M. S., Cummins R. O. and Larsen M. P. (1991). "Numerators, denominators, and survival rates: reporting survival from out-of-hospital cardiac arrest." Am J Emerg Med **9** (6): 544-6.

Eisenberg M. S., Horwood B. T., Cummins R. O., Reynolds-Haertle R. and Hearne T. R. (1990). "Cardiac arrest and resuscitation: a tale of 29 cities." Annals of emergency medicine **19**(2): 179-86.

Elam J. O. (1977). Rediscovery of expired air methods for emergency ventilation. Advances in Cardiopulmonary Resuscitation. P. Safar. New York, Springer Verlag**:** 263-265.

ERC (2000). "Part 3: adult basic life support. European Resuscitation Council." Resuscitation **46**(1-3): 29-71.

ERC (2000). "Part 6: advanced cardiovascular life support. Section 2: defibrillation. European Resuscitation Council." Resuscitation **46**(1-3): 109-13.

ERC (2005). "European Resuscitation Council Guidelines for Resuscitation 2005." Resuscitation **67(Suppl)**: S1-190.

Ewy G. A. (2007). "Cardiac arrest--guideline changes urgently needed." Lancet **369**(9565): 882-4.

Ewy G. A., Zuercher M., Hilwig R. W., Sanders A. B., Berg R. A., Otto C. W., Hayes M. M. and Kern K. B. (2007). "Improved neurological outcome with continuous chest compressions compared with 30:2 compressions-to-ventilations cardiopulmonary resuscitation in a realistic swine model of out-of-hospital cardiac arrest." Circulation **116** (22): 2525-30.

Fischer E. G. and Ames A., III (1972). "Studies on Mechanisms of Impairment of Cerebral Circulation Following Ischemia: Effect of Hemodilution and Perfusion Pressure." Stroke **3**(5): 538-542.

Fisher J., Vaghaiwalla F., Tsitlik J., Levin H., Brinker J., Weisfeldt M. and Yin F. (1982). "Determinants and clinical significance of jugular venous valve competence." Circulation **65**(1): 188-96.

Florence G. and Seylaz J. (1992). "Rapid autoregulation of cerebral blood flow: a laser-Doppler flowmetry study." J Cereb Blood Flow Metab **12**(4): 674-80.

Gallagher E. J., Lombardi G. and Gennis P. (1995). "Effectiveness of bystander cardiopulmonary resuscitation and survival following out-of-hospital cardiac arrest." JAMA **274**(24): 1922-5.

Gando S., Kameue T., Nanzaki S. and Nakanishi Y. (1997). "Massive fibrin formation with consecutive impairment of fibrinolysis in patients with out-of-hospital cardiac arrest." Thromb.Haemost. **77**(2): 278-282.

Gando S., Nanzaki S., Morimoto Y., Kobayashi S. and Kemmotsu O. (1999). "Tissue Factor and Tissue Factor Pathway Inhibitor Levels during and after Cardiopulmonary Resuscitation." Thrombosis Research **96**(2): 107-113.

Gottlieb R. (1896). "Ueber die Wirkung der Nebennierenextracte auf Herz und Blutdruck." Naunyn-Schmiedeberg's Archives of Pharmacology **38**: 99-112.

Gueugniaud P. Y., David J. S., Chanzy E., Hubert H., Dubien P. Y., Mauriaucourt P., Bragança C., Billères X., Clotteau-Lambert M. P., Fuster P., Thiercelin D., Debaty G., Ricard-Hibon A., Roux P., Espesson C., Querellou E., Ducros L., Ecollan P., Halbout L., Savary D., Guillaumée F., Maupoint R., Capelle P., Bracq C., Dreyfus P., Nouguier P., Gache A., Meurisse C., Boulanger B., Lae C., Metzger J., Raphael V., Beruben A., Wenzel V., Guinhouya C., Vilhelm C. and Marret E. (2008). "Vasopressin and epinephrine vs. epinephrine alone in cardiopulmonary resuscitation." N Engl J Med **359**(1): 21-30.

Gundersen K., Nysæther J., Kvaløy J. T., Kramer-Johansen J. and Eftestøl T. (2009). "Chest compression quality variables influencing the temporal development of ROSC-predictors calculated from the ECG during VF." Resuscitation **80**(2): 177-182.

Halperin H., Tsitlik J., Guerci A., Mellits E., Levin H., Shi A., Chandra N. and Weisfeldt M. (1986). "Determinants of blood flow to vital organs during cardiopulmonary resuscitation in dogs." Circulation **73**(3): 539.

Hanche-Olsen T. and Nielsen E. W. (2002). "High survival in out-of-hospital cardiopulmonary resuscitation--7 years' incidence according to the Utstein template in a small town in Northern Norway." Eur J Emerg Med **9**(1): 19-24.

Hartveit F. and Halleraker B. (1970). "Intravascular changes in kidneys and lungs after external cardiac massage: a preliminary report." J Pathol. **102**(1): 54-58.

Hekmatpanah J. (1973). "Cerebral blood flow dynamics in hypotension and cardiac arrest." Neurology **23**(2): 174-180.

Herlitz J., Bahr J., Fischer M., Kuisma M., Lexow K. and Thorgeirsson G. (1999). "Resuscitation in Europe: a tale of five European regions." Resuscitation **41**(2): 121-131.

Herlitz J., Ekstrom L., Wennerblom B., Axelsson A., Bang A. and Holmberg S. (1994). "Effect of bystander initiated cardiopulmonary resuscitation on ventricular fibrillation and survival after witnessed cardiac arrest outside hospital." Br Heart J **72**(5): 408-12.

Herlitz J., Engdahl J., Svensson L., Angquist K. A., Young M. and Holmberg S. (2005). "Factors associated with an increased chance of survival among patients suffering from an out-of-hospital cardiac arrest in a national perspective in Sweden." American Heart Journal **149**(1): 61-66.

Hoffman B. B. (2001). Catecholamines, sympathomimetic drugs and adrenergic receptor antagonists. Goodman & Gilman´s The pharmacological basis of therapeutics. J. G. L. Hardman, L.E. Gilman, A.G. London, McGraw-Hill**:** 215-268.

Hoffman B. B. (2001). Neurotransmission, the autonomic and somatic nervous system. Goodman & Gilman´s the pharmacological basis of therapeutics. J. G. L. Hardman, L.E. Gilman, A.G. London, McGraw-Hill**:** 115-153.

Holmberg M., Holmberg S. and Herlitz J. (2002). "Low chance of survival among patients requiring adrenaline (epinephrine) or intubation after out-of-hospital cardiac arrest in Sweden." Resuscitation **54**(1): 37-45.

Holmberg M., Holmberg S., Herlitz J. and Registry S. C. A. (2001). "Factors modifying the effect of bystander cardiopulmonary resuscitation on survival in out-of-hospital cardiac arrest patients in Sweden." Eur Heart J **22**(6): 511-9.

Holmes H. R., Babbs C. F., Voorhees W. D., Tacker W. A., Jr. and de G. B. (1980). "Influence of adrenergic drugs upon vital organ perfusion during CPR." Crit Care Med **8**(3): 137-140.

Idris A. H., Becker L. B., Ornato J. P., Hedges J. R., Bircher N. G., Chandra N. C., Cummins R. O., Dick W., Ebmeyer U., Halperin H. R., Hazinski M. F., Kerber R. E., Kern K. B., Safar P., Steen P. A., Swindle M. M., Tsitlik J. E., von Planta I., von Planta M., Wears R. L. and Weil M. H. (1996). "Utstein-style guidelines for uniform reporting of laboratory CPR research. A statement for healthcare professionals from a Task Force of the American Heart Association, the American College of Emergency Physicians, the American College of Cardiology, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, the Institute of Critical Care Medicine, the Safar Center for Resuscitation Research, and the Society for Academic Emergency Medicine." Resuscitation **33**(1): 69-84.

Idris A. H., Staples E. D., O'Brien D. J., Melker R. J., Rush W. J., Del Duca K. D. and Falk J. L. (1994). "Effect of ventilation on acid-base balance and oxygenation in low blood-flow states." Crit Care Med **22**(11): 1827-34.

Idris A. H., Wenzel V., Becker L. B., Banner M. J. and Orban D. J. (1995). "Does hypoxia or hypercarbia independently affect resuscitation from cardiac arrest?" Chest **108**(2): 522-8.

Indik J. H., Donnerstein R. L., Berg R. A., Hilwig R. W., Berg M. D. and Kern K. B. (2007). "Ventricular fibrillation frequency characteristics are altered in acute myocardial infarction." Crit Care Med **35**(4): 1133-8.

Indik J. H., Donnerstein R. L., Kern K. B., Goldman S., Gaballa M. A. and Berg R. A. (2006). "Ventricular fibrillation waveform characteristics are different in ischemic heart failure compared with structurally normal hearts." Resuscitation **69**(3): 471-7.

Johansson J., Gedeborg R., Basu S. and Rubertsson S. (2003). "Increased cortical cerebral blood flow by continuous infusion of adrenaline (epinephrine) during experimental cardiopulmonary resuscitation." Resuscitation **57**(3): 299-307.

Johansson J., Ridefelt P., Basu S. and Rubertsson S. (2004). "Antithrombin administration during experimental cardiopulmonary resuscitation." Resuscitation **62**(1): 71-78.

Keen W. W. (1904). "A case of total laryngectmy (unsuccessful) and a case of abdominal hysterectomy (successful), in both of which massage of the heart for chloroform collapse was employed, with notes of 25 other cases of cardiac massage." Therap Gaz **28**: 217-221.

Kerber R. E. and Sarnat W. (1979). "Factors influencing the success of ventricular defibrillation in man." Circulation **60**(2): 226-30.

Kern K. B., Cragan D., Zuercher M., Hilwig R., Berg R. A. and Ewy G. A. (2007). "Post resuscitation myocardial microcirculatory dysfunction is ameliorated with platelet glycoprotein IIb/IIIa inhibition." Circulation **116**: II630-II631.

Kern K. B., Ewy G. A., Voorhees W. D., Babbs C. F. and Tacker W. A. (1988). "Myocardial perfusion pressure: a predictor of 24-hour survival during prolonged cardiac arrest in dogs." Resuscitation **16**(4): 241-250.

Kern K. B., Hilwig R., Berg R. A. and Ewy G. A. (2006). "Post resuscitation myocardial microcirculatory dysfunction after prolonged ventricular fibrillation." Circulation **114**: II350-II351.

Kern K. B., Hilwig R. W., Berg R. A., Sanders A. B. and Ewy G. A. (2002). "Importance of continuous chest compressions during cardiopulmonary resuscitation: improved outcome during a simulated single lay-rescuer scenario." Circulation **105**(5): 645-649.

Kern K. B., Lancaster L., Goldman S. and Ewy G. A. (1990). "The effect of coronary artery lesions on the relationship between coronary perfusion pressure and myocardial blood flow during cardiopulmonary resuscitation in pigs." Am Heart J **120**(2): 324-33.

Kirkeby O. J., Rise I. R., Nordsletten L., Skjeldal S., Hall C. and Risoe C. (1995). "Cerebral blood flow measured with intracerebral laser-Dopplerflow probes and radioactive microspheres." J Appl.Physiol **79**(5): 1479-1486.

Klouche K., Weil M. H., Sun S., Tang W. and Zhao D. H. (2003). "A comparison of alpha-methylnorepinephrine, vasopressin and epinephrine for cardiac resuscitation." Resuscitation **57**(1): 93-100.

Kolar M., Krizmaric M., Klemen P. and Grmec S. (2008). "Partial pressure of end-tidal carbon dioxide successful predicts cardiopulmonary resuscitation in the field: a prospective observational study." Crit Care **12**(5): R115.

Koster RW B. L., Nolan JP, Zideman D. (2008). "Advisory statement of the European Resuscitation Counsil on Basic Life Support." Retrieved 02 11, 2008, from http://www.erc.edu/index.php/docLibrary/en/viewDoc/775/3/.

Kouwenhoven W. B., Jude J. R. and Knickerbocker G. G. (1960). "Closed-chest cardiac massage." JAMA **173**: 1064-7.

Kramer-Johansen J., Edelson D. P., Abella B. S., Becker L. B., Wik L. and Steen P. A. (2007). "Pauses in chest compression and inappropriate shocks: a comparison of manual and semi-automatic defibrillation attempts." Resuscitation **73**(2): 212-20.

Kramer-Johansen J., Edelson D. P., Losert H., Köhler K. and Abella B. S. (2007). "Uniform reporting of measured quality of cardiopulmonary resuscitation (CPR)." Resuscitation **74** (3): 406-17.

Kramer-Johansen J., Myklebust H., Wik L., Fellows B., Svensson L., Sorebo H. and Steen P. A. (2006). "Quality of out-of-hospital cardiopulmonary resuscitation with real time automated feedback: A prospective interventional study." Resuscitation **71**(3): 283-292.

Kumano H., Shimomura T., Furuya H., Yomosa H., Okuda T., Sakaki T. and Kuro M. (1993). "Effects of flumazenil during administration of midazolam on pial vessel diameter and regional cerebral blood flow in cats." Acta Anaesthesiol Scand **37**(6): 567-70.

Langhelle A., Tyvold S. S., Lexow K., Hapnes S. A., Sunde K. and Steen P. A. (2003). "In-hospital factors associated with improved outcome after out-of-hospital cardiac arrest. A comparison between four regions in Norway." Resuscitation **56**(3): 247-263.

Larsen M. P., Eisenberg M. S., Cummins R. O. and Hallstrom A. P. (1993). "Predicting survival from out-of-hospital cardiac arrest: a graphic model." Annals of emergency medicine **22**(11): 1652-8.

Lexow K. and Sunde K. (2007). "Why Norwegian 2005 guidelines differs slightly from the ERC guidelines." Resuscitation **72**(3): 490-2.

Li X., Fu Q. L., Jing X. L., Li Y. J., Zhan H., Ma Z. F. and Liao X. X. (2006). "A meta-analysis of cardiopulmonary resuscitation with and without the administration of thrombolytic agents." Resuscitation **70**(1): 31-6.

Li Y., Ristagno G., Bisera J., Tang W., Deng Q. and Weil M. H. (2008). "Electrocardiogram waveforms for monitoring effectiveness of chest compression during cardiopulmonary resuscitation." Crit Care Med **36**(1): 211-5.

Lindner K. H., Prengel A. W., Pfenninger E. G., Lindner I. M., Strohmenger H. U., Georgieff M. and Lurie K. G. (1995). "Vasopressin improves vital organ blood flow during closed-chest cardiopulmonary resuscitation in pigs." Circulation **91**(1): 215-221.

Loeckinger A., Kleinsasser A., Wenzel V., Mair V., Keller C., Kolbitsch C., Recheis W., Schuster A. and Lindner K. H. (2002). "Pulmonary gas exchange after cardiopulmonary resuscitation with either vasopressin or epinephrine." Crit Care Med **30**(9): 2059-2062.

Lund I. and Skulberg A. (1976). "Cardiopulmonary resuscitation by lay people." Lancet **2** (7988): 702-4.

Lurie K. G., Zielinski T., McKnite S., Aufderheide T. and Voelckel W. (2002). "Use of an inspiratory impedance valve improves neurologically intact survival in a porcine model of ventricular fibrillation." Circulation **105**(1): 124-9.

Ma M. H., Hwang J. J., Lai L. P., Wang S. M., Huang G. T., Shyu K. G., Ko Y. L., Lin J. L., Chen W. J. and Hsu K. L. (1995). "Transesophageal echocardiographic assessment of mitral valve position and pulmonary venous flow during cardiopulmonary resuscitation in humans." Circulation **92**(4): 854-61.

Maass D. (1892). "Die methode der wiederbelebung bei herztod nach chloroformeinathmung." Ber Klin Wschr **12**: 265.

Maron B. J., Epstein S. E. and Roberts W. C. (1983). "Hypertrophic cardiomyopathy: a common cause of sudden death in the young competitive athlete." Eur Heart J **4 Suppl F**: 135-44.

McKay D. G., Latour J. G. and Parrish M. H. (1970). "Activation of Hageman factor by alpha-adrenergic stimulation." Thromb.Diath.Haemorrh. **23**(3): 417-422.

Michael J. R., Guerci A. D., Koehler R. C., Shi A. Y., Tsitlik J., Chandra N., Niedermeyer E., Rogers M. C., Traystman R. J. and Weisfeldt M. L. (1984). "Mechanisms by which epinephrine augments cerebral and myocardial perfusion during cardiopulmonary resuscitation in dogs." Circulation **69**(4): 822-835.

Mills D. C. and Roberts G. C. (1967). "Effects of adrenaline on human blood platelets." J Physiol **193**(2): 443-53.

Mortberg E., Cumming P., Wiklund L., Wall A. and Rubertsson S. (2007). "A PET study of regional cerebral blood flow after experimental cardiopulmonary resuscitation." Resuscitation **75**(1): 98-104.

Mosher P., Ross J., Mcfate P. A. and Shaw R. F. (1964). "Control of Coronary Blood Flow by an Autoregulatory Mechanism." Circ Res **14**(3): 250.

Myerburg R. J., Fenster J., Velez M., Rosenberg D., Lai S., Kurlansky P., Newton S., Knox M. and Castellanos A. (2002). "Impact of Community-Wide Police Car Deployment of Automated External Defibrillators on Survival From Out-of-Hospital Cardiac Arrest." Circulation **106**(9): 1058-1064.

Neurauter A., Eftestol T., Kramer-Johansen J., Abella B. S., Sunde K., Wenzel V., Lindner K. H., Eilevstjonn J., Myklebust H., Steen P. A. and Strohmenger H. U. (2007). "Prediction of countershock success using single features from multiple ventricular fibrillation frequency bands and feature combinations using neural networks." Resuscitation **73**(2): 253-263.

Nichol G. and Baker D. (2007). The epidemiology of sudden death. Cardiac Arrest: The Science and Practice of Resuscitation Medicine. N. A. Paradis, H. R. Halperin, K. B. Kern, V. Wenzel and D. Chamberlain. Cambridge, Cambridge University Press**:** 26-48.

Nichol G., Stiell I. G., Laupacis A., Pham B., De Maio V. J. and Wells G. A. (1999). "A cumulative meta-analysis of the effectiveness of defibrillator-capable emergency medical services for victims of out-of-hospital cardiac arrest." Ann Emerg Med **34**(4 Pt 1): 517-25.

Nichol G., Thomas E., Callaway C. W., Hedges J., Powell J. L., Aufderheide T. P., Rea T., Lowe R., Brown T., Dreyer J., Davis D., Idris A. and Stiell I. (2008). "Regional variation in out-of-hospital cardiac arrest incidence and outcome." JAMA **300**(12): 1423-31.

Niemann J., Rosborough J., Hausknecht M., Garner D. and Criley J. (1981). "Pressure-synchronized cineangiography during experimental cardiopulmonary resuscitation." Circulation **64**(5): 985.

Niemann J. T., Haynes K. S., Garner D., Rennie C. J., 3rd, Jagels G. and Stormo O. (1986). "Postcountershock pulseless rhythms: response to CPR, artificial cardiac pacing, and adrenergic agonists." Ann Emerg Med **15**(2): 112-20.

Noc M., Weil M. H., Tang W., Sun S., Pernat A. and Bisera J. (1999). "Electrocardiographic prediction of the success of cardiac resuscitation." Crit Care Med **27**(4): 708-714.

Olasveengen T. M., Eftestol T., Gundersen K., Wik L. and Sunde K. (2009). "Acute ischemic heart disease alters ventricular fibrillation waveform characteristics in out-of hospital cardiac arrest." Resuscitation **80**(4): 412-7.

Olasveengen T. M., Sunde K., Thowsen J. and Steen P. A. (2008). "Prospective randomized controlled trial on the effect of intravenous drug administration on survival to hospital discharge after out-of-hospital cardiac arrest." Circulation **118**(18 supplement): S1447.

Olasveengen T. M., Vik E., Kuzovlev A. and Sunde K. (2009). "Effect of implementation of new resuscitation guidelines on quality of cardiopulmonary resuscitation and survival." Resuscitation **80**(4): 407-11.

Olasveengen T. M., Wik L., Kramer-Johansen J., Sunde K., Pytte M. and Steen P. A. (2007). "Is CPR quality improving? A retrospective study of out-of-hospital cardiac arrest." Resuscitation **75**(2): 260-6.

Olasveengen T. M., Wik L. and Steen P. A. (2008). "Standard basic life support vs. continuous chest compressions only in out-of-hospital cardiac arrest." Acta Anaesthesiol Scand **52**(7): 914-9.

Ornato J. P. (1993). "Hemodynamic monitoring during CPR." Ann Emerg Med **22**(2 Pt 2): 289-95.

Page R. L., Joglar J. A., Kowal R. C., Zagrodzky J. D., Nelson L. L., Ramaswamy K., Barbera S. J., Hamdan M. H. and McKenas D. K. (2000). "Use of automated external defibrillators by a U.S. airline." The New England Journal of Medicine **343**(17): 1210-1216.

Paradis N. A., Martin G. B., Rivers E. P., Goetting M. G., Appleton T. J., Feingold M. and Nowak R. M. (1990). "Coronary perfusion pressure and the return of spontaneous circulation in human cardiopulmonary resuscitation." JAMA: The Journal of the American Medical Association **263**(8): 1106-1113.

Pell J. P., Sirel J. M., Marsden A. K., Ford I., Walker N. L. and Cobbe S. M. (2003). "Presentation, management, and outcome of out of hospital cardiopulmonary arrest: comparison by underlying aetiology." Heart **89**(8): 839-42.

Prengel A. W., Lindner K. H. and Keller A. (1996). "Cerebral oxygenation during cardiopulmonary resuscitation with epinephrine and vasopressin in pigs." Stroke **27**(7): 1241-8.

Ravanat C., Freund M., Dol F., Cadroy Y., Roussi J., Incardona F., Maffrand J. P., Boneu B., Drouet L. and Legrand C. (1995). "Cross-reactivity of human molecular markers for detection of prethrombotic states in various animal species." Blood Coagul.Fibrinolysis **6** (5): 446-455.

Rea T. D., Helbock M., Perry S., Garcia M., Cloyd D., Becker L. and Eisenberg M. (2006). "Increasing Use of Cardiopulmonary Resuscitation During Out-of-Hospital Ventricular Fibrillation Arrest: Survival Implications of Guideline Changes." Circulation **114**(25): 2760-2765.

Rea T. D., Shah S., Kudenchuk P. J., Copass M. K. and Cobb L. A. (2005). "Automated External Defibrillators: To What Extent Does the Algorithm Delay CPR?" Annals of Emergency Medicine **46**(2): 132-141.

Redberg R. F., Tucker K. J., Cohen T. J., Dutton J. P., Callaham M. L. and Schiller N. B. (1993). "Physiology of blood flow during cardiopulmonary resuscitation. A transesophageal echocardiographic study." Circulation **88**(2): 534-42.

Refsum H. E., Opdahl H. and Leraand S. (1997). "Effect of extreme metabolic acidosis on oxygen delivery capacity of the blood--an in vitro investigation of changes in the oxyhemoglobin dissociation curve in blood with pH values of approximately 6.30." Crit Care Med **25**(9): 1497-1501.

Reinier K., Stecker E. C., Vickers C., Gunson K., Jui J. and Chugh S. S. (2006). "Incidence of sudden cardiac arrest is higher in areas of low socioeconomic status: a prospective two year study in a large United States community." Resuscitation **70**(2): 186-92.

Ristagno G., Tang W., Huang L., Fymat A., Chang Y. T., Sun S., Castillo C. and Weil M. H. (2009). "Epinephrine reduces cerebral perfusion during cardiopulmonary resuscitation." Crit Care Med **37**(4): 1408-15.

Robicsek F. and Littmann L. (1983). "The first reported case of external heart massage (János Balassa)." Clinical cardiology **6**(11): 569, 571.

Safar P. (1958). "Ventilatory efficacy of mouth-to-mouth artificial respiration; airway obstruction during manual and mouth-to-mouth artificial respiration." Journal of the American Medical Association **167**(3): 335-41.

Safar P. (1976). "Amelioration of brain damage after 12 minutes' cardiac arrest in dogs." Archives of neurology **33**(2): 91-95.

Sanders A. B., Kern K. B., Berg R. A., Hilwig R. W., Heidenrich J. and Ewy G. A. (2002). "Survival and neurologic outcome after cardiopulmonary resuscitation with four different chest compression-ventilation ratios." Annals of emergency medicine **40**(6): 553-62.

Sato Y., Weil M. H., Sun S., Tang W., Xie J., Noc M. and Bisera J. (1997). "Adverse effects of interrupting precordial compression during cardiopulmonary resuscitation." Crit Care Med **25**(5): 733-736.

Sayre M., Berg R. A., Cave D. M., Page R. L., Potts J. and White R. D. (2008). "Hands-Only (Compression-Only) Cardiopulmonary Resuscitation: A Call to Action for Bystander Response to Adults Who Experience Out-of-Hospital Sudden Cardiac Arrest: A Science Advisory for the Public From the American Heart Association Emergency Cardiovascular Care Committee." Circulation **117**(16): 2162.

Schleien C. L., Koehler R. C., Shaffner D. H. and Traystman R. J. (1990). "Blood-brain barrier disruption following CPR in piglets." Acta Neurochir Suppl (Wien) **51**: 213-5.

Sinha S. K., Moss A. J. and Calkins G. (2007). The etiology of sudden death. Cardiac Arrest: The Science and Practice of Resuscitation Medicine N. A. Paradis, H. R. Halperin, K. B. Kern, V. Wenzel and D. Chamberlain. Cambridge, Cambridge University Press**:** 229-235.

Smith B. S. and Gandhi P. J. (2001). "Pharmacokinetics and pharmacodynamics of low-molecular-weight heparins and glycoprotein IIb/IIIa receptor antagonists in renal failure." J Thromb.Thrombolysis. **11**(1): 39-48.

Snyder D. and Morgan C. (2004). "Wide variation in cardiopulmonary resuscitation interruption intervals among commercially available automated external defibrillators may affect survival despite high defibrillation efficacy." Crit Care Med **32**(9 Suppl): S421-S424.

SOS-KANTO (2007). "Cardiopulmonary resuscitation by bystanders with chest compression only (SOS-KANTO): an observational study." Lancet **369**(9565): 920-6.

Steen S., Liao Q., Pierre L., Paskevicius A. and Sjoberg T. (2003). "The critical importance of minimal delay between chest compressions and subsequent defibrillation: a haemodynamic explanation." Resuscitation **58**(3): 249-58.

Stiell I. G., Wells G. A., Field B., Spaite D. W., Nesbitt L. P., De Maio V. J., Nichol G., Cousineau D., Blackburn J., Munkley D., Luinstra-Toohey L., Campeau T., Dagnone E., Lyver M. and Group O. P. A. L. S. S. (2004). "Advanced cardiac life support in out-of-hospital cardiac arrest." N Engl J Med **351**(7): 647-56.

Stults K. R., Brown D. D. and Kerber R. E. (1986). "Efficacy of an automated external defibrillator in the management of out-of-hospital cardiac arrest: validation of the

diagnostic algorithm and initial clinical experience in a rural environment." Circulation **73**(4): 701-709.

Sunde K., Eftestøl T., Askenberg C. and Steen P. A. (1999). "Quality assessment of defribrillation and advanced life support using data from the medical control module of the defibrillator." Resuscitation **41**(3): 237-47.

Sunde K., Pytte M., Jacobsen D., Mangschau A., Jensen L. P., Smedsrud C., Draegni T. and Steen P. A. (2007). "Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest." Resuscitation **73**(1): 29-39.

Sunde K., Wik L., Naess P., Grund F., Nicolaysen G. and Steen P. A. (1998). "Improved haemodynamics with increased compression-decompression rates during ACD-CPR in pigs." Resuscitation **39**(3): 197-205.

Sunde K., Wik L., Naess P. A., Ilebekk A., Nicolaysen G. and Steen P. A. (1998). "Effect of different compression--decompression cycles on haemodynamics during ACD-CPR in pigs." Resuscitation **36**(2): 123-31.

Tang W., Weil M. H., Gazmuri R. J., Sun S., Duggal C. and Bisera J. (1991). "Pulmonary ventilation/perfusion defects induced by epinephrine during cardiopulmonary resuscitation." Circulation **84**(5): 2101-7.

Tang W., Weil M. H., Sun S., Noc M., Yang L. and Gazmuri R. J. (1995). "Epinephrine increases the severity of postresuscitation myocardial dysfunction." Circulation **92**(10): 3089-93.

Taw R. L. (1991). "Dr. Friedrich Maass: 100th anniversary of "new" CPR." Clinical cardiology **14**(12): 1000-2.

Valenzuela T. D., Kern K. B., Clark L. L., Berg R. A., Berg M. D., Berg D. D., Hilwig R. W., Otto C. W., Newburn D. and Ewy G. A. (2005). "Interruptions of Chest Compressions During Emergency Medical Systems Resuscitation." Circulation **112**: 1259-1265.

Valenzuela T. D., Roe D. J., Nichol G., Clark L. L., Spaite D. W. and Hardman R. G. (2000). "Outcomes of Rapid Defibrillation by Security Officers after Cardiac Arrest in Casinos." The New England Journal of Medicine **343**(17): 1206-1209.

van Alem A. P., Vrenken R. H., de Vos R., Tijssen J. G. and Koster R. W. (2003). "Use of automated external defibrillator by first responders in out of hospital cardiac arrest: prospective controlled trial." BMJ **327**(7427): 1312.

Voelckel W. G., Lurie K. G., McKnite S., Zielinski T., Lindstrom P., Peterson C., Wenzel V., Lindner K. H. and Benditt D. (2002). "Effects of epinephrine and vasopressin in a piglet model of prolonged ventricular fibrillation and cardiopulmonary resuscitation." Crit Care Med **30**(5): 957-962.

Weaver W. D., Cobb L. A., Dennis D., Ray R., Hallstrom A. P. and Copass M. K. (1985). "Amplitude of ventricular fibrillation waveform and outcome after cardiac arrest." Ann Intern Med **102**(1): 53-5.

Weaver W. D., Cobb L. A., Hallstrom A. P., Copass M. K., Ray R., Emery M. and Fahrenbruch C. (1986). "Considerations for improving survival from out-of-hospital cardiac arrest." Annals of emergency medicine **15**(10): 1181-6.

Weaver W. D., Hill D., Fahrenbruch C. E., Copass M. K., Martin J. S., Cobb L. A. and Hallstrom A. P. (1988). "Use of the automatic external defibrillator in the management of out-of-hospital cardiac arrest." The New England Journal of Medicine **319**(11): 661-666.

Weil M. H., Rackow E. C., Trevino R., Grundler W., Falk J. L. and Griffel M. I. (1986). "Difference in acid-base state between venous and arterial blood during cardiopulmonary resuscitation." N Engl J Med **315**(3): 153-6.

Weil-Malherbe H., Axelrod J. and Tomchick R. (1959). "Blood-brain barrier for adrenaline." Science **129**(3357): 1226-7.

Weisfeldt M. L. and Becker L. B. (2002). "Resuscitation after cardiac arrest: a 3-phase time-sensitive model." JAMA **288**(23): 3035-8.

Weitz J. I. (1997). "Low-molecular-weight heparins." The New England Journal of Medicine **337**(10): 688-698.

Wenzel V., Krismer A. C., Arntz H. R., Sitter H., Stadlbauer K. H. and Lindner K. H. (2004). "A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation." N.Engl.J.Med. **350**(2): 105-113.

Wenzel V., Lindner K. H., Krismer A. C., Miller E. A., Voelckel W. G. and Lingnau W. (1999). "Repeated administration of vasopressin but not epinephrine maintains coronary perfusion pressure after early and late administration during prolonged cardiopulmonary resuscitation in pigs." Circulation **99**(10): 1379-1384.

Wenzel V., Lindner K. H., Krismer A. C., Voelckel W. G., Schocke M. F., Hund W., Witkiewicz M., Miller E. A., Klima G. u., Wissel J. o., Lingnau W. and Aichner F. T. (2000). "Survival with full neurologic recovery and no cerebral pathology after

prolonged cardiopulmonary resuscitation with vasopressin in pigs." J Am Coll Cardiol **35** (2): 527.

Wenzel V., Lindner K. H., Prengel A. W., Maier C., Voelckel W., Lurie K. G. and Strohmenger H. U. (1999). "Vasopressin improves vital organ blood flow after prolonged cardiac arrest with postcountershock pulseless electrical activity in pigs." Crit Care Med **27**(3): 486-492.

Werner J., Greene H., Janko C. and Cobb L. (1981). "Visualization of cardiac valve motion in man during external chest compression using two-dimensional echocardiography. Implications regarding the mechanism of blood flow." Circulation **63**(6): 1417.

White R. D., Asplin B. R., Bugliosi T. F. and Hankins D. G. (1996). "High discharge survival rate after out-of-hospital ventricular fibrillation with rapid defibrillation by police and paramedics." Ann Emerg Med **28**(5): 480-5.

Wik L., Hansen T. B., Fylling F., Steen T., Vaagenes P., Auestad B. H. and Steen P. A. (2003). "Delaying defibrillation to give basic cardiopulmonary resuscitation to patients with out-of-hospital ventricular fibrillation: a randomized trial." JAMA **289**(11): 1389-1395.

Wik L., Kramer-Johansen J., Myklebust H., Sorebo H., Svensson L., Fellows B. and Steen P. A. (2005). "Quality of Cardiopulmonary Resuscitation During Out-of-Hospital Cardiac Arrest." JAMA **293**(3): 299-304.

Wik L., Steen P. A. and Bircher N. G. (1994). "Quality of bystander cardiopulmonary resuscitation influences outcome after prehospital cardiac arrest." Resuscitation **28**(3): 195-203.

Winkler M., Mauritz W., Hackl W., Gilly H., Weindlmayr-Goettel M., Steinbereithner K. and Schindler I. (1998). "Effects of half the tidal volume during cardiopulmonary resuscitation on acid-base balance and haemodynamics in pigs." Eur J Emerg Med **5**(2): 201-206.

Xie J., Weil M. H., Sun S., Tang W., Sato Y., Jin X. and Bisera J. (1997). "High-energy defibrillation increases the severity of postresuscitation myocardial dysfunction." Circulation **96**(2): 683-688.

Xie J., Weil M. H., Sun S., Yu T. and Tang W. (2004). "Spontaneous gasping generates cardiac output during cardiac arrest." Crit Care Med **32**(1): 238-40.

Yannopoulos D., Aufderheide T. P., Gabrielli A., Beiser D. G., McKnite S. H., Pirrallo R. G., Wigginton J., Becker L., Hoek T. V., Tang W., Nadkarni V. M., Klein J. P., Idris A. H. and

Lurie K. G. (2006). "Clinical and hemodynamic comparison of 15:2 and 30:2 compression-to-ventilation ratios for cardiopulmonary resuscitation*." Crit Care Med.

Yu T., Weil M. H., Tang W., Sun S., Klouche K., Povoas H. and Bisera J. (2002). "Adverse Outcomes of Interrupted Precordial Compression During Automated Defibrillation." Circulation **106**(3): 368-372.

Zhang Z. G., Zhang Q. Z., Cheng Y. N., Ji S. L. and Du G. H. (2007). "Antagonistic effects of ultra-low-molecular-weight heparin against cerebral ischemia/reperfusion injury in rats." Pharmacol Res **56**(4): 350-5.

Zoll P. M., Linenthal A. J., Gibson W., Paul M. H. and Norman L. R. (1956). "Termination of ventricular fibrillation in man by externally applied electric countershock." N Engl J Med **254**(16): 727-32.

12. Reprint of papers I-IV

I

This article is removed.

II

This article is removed.

III

This article is removed.

IV

This article is removed.