Clinical and experimental insights into the use of mechanical chest compressions during prolonged resuscitation in the coronary catheterization laboratory

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Title and subtitle: Clinical and experimental insights into the use of mechanical chest compressions during prolonged resuscitation in the coronary catheterization laboratory

INTRODUCTION. Prolonged cardiopulmonary resuscitation (CPR) with manual chest compressions (CC) during simultaneous percutaneous coronary intervention (PCI) is exceedingly difficult, with high mortality rates. The use of a mechanical CC (MCC) device can overcome the ordeal of manual CC. The aims of this thesis were to investigate the impact of the introduction of the LUCAS™ MCC device in the cath-lab (Papers I and II); to develop a structured approach in advanced CPR during simultaneous PCI (Paper III); to study myocardial perfusion and blood flow during MCC with and without EPI (Papers IV and V).

MATERIAL and METHODS. A retrospective analysis (5 years) and a prospective follow up study (4 years) with patients treated with MCC during simultaneous PCI were performed. Circumstances leading to the cardiac arrest, and patient and PCI outcomes were investigated (Papers I and II). A structured physiology-guided CPR approach during simultaneous PCI was developed (Paper III). In both animal studies (Papers IV and V) circulation was maintained with MCC during ventricular fibrillation. Coronary blood flow (APV) and coronary perfusion pressure (CPP) were analysed (Papers IV and V), with the addition of amplitude spectrum area (AMSA) in Paper V. The animals in Paper V were randomised to four injections of EPI or saline (control) during the MCC period.

RESULTS. Forty-three patients were included in Paper I and 32 patients in Paper II. Twenty-five percent were discharged from hospital in good neurological condition in each study. Seventy-six percent (Paper I) and 81% (Paper II) were successfully treated with PCI. In Paper III, the development of a structured physiology-guided CPR approach in the cath-lab led to better CPR teamwork during the CPR effort. Coronary artery APV was good throughout the MCC period with a good correlation to CPP (Paper IV). In Paper V, epinephrine significantly increased CPP in 3/4 injections; APV was increased only after the first injection, and no increase was seen in AMSA.

CONCLUSIONS. The use of MCC during prolonged CPR has been shown to be feasible, safe, with good PCI results, and can save lives. Mechanical chest compressions can maintain normal coronary blood flow in the experimental laboratory. Epinephrine decreases myocardial circulation despite increased CPP.

Key words: Cardiac arrest, mechanical chest compressions, PCI, survival, coronary artery blood flow, epinephrine

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Clinical and experimental insights into the use of mechanical chest compressions during prolonged resuscitation in the coronary catheterization laboratory

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To my wife Sophia, our son Christopher, my children Hannah and Max

Contents

Abstract

INTRODUCTION. Cardiac arrest (CA) in the coronary catheterization laboratory (cath-lab) is not uncommon and in most cases is solved with defibrillation or with a shorter period of chest compressions (CC). However, prolonged, high quality cardiopulmonary resuscitation (CPR) with manual CC during simultaneous percutaneous coronary intervention (PCI) is exceedingly difficult to perform and mortality rates are high. In 2003 the LUCAS™ mechanical CC (MCC) device was introduced and was brought to the cath-lab. Vital parameters are routinely monitored in the cath-lab. However, in CPR efforts during simultaneous PCI, little notice was taken of those vital parameters and the situations were often characterized by unstructured CPR teamwork with suboptimal CPR efforts. When CA occurred, patients' circulation was maintained with MCC during the simultaneous coronary angiogram, and it was noticed that the coronary artery blood flow was visually almost normal in several cases. On the contrary, when epinephrine (EPI) was administered according to current CPR guidelines, the angiographic visualization and the assessment of the coronary anatomy were impaired. Moreover, several human studies have showed that EPI might even be harmful. Therefore, the aims of this thesis were to investigate the impact of the introduction of the LUCAS™ MCC system in the cath-lab during simultaneous coronary/cardiac intervention (Papers I and II); to organize and optimize the advanced CPR effort during simultaneous PCI (Paper III); to study coronary artery blood flow correlated to coronary perfusion pressure (CPP) (Paper IV) and to study the impact of repeated administrations of EPI on coronary artery blood flow, CPP and bioelectrical activity, measured by amplitude spectrum area (AMSA) (Paper V).

MATERIAL and METHODS. A retrospective analysis was performed consisting of patients who suffered CA in the cath-lab at the Skåne University Hospital, Lund, Sweden, and who were in the need of prolonged CPR with MCC during simultaneous PCI between 2004 and 2008. A prospective follow up study with the same inclusion criteria was performed between 2009 and 2013. Circumstances leading to the CA, different resuscitation parameters, and patient and PCI outcomes were investigated. The survival rate six months after hospital discharge was evaluated in a mixture consisting of the survivors from Papers I and II. For comparison, a group of patients suffering CA in the cath-lab, who required prolonged CPR with manual CC, were evaluated. A detailed educational program took place, based on the experience of the retrospective analysis and ten consecutive patients in the prospective study, literature studies of vital resuscitation parameters and CPR teamwork. A structured, physiology-guided CPR team approach during simultaneous PCI was developed (Paper III). In both animal studies (Papers IV and V), VF was induced and left untreated for one

minute. Circulation was maintained with MCC for 10 (Paper IV) and 15 minutes (Paper V). Measurements of coronary blood flow in the left anterior descending coronary artery (LAD) were made at baseline and during VF with a catheter-based Doppler flow wire measuring average peak velocity (APV), and CPP was calculated over the same period (Paper IV). In the second animal study (Paper V), pigs were randomised 1:1:1 to EPI 0.02 mg/kg/dose, EPI 0.03 mg/kg/dose or saline (control). Four EPI/saline-injections were administered, and the effects on CPP, APV and AMSA were recorded. Comparisons were made between the controls and the two EPI groups, a combination of the two EPI groups, and EPI-all.

RESULTS. Forty-three patients were included in Paper I (33 patients with ST-elevation myocardial infarction (STEMI), seven non-STEMI, two planned PCI and one referred for pericardiocentesis). Seventy-six percent were successfully treated with PCI. Eleven patients (25%) were discharged from hospital in good neurological condition. In Paper II, 32 patients were included: 24 STEMI, four non-STEMI, two planned PCI, one angiogram and one intra-aortic counter pulsation balloon pump insertion. Eighty-four percent were successfully treated with PCI. Eight patients (25%) were discharged alive from hospital in good neurological condition. Survival in the merged group after six months was 84%. Ten patients were included in the group treated with manual CC, with one survivor. In Paper III, improved personnel education and the development of a structured, physiology-guided advanced CPR approach led to better teamwork with critical evaluation of vital parameters during the CPR effort. Coronary artery APV (Paper IV) was higher when circulation was maintained by MCC compared to normal circulation. There was a good correlation between APV and CPP. In Paper V, compared to the control group, maximum peak of CPP (P_{max}) after injections one and two was significantly increased in the EPI-all group; after injections two and three in the EPI 0.02 group and after injection one in the EPI 0.03 group. Coronary artery APV increased only after the first injection in both the EPI-all and the EPI 0.03 group compared to the control group. No increase of AMSA was seen after any injection of EPI. Seven out of 12 animals (58%) in each EPI group versus 10 out of 12 (83%) achieved spontaneous circulation after defibrillation.

CONCLUSIONS. The use of the LUCAS™ MCC device in the cath-lab during CPR in conjunction with cardiac /coronary intervention has proven to be feasible, safe to use, without impairment of the PCI result and can save lives. The visualized normal coronary artery blood flow seen in CA patients when circulation was maintained by MCC during a simultaneous coronary angiogram was objectively confirmed in the first animal study. Thus the coronary artery blood flow was significantly increased during MCC compared to normal circulation and the correlation between APV and CPP was good. Epinephrine, when administered according to current CPR guidelines, only increases coronary artery blood flow after the first out of four injections and did not improve AMSA despite increased CPP.

Papers

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

I.   Cardiac arrest in the catheterization laboratory: A 5-year experience of using mechanical chest compressions to facilitate PCI during prolonged resuscitation efforts. Resuscitation 2010, 81:4. 383 - 387

II. Mechanical Chest Compressions in the Coronary Catheterization Laboratory to Facilitate Coronary Intervention and Survival in Patients Requiring Prolonged Resuscitation Efforts. Manuscript. Submitted American Heart Journal

III. A Structured Approach for Treatment of Prolonged Cardiac Arrest Cases in the Coronary Catheterization Laboratory using Mechanical Chest Compressions. *Int J Cardiovasc Res 2013, 2:4.*

IV. Evaluation of Coronary Blood Flow Velocity during Cardiac Arrest with Circulation Maintained through Mechanical Chest Compressions in a Porcine Model. BMC Cardiovascular Disorders 2011, 11:73

V.   Repeated epinephrine doses during prolonged cardiopulmonary resuscitation have limited effects on myocardial blood flow: a randomized porcine study. BMC Cardiovascular Disorders 2014, 14:199

List of abbreviations

ABP	Arterial blood pressure (mmHg)
AMI	Acute myocardial infarction
AMSA	Amplitude spectrum area (mV·Hz)
APV	Average peak velocity (cm/s)
BP	Blood pressure
CA	Cardiac arrest
Cath-lab	Coronary catheterization laboratory
CC	Chest compression
CO_2	Carbon dioxide
CPC	Cerebral performance category
CPP	Coronary perfusion pressure (mmHg)
CPR	Cardiopulmonary resuscitation
CS	Cardiogenic shock
CVP	Central venous pressure (mmHg)
ECG	Electrocardiography
$ETCO_2$	End tidal carbon dioxide (kPa)
EPI	Epinephrine
kPa	Kilopascal
MCC	Mechanical chest compression
MI	Myocardial infarction
mmHg	Millimetre mercury
mmol/l	Millimol per litre
PCI	Percutaneous coronary intervention
PEA	Pulseless electrical activity
pH	Hydrogen ion activity

SctO$_2$ Cerebral oximetry (%)

SpO$_2$ Pulse wave oxygenation (%)

TIMI flow   Thrombolysis in myocardial infarction flow

VF   Ventricular fibrillation

VT   Ventricular tachycardia

Introduction

Modern treatment of coronary artery disease such as an AMI, consists primarily of mechanical restoration of the blood flow of the occluded coronary artery by PCI. Occasionally the situation is complicated by a sudden CA. Ideally the situation is solved with a short period of CC or a defibrillation with a limited interruption of the PCI. Cardiac arrest due to an AMI in the cath-lab is not uncommon, approximately 1.3% in a study from the late 1990s [1] and in overall CA during any procedure, the incidence is 0.22% [2]. According to the Swedish CPR register, the survival rate for CA victims in the cath-lab is 65% [3], but many of these CA cases are thought to be VF or pulseless VT, treated with either a single or a few defibrillation attempts or a shorter period of CC. However, when this initial CPR treatment fails, and turns in to a prolonged advanced CPR treatment with manual CC, mortality rates are high [4]. There are several contributory factors. Firstly, to perform good manual CC with the cath-lab table extended and elevated is exceedingly difficult. Secondly, the extended table causes a trampoline effect, and thirdly, the fluorescence tubes block the area for the CC provider. To perform high quality CC it is necessary to retract and lower the table and retract the fluorescence tubes and these actions interrupt the potentially lifesaving intervention. With the advent of the LUCAS™ MCC device in 2003, which performs CC according to current guidelines [5], it became possible to treat patients with refractory CA not responding to normal advanced CPR treatment, and to continue with the PCI during MCC without interruptions [6, 7]. We therefore developed a retrospective registry covering the period 1 January 2004 - 31 December 2008 to study the incidence and outcomes of prolonged CA in the cath-lab where patients needed prolonged advanced CPR using MCC during simultaneous PCI (Paper I). A prospective follow-up study (9 April 2009 – 9 April 2013) was performed to re-evaluate outcomes, six month survival and PCI results, among patients who suffered a CA in the cath-lab and needed prolonged A-CPR including MCC during simultaneous PCI (Manuscript Paper II). Initially, the CPR situation using MCC in the cath-lab during simultaneous PCI was notable for the lack of a structured approach concerning teamwork, familiarity with the cath-lab environment, knowledge of the monitoring possibilities of vital physiological parameters such as ABP, $ETCO_2$ and SpO_2 and their value for predicting ROSC. Therefore, a protocol was developed describing a physiological approach in CA situations with prolonged advanced CPR including MCC and simultaneous PCI (Paper III). When assessing flow in coronary arteries during coronary angiogram and PCI, the visual TIMI flow scale is often used, where TIMI-0 means no flow and TIMI-III flow represents normal flow [8]. During interventions in the CA patients whose circulation was maintained with MCC, it was

observed that the LUCAS™ device could perform a visual TIMI-III flow in the coronary arteries [9], (Paper I). But to translate this indirect information to actual measurements in humans with CA treated with MCC is extremely difficult. We therefore conducted an animal CA study where the relationship between coronary artery blood flow velocity was correlated to CPP during prolonged CPR with MCC (Paper IV). In advanced CPR guidelines the use of EPI has a Class IIb (level of evidence C) immediately if a non-shockable rhythm (asystole or PEA) is present and after four minutes after first defibrillation if there is a shockable rhythm (VF or pulseless VT), and thereafter every fourth minute [5, 10]. However, a CA in the cath-lab is instantaneously attended and the use of EPI according to current guidelines can be questioned. Based upon the knowledge that the LUCAS™ device produces sufficient values of CPP [11-13], (Paper IV), cerebral cortical blood flow [14] and TIMI flow [9], (Paper I) the use of EPI according to current guidelines seems redundant. Further, when EPI was administered to patients with prolonged CA in the cath-lab, there was indeed a significant peak in blood pressure but a clearly visible constriction of the coronary arteries which blurred any assessment of them. Epinephrine also impairs cardiac output measured by $ETCO_2$ [15]. Furthermore, there is evidence of a positive relationship between cumulative dose of EPI administered and a worse neurological outcome [16, 17]. Randomised out-of-hospital CA trials do not support the use of EPI in terms of increased survival at discharge from hospital [18, 19]. With this knowledge it was necessary to conduct a study where the use of guideline administered EPI in the setting of a CA in the cath-lab was evaluated.

Background

Treatment of acute myocardial infarction

An MI is typically caused by a plaque rupture in the coronary artery where a thrombus formation of platelets, red and white blood cells and fibrin causes a coronary artery occlusion which leads to an interruption of blood to the affected myocardium. Originally, treatment consisted mainly of symptomatic care with strict bed rest with careful mobilization after several weeks [20]. Later the use of fibrinolytic agents was introduced and gave the attending cardiologist an effective treatment option which dramatically reduced mortality and morbidity [21]. Despite the good results, there were still a large number of patients where the fibrinolytic result was unsuccessful.

With the development of peripheral percutaneous artery interventions in the 1960s, Dr. Andreas Gruentzig performed the first PCI on coronary arteries in conscious human patients in 1977 [22]. During the 1980s the mechanical restoration of coronary blood flow in patients with AMI using this technique was further developed by Meier

and Hartzler [23, 24] and studies showed that this technique was superior to fibrinolytic therapy [25]. The evolution of treatment with this technique took major steps forward, with increasing numbers of patients with AMI being brought to the cath-lab, when studies could show superior results even outside high expertise centres, and also when patients had to be transferred from a hospital without PCI-facilities to a PCI centre [26, 27].

Principles of PCI

An introducer sheath is inserted in either the radial or the femoral artery. A guide wire is inserted through the sheath up to the aortic valve, upon which a catheter is advanced to the ostium of the coronary artery (left or right ostium). To visualize the coronary arteries, contrast is injected though the catheter during simultaneous fluoroscopy. A thin metal wire is inserted into the artery through the catheter, passing the occlusion. A folded balloon or a stent is placed on the wire and introduced into the artery and then inflated at the site of the occlusion. In order to avoid acute thrombus formation and new cardiac events, anti-thrombotic therapy is administered prior to, during and after the intervention [28]. Normally, these interventions restore blood flow in more than 90% of patients when treated with primary PCI for an AMI [29].

Cardiogenic shock (CS)

Depending on the size of the affected area of the myocardium, typically caused by a proximal occlusion in the LAD or in the LM, the damage in the acute phase can cause a CS in five to eight per cent of patients with AMI [30] and is associated with high mortality rates which have been estimated between 60.9% and 65.4% [31, 32]. The condition is caused by decreased cardiac output, systemic perfusion and tissue hypoxia despite the presence of sufficient intravascular volume leading to the heart's inability to adequately perfuse the tissues.

Cardiac arrest

Cardiac arrest (CA)

One of the most feared complications in an AMI is the development of a CA. This can happen in the acute phase, prior to or during the intervention, as well in the later phase. A CA can also be induced by iatrogenic causes, for example wedging of the catheter in the coronary ostium, coronary artery dissection or a rupture induced by the inflation of a balloon or stent which can cause an acute pericardial tamponade. The rhythm when the CA occurs can be either pulseless VT or VF, asystole or PEA. If a CA occurs,

the most important treatment is a rapid start of effective and accurate CC to sustain circulation to the brain and heart, and to perform early defibrillation when the rhythm of the CA is VF or pulseless VT and then to treat the cause of the CA. The first known defibrillation was performed on humans in early 1948 [33] and treatment with external CC and ventilation as we know it today was first developed by Kouwenhoven and Knickerbocker in 1960 [34].

Training CPR

During CPR treatment, the outcome is not only dependent on the cause of the CA and the patient´s co-morbidity. Cohesive teamwork by the medical emergency team [35, 36], technical skills and the presence of an unequivocal team leader [35-38] are also important. But leadership practice is just as important. [39]. However, a CA situation in the cath-lab is very different from a CA in an ordinary ward. Hence it is important to practice CPR in the cath-lab, both for familiarity with the environment and for teamwork training in tandem with the cath-lab personnel. Another advantage of training in the cath-lab is the opportunity to learn the advanced technologies needed to succeed during such stressful emergent circumstances.

Quality of CPR

Current CPR guidelines presented in 2010 recommend CC at 50 - 60 mm depth with a frequency of 100 – 120 per minute. Ventilation rates are two ventilations every 30 CC cycle, and when intubated, ten inflations during continuous CC [5]. Even though the provider performs excellent CC, the quality of both depth and frequency will be reduced during extended CPR due to rescuer fatigue, and impaired circulation is a consequence [40]. Further, frequent or long-lasting pauses in manual CC are associated with a worse outcome [41-43].

Mechanical CPR

In an effort to overcome the shortcomings of reduced depth and frequency, and also in the hope of a better outcome, the development of MCC devices made its contribution in the early 1960s [44]. The LUCAS™ device (Physio-Control Inc./Jolife AB Sweden), which was introduced in 2002, performs CC and active decompressions with a compression depth of 53±2 mm at a rate of 102 CCs per minute in a 50/50 ratio (Figure 1a). In animal studies MCC with the LUCAS™ device has been proven to create higher cerebral cortical blood flow [14] and CPP compared to manual CC [11, 45]. The other commercial devices available on the market include the band-loading distribution device Autopulse (Zoll Medical, Chelmsford, WA) which came onto the market in 2004 (Figure 1b). In 2003 the Skåne Regional Council placed the LUCAS™ device in all the county's ambulances. Initially, concerns were raised about increased

injuries due to MCC [46, 47], but this has not been seen in other autopsy studies [48, 49]. A large randomised multi-centre study of out-of-hospital CA patients showed that MCC with the LUCAS™ device was as good as manual CC in terms of survival and there was no difference in injuries in either group [50]. The same result was also seen in a randomised out-of-hospital CA study with the Autopulse device in an adjusted cohort [51].
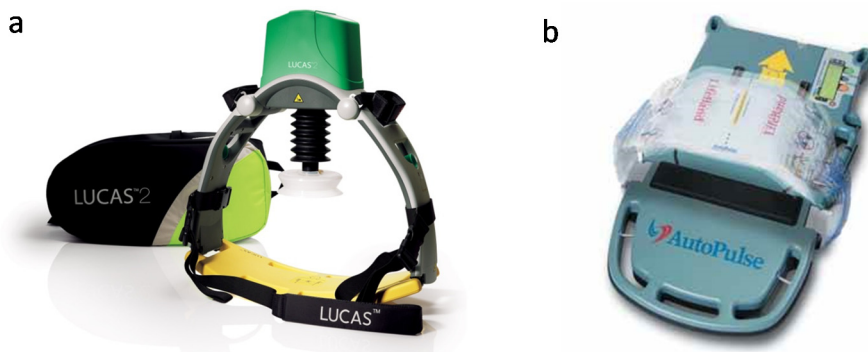
Figure 1
Left (a): The electrical driven LUCAS™ device (Jolife AB, Lund, Sweden). Right (b), Autopulse (Zoll Medical, Chelmsford, WA, USA).

Cardiac arrest in the coronary catheterization laboratory

One consequence of the movement of patients with AMI into the cath-lab for primary PCI due to new treatment results [27, 52, 53] was an increasing amount of CA in the cath-lab. Ideally the situation is solved with a defibrillation or a short period of CC. It is quite the reverse when initial CPR efforts fail and the situation turns into a prolonged CPR operation: the demands are suddenly different. To perform high quality manual CC when the patient is on the cath-lab table is exceedingly difficult. Firstly, when the table is elevated the force from the CC provider is not optimal. Secondly, when the table is fully extended the CCs will be substandard due to the trampoline effect. Thirdly, the CC provider is exposed to an unacceptably high amount of radiation and also hampers the view of the coronary arteries for the interventionist. In order to overcome these obstacles, it is necessary to lower and retract the table, at the cost of interrupting the potentially lifesaving intervention. (Figure 2)

Figure 2

shows the difficulties with manual CC on the cath-lab table. Note the retracted and lowered table, the retracted fluoroscopyfluoroscopy tubes, the angle of the arms of the chest compression provider which reduces force to the chest. (Arranged picture courtesy of Jolife AB.)

Mechanical CPR in the cath-lab

The LUCAS™ device was introduced into the cath-lab in 2004 and this led to several advantages. First of all, when a patient suffered CA during a PCI and the situation was not solved in a few minutes, the use of MCC made it possible to continue the intervention without interruption of CCs. Secondly, the MCC device delivers CCs according to current guidelines without interruptions. Thirdly, the design of the LUCAS™ device, where most parts are radio-lucent (Figure 3), allows the interventionist to continue the intervention and use the fluoroscopy angels normally used with only small adjustments (Figure 4). Several case reports and case series have proven the feasibility of this approach [6, 7, 9].

Figure 3
The LUCAS™ device put into a fluoroscopy field. Note the radio-lucent parts. The back plate is specially designed and manufactured in carbon fibre for use in cath-labs for optimal sight during fluoroscopy.

PCI during mechanical chest compressions

PCI is normally performed on a beating heart with the patient conscious. However, when the patient suffers a CA, it is essential to perform high quality CC without interruptions, ideally with the LUCAS™ device. To wire an occluded vessel during MCC is more difficult than with the patient consciousand there are minor limitations in views during MCC. To obtain exact deployment of a stent, it is often necessary to stop the MCC device for a few seconds and then start again during or immediately after balloon/stent inflation.
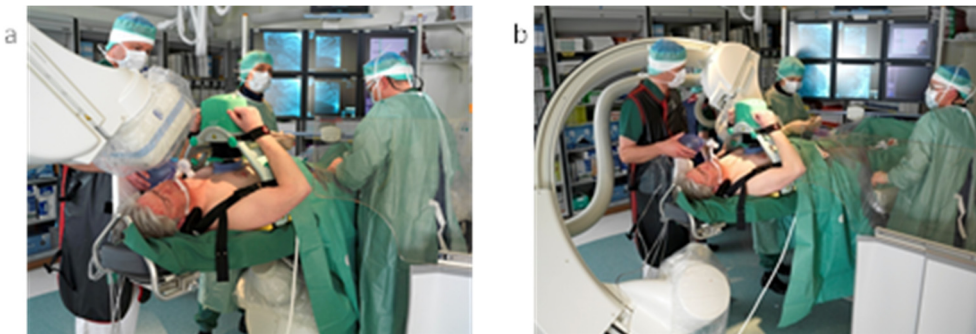
Figure 4
Left (a) shows the fluoroscopyfluoroscopy tube in left anterior cranial oblique position during MCC. Right (b) shows the fluoroscopyfluoroscopy tube in the left anterior caudal oblique position (spider view). Arranged picture, courtesy of Jolife AB.

Cerebral performance category (CPC)

The cerebral performance category scale (CPC) describes the patient's neurological status in five categories and was adopted from the Glasgow outcome coma scale [54]. This scale can be used in the assessment of neurological function in patients who have survived a CA.

CPC 1: Good cerebral performance (normal life). Able to work and lead a normal life. May have minor psychological or neurological deficits (mild dysphasia, non-incapacitating hemiparesis, or minor cranial nerve abnormalities)

CPC 2: Moderate cerebral disability (disabled but independent). Conscious. Sufficient cerebral function for part-time work in a sheltered environment or independent daily-life activities (dressing, travelling by public transportation, food preparation). May have hemiplegia seizures, ataxia, dysarthria, dysphasia or permanent mental or memory changes.

CPC 3: Severe cerebral disability. (Conscious but disabled and dependent). Conscious but dependent on others for daily support (in an institution or at home with exceptional family effort). Has at least limited cognition. This category includes a wide range of cerebral abnormalities from patients who are ambulatory but have severe memory disturbances or dementia precluding independent existence, to those who are paralyzed and can communicate only with their eyes as in the locked-in syndrome.

CPC 4: Coma vegetative state (unconscious). Unconscious, unaware of surroundings, no cognition. No verbal or psychological interaction with environment.

CPC 5: Brain dead. Certified brain dead or dead by traditional criteria.

Physiology

Arterial blood pressure (ABP)

Normal systolic ABP values range from 100 – 130 mmHg with 60 – 90 mmHg for diastolic values. In a CA situation, ABP falls dramatically. In CPR situations the level of systolic ABP depends on the CC quality, e.g. rate, depth and minimized interruptions [55]. Currently there are no recommendations of the optimal level of systolic ABP that can predict ROSC. However, in some animal studies, values of 70 – 80 mmHg in systolic ABP and diastolic values > 25 – 40 mmHg have been proposed [11, 56, 57]. Figures 5 and 6 show the intra-aortic BP in a patient who is suffering a CA. The cath-lab personnel initiate manual CC (Figure 5). The situation is not solved in due time, and thus the LUCAS™ device is deployed and started, giving a more stable compression depth and rate leading to a consistent and better ABP (Figure 6).
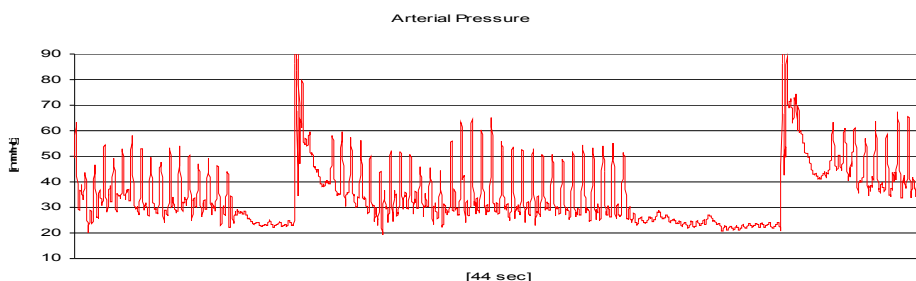
Figure 5
shows the development of intra-aortic blood pressure during 44 seconds of manual chest compressions in a patient suffering cardiac arrest on the cath-lab table. Note the narrow spikes, the inconcistency in the systolic values, and the interruptions for ventilation. mmHg = millimetre mercury.
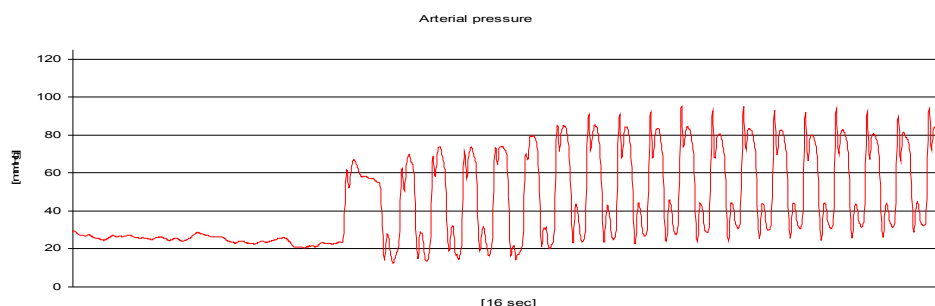
Figure 6
shows the development of intra-aortic blood pressure during 16 seconds after initiation of mechanical chest compressions in a patient suffering cardiac arrest on the cath-lab table. mmHg = millimetre mercury.

Central venous blood pressure (CVP)

In normal physiology the mean CVP measured in the right atrium is generally low, between 0 – 8 mmHg. However, in a CA situation CVP is dramatically elevated because of the no flow situation where the right atrium and right ventricle are filled with returning blood and eventually distended [58, 59].

Coronary perfusion pressure (CPP)

Coronary perfusion pressure is thought to represent the perfusion pressure in the myocardium. The calculated value is the pressure difference between the aortic end diastolic pressure and the right atrial end diastolic pressure (a – b = c) (Figure 7) [60].

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Closed chest animal CA models are frequently used in CPR studies and the methods for calculating CPP in these studies are well established [45, 61, 62]. Studies in humans and in animals have demonstrated a positive correlation between CPP and ROSC [11, 45, 62-64]. In humans the lower cut-off threshold for the possibility of attaining ROSC following a defibrillation is 15 mmHg, as shown by Paradis and co-workers [63]. Recently one study has suggested that it is the total dose of perfusion over time which may be more important than a threshold in CPP for the possibility of attaining ROSC [64].
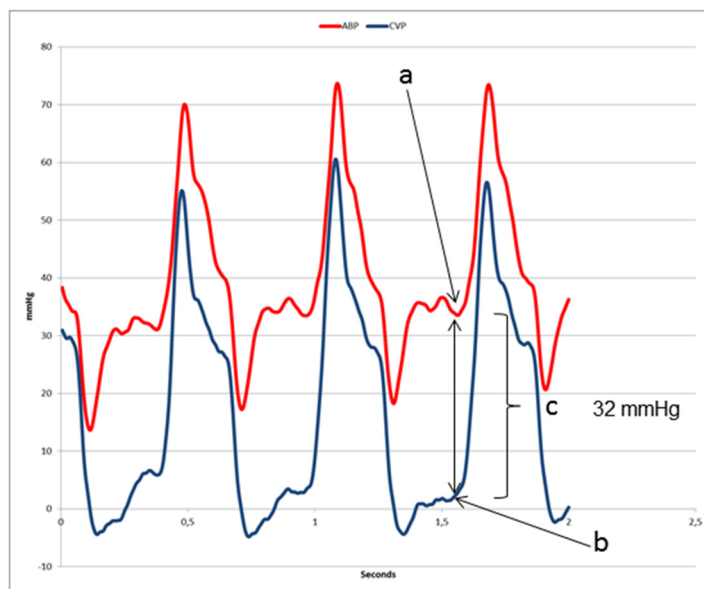
Figure 7
shows the intra-aortic blood pressure curve (red curve) and the right atrial blood pressure (blue curve) during MCC in a patient suffering CA on the cath-lab table. Arrows indicate (a) arterial and (b) right atrial end diastolic values. The clammer represents the difference between the intra-aortic diastolic value and the right atrial end diastolic value. (c) = coronary perfusion pressure (CPP), which is 32 mmHg in this example.

Blood flow velocity in the coronary arteries

Measurements of intracoronary blood flow velocity can be performed by using a Doppler flow wire. A Doppler transducer is placed at the tip of a 0.014 inch wire (Figure 8). The appearance of the Doppler curve during normal sinus rhythm and during MCC is shown in Figure 9. The preferred variable is APV which is the averaged value of the instantaneous peak velocity blood flow samples over the last two cardiac cycles in cm/s. This method has previously been used to measure coronary blood flow

before and after PCI in patients with stable circulation [65-68] or when correlating other modalities for measuring coronary blood flow [69, 70]. Figure 10 shows the principle of the placement of a Doppler wire in the LAD.
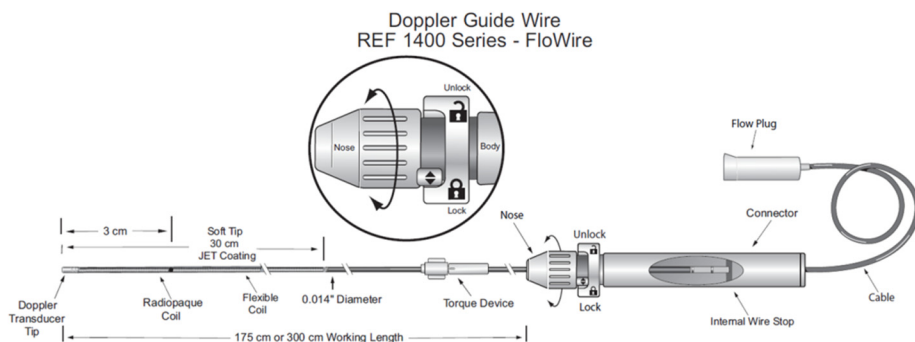
Figure 8
Volcano Doppler FloWire (Volcano Corp., Rancho Cordova, CA, USA)
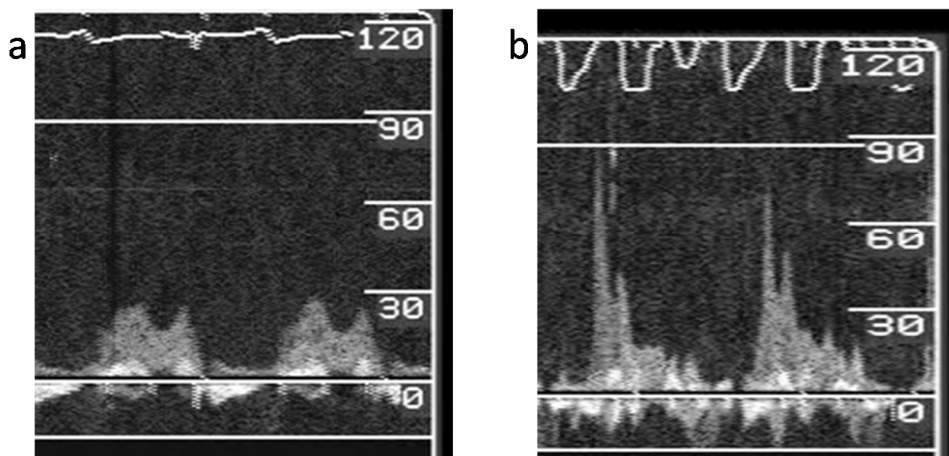
Figure 9
Left (a) Doppler flow velocity curve in the left descendent coronary artery (LAD) during sinus rhythm. Right (b) Doppler flow velocity curve in the LAD during MCC. Velocity is shown in cm/s.
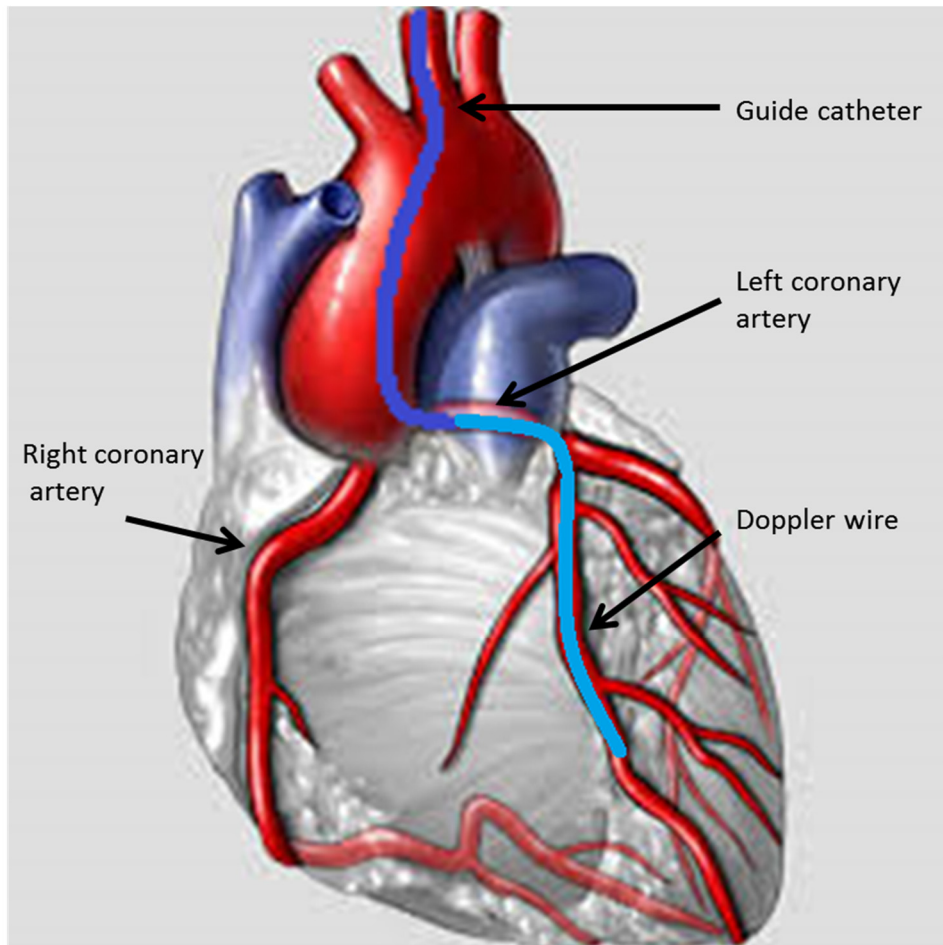
Figure 10
shows a drawing of a guiding catheter with the tip at the left coronary main artery ostium with a Doppler wire in the left anterior descending artery.

TIMI flow

Assessment of TIMI flow is basically a visual estimate of the filling of the coronary arteries with contrast media [8]. It is graded from TIMI 0 (no flow) to TIMI III, normal coronary artery flow. TIMI flow estimation is used routinely when performing a coronary angiogram or PCI. Mechanical chest compressions performed with the LUCAS™ device have been shown to produce a TIMI III flow in coronary arteries in patients who suffer a CA treated with MCC during simultaneous PCI [9, 13, 40] (Paper I). TIMI flow has also been shown to be a surrogate marker for CPP [13].

Blood gases in normal circulation and during CPR

In normal circulation, pH is between 7.37 and 7.47 and reflects the relationship between acid and base in the body. In CA victims and during CPR, pH is decreased, reflecting the anaerobic metabolism and accumulation of H^+ -ions and hence lower pH.

Cerebral oximetry (SctO$_2$)

Cerebral oximetry (SctO$_2$) measures the mix of oxyhaemoglobin and deoxyhaemoglobin in the regional space of microvasculature - arterioles, venules and capillaries in the brain [71, 72]. Absolute oximetry with fibre optic laser spectroscopy uses four different wavelengths at a depth of 2.5 cm in the brain excluding skin and bone perfusion (FORE-SIGHT, Casmed, Brandford, CT, USA) (Figures 11 and 12). The lower safe threshold for FORE-SIGHT SctO$_2$ values has been estimated at 55% and normal values range from 65 to 70% [73, 74]. Cerebral oximetry is routinely used in vascular surgery, cardiac surgery [74, 75], carotid endarterectomy [76], and in neonatal intensive care [77]. However, information on the use of SctO$_2$ during CA is limited [78-82].
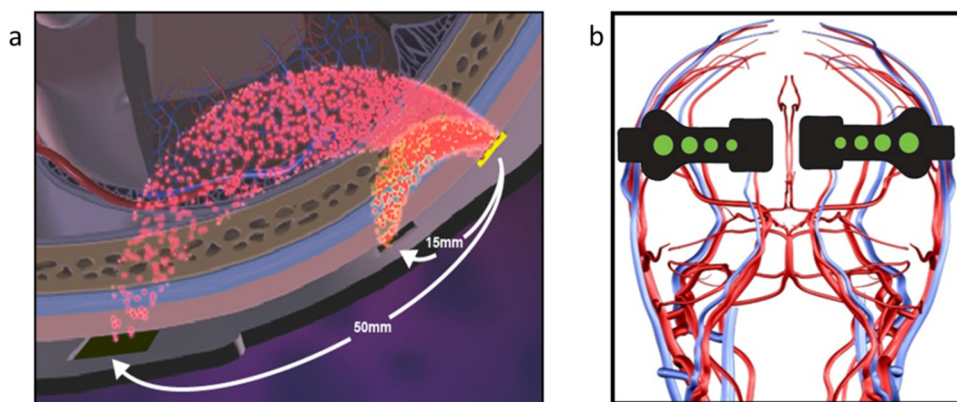
Figure 11
Left (a) Principle of penetration of Near Infrared Spectroscopy (NIRS) and the absorbtion of NIRS from skin and bone obtained at 15 mm from the light souce, and skin, bone and gray matter of the brain at 50 mm from the light source. Right (b) Principle of the placement of the NIRS electrodes on the forehead. (Used with permission from Casmed, WN, USA.)

Figure 12
The FORE-SIGHT Cerebral oximetry device (Casmed, WN, USA.) (Used with permission from Casmed, WN, USA.)

Pulsewave oxygenation (SpO$_2$)

Non-invasive SpO$_2$ provides a continuous real-time estimation of the oxygen saturation of haemoglobin within arteries proximal to the precapillary sphincters. This monitoring equipment is widely used in several wards such as coronary care units, intensive care units, emergency rooms, surgery wards, etc. (Figure 13) Normal SpO$_2$ varies between 96% and 99%. In patients with CA, SpO$_2$ is generally low and there are a limited amount of studies using SpO$_2$ in the monitoring of resuscitation attempts in CA. One study using pulse oximetry in CPR found it equivocal [83] while another found it feasible [84].

Figure 13
This figure shows the utilization of a pulse oximeter.

End tidal carbon dioxide (ETCO$_2$)

In the lungs the deoxygenated blood exchanges CO_2 as a bicarbonate ion which is the by-product of cellular metabolism. The value of exhaled CO_2 varies with the physical and chemical demands on the cellular metabolism reflecting changes in pCO_2, pH and pO_2 with the goal of normalizing these parameters. For many years, the measurement of ETCO$_2$ has been a method used by anaesthesiologists to confirm correct placement of the endotracheal tube [85]. In an animal CA study and in an animal shock study (haemorrhagic, septic and cardiogenic), ETCO$_2$ has been shown to correlate to cardiac output [86, 87]. Cardiac output correlated to ETCO$_2$ has also been studied in humans [88]. Further, in both human and animal studies, ETCO$_2$ has been shown to be a useful predictor of the possibility to obtain ROSC during CPR [89-91]. This finding also led to the ability to assess the quality of CC in terms of the value of ETCO$_2$ [92, 93]. Figure 14 shows examples on the ETCO$_2$ curve.
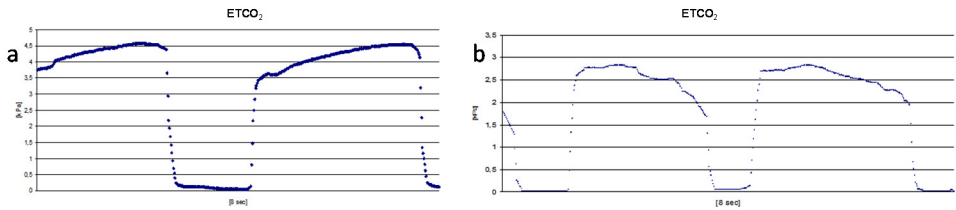
Figure 14
Left (a) End tidal carbon dioxide (ETCO$_2$) curve during normal ventilation. Right (b) ETCO$_2$ curve during mechanical chest compressions. kPa = Kilopascal.

Amplitude spectrum area (AMSA)

AMSA represents the sum of the products of the individual frequencies and the corresponding amplitude (mV·Hz) of the VF wavelets derived from the ECG (Figure 15) [94]. AMSA has proven to be a strong predictor both for successful defibrillation as well as a strong negative predictor for defibrillation failure [94, 95]. Further, one animal study has shown that there is a positive correlation between AMSA and CPP [96] which is a known predictor for the possibility of attaining ROSC following a defibrillation [63]. In humans, several studies show the usefulness of AMSA in predicting successful defibrillation attempts in VF CA victims [97-100].
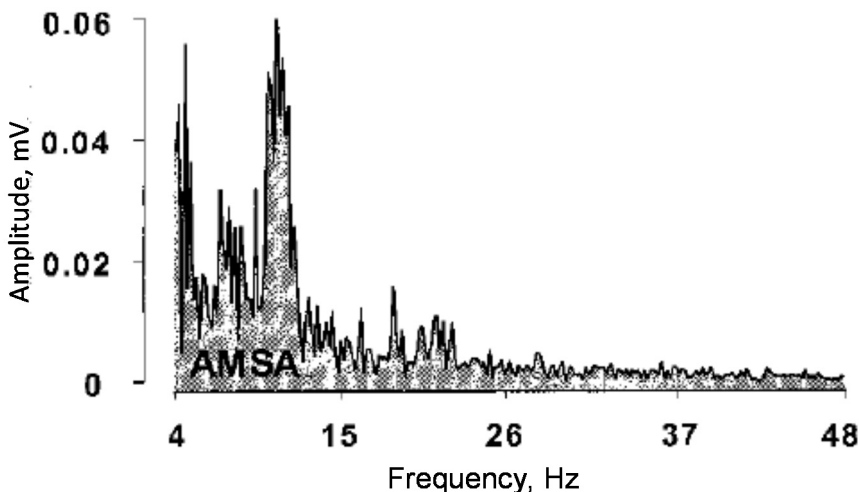
Figure 15
A representative example of amplitude frequency relationship. The area under the curve defines the amplitude spectrum area, AMSA. (Marn-Pernat et al. Crit Care Med 2001 Vol 29, No 12).

Epinephrine (EPI)

Epinephrine is a hormone that is endogenously produced by the adreno-medullary glands and other chromaffin tissue and which acts like a circulating hormone. Epinephrine stimulates α_1 and α_2, β_1 and β_2 receptors. Via its α_1-adrenergic effect on the arteries and arterioli it causes vasoconstriction in the skin, mucosa, abdominal organs and veins [101]. Further, when stimulating both α_1 and α_2 adrenoreceptors in the myocardium, predominantly α_2 adrenoreceptors in the arterioli, it causes vasoconstriction [102]. Epinephrine has been recommended in cardiac arrest CPR situations since 1962, when Redding and Pearson were able to show improved survival in dogs resuscitated from CA using EPI, [103] and ever since that, it has been established in resuscitation guidelines (Class 2b LOE A) [5, 10, 104-106]. Due to the α_1 adrenoreceptor vascular effects, EPI has been proven to increase CPP during CPR and as a result of that, it has improved the possibility of attaining ROSC in animal studies [15, 107] as well as in human studies, where more CA victims attain ROSC and are admitted to hospital [18, 19]. On the other hand, when stimulating the β adrenoreceptors, oxygen consumption rises and reduces sub-endocardial perfusion [108]. Furthermore, in animal studies EPI causes constriction in the cortical capillaries in the brain during CPR as well as in the microcirculatory blood flow in gingival mucosa [109, 110]. Epinephrine also impaired $ETCO_2$ and cardiac output in an animal study [15, 108]. Several studies have failed to show an increased survival rate to discharge from hospital in patients who received EPI during the resuscitation effort [18, 19], and in survivors an even worse neurological outcome has been observed in the EPI groups [16, 17]. In one large registry study, Warren et al. concluded that CA victims of in-hospital CA resuscitated with less frequent doses of EPI than recommended had a more favourable outcome [111]. Despite the conflicting data, the use of EPI in current resuscitation guidelines is still recommended [5].

Aim of the study

The aim of this study was to evaluate the effect of the introduction of the LUCAS™ MCC in the cath-lab in CA situations where the patients required prolonged CPR including MCC during simultaneous cardiac or coronary intervention. In 2003 the LUCAS™ device was introduced into clinical operation without any randomised trial in this particular field. It was therefore important to evaluate feasibility, safety, interventional results during simultaneous MCC, and both short and long term survival in a larger cohort than previously published [6, 7, 9]. Moreover, the CPR situation in the cath-lab was marked to a certain extent by a lack of teamwork structure, a lack of awareness of options for monitoring vital parameters, and limited knowledge of vital parameter physiological cut-off values during CPR. Hence there was a need for a structured approach in CPR situations in the cath-lab during simultaneous PCI. When CA patients had their blood circulated with MCC during a simultaneous coronary angiogram, it was noticed that there was a TIMI-III flow in the coronary arteries of several patients which has also been seen in other studies [9, 13, 40]. Moreover, when EPI was administrated to patients who suffered a CA in the cath-lab and who required prolonged CPR including MCC, it was noticed that repeated injections of EPI gave a significant but short-lasting peak in ABP, constricting coronary arteries and aggravating both the assessment of the anatomical structure and the progress of the intervention. In addition, several studies revealed that EPI could even be harmful [16-19]. Based on these observations and studies, the use of EPI according to current guidelines was questioned. Two exploratory animal CA studies were conducted to study the physiological effect of MCC on APV and CPP and the effects of EPI on CPP, APV and AMSA during MCC. As a result, five papers have been produced describing:

- a retrospective analysis including patients between 1 January 2004 and 31 December 2008 where the frequency and survival rate in patients who were referred to the cath-lab with sustained circulation and who at some point during the intervention suffered a CA, thus requiring prolonged CPR including MCC during simultaneous PCI, were studied (Paper I).

- a second study with prospectively enrolled patients with the same inclusion criteria as those above between 9 April 2009 and 9 April 2013. In this cohort, circumstances leading to CA, resuscitation parameters and outcomes were evaluated. Specifically survival rate at discharge from hospital and 6-month survival in a mixture of the survivors from Paper I and II were assessed. We also investigated duration of MCC in the CA situation (Paper II).

- proceedings, teamwork, comprehension and assessment of vital parameters in prolonged CPR with MCC during simultaneous PCI. This was based on the insights and experience obtained from the first study, an analysis of 10 consecutive patients from the prospective study, a case report on five patients suffering CA in the cath-lab where we also measured $SctO_2$ along with studies of articles investigating CPR training and leadership and the impact on survival of examining vital parameters during CPR (Paper III).

- a closed-chest animal CA model where the correlation between CPP and APV in the coronary artery during prolonged CPR with MCC was studied (Paper IV).

- a closed-chest animal CA model where the impact of guideline administered EPI during prolonged CPR with MCC on CPP, APV and AMSA was studied (Paper V).

Material and Methods

Patient selection in Papers I and II

Patients recruited for the retrospective analysis and the prospective study were treated at the cath-lab at Skåne University Hospital in Lund, which is a tertiary centre in southern Sweden that performs PCIs 24 hours a day, seven days a week, and serves a population of 1.2 million inhabitants. Patients in the retrospective registry (1 January 2004 - 31 December 2008) were localized through the local hospital CA registry and in the study covering the time period 9 April 2009 – 9 April 2013, patients were prospectively recruited. Among those who suffered a CA in the cath-lab, patients were included if immediate resuscitation efforts (prompt defibrillation/manual CCs) failed and there was consensus among the attending cardiologist, anaesthesiologist and the PCI operator that MCCs were indicated. The reason for referral to the cath-lab for the included patients were elective coronary angiogram, primary PCI in STEMI patients, sub-acute PCI in non-STEMI patients, planned PCI, insertion of an intra-aortic balloon counter pulsation pump or treatment of cardiac tamponade. In the retrospective analysis similar patients (requiring >one minute of manual CC and tracheal intubation) in which no MCC device was used in the same time span, were evaluated. For comparison, patients who suffered CA in the cath-lab and who were treated with manual CC ≥ ten minutes, between 1999 and 2003 (prior to the introduction of MCC devices in the cath-lab) were analysed using the local hospital CA registry. Inclusion criteria were the same as for those treated with MCC. In the prospective study informed consent was obtained either from survivors or from relatives.

Prolonged CPR was defined as an episode of CA necessitating a period of several minutes of manual CC, followed by the use of MCC.

All patient charts and medical files were examined in both studies. Autopsy reports were examined in the retrospective analysis. Analysis of deaths of patients who were discharged alive from hospital was found in the Swedish registry for cause of death.

The patients included in the retrospective analysis were divided into two outcome groups (Group 1: in-hospital death; Group 2: discharged from hospital alive). In the prospective study, patients were divided into four outcome groups (Group 1: whole group; Group 2: expired in the cath-lab; Group 3: discharged from the cath-lab with circulation and Group 4: discharged alive from hospital in good neurological condition).

In both studies, patient demography, indication for admission to the cath-lab, culprit lesion and cardiac rhythm at the time of the CA were assessed. In the prospective study, circulatory state at the time of arrival in the cath-lab was assessed. The predefined endpoints in both studies were mortality status on departure from the cath-lab; successful PCI, assessed by TIMI flow, or <50% residual stenosis and discharge from hospital in CPC 1 or 2 representing a good neurological outcome. The MCC time was calculated for the two groups in Paper I and for all our groups in Paper II.

In the prospective study the use of vasoactive drugs was assessed.

The six-month survival rate was analysed in a merged group that consisted of patients discharged from hospital in good neurological condition from Paper I and Paper II.

Chest compressions

In Paper I the LUCAS™ V1 MCC device (European version) was used between 1 January 2004 and 31 December 2007. Between 1 January 2008 and 31 December 2008, the LUCAS™ V2 MCC device (US version) was used. It has the same operating parameters as LUCAS™ V1 except for the decompression force, which is set to a maximum of 13 N.

In Paper II, the LUCAS™ V2 (US version), and later the electrically driven LUCAS™ 2 chest compression system (Physio-Control/Jolife AB, Lund, Sweden) was used.

Patient selection and methods in Paper III

Ten consecutive patients with prolonged CA in the cath-lab were analysed [12] together with five other patients where $SctO_2$ was added to the other vital parameters (ABP, CPP, $ETCO_2$, SpO_2) [112]. Several deficiencies in monitoring and teamwork were noticed. Four areas which needed improvement were identified from this data: (1) the understanding of the importance of teamwork and leadership within the unique circumstances of a prolonged CPR effort in the cath-lab. (2) the importance of practical simulations within the cath-lab setting. (3) an understanding of the vital physiological parameters for the successful restoration of spontaneous circulation. (4) familiarity with the advanced technology needed to succeed during such emergent and stressful circumstances. Several studies addressing teamwork [35-37], leadership [35, 39], technical skills [38], vital parameters such as ABP [11, 56, 57], CPP [11, 45, 62, 63, 96], SpO_2 [83, 84], $ETCO_2$ [89-91, 113] and $SctO_2$ [78-82, 114, 115] were studied. In addition, the importance of correct positioning over the heart during CC [116-119] and ventilation rate were brought to light [120].

Mechanical chest compressions were performed using a LUCAS™ V2 (US version) and a LUCAS™2 device. Parameters of ECG, ABP, CVP, SpO_2 and $ETCO_2$ were monitored on an IntelliVue MP90 monitoring system (Philips, Eindhoven, The Netherlands), and $SctO_2$ was monitored using the FORE-SIGHT monitoring system (CAS Medical Systems Inc., Branford, CT, US). TIMI flow in non-occluded vessels was assessed as done routinely during PCI [8]. The hemodynamic parameters were recorded every 2nd to 5th millisecond on an external PC computer using custom made software and evaluated using LabChart 7 (AD Instruments Corp., Colorado Springs, CO, US). Coronary perfusion pressure was calculated as described earlier [60].

Animal studies

Two animal studies were carried out. In both studies Swedish Landrace pigs were used. The pig has a coronary anatomy similar to humans which makes it suitable for coronary cardiac experiments [121].The ideal size of the pig is 20 – 30 kg because at this weight the size of the heart is identical to that of an adult human heart [122]. However, occasionally at this size, the foramen ovale has not been closed, which can cause unexpected results during the experiment, which in turn may lead to exclusion from the study.

Animal preparation

Methods

In Paper IV (n = 11) and Paper V (n = 36), Swedish Landrace pigs were used with a mean weight of 31 ±1.5 kg (range 28 – 31kg) in paper IV and a mean weight of 38 ±4.1 kg (range 32 – 46 kg) in paper V.

Anaesthesia

The animals in both studies were fasted over night with free access to water. In Paper IV, the animals were anaesthetized with an induction dose of intramuscular ketamine (30 mg/kg) (Ketamine 100mg/ml, Intervet, Danderyd, Sweden). Sodium thiopental (5-8 mg/kg) (Pentothal 100 mg/ml, Abbott, Stockholm, Sweden) and atropine (0.015mg/kg) were given intravenously before tracheotomy. Anaesthesia and muscular paralysis were maintained with a continuous infusion of 10 ml/h of a 0.9% saline solution containing ketamine (16 mg/ml) and pancuronium (0.6 mg/ml).

In Paper V, the animals were pre-medicated with Ketaminol 15 mg/kg (Ketamine 100mg/ml, Intervet, Danderyd, Sweden), and Rompun 0.1ml/kg (Xylazin 20 mg/ml, Bayer AG, Leverkusen, Germany), intramuscularly. The anaesthetic induction was accomplished with thiopental 12.5 mg/kg (Pentothal 100 mg/ml, Abbott, Stockholm, Sweden). The animals were orally intubated with cuffed endotracheal tubes. For maintenance of anaesthesia a slow infusion of 1μg/ml fentanyl (Fentanyl, Pharmalink AB, Stockholm, Sweden) in buffered glucose (25 mg/ml) was started at a rate of 2 ml/min and adjusted as needed. Meprobamat (Mebumal DAK, Copenhagen, Denmark) and thiopental was titrated if needed in small bolus doses.

Ventilator settings

In the first animal study (Paper IV), a Boussignac endotracheal tube, 7 mm internal diameter (Laboratoires Pharmaceutiques VYGON, Ecouen, France) was used as an ordinary endotracheal tube for ventilation. After tracheotomy it was connected to a Servo Ventilator 300 (Siemens, Solna, Sweden) using pressure-regulated (max 30 cm H_2O = 23 mmHg) and volume-controlled intermittent positive pressure ventilation (IPPV). Normoventilation $ETCO_2$ (around 5.3 kPa = 40 mmHg) was obtained by using a tidal volume of 8 ml/kg body weight, 20 breaths/min, a PEEP of 5 cm H_2O (6 mmHg) and a FiO_2 of 0.21. End tidal carbon dioxide was measured by CO_2SMO Plus Respiratory Profile Monitor Model 8100 (Novametrix Medical Systems Inc., Wallingsford, CT, USA) with a CO_2 sensor (REF 6719) connected to the proximal end of the Boussignac tube.

In the second animal study (Paper V), the animals were orally intubated with cuffed 7 mm inner lumen endotracheal tubes. Mechanical ventilation was established with a Siemens-Elema 900B ventilator (Siemens, Solna, Sweden) in the volume-controlled mode, adjusted in order to obtain normoventilation (4.5 – 5.5 kPa). The animals were ventilated with a mixture of nitrous oxide (70%), oxygen (30%) and normal air. End tidal carbon dioxide was monitored by a Circuit $ETCO_2$ Sensor (Philips Medical Systems, Andover, MA, USA) connected to an IntelliVue MP90 monitoring system (Philips, Eindhoven, The Netherlands).

Catheterization of LAD

In both animal experiments, a 6 F introducer sheath (Boston Scientific Scimed, Maple Grove, MN, USA) was inserted using the Seldinger technique into the surgically exposed left carotid artery and a 6F JL 3.5 Wiseguide™ (Boston Scientific Scimed, Maple Grove, MN, USA) catheter was then inserted through the introducer with the tip at the ostium of the left main coronary artery. The catheter was used to place a 0.014 inch, 12 MHz pulsed Doppler flow velocity transducer (FloWire® Volcano Inc., San Diego, CA, USA) into the mid-portion of the LAD. Continuous coronary flow velocity profiles were displayed and recorded using the Doppler flow wire connected to a FloMap monitor (Cardio Metrics, Mountain View, CA, USA).

General catheterizations and monitoring

In the first animal study (Paper IV), two catheters (Secalon-T-over-needle catheter, 16G/1.70/130 mm) for monitoring the aortic pressure and CVP were introduced via direct puncture of the right carotid artery and the right jugular vein respectively, in order to avoid ligation of the artery. The tip of the arterial catheter was inserted into the thoracic aorta and the central venous catheter was placed with the tip in the right atrium. The fluid-filled catheters were connected via short tubes to pressure transducers.

A temperature probe was placed in the oesophagus and ECG was obtained by three electrodes glued to the chest. The following variables were continuously sampled (100 – 500 Hz) to a computer supplied with a data acquisition system (Testpoint, Capital Equipment Corporation, Billerica, Massachusetts, USA): body temperature, ECG, intra thoracic AP, CVP, CPP, APV, $ETCO_2$.

All radiological procedures were performed in an experimental cath-lab (GE Healthcare, Chalfont St Giles, UK).

In the second animal study (Paper V), the pigs were continuously monitored with ECG, $ETCO_2$, SpO_2 on an IntelliVue MP90 monitoring system (Philips, Eindhoven, The Netherlands). Unfractioned heparin (10 000 IU) (LEO Pharma AB, Malmoe, Sweden) was given intravenously at the start of the catheterization. A 6 Fr pigtail catheter was placed with the tip in the proximal thoracic aorta for obtaining ABP. A 9 F introducer sheath (Boston Scientific Scimed, Maple Grove, MN, USA) was inserted into the surgically exposed right jugular vein. A 7.5 F Continuous Cardiac Output Pulmonary Artery Catheter™ (Edwards Life Sciences, Irvine, CA, USA) was inserted into a pulmonary artery. Arterial blood pressure and CVP were continuously measured using separate transducers (AD Instruments Inc., Colorado Springs, CO, USA). Arterial BP, CVP and APV were digitally recorded using Chart v4.2 (AD Instruments Inc., Colorado Springs, CO, USA). The procedures were performed in an experimental cath-lab (Shimadzu Corp., Kyoto, Japan).

Induction of VF

In the first animal study (Paper IV), VF was induced with a 5-20 mA, 6 Hz and 30 V alternating current delivered to the epicardial surface via a needle electrode. In the second animal study (Paper V), VF induction was executed with a 9 V direct current battery (Duracell, Procter & Gamble, Cincinnati, OH, USA) with one pole connected to a needle inserted into the skin surface and the other pole connected to a needle which was inserted to the epicardial surface with a stimulation time of 5 – 10 seconds. Circulatory arrest was confirmed by an instant loss of ABP, flow velocity in LAD and an ECG showing VF.

CPR during the experiments

Chest compressions in both experiments were performed with the LUCAS™2 MCC device (Physio-Control Inc./Jolife AB, Sweden).

Defibrillation

Defibrillations in both animal studies were performed with a Lifepack™ 12 (Physio-Control, Redmond, WA, USA).

Blood gas analysis

Blood gas, haemoglobin and electrolytes were analysed directly after a sample had been obtained, using a blood gas analyser (ABL 505, Radiometer, Copenhagen Brönshöj, Denmark).

Experimental protocol (Paper IV)

A flow chart of the experiment is presented in Figure 16. At baseline when all parameters were stable, VF was induced, upon which ventilation was stopped. Following 60 seconds of VF, CPR was started using the LUCAS™2 and ventilation was initiated at a rate of ten manual inflations per minute. Continuous measurements of ECG, body temperature, ABP, CVP and CPP were performed. APV was documented by both a VHS recorder and by digital recording. After ten minutes of CPR the pigs were defibrillated. If ROSC was not obtained after the first defibrillation, EPI 0.01 mg/kg was given in the central venous catheter and another defibrillation attempt was made after two minutes, if VF persisted. Repeated doses of EPI and defibrillation attempts were performed as needed for a total of three times, with two-minute intervals of CC between each dose. After the third dose of EPI, CPR was continued for two minutes and then terminated. When ROSC was obtained, measurements continued for 15 minutes with a ventilation rate of 20 breaths per minute with 100% oxygen in the respirator setting described above. Blood gas was obtained at baseline and after 9 minutes of MCC.
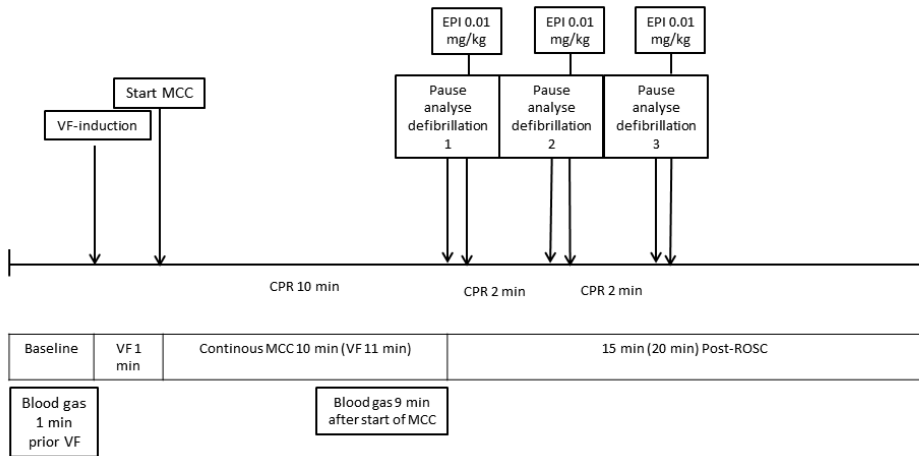
Figure 16
Experimental timeline. MCC= mechanical chest compressions. VF = ventricular fibrillation. CPR = cardiopulmonary resuscitation. EPI = epinephrine. min = minutes. ROSC = return of spontaneous circulation.

Experimental Protocol (Paper V)

A flow chart of the experiment is presented in Figure 17. When baseline was obtained, the pigs were randomised in a 1:1:1 ratio by one researcher to receive either EPI 0.02 mg/kg/dose, EPI 0.03mg/kg/dose or NaCl as a control group diluted to 10 ml. The remainder of the researchers were blinded to the randomization result. Ventricular fibrillation was induced and ventilation was stopped. After one minute of VF the LUCAS™ device was started with manual ventilation at a rate of eight to ten inflations per minute with 100% oxygen. At five, eight, 11 and 14 minutes after VF induction, an injection of EPI 0.02 mg/kg/dose or 0.03 mg/kg/dose or NaCl was administered via a cannula in a vein in the ear. The chosen time interval for administration of EPI/NaCl was according to current CPR guidelines [5]. The rationale behind a 16-minute VF period (1 minute of untreated VF followed by 15 minutes of MCC) was an attempt to reflect a CA situation in the human cath-lab with prolonged advanced CPR in connection with PCI (Paper I).
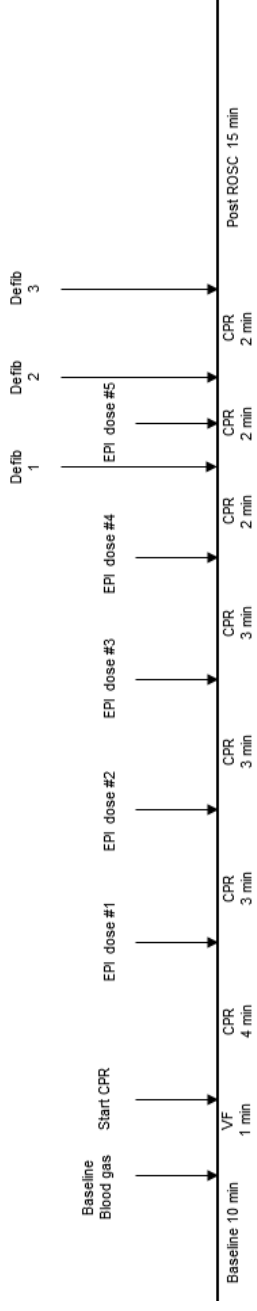
Figure 17

Experimental timeline. MCC= mechanical chest compressions. VF = ventricular fibrillation. CPR = cardiopulmonary resuscitation. EPI = epinephrine. min = minutes. ROSC = return of spontaneous circulation. Drug administration either 0.02 mg EPI/kg/dose or 0.03 mg EPI/kg/dose or NaCl , was given after 4 minutes of MCC and then every 3rd minute during the 15 minutes of MCC. Three defibrillation attempts were made if necessary.

After 16 minutes of MCC, the first defibrillation was attempted. If ROSC was not obtained, MCC was continued for two minutes and then briefly stopped in order to analyse the rhythm. After 17 minutes, a fifth dose of EPI or NaCl according to the randomization was administered. If VF persisted, a second defibrillation attempt was performed or MCC was continued if it was a non-defibrillatable rhythm. If ROSC was not obtained after the second defibrillation MCC was continued for two more minutes, followed by a short stop for rhythm analysis and then MCC was continued with defibrillation if appropriate. If the animals did not obtain ROSC after three cycles, the CPR effort was stopped. Return of spontaneous circulation was defined as a systolic BP > 60 mmHg for 15 minutes after regaining spontaneous circulation. Blood gas was obtained at baseline.

Measurements

In both animal studies maximum, mean and minimum ABP and CVP were continuously measured. In both animal studies CPP was calculated as the difference between the thoracic intra-aortic pressure and the right atrial pressure in the end-decompression phase which was defined between 0.1 and 0.05 seconds before the start of next compression [60].

In the first animal study, Doppler time periods which were visually free from noise and had a typical Doppler curve-like shape on the VHS recording tape where used for analysis of APV measurement (Figure 18). Time periods that were obviously artefacts were excluded. Arterial blood pressure, CVP and APV signals were sampled 50 times/second and the mean values were recorded every fifth second during the whole experiment, using a computer supplied with a data acquisition system (Test Point, Capital Equipment Corporation, Bilerica, MA, USA).
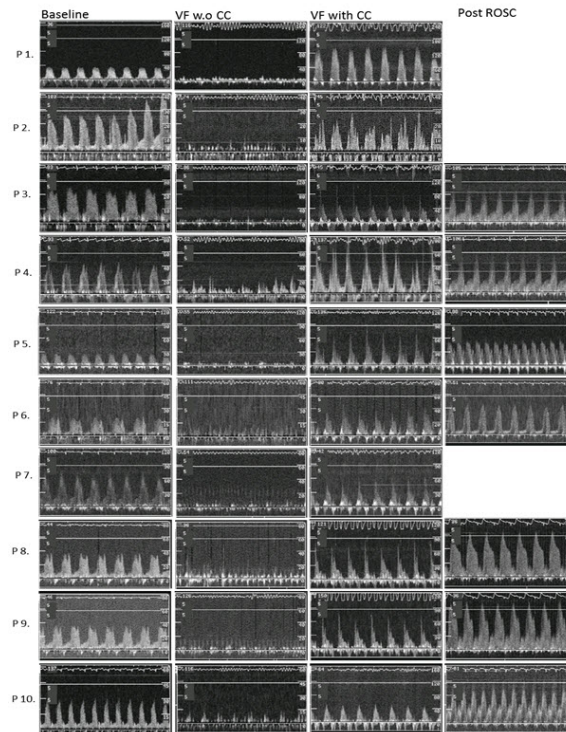
Figure 18
Doppler flow measurement from which the APV is calculated, shown for all periods of the experiments and each pig (P n), baseline sinus rhythm (Baseline), untreated VF (VF without CC), VF during chest compressions (VF with CC) and post return of spontaneous circulation (Post ROSC). Note the difference in scale on the y-axis, which is due to automatic adjustments made by the FloMap monitor.

In the second animal study, ABP and CVP were continuously measured using a sampling rate at 1000 Hz (AD Instruments Inc., Colorado Springs, CO, USA). Hemodynamic parameters were digitally recorded using Chart v4.2 (AD Instruments Inc., Colorado Springs, CO, USA). Baseline values of ABP, CVP, APV, heart rate and ETCO$_2$ were obtained as a median value of 10 seconds, at 20 and 10 seconds prior to VF. The maximum peak of CPP (P$_{max}$) was depicted at 20, 60, 120, and 180 seconds after initiation of MCC, at the time of every EPI injection, and when CPP reached the highest value after each injection. In the control group, CPP was depicted 90 seconds after each NaCl injection. Continuous coronary APV was displayed and recorded using the Doppler flow wire connected to the FloMap monitor transmitted into Chart v4.2 (AD Instruments Inc., Colorado Springs, CO, USA). The APV was analysed in visual artefact free zones concomitantly with P$_{max}$.

Analogue ECG signals were digitized and converted from a time to a frequency domain by fast Fourier transformation at a sampling rate of 250 Hz. The amplitude spectrum

area was calculated as the sum of the products of individual frequencies between eight and 48 Hz at P_{max}. The measurements were performed throughout the 16 minutes of VF as median values of every ten-second period.

Times to P_{max} were analysed in the EPI groups. Survival was defined as stable ROSC for 15 minutes after successful defibrillation and was assessed in each group.

All analyses of these parameters were performed on the three groups and on a merged group including the two EPI groups (EPI-all).

Statistical methods

In all statistical comparisons, P-values < 0.05 were considered to be significant.

1. In the retrospective analysis (Paper I), continuous data are given as mean and standard error of the mean (SEM). Categorical variables are given as numbers or percentages. No statistical comparisons were made due to the limited amount of patients.

2. In the prospective study of patients suffering CA in the cath-lab who required prolonged CPR (Paper II), continuous data are given as mean±SD, and median and range when appropriate. Categorical variables are given as numbers or percentages. For non-parametric statistics, the Mann-Whitney U-test was used for comparing age and MCC time between the outcome groups.

3. In Paper III, hemodynamic parameters, SpO_2 and $ETCO_2$ are presented as mean ±SD of different time intervals of the MCC period for each of the ten patients.

4. In the first animal study (Paper IV), all values are presented as mean ± standard deviation (SD). The Mann-Whitney U-test was used to compare unpaired independent continuous variables between baseline measurements of APV and APV during MCCs as well as for analysing differences between blood gases. To test the null-hypothesis for correlation between APV and CPP, a correlation z-test was used. Multiple continuous statistical comparisons were made between baseline APV, each two-minute period and in the blood gas analysis. We therefore used the Bonferroni correction on all p-values.

5. In the second animal study (Paper V), quantitative data are given as mean±SD. Categorical variables are given as numbers or percentages. Fischer's exact test was used to compare categorical variables. Continuous variables are presented as median, 25th and 75th percentile. The Mann-Whitney U-test was used for comparing unpaired independent continuous variables in ABP, CVP, $ETCO_2$, APV, heart rate and blood gas analyses at baseline. During the MCC period the Mann-Whitney U-test was used to compare APV, CPP and AMSA between the control group, EPI-all, EPI-0.02 mg/kg and EPI-0.03 mg/kg. The Kruskal-Wallis test was used when comparing multiple median values in time to P_{max} after each EPI administration between the different EPI groups.

Ethical considerations

In the prospective study (Paper II), the local ethics Review Board (667/2009) accepted the study. Written informed consent had to be accepted and signed, either by survivors or by relatives if the patient was diseased. In the case of patients who did not survive their CA, their relatives were contacted by telephone some weeks to some months after the patient had expired. The purpose was to inform and ask for permission to include the deceased family member. Practically all the relatives found the telephone call positive. In many of those telephone calls they felt that they had an opportunity to ask questions and get explanations, which they had possibly already received at the hospital but had forgotten or never heard due to shock. Thereafter they received the written information release form to sign and return by mail. For those who survived, the information was given primarily in the coronary care unit. Coronary artery blood flow measured with a Doppler flow wire during CPR with MCC and during the influence of EPI administered according to current CPR guidelines has not been studied further. To perform such an experiment in humans was considered unethical. Hence animal studies were the only option for these studies. The institutional Review Board for animal experimentation at Lund University, Sweden, approved the experimental protocols, M 184-06, for the study in Paper IV, and M 192-10 for the study in Paper V. The animals in both studies received humane care in compliance with *The Guide for the Care and Use of Laboratory Animals*, published by the National Institutes of Health (NIH publication 85 – 23, revised 1985) and the *European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes* (1986).

Results

Paper I

During the 5-year period of the retrospective analysis, more than 6300 PCIs were performed. Forty-three patients were included in the registry fulfilling the inclusion criteria. Patient demographics are presented in Table 1. The vast majority were admitted to the cath-lab because of an ongoing STEMI, followed by non-STEMI, elective PCI and cardiac tamponade. The majority of the patients had their culprit lesion in LM and LAD (n = 34, 81%). In most cases the presenting rhythm at the time of the CA was a non-shockable rhythm (PEA and asystole, n = 37, 86%) (Table 1). In five of the patients a myocardial rupture was revealed at the intervention. These patients died and were considered to be beyond saving from the start.

Table 1 Patient characteristics and outcomes
Background information on the 43 patients, the indication for the procedure in the cath-lab, the culprit coronary artery and the initial rhythm of the cardiac arrest. AMI: acute myocardial infarction. PCI: percutaneous coronary intervention. CABG: coronary artery by-pass grafting. STEMI: ST-elevation myocardial infarction. NSTEMI: non-ST-elevation myocardial infarction. LM: left main artery. LAD: left anterior descending artery. Cx: left circumflex artery. RCA: right coronary artery. VF: ventricular fibrillation. VT: ventricular tachycardia. PEA: pulseless electrical activity.

	n (%)	In-hospital death	Discharged alive
Patient history			
Hypertension	24 (56%)	16	8
Diabetes	11 (25.5%)	10	4
Hyperlipidaemia	15 (35%)	10	7
Smoker/ex-smoker	22 (51%)	16	3
Previous MI	12 (28%)	8	4
Previous PCI	5 (11.5%)	5	0
Previous CABG	6 (14%)	5	1
Indication for cath-lab procedure			
STEMI	33 (77%)	27	6
NSTEMI	7 (16.1%)	3	4
Elective PCI	2 (4.6%)	0	2
Tamponade	1 (2.3%)	1	0
Culprit lesion in coronary patients (n=42)			
LM	9 (21%)	6	3
LAD	25 (60%)	20	5
LCx	2 (4.7%)	0	2
RCA	6 (14.3%)	5	1
Initial rhythm at cardiac arrest (n=43)			
VF/VT	6 (14%)	2	4
PEA	28 (65%)	25	3
Asystole	9 (21%)	4	5

Thirty-five PCIs were performed on the 43 patients and of these, 31 were performed during MCC. The success rate was 76% in terms of TIMI II or III flow or <50% residual stenosis. In the remaining interventions the reasons for an unsuccessful result were mainly peripheral embolism, no reflow and complex lesions and not due to the use of MCC with the LUCAS™ device (Table 2).

Table 2. Procedural data of the 43 patients
In the cath-lab a technically successful PCI was defined as achieving a residual stenosis in the coronary artery < 50% with TIMI II or III blood flow. PCI: percutaneous coronary intervention. IABP: intra-aortic balloon counter pulsation pump. TIMI blood flow: a grading scale developed by the Thromolysis in Myocardial Infarction study group in which TIMI II or III indicates successful reperfusion.

Procedural data	N (%)	In-hospital death	Discharged alive
Angiography only	6 (15%)	5	1
PCI successful	27 (76%)	16	11
PCI unsuccessful	8 (24%)	8	0
Use of IABP	19 (43%)	9	10

The total MCC time for the whole group was mean 28 minutes, SEM±3.4 minutes (range 1 – 90 minutes). Seventeen patients were discharged from the cath-lab with circulation. Of those, 12 patients were eventually discharged from hospital, 11 of them in good neurological condition (CPC 1) (Figure 19). This represents a 25% survival rate in this patient category. The MCC treatment time in this group was mean 16.5 minutes, SEM ± 3.8 (range 1 – 50 minutes). Rib fractures were present in all the survivors and in one patient a spleen and gastric rupture arose due to user error with the MCC device. Only six autopsies were performed on the remaining 31 patients, with findings of rib fractures in all six patients, sternal fractures in five, and one patient had minor bleeding around the aortic arch without rupture.
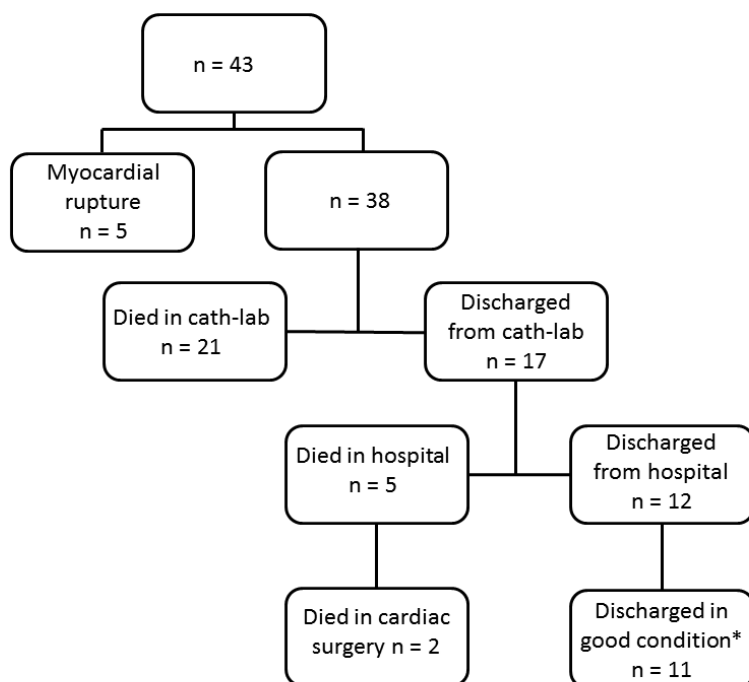
Figure 19
Flow chart illustrating the outcomes of the study patients. * Cerebral performance category 1.

Paper II

Thirty-two patients were included during the study period. For patient demographics see Table 3. Patient characteristics such as the indications for the cath-lab procedure, culprit lesion, circulatory state upon arrival in the cath-lab, and rhythm when the CA occurred, are presented in Table 4.

Table 3. Patient demographics.
Cath-lab = coronary catheterization laboratory. MI = myocardial infarction. PCI = percutaneous coronary intervention. CABG = coronary artery by-pass grafting.

	All patients	Expired Cath-lab	Discharged Cath-lab	Discharged Hospital
	n=32 (%)	17 (53)	15 (47)	8 (25)
Patient History				
Age	70.9±12.9	73±10	68.3±15.2	68.1±18.8
Gender (male)	20 (63%)	11(65)	9 (60)	4 (50)
Hypertension	18 (56%)	9 (53)	9 (60)	7 (86)
Diabetes	8 (25%)	6 (35)	2 (13)	2 (25)
Hyperlipidaemia	9 (28 %)	7 (41)	2 (13)	2 (25)
Smoker/Ex-smoker	14 (44%)	7 (41)	7 (47)	4 (50)
Previous MI	9 (28%)	4 (24)	5 (33)	4 (50)
Previous PCI	3 (9%)	1 (6)	2 (13)	2 (25)
Previous CABG	4 (13%)	3 (18)	1 (7)	1 (13)

In one specific patient, the reason for referral for the intra-aortic balloon counter pulsation insertion was therapy-resistant VT with CS. In the patients referred for planned PCI and non-STEMI, complications such as, for example, thrombus formation, vessel rupture and dissection, caused the CA. One of the patients with non-STEMI was in CS at the time of arrival in the cath-lab. The patient, who was referred for an elective pre-operative coronary angiogram for surgery on the aortic valve, deteriorated into PEA due to aortic stenosis and reduced systolic left ventricular function.

Seventeen patients expired in the cath-lab. Fifteen patients left the cath-lab with circulation, of whom eight were discharged from hospital in CPC 1 - 2. During the study period (9 April 2009 – 9 April 2013), 8738 patients were admitted to the cath-lab for an invasive cardiac or coronary procedure. In total, 3368 patients were evaluated with a coronary angiogram only and 5370 patients were treated with PCI (acute or

elective) whereof 2728 were treated for STEMI. Of these, 116 patients were in CS when admitted to the cath-lab. There was no statistical age difference between the patients who expired in the cath-lab and those who were discharged from the cath-lab with circulation (p = 0.37) or those discharged from hospital (p = 0.64). Successful PCI defined as TIMI-II-III or <50% residual stenosis, PCI during mechanical CC, and treatment time with mechanical CC are presented in Table 5. There was a statistically significant difference in duration of mechanical CC when comparing patients who expired in the cath-lab to those discharged from the cath-lab with circulation (p = 0.02) and to those discharged from hospital (p = 0.004). At least one vasoactive drug (norepinephrine, EPI or dobutamine) was administered either intermittently or as a continuous infusion to 29 patients, and the majority received a combination of these drugs during the procedure.

Table 4.
Indication for referral to the coronary catheterization laboratory, culprit lesion, circulatory state upon arrival in the cath-lab, rhythm at the time of the cardiac arrest. Cath-lab = coronary catheterization laboratory. STEMI = ST elevation myocardial infarction. NSTEMI = non-ST elevation myocardial infarction. PCI = percutaneous coronary intervention. LM = left main coronary artery. LAD = left anterior descendent coronary artery. LCx = left circumflex coronary artery. RCA = right coronary artery. VT = ventricular tachycardia. VF = ventricular fibrillation. PEA = pulseless electrical activity.

	All patients	Expired Cath-lab	Discharged Cath-lab	Discharged Hospital
	n = 32 (%)	17 (53)	15 (47)	8 (25)
Indication for cath-lab procedure				
STEMI	24 (75)	15 (88)	9 (60)	4 (50)
Non-STEMI	4 (13)	1 (6)	3 (20)	2 (25)
Elective PCI	2 (6)	1 (6)	1 (7)	1 (13)
Other	1 (3)	0	1 (7)	1 (13)
Angiogram	1 (3)	0	1 (7)	0 (0)
Culprit lesion in coronary patients				
LM	10 (31)	6 (35)	4 (27)	2 (25)
LAD	12 (38)	7 (41)	4 (27)	2 (25)
LCx	2 (6)	0	3 (20)	2 (25)
RCA	6 (19)	4 (24)	2 (13)	1 (13)
Other	2 (6)	0	2 (13)	1 (13)
Circulatory state upon arrival in the cath-lab				
Cardiogenic shock	20 (62)	12 (71)	8 (53)	2 (25)
Initial rhythm at cardiac arrest				
VT/VF	5 (16)	1 (6)	4 (27)	2 (25)
PEA	22 (69)	14 (82)	8 (53)	4 (50)
Asystole	5 (16)	2 (12)	3 (20)	2 (25)

The manual CC group

Ten patients (eight men) with a mean age of 67.9 ±6.3 years suffered CA and required prolonged advanced resuscitation efforts with manual CC in the cath-lab between 1 January 1999 and 31 December 2003. Eight of these were referred due to a STEMI, one patient had a non-STEMI, and one patient had developed a ventricular septum defect due to a STEMI a few days earlier. Seven patients were in CS when admitted to the cath-lab. Two patients had a shockable rhythm at the time of the CA. Six patients were treated with PCI during manual CC, with 50% PCI success rate. The median time with manual CC for the whole group (n = 10) was 20 minutes (range 15 – 75) for those who expired in the cath-lab (n = 6); 25 minutes (range 15 – 60) for those discharged from the cath-lab (n = 4), and 15 minutes for the patient discharged from hospital in CPC 1 (n = 1).

Six-month survival rate

In the merged group with survivors discharged from hospital in CPC 1 from the previous study (n = 11) (Paper I) and the current study (n = 8), there was an 84% survival rate at six months (n = 16) (Figure 19).

Table 5. Cath-lab procedural data.
Cath-lab = coronary catheterization laboratory. PCI = percutaneous coronary intervention. MCC = mechanical chest compression. IABP = intra-aortic counter pulsation pump. CC = chest compression. CC times are presented as median minutes (range).

	All patients n=32 (%)	Expired Cath-lab 17 (53)	Discharged Cath-lab 15 (47)	Discharged Hospital 8 (25)
Procedural data				
Angiography during MCC	5 (16)	2 (12)	3 (20)	2 (25)
PCI during MCC	27 (87)	16 (94)	11 (73)	6 (75)
PCI successful	25 (81)	12 (71)	13 (87)	6 (75)
PCI unsuccessful	6 (20)	5 (29)	1 (7)	1 (12.5)
Use of concomitant IABP	12 (38)	3 (18)	9 (60)	4 (50)
CC time	34 (5-90)	42.5(10-75)	15 (5-90)	10 (5-52)
Thoracic surgery	4 (13)	0	4 (27)	2 (25)
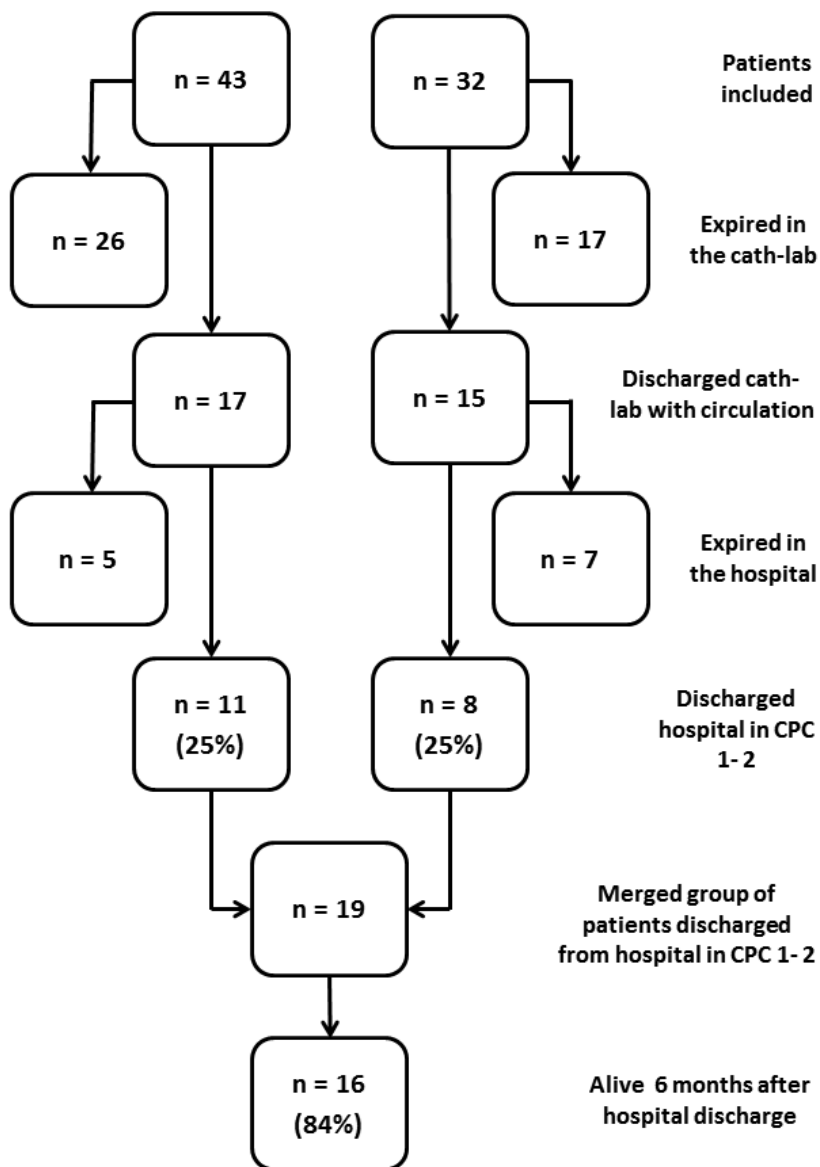
Figure 20.
Flow-chart showing the included patients (Paper I left, Paper II right) requiring prolonged advanced resuscitation including mechanical chest compressions during percutaneous coronary/cardiac interventions. Cath-lab = coronary catheterization laboratory. CPC = cerebral performance category.

Paper III

The results of analysing the monitored patients and studying the CPR situations revealed several deficiencies among the personnel involved. Firstly there was a lack of understanding of the importance of teamwork and leadership within the unique circumstances of a prolonged CPR effort in the cath-lab and the importance of practical simulations within the cath-lab setting. Secondly, there was a lack of understanding of the vital physiological parameters for the successful restoration of spontaneous circulation. Thirdly, there was a lack of familiarity with the advanced technology needed to succeed during such emergent and stressful circumstances.

The result of the initial analysis also showed specific difficulties such as:

1. The complex collaboration required during CPR in the cath-lab between different categories of personnel was not fully appreciated in the beginning. This resulted in suboptimal teamwork.

2. Only two patients had all physiological parameters collected. We found long periods without recorded ABP data for all patients. In one patient three vital parameters were at suboptimal levels without any corrective action taken to optimize these parameters. The recommended ventilation rate during CPR was not often followed (hyperventilation). We also found numerous variations in artefacts on the recorded $ETCO_2$ curve (Figure 22). ECG leads and the SpO_2 probe fell off frequently and were not always placed on the patient again. In Table 6, the physiological variables, outcomes, CC time and the use of vasopressor drugs in the ten patients are presented

3. The monitor in the cath-lab was optimized for ischemic monitoring (Figure 21b).

4. The CPR algorithm was practiced in a separate training area, but not specifically in the cath-lab procedure room, so staff did not experience the real life space and other limitations in these situations.

5. The extra equipment needed for resuscitation efforts blocked the movement of people in the room as well as the movements of the fluoroscopy equipment.

6. Individuals in the team were not trained to react in response to the measured physiological parameters, partly due to lack of knowledge of important, minimally acceptable levels needed to secure ROSC.

Hence a new physiology-guided advanced CPR approach adapted for the cath-lab was developed. A flow chart (Figure 23) and 20 points listed below describe this approach. To successfully launch the implementation of the new approach, several lectures were held for personnel in the medical emergency team (cardiologists, anaesthesiologists,

anaesthetic nurses, interventionists, cath-lab nurses and assistant nurses) which included >200 people. Focus was put on training CA scenarios in the cath-lab, teamwork and an understanding of the minimally acceptable levels of vital parameters needed for successful resuscitation.

Table 6

Vital parameters, outcomes, CPR time, the use of vasopressor substances in ten patients suffering CA in the cath-lab during simultaneous PCI. ABP = arterial blood pressure. CVP = central venous pressure. SpO$_2$ = index finger saturation. ETCO$_2$ = end tidal carbon dioxide. nd = not determined due to artefacts. nr = not registered or lost during procedure. ROSC = return of spontaneous circulation. CPC = cerebral performance category.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
	Mean SD	MeanSD	Mean SD	Mean SD	Mean SD	Mean SD	Mean SD	Mean SD	Mean SD	Mean SD
ABP Systolic [mmHg]	114±18	133±4	63±2	50±18	87±7	85±6	34±3	139±19	117±15	81±10
ABP Diastolic [mmHg]	2±12	10±4	39v3	22±8	59±4	7±6	20±2	nd	31±18	12±10
ABP Mean [mmHg]	40±4	51±3	46±4	31±10	68±7	33±6	25±2	43±9	60±16	35±9
CVP Systolic [mmHg]	123±10	95±4	nr	nr	nr	nr	46±2	169±17	70±10	nr
CVP Diastolic [mmHg]	15±11	-12±3	nr	nr	nr	nr	6±9	nd	13±6	nr
CVP Mean [mmHg]	52±13	24±3	nr	nr	nr	nr	19±1	36±8	32±7	nr
SpO$_2$ [%]	82±8	81±0	95±0	77±6	78±4	nr	64±3	nr	nr	nr
ETCO$_2$ [kPa]	2,4±0,4	3,5±0,3	2,8±0,5	nr	nr	nr	nr	nr	3,1±0,7	nr
Outcome	ROSC (312 h)	Dead in cath-lab	ROSC (216h)	Dead in cath-lab	ROSC (13 h)	CPC 1	Dead in cath-lab	Dead in cath-lab	CPC 1	Dead in cath-lab
CPR time (minutes)	45	50	15	75	35	10	50	30	45	70
Norephinephrine	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Epinephrine	YES	NO	No	YES	YES	NO	YES	YES	No	YES
Dobutamine	YES	YES	YES	YES	YES	NO	NO	NO	NO	NO
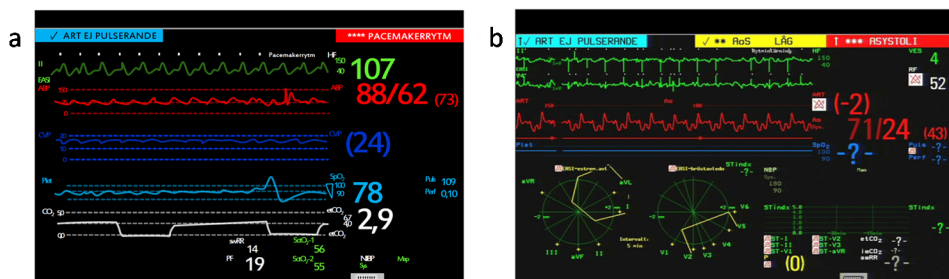
Figure 21

Left (a) Monitor screen designed for CPR-CA arrest situations displaying vital physiological parameters. Green line = ECG, red line = intra-aortic arterial blood pressure, dark blue line = central venous pressure (CVP), light blue line = pulse oximetry (SpO_2), white line = end tidal carbon dioxide ($ETCO_2$), green figures bottom = cerebral oximetry $SctO_2$ values.

Right (b) Monitor screen primarily designed for ischemic monitoring in the cath-lab. Green line = ECG, red line = intra-aortic arterial blood pressure, dark blue line = pulse oximetry (SpO_2), green circles = ischemic monitoring.

Specific recommendations

- SpO_2, ECG and ABP should be measured from the start of all interventions in the cath-lab.

- In case of a CA, defibrillate as early as possible if indicated by rhythm. All these cases are instantaneously attended and do not have a high volume load on the venous side [58, 123]. After defibrillation, start CC immediately if the patient does not obtain instantaneous ROSC.

- Alert the medical emergency team, whose swift arrival should be in 60 - 90 seconds.

- Select a team leader (most often the cardiologist).

- If the CA situation has not been solved in a few minutes with manual CC and defibrillations, apply the MCC device and start CCs (30 CC followed by two ventilations) for patients not intubated. The MCC device should be placed in the cath-lab for quick access and deployment.

- When the patient is intubated, switch to continuous MCCs and a ventilation rate of ten per minute. Ventilation has to be modified to avoid high intra-thoracic pressures. Intermittent manual ventilation between compressions is usually possible. When blood gases are available, ventilation should aim at normoventilation. Blood gases should also be used for adjustment of acidosis if needed.

- To simplify an instant overview of the vital parameters, use a specially designed monitor screen showing one continuous ECG lead, two ABP curves, one CVP curve (optional), one $ETCO_2$ curve, one SpO_2 curve and values for $SctO_2$ (Figure 21a).

- As soon as the patient is intubated start monitoring $ETCO_2$. However, be aware of compression artefacts in the $ETCO_2$ curve during MCC (Figure 22). To correctly assess the curve, stop the MCC device, perform two inflations and assess the $ETCO_2$ curve.

- If the patient has a shock-resistant VF, continue MCC and proceed with PCI in order to open the occlusion, rather than continue with further defibrillation attempts while the culprit coronary vessel remains occluded.

- Place the equipment brought by the medical emergency team in dedicated zones marked on the floor, so as not to interfere with the needed fluoroscopic projections.

- Optimize physiological parameters according to Table 7. Since CPP cannot be calculated instantaneously, TIMI flow might be used as a surrogate marker. If systolic ABP is below 70 mmHg, rule out cardiac tamponade, reposition the LUCAS™ device, consider changing the ventilation rate, or administer norepinephrine [124] or an infusion of EPI [125]. Be careful with the latter to avoid high dose EPI.
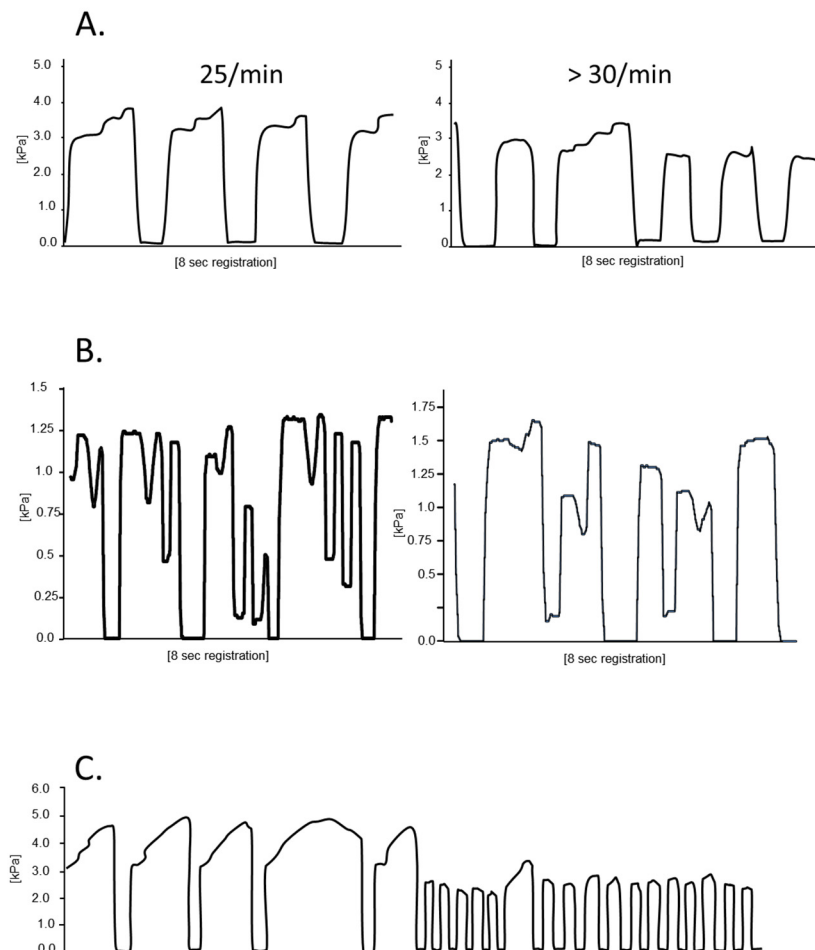
Figure 22

When analysing ETCO$_2$ during CCs, be aware that MCC can cause compression artefacts and also avoid hyper-ventilation. A: Shows two examples from the analysed patients where hyperventilation was seen during CC. B: Shows some examples of the artefacts that were noticed on the ETCO$_2$ registration. C: Shows an example of the difference between ETCO2 levels (decreasing from ~5 kPa to ~3 kPa) in an ETCO$_2$ curve with and without CC artefacts.

Table 7

Target values for vital physiological parameters during the resucitation in the cath-lab. AoD = aortic diastolic pressure. RaD = right atrial diastolic pressure. TIMI = thrombolysis in myocardial infarction. mmHg = millimetre mercury. kPa = kilopascal.

Parameter		Target value
Arterial blood pressure (ABP)	Systolic	>70 mmHg
	Diastolic	>40 mmHg
Central venous pressure (CVP)	Diastolic	<25 mmHg
Coronary perfusion pressure (CPP)	(AoD-RaD)	>15 mmHg
End tidal carbon dioxide (ETCO$_2$)	Mean	>10 mmHg or >2 kPa
Pulse oximetry (SpO$_2$)		>80 %
Cerebral oximetry (SctO$_2$)		>45 %
Coronary flow		TIMI-3

- Apply the electrodes for SctO$_2$ on the patient's forehead as soon as possible if available.

- At the interventionist´s discretion, an introducer could be inserted in the femoral vein, both in order to place a pigtail catheter in the right atria for measuring CVP and to serve as a central venous line for infusions and drug administration.

- Collaboration between the anaesthesiologist and cardiologist is key in all efforts to optimize vital parameters.

- In the relatively rare cases of pulmonary oedema, an adjustable PEEP valve could be tried. When ROSC has been attained, intermittent positive pressure ventilation using a conventional intensive care unit ventilator can be started.

- Record physiology parameters and communicate them to the team leader and anaesthesiologist repeatedly or when dramatic change occurs. Every person in the cath-lab has the responsibility to react to unsatisfactory physiology parameters.

- Consider initiation of therapeutic hypothermia/target temperature management as soon as possible.

- If successful PCI is accomplished and the patient has a shockable rhythm, defibrillate during MCC. If unsuccessful, consider one bolus injection of EPI (1 mg) followed by defibrillation.

- If successful PCI is accomplished and the patient has PEA or asystole, continue MCC for 15 – 20 minutes followed by an infusion of EPI for approximately two to three minutes. Then administer a bolus dose of 1 mg of EPI in the right atria. Continue MCC for at least ten minutes after last drug delivery before termination of resuscitation efforts.

- If successful PCI is accomplished and the patient has obtained ROSC, deploy a left ventricular assist device if needed. Prepare for further post-resuscitation treatment in the intensive care unit according to guideline recommendations [126] or local directive.

These points, together with the flow chart shown in Figure 23, were put into a pocket folder and given to all personnel involved in the medical emergency team and to all cath-lab personnel.

Due to this education (theoretical and practical), personnel felt more secure and comfortable in their roles when real CA situations arose in the cath-lab and they experienced a more success-oriented result.
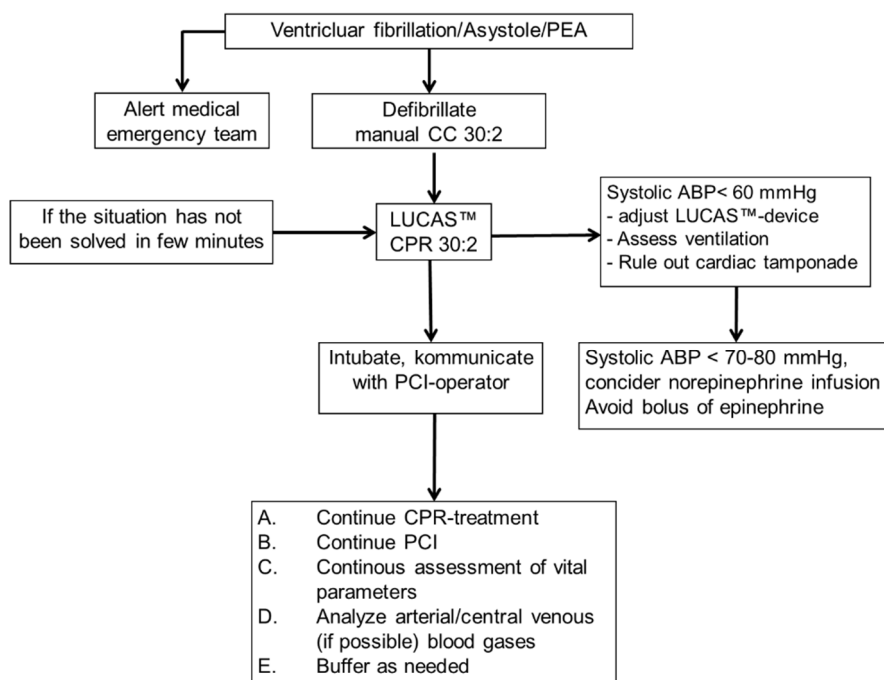
Figure 23
shows a flow chart visualizing the important steps and decision points in the physiology-guided CPR approach in CA situations in the cath-lab during simultaneous PCI. PEA = pulseless electrical activity. CC = chest compression. CPR = cardiopulmonary resuscitation. ABP = intra-aortic arterial blood pressure.

Paper IV

The baseline variables for the ten pigs analysed are shown in Table 8. The blood pressure and APV (APV noise-free period was s: 0 – 2 min: six pigs = 66 ±47 s, 2 – 4 min: seven pigs = 114 ±11 s, 4 – 6 min: seven pigs = 99 ±38 s, 6 – 8 min: nine pigs = 68 ±46 s, 8 – 10 min: seven pigs = 84 ±40 s) are shown in Table 10. The statistical comparison revealed a significant ($P <0.0005$) increase in coronary blood flow with MCC compared to baseline (sinus rhythm, at a frequency of 97±16) at each time interval, ranging between a 12 and 39% increase (Table 8).

Table 8
Measurements of intra-aortic arterial blood pressure, central venous pressure, coronary perfusion pressure and average peak blood flow velocity. Mean values ±SD during baseline, during 0 – 2 minutes, 2 – 4 minutes, 4 – 6 minutes, 6 – 8 minutes and 8 – 10 minutes of mechanical chest compressions. Min = minimum. AP = intra-aortic arterial blood pressure. Max = maximum. CVP = central venous blood pressure. CPP = coronary perfusion pressure. APV = average peak blood flow velocity. mmHg = millimetre mercury. cm/s = centimetre per second.

Variable/time	Baseline	0-2 min	2-4 min	4-6 min	6-8 min	8-10 min
Min AP [mmHg]	101.1 ±1.1	16.9 ±2.3	14.1 ±1.1	11.9 ±1.2	8.5 ±1.2	5.6 ±1.3
Mean AP [mmHg]	115.7 ±1.2	35.7 ±3.3	38.0 ±0.7	36.3 ±1.4	33.8 ±0.8	37.8 ±1.3
Max AP [mmHg]	129.3 ±1.5	65.9 ±6.4	69.9 ±0.8	68.0 ±1.1	66.2 ±0.9	65.6 ±0.9
Min CVP [mmHg]	1.7 ±0.5	1.9 ±1.3	1.2 ±0.2	1.1 ±0.2	8.1 ±0.2	1.0 ±0.3
Mean CVP [mmHg]	3.5 ±0.2	23.2 ±1.7	23.7 ±0.4	23.8 ±0.8	24.8 ±0.4	24.2 ±0.6
Max CVP [mmHg]	5.2 ±1.8	59.5 ±8.4	67.9 ±1.1	66.7 ±1.7	69.7 ±0.9	70.1 ±1.2
CPP [mmHg]	98.0 ±2.0	24.3 ±1.4	24.1 ±0.5	23.6 ±1.3	21.5 ±1.2	20.6 ±1.5
APV [ml/min]	14.3 ±1.0	20.0 ±1.2	18.9 ±0.5	17.8 ±0.9	17.3 ±0.9	16.0 ±1.1

Arterial pressure and CVP over the total study period are presented in Figure 24. The progress of calculated CPP and the measured intracoronary APV are shown during the experimental period in Figure 24. APV values could not be calculated correctly in the ROSC period due to technical disturbances. However, there is a hyperemic period evidenced by increased AP and CPP that is shown in Figures 24 and 25 indicating that increased Doppler flow is evident. However, this cannot be proven due to the technical problems we experienced.
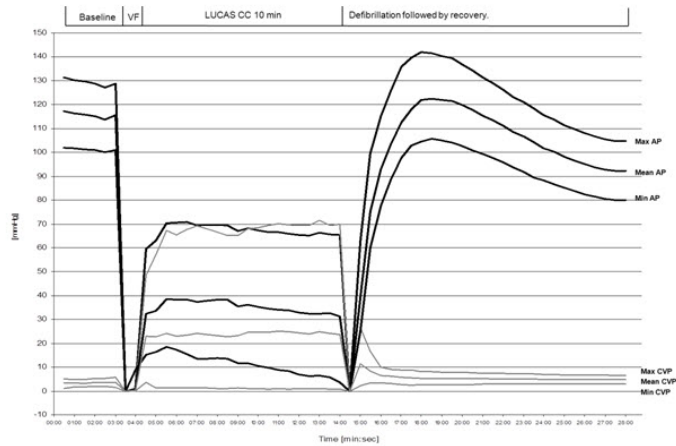
Figure 24

The development of minimum, mean and max (Min, Mean and Max) intra-thoracic aortic pressure and right atrial pressure during the total experimental period (28 minutes). Data are presented as the mean value of the 30-second periods of analysed data, and each individual pig's data are time-adjusted to the same length for each period of the experiments.
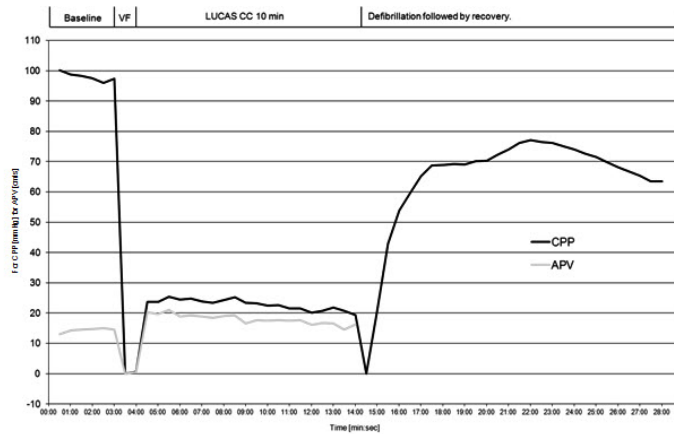
Figure 25

The development of the calculated mean coronary perfusion pressure (CPP in mmHg) over the total experimental period (28 minutes) and the development of coronary artery flow velocity (cm/s) during the experimental period. Coronary flow is not shown after ROSC due to technical problems after defibrillation. Data are presented as the mean value of the 30-second periods of analysed data, and each individual pig's data are time-adjusted to the same length for each period of the experiments.

Correlation analysis between calculated CPP and APV was performed for the entire ten minute period of MCC. A significant correlation (R = 0.761, R^2 = 0.6 and P-value <0.0001) between the calculated CPP and APV during MCC was seen (Figure 26).
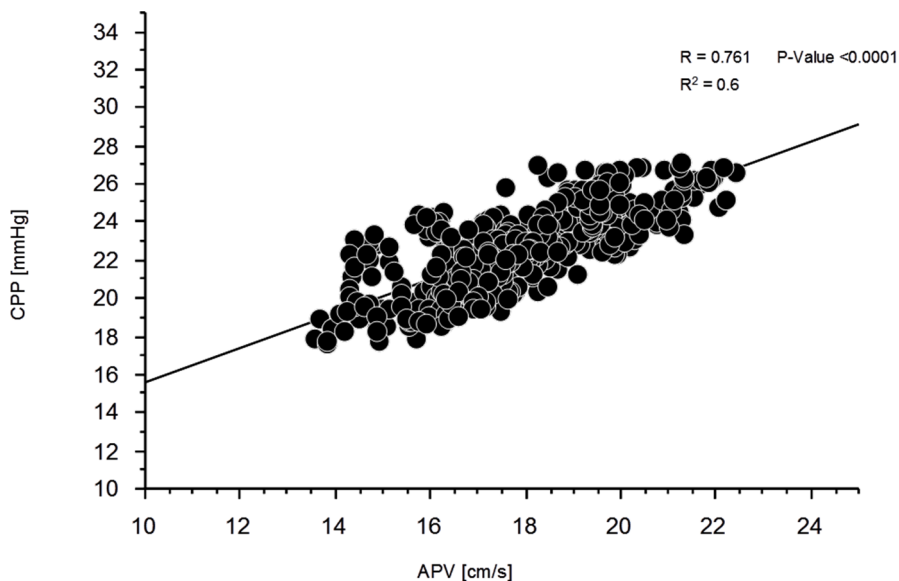
Figure 26
Correlation of coronary perfusion pressure (CPP) and average blood flow peak velocity (APV). Shows the correlation of calculated CPP and APV during the 10 minutes of mechanical chest compressions. To test the null-hypothesis for CPP and APV correlation, the Z-test was used.

Arterial blood gas values are shown in Table 9. There was a significant fall between base line and after ten minutes of MCC in pH and BE, but lactate was significantly elevated as well as glucose. The significant difference in pH, lactate and glucose also persisted following 20 minutes of ROSC, but BE stabilized and PO_2 increased.

Table 9

Measurements of blood gas, haemoglobin, lactate, electrolytes and glucose at baseline and after ten minutes of MCC. Data are presented as mean ±SD, n= 10. ns= not significant. pH = hydrogen ions. pCO_2 = partial pressure carbon dioxide. pO_2 = partial pressure oxygen. ABE = arterial base excess. Hb = haemoglobin. Na = sodium. K = potassium. Ca = calcium.

Variable	Baseline Arterial		10 min Arterial		P-value	ROSC 20 min Arterial		P-value
	Mean	±SD	Mean	±SD		Mean	±SD	
pH	7.350	±0.026	7.257	±0.060	0.012	7.287	±0.050	0.014
PCO₂	5.8	±0.63	6.5	±1.30	ns	6.4	±0.83	ns
PO₂	14.3	±6.9	27.5	±18.6	ns	48.75	±17.7	0.042
ABE	-1.7	±1.4	-6.0	±1.4	0.002	-3.97	±1.6	ns
Lactate	1.42	±0.47	4.35	±1.33	0.02	3.86	±1.02	0.002
Hb	108	±10	120	±11	ns	114	±10	ns
Na	137	±2,1	136	±2.7	ns	136	±2.8	ns
K	3.96	±0.24	4.59	±0.89	ns	3.86	±0.34	ns
Ca	1.33	±0.04	1.35	±0.06	ns	1.27	±0.05	ns
Glucose	6.6	±1.4	11.5	±2.2	0.002	11.79	±3.15	0.008

ROSC

Seven animals regained ROSC following the first defibrillation attempt; two pigs required three defibrillation attempts to attain ROSC and two pigs did not obtain ROSC following defibrillation at the end of the ten-minute episode of VF, one of which was excluded due to misplacement of the device before start of CC.

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No difference was seen during the baseline period regarding analysed measurements between any groups (Table 10).

Table 10.

Baseline parameters. NaCl = Saline. EPI = epinephrine. Syst = systolic. ABP = arterial blood pressure (mmHg). Diast = diastolic. Max = maximum. CVP = central venous pressure (mmHg). Min = minimum. $ETCO_2$ = end tidal carbon dioxide (kPa). APV = average peak velocity (cm/s). Heart rate (beats/minute). PCO_2 = partial pressure carbon dioxide (kPa). PO_2 = partial pressure oxygen (kPa). ABE = arterial base excess (mmol/l). All values are expressed as median, 25th and 75th interquartile.

	NaCl (n=12)		EPI all (n=24)		p-value	EPI 0.02 mg/kg/dose (n=12)		p-value	EPI 0.03 mg/kg/dose (n=12)		p-value
Syst ABP	152	(137 - 167)	151	(136 - 163)	0.5347	149	(136 - 172)	0.4357	152	(136 - 172)	0.7950
Diast ABP	96	(79 - 122)	96	(89 - 106)	0.6996	93	(89 - 99)	0.7075	100	(78 - 107)	0.7950
Mean ABP	115	(99 - 139)	114	(105 - 124)	0.5347	113	(105 - 118)	0.5067	116	(94 - 126)	0.7075
Max CVP	12	(10 - 13)	11	(10 - 13)	0.6505	11	(10 - 13)	0.5444	11	(10 - 13)	0.8852
Min CVP	8	(5 - 10)	7	(6 - 8)	0.4502	7	(4 - 8)	0.2855	7	(6 - 9)	0.8399
Mean CVP	10	(8 - 11)	9	(8 - 11)	0.7944	9	(8 - 11)	0.7350	9	(8 - 11)	0.9310
$ETCO_2$	4.9	(4.3 - 5.0)	4.5	(4.1 - 4.9)	0.5642	4.8	(4.4 - 5.0)	0.8691	4.3	(4.0 - 4.7)	0.2727
APV	17	(12 - 28)	17	(12 - 24)	0.7677	20	(13 - 26)	0.8399	15	(11 - 21)	0.4417
Heart rate	88	(58 - 97)	75	(64 - 91)	0.7455	77	(71 - 93)	0.8955	71	(56 - 90)	0.4701
pH	7.473	(7.420-7.505)	7.484	(7.402-7.510)	0.9331	7.468	(7.414-7.529)	0.7950	7.485	(7.3875-7.503)	0.6650
PCO_2	5.3	(5.0-6.5)	5.4	(5.1-5.9)	0.7246	5.5	(5.1-5.9)	0.9310	5.2	(4.9-5.9)	0.6236
PO_2	27.2	(16.6-37.1)	20.2	(17.2-33.9)	0.6030	23.0	(17.3-33.2)	0.8174	20.2	(16.4-33.9)	0.5254
ABE	6.0	(4.6-7.3)	5.9	(2.8-7.8)	0.9065	6.8	(3.2-8.7)	0.7075	5.5	(2.5-6.1)	0.2855

CPP

During the first four minutes of MCC and at the time of the first EPI injection, there were no significant differences in CPP between the control group (n=12), EPI-all group (n=24), EPI 0.02 mg/kg/dose (n=12) or EPI 0.03 mg/kg/dose (n=12) (Table 11, Figures 27a – 27c). During the subsequent period of MCC there was a significant increase in CPP at P_{max} after EPI injections one and two in the EPI-all group (p = 0.022, p = 0.016), compared to the control group but not after injections three and four (Table 11, Figure 27a). There was a significant increase in CPP after injections two and three in EPI 0.02mg/kg/dose compared to the control group (p = 0.023, p = 0.027) (Table 11, Figure 27b). When comparing the EPI 0.03 mg/kg/dose to the control group, there was a statistical significant difference at P_{max} following injection one (p = 0.013) but not at P_{max} following injections two, three and four (Table 11, 27c).

Table 11.

Physiological values of CPP during 15 minutes of MCC. CPP = coronary perfusion pressure (mmHg). NaCl = saline. EPI = epinephrine. MCC = mechanical chest compressions. Inj = injection a: n = 12, b: n = 11, c: n = 10, d: n = 24, e: n = 23, f: n = 22, g: n = 21. Peak values at 20, 60, 120, 180 seconds after start of MCC, at each time point of the 4 drug injections (4, 7, 10, 13 minutes after start of MCC) and the corresponding peak to each injection for NaCl compared to EPI. All values are expressed as median, 25th and 75th interquartile.

	CPP NaCl (n = 12)		CPP EPI-all (n = 24)		P-value	CPP EPI 0.02 mg/kg dose (n = 12)		P-value	CPP EPI 0.03 mg/kg/ dose (n = 12)		P-value
MCC 20 s	30	(23-42)[a]	27	(12-40)[c]	0.4141	28	(12-46)[b]	0.7818	26	(18-37)[a]	0.2855
MCC 60 s	31	(23-36)[a]	25	(16-45)[d]	0.9331	34	(14-46)[a]	0.6650	25	(21-46)[a]	0.7950
MCC 120 s	28	(14-36)[a]	27	(9-47)[e]	0.7152	25	(16-49)[b]	0.5588	29	(25-52)[b]	0.6891
MCC 180 s	29	(14-39)[a]	27	(13-42)[f]	0.8712	25	(14-44)[b]	1.0000	29	(21-53)[c]	0.9737
Inj #1	29	(10-40)[b]	27	(11-49)[n]	0.9368	31	(11-48)[b]	0.9476	27	(14-57)[c]	0.9719
Peak #1	29	(11-41)[c]	44	(31-78)[e]	0.0219	38	(28-78)[b]	0.1489	47	(39-77)[a]	0.0134
Inj #2	29	(15-41)[b]	25	(16-38)[e]	1.0000	19	(10-44)[a]	0.6009	27	(24-50)[b]	0.5545
Peak #2	28	(12-36)[c]	39	(31-59)[e]	0.0160	50	(31-65)[a]	0.0229	37	(29-56)[b]	0.0620
Inj #3	32	(18-35)[c]	27	(11-36)[d]	0.9849	12	(7-38)[a]	0.6209	27	(25-39)[a]	0.6682
Peak #3	28	(10-38)[c]	39	(29-50)[e]	0.1434	42	(32-50)[a]	0.0265	35	(28-64)[a]	0.1213
Inj # 4	31	(21-32)[b]	26	(12-38)[f]	0.9848	13	(11-43)[c]	0.5974	27	(23-39)[a]	0.6891
Peak #4	24	10-37)[c]	32	(24-45)[e]	0.1894	32	(22-47)[b]	0.2453	33	(29-44)[a]	0.2766

APV

During the first four minutes of VF there were no statistically significant differences in APV between any groups. During the following period of MCC there was a significant increase in APV after injection one when comparing the control group

to the EPI groups, except for the EPI 0.02 mg/kg/dose group, in which the APV increase was only borderline (p = 0.056). We could not detect any change in APV after the subsequent EPI injections (Table 12, Figures 28a – 29c).

Table 12.
Physiological values of APV during 15 minutes of MCC. APV = average peak velocity (cm/s, NaCl = saline. EPI = epinephrine. MCC = mechanical chest compressions. Inj = injection, a: n = 12, b: n = 11, c: n = 10, d: n = 9, e: n = 8, f: n = 7, g: n = 24, h: n = 23, i: n = 21, j: n = 19, k: n = 18, l: n = 17, m: n = 16. Peak values at 20, 60, 120, 180 seconds after start of MCC, at each time point of the 4 drug injections (4, 7, 10, 13 minutes after start of MCC) and the corresponding peak to each injection for NaCl compared to EPI. All values are expressed as median, 25th and 75th interquartile.

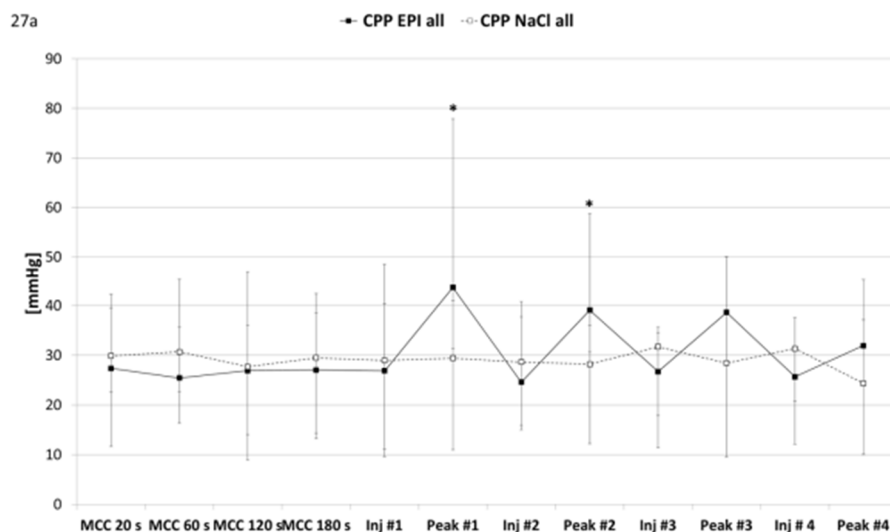|	APV NaCl (n = 12)		P-value	APV EPI-all (n = 24)		P-value	APV EPI 0.02 mg/kg/dose (n = 12)		P-value	APV EPI 0.03mg/kg/dose (n = 12)		P-value
MCC 20 s	19	(12-28) [a]		18	(12-22) [h]	0.3571	20	(13-24) [a]	0.5444	16	(11-32) [b]	0.3401
MCC 60 s	20	(15-29) [a]		20	(11-24) [h]	0.4141	21	(12-25) [a]	0.8399	17	(10-22) [b]	0.2071
MCC 120 s	17	(12-25) [a]		14	(9-21) [h]	0.3220	14	(10-21) [a]	0.4025	10	(8-21) [b]	0.3401
MCC 180 s	24	(17-29) [a]		17	(11-26) [g]	0.0901	14	(10-30) [a]	0.0606	18	(12-24) [b]	0.1316
Inj #1	13	(12-20) [c]		16	(8-20) [m]	0.8536	16	(9-20) [c]	0.9646	14	(7-25) [c]	0.6893
Peak #1	11	(9-15) [c]		19	(15-26) [j]	0.0109	19	(12-23) [c]	0.0561	19	(15-42) [b]	0.0183
Inj #2	12	(8-18) [e]		12	(9-20) [i]	0.8262	10	(8-16) [b]	0.5915	15	(12-21) [b]	0.2303
Peak #2	16	(6-19) [e]		17	(13-31) [l]	0.1899	18	(13-36) [d]	0.1629	15	(13-35) [c]	0.4309
Inj #3	13	(11-20) [d]		14	(7-22) [k]	0.5892	16	(9-26) [c]	0.9674	12	(7-18) [c]	0.3606
Peak #3	13	(9-22) [b]		19	(14-31) [j]	0.5892	19	(15-29) [a]	0.1661	19	(14-33) [f]	0.3191
Inj # 4	15	(9-20) [b]		17	(9-21) [j]	0.9314	19	(8-29) [d]	0.8792	16	(10-21) [c]	1.0
Peak #4	12	(8-21) [b]		15	(10-29) [m]	0.6749	14	(12-22) [c]	0.6497	17	(8-37) [c]	0.8365

AMSA

There were no statistical differences in AMSA, when comparing the control group to any of the EPI groups. (Table 13, Figures 29a – 29c).

Table 13.
Physiological values of AMSA during 15 minutes of MCC. AMSA= amplitude spectral area (mV·Hz). NaCl = saline. EPI = epinephrine. MCC = mechanical chest compressions. Inj = injection, a: n = 12, b: n = 10, c: n = 9, d: n = 21, e: n = 6. Peak values at 20, 60, 120, 180 seconds after start of MCC, at each time point of the 4 drug injections (4, 7, 10, 13 minutes after start of MCC) and the corresponding peak to each injection for NaCl compared to EPI. All values are expressed as median, 25th and 75th interquartile.

	AMSA NaCl	EPI All	p-value	AMSA 0.02mg/kg/dose	EPI p-value	AMSA 0.02mg/kg/dose	EPI p-value
MCC 20 s	12.1 (9.6-14.0)[b]	13.0 (10.9-16.0)[d]	0.4099	13.0 (11.8-13.0)[c]	0.3913	13.1 (10.6-15.0)[a]	0.5752
MCC 60 s	12.4 (10.8-15.3)[b]	14.4 (11.4-16.8)[d]	0.4990	13.7 (10.8-17.6)[c]	0.7751	14.6 (13.0-15.8)[a]	0.4288
MCC 120 s	13.8 (12.1-16.3)[b]	16.0 (14.2-18.7)[d]	0.1974	16.0 (14.2-19.8)[c]	0.1779	15.5 (13.8-17.6)[a]	0.3734
MCC 180 s	14.7 (13.3-17.9)[b]	17.0 (12.8-19.0)[d]	0.3749	17.0 (12.8-19.3)[c]	0.4877	17.0 (15.3-18.3)[a]	0.4288
Inj #1	14.3 (12.7-16.8)[b]	15.9 (13.9-16.7)[d]	0.4725	15.4 (9.7-16.7)[c]	0.4142	16.1 (13.3-16.7)[a]	0.6682
Peak #1	14.7 (11.5-15.9)[b]	14.6 (13.0-16.2)[d]	0.6121	14.6 (13.8-15.9)[c]	0.7133	14.7 (12.7-16.2)[a]	0.6444
Inj #2	13.9 (11.0-15.4)[b]	14.0 (11.6-14.5)[d]	0.8824	14.3 (13.0-14.9)[c]	0.7751	13.8 (11.6-14.3)[a]	0.6209
Peak #2	13.5 (10.4-14.7)[b]	12.5 (11.0-14.6)[d]	1.0000	13.1 (11.9-17.5)[c]	0.5956	12.2 (10.4-13.9)[a]	0.6682
Inj #3	13.7 (11.4-14.8)[b]	11.5 (9.7-13.8)[d]	0.2285	11.5 (10.2-20.9)[c]	0.5676	11.2 (9.5-11.7)[a]	0.1616
Peak #3	12.7 (10.6-15.5)[b]	12.5 (11.1-14.5)[d]	0.9831	13.1 (10.2-20.9)[c]	0.5954	12.2 (11.3-14.3)[a]	0.7169
Inj # 4	13.9 (11.3-15.3)[b]	11.0 (9.7-13.5)[d]	0.1696	11.8 (10.5-14.3)[c]	0.6534	10.6 (8.8-12.2)[a]	0.0806
Peak #4	14.0 (11.4-15.3)[e]	11.0 (8.9-15.9)[d]	0.8841	16.8 (9.9-11.1)[c]	0.3165	9.9 (8.8-14.3)[a]	0.2814

Figure 27a
Development of CPP in the combined group – EPI-all (0.02 mg EPI/kg/dose and 0.03 mg EPI/kg/dose) compared to control group (NaCl) during the MCC period (15 minutes). Significant difference between the EPI group compared to control group, * = p <0.05. CPP = coronary perfusion pressure. EPI = epinephrine. MCC = mechanical chest compressions. Inj = injection.
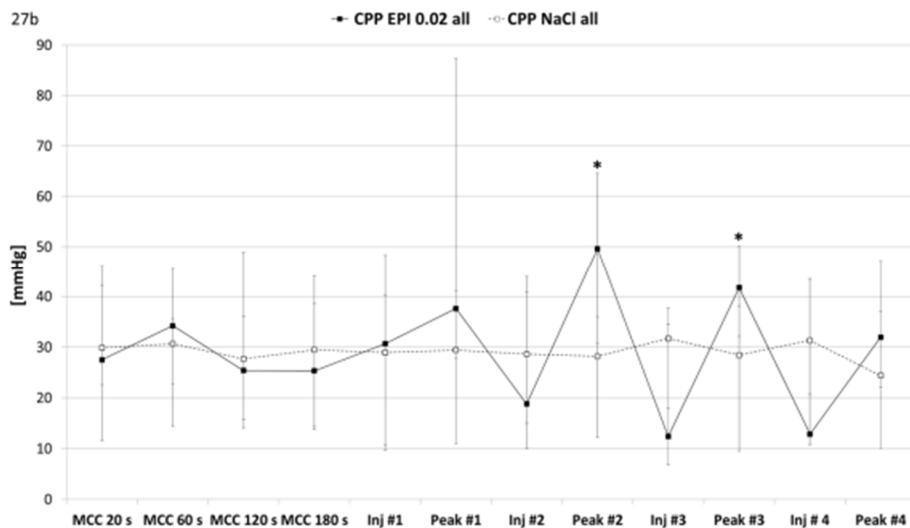
Figure 27b
Development of CPP in 0.02 mg EPI/kg/dose compared to control group during the MCC period (15 minutes). Significant difference between the EPI group compared to control group, * = p <0.05. CPP = coronary perfusion pressure. EPI = epinephrine. MCC = mechanical chest compressions. Inj = injection.
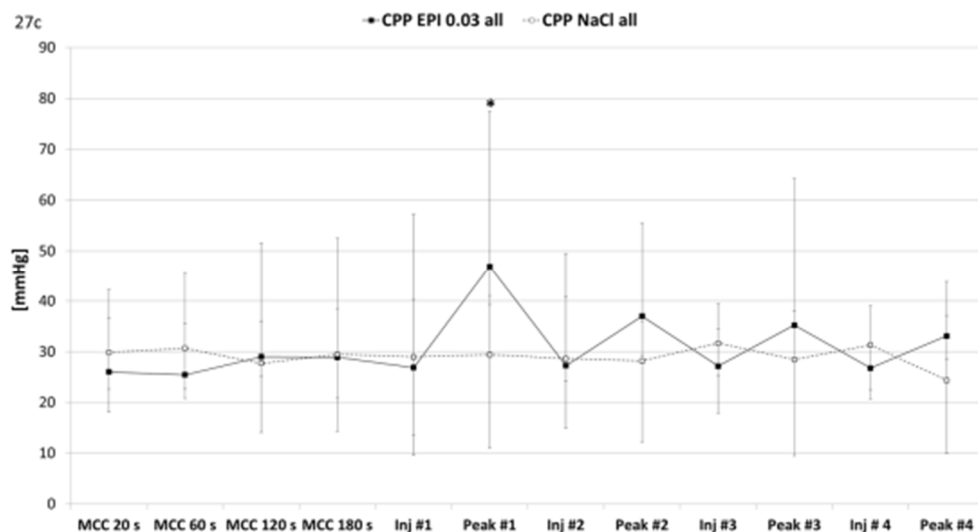
Figure 27c
Development of CPP in 0.03 mg EPI/kg/dose compared to control group during the MCC period (15 minutes). Significant difference between the EPI group compared to control group, * = p <0.05. CPP = coronary perfusion pressure. EPI = epinephrine. MCC = mechanical chest compressions. Inj = injection.

Figure 28a
Development of APV in the combined group – EPI-all, (0.02 mg EPI/kg/dose and 0.03 mg EPI/kg/dose) compared to control group (NaCl) during the MCC period (15 minutes). Significant difference between EPI group compared to control group, * = p <0.05. APV = average peak velocity. EPI = epinephrine. MCC = mechanical chest compressions. Inj = injection.

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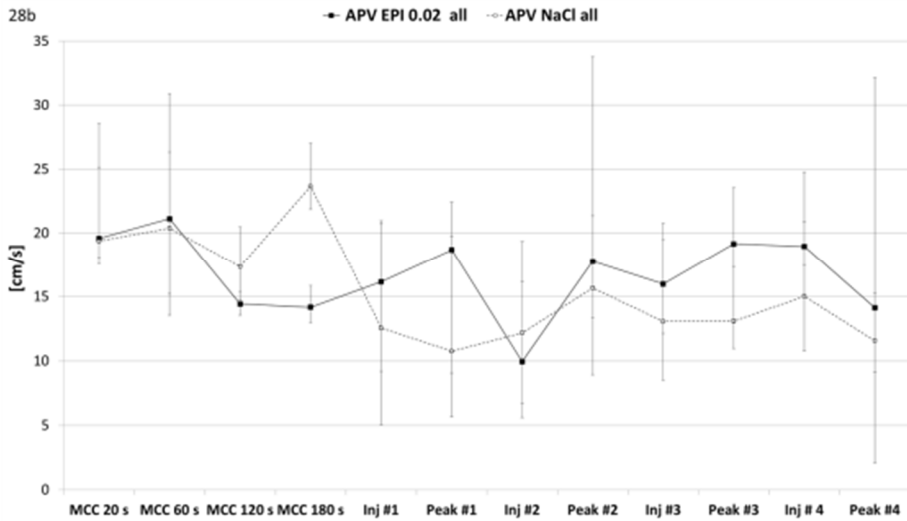
Figure 28b
Development of APV in 0.02 mg EPI/kg/dose compared to control group during the MCC period (15 minutes). APV = average peak velocity. EPI = epinephrine. MCC = mechanical chest compressions. Inj = injection.
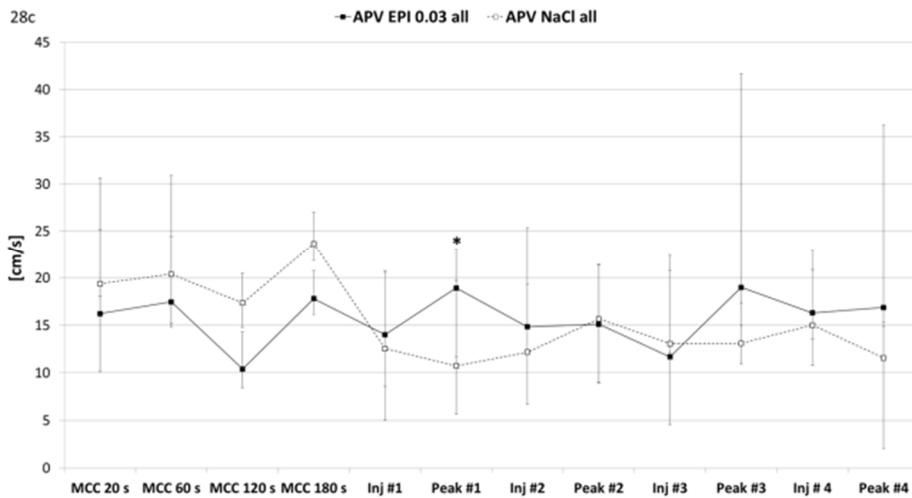
Figure 28c
Development of APV in 0.03 mg EPI/kg/dose compared to control group during the MCC period (15 minutes). Significant difference between EPI group compared to control group, * = p <0.05. APV = average peak velocity. EPI = epinephrine. MCC = mechanical chest compressions. Inj = injection.
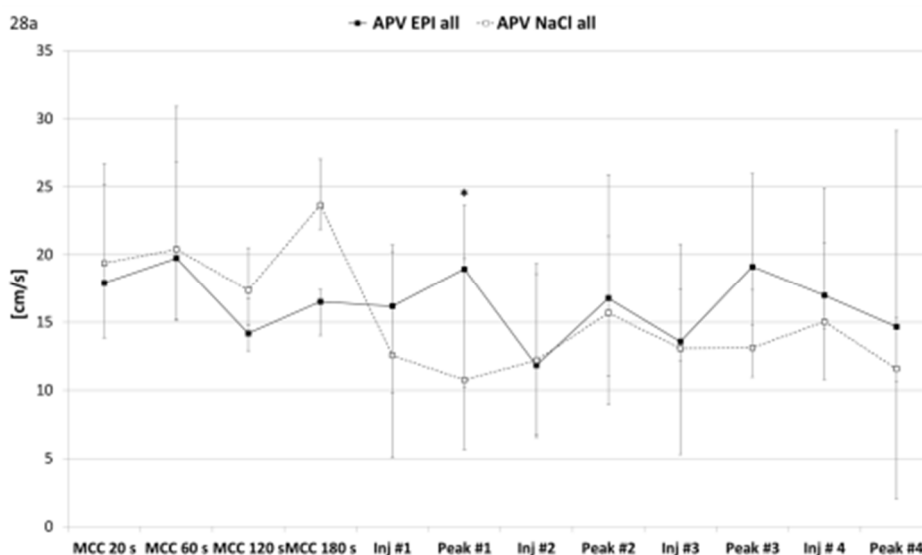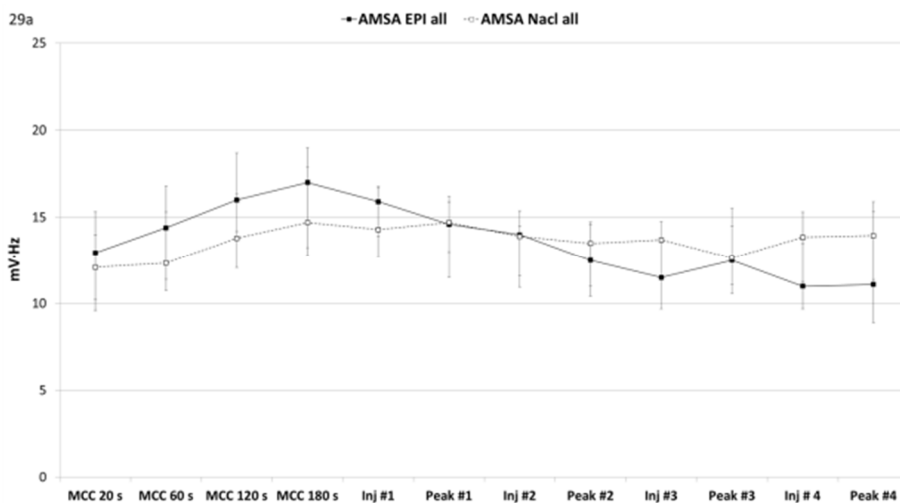
Figure 29a
Development of AMSA in the combined group – EPI-all, (0.02 mg EPI/kg/dose and 0.03 mg EPI/kg/dose) compared to NaCl during the MCC period (15 minutes). AMSA = amplitude spectrum area. EPI = epinephrine. MCC = mechanical chest compressions. Inj = injection.
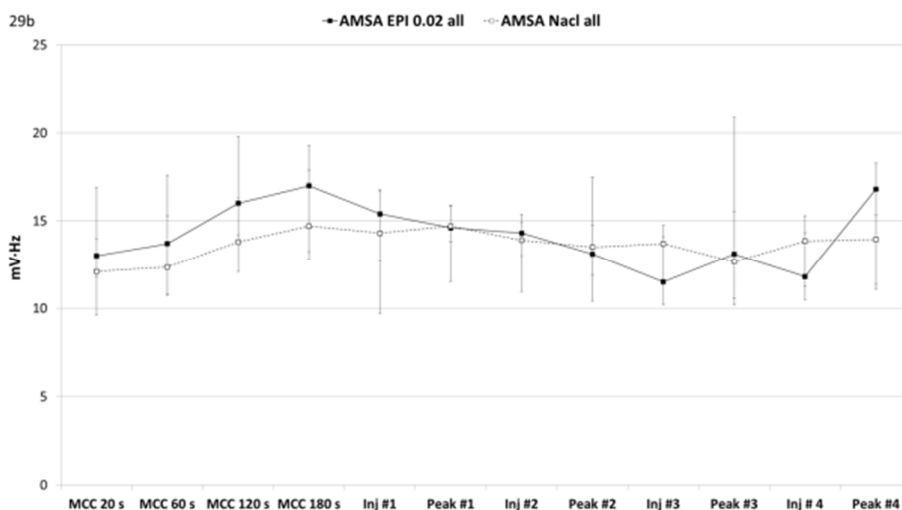
Figure 29b
Development of AMSA in 0.02 mg EPI/kg/dose compared to control group during the MCC period (15 minutes). AMSA = amplitude spectrum area. EPI = epinephrin., MCC = mechanical chest compressions. Inj = injection.
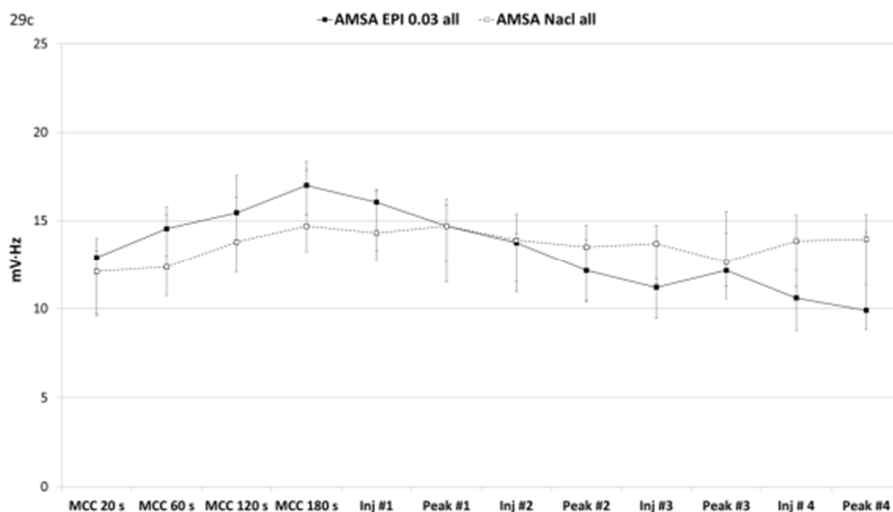
Figure 29c
Development of AMSA in 0.03 mg EPI/kg/dose compared to control group during the MCC period (15 minutes). AMSA = amplitude spectrum area. EPI = epinephrine. MCC = mechanical chest compressions. Inj = injection.

Time to maximum peak of CPP

The median time to P_{max} following the EPI injections was 50 seconds (interquartile range 48 to 52) seconds (Table 3). There were no significant differences in time to P_{max} between the EPI groups following injections one to four (Table 14).

Table 14
Time duration from drug administration to peak time (seconds) /P_{max} of CPP for the 4 different drug injections. Inj = injection. mg = milligram. kg = kilogram. a; n = 12, b; n = 11, c; n = 23. All values are expressed as median, 25th and 75th interquartile.

		Inj #1	Inj #2	Inj #3	Inj #4	P-value
Epinephrine all		51 (32-66)c	53 (41-58)c	49 (41-70)c	56 (44-78)c	0.392
Epinephrine mg/kg/dose	0.02	48 (39-49)b	48 (40-52)a	52 (50-60)a	47 (43-59)b	0.44
Epinephrine mg/kg/dose	0.03	48 (38-60)a	51 (40-56)b	51 (46-62)b	49(44-65)a	0.44

ROSC

Return of spontaneous circulation was achieved in 10 out of 12 animals (84%) in the control group compared with seven out of 12 (58%) in each EPI group (p=0.37).

Discussion

The use of MCC in the cath-lab during simultaneous PCI has been shown to be feasible, safe and can save lives. Over the nine years (2004 – 2013) covered by Papers I and II, 11 720 patients underwent PCI (elective, sub-acute or primary PCI) and of those 75 patients (0.64%) suffered a protracted CA in the cath-lab. The LUCAS™ mechanical CC system offers a valuable tool in these cases. The device performs high quality CC according to current CPR guidelines, without interruptions, and is easy to deploy. The radio-lucent design of most parts allows for fluoroscopy in all preferred angles during an intervention.

The majority of coronary interventions were performed during MCC with a success rate of 76% (Paper I) and 80% (Paper II), defined as TIMI II-III flow, as compared to PCI results in primary PCI with a 90% success rate [29]. This result indicates that the use of MCC is feasible and does not impair the progress of the coronary or cardiac intervention or substantially reduce the PCI result.

Questions have been raised regarding severe injuries caused by MCC compared to manual CC [46, 47] while other studies were unable to confirm this [48, 49]. In autopsy reports in Paper I (n=6), all had rib fractures and five had sternal fractures. In one autopsy there was minor bleeding around the aortic arch without rupture. Of the survivors, all suffered rib fractures and possibly sternal fractures. In one of the survivors, there was a gastric and spleen rupture due to mal-apposition of the MCC device, but the patient was successfully surgically treated. Thus, with the device correctly deployed, its utilization in the cath-lab is safe.

Survival rates at discharge from hospital after in-hospital CA vary widely, from 17 to 65% [3, 127-131], as do the causes of the CA [3, 127-131]. In some studies, subgroups such as patients < 65 years of age [129] or patients suffering a CA during a procedure or experiencing their CA in the emergency department [127] were excluded. Other factors that differ are a high amount of initial shockable rhythm (49% and 39%) [130, 131]. Herlitz et al. (data from the Swedish CPR registry) showed a 65% survival rate in patients who had their CA in the cath-lab [3]. In a newly published study by Demidova et al., the incidence of reperfusion VF associated with primary PCI was found to be 1.9% yearly with a survival rate of 81.7% at hospital discharge [132].

In Papers I and II, the survival rate was 25%. All these patients were discharged from hospital in good neurological condition (CPC 1 – 2). In the merged group including the survivors at hospital discharge, 84% were alive after 6 months. Thus, the use of the MCC device has probably increased survival in this group.

The population in Papers I and II consisted of patients with CA due to cardiac ischemic causes and there were no restrictions in upper age or procedure. There was a low amount of initial shockable rhythm causing the CA, which might be explained by the fact that all cases that were solved with one or a few defibrillation attempts, such as reperfusion VF, were excluded. The latter circumstance is probably an explanation for the difference in survival rate presented by Herlitz et al. [3] compared to the survival rate in Papers I and II. Since no other studies have described a similar population, these differences make comparisons delicate.

The DANAMI-2 trial in 2003 showed that primary PCI was superior to fibrinolytic therapy in STEMI patients [27]. Hochman et al. showed a survival benefit in patients in CS treated with early invasive strategy, both in the short- and long-term perspective [52, 53]. The results from these studies contributed to new treatment recommendations, which may have increased referrals to the cath-lab of patients in a more severe cardio-vascular circulatory condition with a higher risk of developing CA. When comparing historical data to current data, indications for referral to the cath-lab may have changed over time. Over a four year period (1999 – 2003) prior to the introduction of the LUCAS™ device, only 10 patients with one survivor were treated with prolonged CPR with manual CC in the cath-lab. The introduction of the new treatment recommendations [133] corresponds to the introduction of the use of MCC in the cath-lab. This may explain the difference in the numbers of patients in the pre-MCC era (n=10) compared to the MCC era (n=75) suffering CA requiring prolonged CPR.

Physiological parameters in cardiopulmonary resuscitation

The cath-lab offers a unique opportunity to treat and monitor physiological response during prolonged CPR in CA. The personnel involved can react immediately to changes in vital parameters and evaluate given therapy in tandem with continued cardiac/coronary intervention. Though the absolute minimum values in vital parameters for obtaining ROSC are unknown, some reasonable recommendations are possible. Animal studies have suggested a systolic ABP of at least 70 – 80 mmHg, diastolic values > 25 to around 40 mmHg and mean ABP > 40 mmHg [11, 56, 57]. In human studies a diastolic ABP > 25 mmHg [55] and a CPP > 15 mmHg [63] have been suggested. Values of $ETCO_2$ > 2.0 kPa have been proposed in several studies [87, 90] and SpO_2 > 80% has been proposed in a few reports [83, 84]. Hence, to achieve these values, high quality CPR as well as the position of the CC pressure point [93, 116-119], and the ventilation rate might be important [120]. When analysing $ETCO_2$ during CCs, one should be aware that CC can cause compression artefacts. Positive pressure ventilation during MCC can result in baro-trauma, so if possible, experienced personnel should be assigned this task. Other reasons for suboptimal values in

physiological parameters such as cardiac tamponade must also be ruled out simultaneously.

The use of cerebral oximetry (SctO$_2$) in CA situations has been found to be feasible [134] and able to predict ROSC [135]. Yet an editorial ask if the increase of SctO$_2$ during CPR is instead an early indicator of ROSC [136]. In a small pilot study (n=5), the monitoring of SctO$_2$ in CA situations in the cath-lab was found to be feasible. However, due to the small number of patients further conclusions could not be drawn [112].

Coronary artery blood flow velocity and coronary perfusion pressure

In Paper IV there was a significant correlation between CPP and APV during VF with circulation maintained by MCC. During ongoing MCCs, APV was equal or higher than baseline levels. Simultaneously, the CPP was well above 20 mmHg.

After ROSC, CPP approaches the baseline value. In APV there is an initial increase but this gradually decreases to the baseline values. One can speculate that the APV value is primarily driven by hyperaemia caused by a post-ischemic state and probably a release of a number of endogenous substances such as adenosine tri-phosphate and catecholamines, which is known to be extremely high in this situation in human and animal resuscitation [137-139]. Coronary perfusion pressure, however, is a theoretical calculation which does not take into account a dilatation or constriction of the capillary bed of the myocardium, which is of course of great importance for the actual coronary flow when measuring APV.

Some animal studies have shown evidence of good coronary flow measured by CPP [11, 45] and case studies have documented visually normalized coronary blood flow (TIMI III) in CA patients with circulation maintained with MCC [7, 9] and Paper I. Thus the findings in Paper IV support the findings in these studies, namely that effective circulation ca be maintained by MCC during prolonged CA.

Epinephrine in cardiopulmonary resuscitation

Human and experimental studies have shown that a CPP above 15 mmHg increases the possibility of attaining ROSC following defibrillation [62-64, 94, 140]. Hence, to strive towards a CPP greater than 15 mmHg during CPR seems logical. Several experimental studies have shown that an EPI-induced increase of CPP leads to a higher probability of subsequent ROSC [15, 62, 64]. However, it is important to stress that in these studies only one injection of EPI was administered. The use of repetitive doses of one mg EPI every fourth to fifth minute as recommended in current guidelines for CPR [5] has been shown to have a positive effect on attaining ROSC but to have a

worse neurological/survival outcome at discharge from hospital [16, 19]. This has also been observed when using higher cumulative doses of EPI [17].

The goal in Paper V was to simulate a CA in the cath-lab, with a short period of untreated VF, followed by repeated administrations of EPI during CPR in conjunction with defibrillation-resistant VF. Repeated EPI injections increased CPP in three out of four injections with a subsiding effect after the third injection. On the contrary, in the control group CPP remains stable throughout the VF period. The increase in CPP only transfers the first injection into a significant increase in APV. Thus, the increase in CPP after EPI injections two and three indicate a rise in local vascular resistance and a lesser amount of oxygenated blood reaching the myocardium. These findings correspond to the findings of Brown et al., using standard doses of EPI [141]. In studies investigating repeated EPI injections, Bar-Joseph et al. showed a significant increase in CPP only after the first injection of repeated doses of high dose EPI (0.1mg/kg) [142]. Cairns et al. showed a significant increase in CPP only in the animals that attained ROSC after the first EPI injection followed by defibrillation [143]. The studies by Bar-Joseph et al. and Cairns et al. used longer periods of untreated VF simulating out-of-hospital CA, higher doses of EPI and defibrillation attempts after each injection of EPI [142, 143].

In regard to coronary pressures and their influence on bioelectrical activity during VF, a high CPP correlates to a high AMSA in some studies [94, 96]. Similar to the findings in Paper V, Achleitner et al. showed an elevated mean fibrillation frequency and VF mean amplitude during basic life support, i.e. without the influence of administered EPI [144]. On the contrary, AMSA showed an insignificant tendency to decline in the EPI groups in Paper V despite the increase in CPP, which is similar to previous findings [144]. Despite different CPR methods and EPI dosages, the results in AMSA were similar in a previous study [144] compared to the findings in Paper V. This may have contributed to a successful defibrillation in only 7 out of 12 animals in each EPI group. A possible explanation for this result may be an increased vascular resistance induced by EPI resulting in a decreased myocardial microcirculatory blood flow, which has also been described in capillaries of the brain [109].

Thus, the lack of effects on APV and AMSA following the repeated doses of EPI may be a result of a successively diminished myocardial tissue perfusion caused by EPI. The initial injection of EPI may serve a purpose, but repeated injections may not be beneficial and may, in fact, be detrimental in subjects with VF whose circulation is reasonable with CC.

According to the physiology-guided CPR approach in the cath-lab described in Paper III, restrained use of indiscriminate injections of bolus doses of EPI should be considered when patients are sufficiently circulated by MCC. The findings in Papers IV and V, and the negative effects of EPI found in other studies [15-17, 19, 109], support this approach. However, in special circumstances, the addition of

norepinephrine [28, 124] or a low dose infusion of EPI might be necessary to preserve acceptable physiology [125].

Treatment perspective of delayed defibrillation and physiology-guided resuscitation

When patients deteriorate into refractory VF in the cath-lab, it is mainly due to an occluded coronary artery. The approach with delayed defibrillation until the vessel is opened, described in Paper III and previously suggested by Kern et al. [123], has been successful to some extent [145-147] and may offer further evidence for sufficient circulation in defibrillation-resistant VF. If the patient is in PEA/asystole, PCI should be continued during MCC. During the PCI procedure, the focus is on optimizing each vital physiological parameter during the intervention. When successful reperfusion with PCI is accomplished, additional CPR efforts are continued including norepinephrine and/or an infusion of EPI if needed and as described in Paper III.

Future perspectives

Another approach to further increasing survival in the cath-lab might be the introduction of extracorporeal membranous oxygenation, which has been used in CA treatment situations with some success [148-150]. If implementing this strategy, the challenge will be to choose the "right" patient, namely one who is already in CA. In a Japanese study of patients suffering CA who were treated with extracorporeal membranous oxygenation, the authors found that patients with refractory VF or pulseless VT without any evidence of developing signs of multiple organ dysfunction, had a favourable outcome [151]. Nevertheless, to improve the chances of successful results in this scenario, it is again important to optimize the prerequisites such as teamwork, knowledge of vital parameters and optimal quality of CC and ventilation prior to the initiation of the extracorporeal membranous oxygenation.

Another option is to prevent the patient's CA. In the group in our study where the patients expired, most of them were in CS at the time of admission and suffered CA during the intervention. A possible tool for selection might be blood lactate in STEMI patients with CS, which has been shown to be a predictor of mortality [152, 153]. It might be possible in this group that patients could be selected for extracorporeal membranous oxygenation [154, 155] or Impella® [156] before the CA occurs. Both the strategy with Impella® in patients with acute MI complicated by CS [157] as well as with extracorporeal membranous oxygenation in the setting of OHCA [158] are currently under evaluation in two randomised studies. A novel percutaneous axial catheter pump, the Reitan catheter pump (CardioBridge GmbH, Hechingen,

Germany) has been proven to reduce afterload and increase organ perfusion in animal studies [159], and offer hemodynamic and renal improvement in patients with acutely decompensated severe cardiac failure [160]. Furthermore, the Reitan catheter pump has been proven safe for use during high-risk PCIs [161]. This device might also be suitable in the setting of CS but further studies are necessary.

Conclusions

This thesis included both human and animal CA studies in the setting of prolonged CPR efforts including MCC during simultaneous percutaneous cardiac and coronary intervention in the cath-lab. The use of the LUCAS™ device in this setting has been shown to be feasible without impairment of PCI result; it is safe and can save lives. In the two human studies (Papers I and II) the survival rate at discharge from hospital in good neurological condition was 25% and survival six months after hospital discharge was 84% in a composite of the survivors in Papers I and II. The visualized normal coronary artery blood flow in CA patients when circulation was maintained by MCC was objectively confirmed in Paper IV. When circulation was maintained by MCC, the coronary artery APV was significantly increased compared to baseline values during normal circulation. Thus, MCC can, at minimum, re-establish coronary blood flow in non-diseased coronary arteries during CA. Repeated administration of EPI during CPR when pigs are adequately circulated by means of MCCs does not increase coronary artery APV or improve AMSA despite increased CPP.

Populärvetenskaplig sammanfattning

Bakgrund

Akut hjärtinfarkt orsakas av att en blodådra (kranskärl) i hjärtat täpps till. Tillståndet behandlas vanligtvis med kateterburen teknik med så kallad ballongsprängning av det tilltäppta kranskärlet och anläggande av stent med hjälp av röntgengenomlysning. Detta görs på sektioner oftast kallade kranskärlsröntgen laboratorier. Hjärtstopp i samband med akut hjärtinfarkt på kranskärlsröntgen är inte ovanligt och i de flesta fall behandlas hjärtstoppet med en eller ett par strömstötar eller en kortare tids manuella bröstkompressioner. Däremot är långvarig hjärtlungräddning (HLR) med manuella bröstkompressioner och samtidig ballongvidgning mycket svårt att utföra med god kvalitet och dödligheten är hög i denna patientgrupp. Dels på grund av att det blir en så kallad trampolineffekt vid manuella bröstkompressioner på ett röntgenbord, men även att sikten försämras för den som utför ballongvidgningen eftersom den som utför bröstkompressionerna hindrar röntgenstrålarna och blir själv utsatt för en oacceptabel hög stråldos. År 2003 introducerades en mekanisk brötkompressions apparat (LUCAS™) i Region Skånes alla ambulanser. LUCAS™-apparaten utför bröstkompressioner enligt aktuella HLR riktlinjer. I djurförsök har den visat sig upprätthålla en god cirkulation till hjärtat och till hjärnan. Sedan 2004 har LUCAS™-apparaten varit i bruk på kranskärlsröntgen i Lund. Det medförde att man kunde utföra långvarig HLR med mekaniska bröstkompressioner och samtidig ballongvidgning utan att behöva avbryta för vare sig den ena eller andra åtgärden.

I samband med undersökningar på kranskärlsröntgen övervakas rutinmässigt patientens hjärtrytm, syremättnad och blodtryck. Om patienten är medvetslös och får andningshjälp kan man även mäta koldioxid i utandningsluften. Utandad koldioxid kan användas som mått på hur väl patienten är cirkulerad. I de fall där patienten drabbas av hjärtstopp, ger övervakningen en unik möjlighet att följa HLR-kvaliteten genom att bedöma nivåerna på syremättnad, blodtryck och utandad koldioxid (vitala parametrar). För de flesta i personalstyrkan som ingår i larmgruppen var det en ny och okänd situation med HLR med LUCAS™-apparaten och samtidig ballongvidgning. Situationen var inte sällan ostrukturerad och man tog ingen större hänsyn till möjligheten att använda övervakningen för att bedöma HLR-kvaliteten.

När patienter som fick HLR med LUCAS™-apparaten kunde man i många fall se ett i det närmaste normaliserat blodflöde i kranskärlen. Omvänt såg man, att i de fall där patienterna fick adrenalin direkt i blodet i samband med HLR, försämrades möjligheten att göra en korrekt bedömning av kranskärlen eftersom dessa drog ihop sig

och blev mycket smalare än normalt. Det finns visserligen studier som visar att adrenalin som ges i samband med HLR ökar antalet återupplivade patienter som skrivs in på sjukhuset, men färre skrivs ut levande från sjukhus från denna grupp. Av de som överlever som fått adrenalin är det däremot ingen skillnad jämfört med de som inte fått adrenalin i samband med HLR när de skrivs ut från sjukhus.

Därför syftar denna avhandling (bestående av 5 delarbeten) till att utvärdera effekten av den mekaniska bröstkompressionsapparaten LUCAS™ i samband med långvarig HLR och samtidig behandling av hjärtats kranskärl på människa, att bedöma cirkulationen i hjärtmuskeln när cirkulation upprätthålls av mekaniska bröstkompressioner utan- och med adrenalin, att organisera och optimera HLR-situationen anpassat till kranskärlsröntgen.

Metoder

Utvärderingen har skett i två perioder, 2004 – 2008 och 2009 – 2013. Patienter som drabbades av hjärtstopp på kranskärlsröntgen och krävde långvarig HLR med mekaniska bröstkompressioner och samtidig ballongvidgning inkluderades. Orsak till hjärtstoppet, antal lyckade ballongvidgningar och överlevnad studerades.

Ett strukturerat HLR-protokoll utvecklades, grundat på erfarenheterna från den första utvärderingsstudien och på en del patienter i den andra utvärderingsstudien. Arbeten studerades där man undersökt HLR-kvalitet, och vitalparametrars betydelse i samband med HLR.

Två djur-hjärtstoppstudier utfördes. I den första studien undersöktes betydelsen av mekaniska bröstkompressioner på blodflödet i hjärtats kranskärl. I den andra studien undersöktes effekten av adrenalin (givet enligt dagens riktlinjer för HLR), på blodflödet i hjärtats kranskärl, det beräknade genomströmningstrycket i hjärtmuskeln och den bioelektriska aktiviteten i hjärtmuskelns celler.

Resultat

Första utvärderingsstudien (arbete I) inkluderade 43 patienter. Utav dessa kunde 11 patienter (25%) skrivas ut från sjukhuset med välbevarad hjärnfunktion. Sjuttiofem procent hade akut hjärtinfarkt och 75% av behandlingarna bedömdes som tekniskt lyckade under pågående HLR. Medelbehandlingstiden med bröstkompressioner var 28 minuter för hela gruppen och för de som kunde skrivas ut från sjukhuset var det 16.5 minuter.

Andra utvärderingsstudien (arbete II) inkluderade 32 patienter där 8 patienter (25%) kunde skrivas ut från sjukhuset med välbevarad hjärnfunktion. Även i denna studie var det 75% som hade akut hjärtinfarkt och 81% av behandlingarna under pågående HLR bedömdes som tekniskt lyckade. I en sammanslagen grupp bestående av överlevarna från båda utvärderingsstudierna var överlevnaden 6 månader efter utskrivning 84%.

I arbete III identifierades ett behov av utbildning rörande HLR på kranskärlsröntgen med dess möjligheter att övervaka och optimera patientens cirkulation och syresättning vid pågående HLR med mekaniska bröstkompressioner, kunskap om vitala parametrar; förståelsen av teamarbete i den komplicerade HLR-situationen med samtidig ballongvidning, och HLR-träning på kranskärlsröntgen. Ett HLR-protokoll utarbetades anpassat för kranskärlsröntgen samtidigt som hela personalstyrkan som bemannar hjärtlarmgruppen undervisades och tränades i HLR på kranskärlsröntgen.

I första djurförsöket (arbete IV) ökade blodflödets hastighet i hjärtats kranskärl markant när cirkulation upprätthölls med mekaniska bröstkompressioner jämfört med normal cirkulation, med en hög överensstämmelse med genomströmningstrycket i hjärtmuskeln.

I andra djurförsöket (arbete V) steg genomströmningstrycket i hjärtmuskeln markant efter injektion av adrenalin i 3 av 4 injektioner jämfört med en kontrollgrupp som fick koksalt. Däremot ökade blodflödets hastighet i kranskärlet markant endast efter första adrenalininjektionen. Den bioelektriska aktiveten ökade inte, men en tendens till försämring sågs. I kontrollgruppen återfick 83% egen cirkulation. Endast 58% återfick egen bärande cirkulation i adrenalingruppen.

Slutsatser

Tack vare sin röntgen-genomsläpplighet och förmåga att upprätthålla en god cirkulation gör MCC med LUCAS det möjligt att på ett säkert sätt fortsätta med ballongvidningen trots samtidig långvarig HLR. Behandlingsresultatet är inte nämnvärt försämrat jämfört med då patienten har normal cirkulation. Överlevnaden med välbevarad hjärnfunktion är hög i denna grupp. Sannolikt hade få, om ens några överlevt utan tillgång till mekaniska bröstkompressioner under pågående HLR och samtidig ballongvidning. Det anpassade protokollet för HLR på kranskärlsröntgen upplevs ge en ökad säkerhet och framgångskänsla hos personalen i HLR-situationer på kranskärlsröntgen Det visuellt normaliserade blodflödet i hjärtats kranskärl som sågs vid HLR med MCC blev objektivt bekräftat i den första djurstudien med en god samstämmighet med genomströmningstrycket i hjärtmuskeln. Den andra djurstudien visar att om individen är tillfredsställande cirkulerad med hjälp av mekaniska

bröstkompressioner under pågående HLR tillför upprepade injektioner adrenalin enligt dagens riktlinjer ingen förbättring av blodflödet i hjärtmuskeln.

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Appendix

Original papers I – V

I. Cardiac arrest in the catheterization laboratory: A 5-year experience of using mechanical chest compressions to facilitate PCI during prolonged resuscitation efforts. Resuscitation 2010, 81:4. 383 - 387

II. Mechanical Chest Compressions in the Coronary Catheterization Laboratory to Facilitate Coronary Intervention and Survival in Patients Requiring Prolonged Resuscitation Efforts. Manuscript. Submitted.

III. A Structured Approach for Treatment of Prolonged Cardiac Arrest Cases in the Coronary Catheterization Laboratory Using Mechanical Chest Compressions. Int J Cardiovasc Res 2013, 2:4

IV. Evaluation of Coronary Blood Flow Velocity during Cardiac Arrest with Circulation Maintained through Mechanical Chest Compressions in a Porcine Model. BMC Cardiovascular Disorders 2011, 11:73

V. Repeated epinephrine doses during prolonged cardiopulmonary resuscitation have limited effects on myocardial blood flow: a randomized porcine study. BMC Cardiovascular Disorders 2014, 14:199

Paper I

Clinical paper

Cardiac arrest in the catheterisation laboratory: A 5-year experience of using mechanical chest compressions to facilitate PCI during prolonged resuscitation efforts ☆

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ARTICLE INFO

ABSTRACT

Purpose: Lengthy resuscitations in the catheterisation laboratory carry extremely high rates of mortality because it is essentially impossible to perform effective chest compressions during percutaneous coronary intervention (PCI). The purpose of this study was to evaluate the use of a mechanical chest compression device, LUCAS™, in the catheterisation laboratory, in patients who suffered circulatory arrest requiring prolonged resuscitation.
Materials and methods: The study population was comprised of patients who arrived alive to the catheterisation laboratory and then required mechanical chest compression at some time during the angiogram, PCI or pericardiocentesis between 2004 and 2008 at the Lund University Hospital. This is a retrospective registry analysis.
Results: During the study period, a total of 3058 patients were treated with PCI for ST-elevation myocardial infarction (STEMI) of whom 118 were in cardiogenic shock and 81 required defibrillations. LUCAS™ was used in 43 patients (33 STEMI, 7 non-ST-elevation myocardial infarction (NSTEMI), 2 elective PCIs and 1 patient with tamponade). Five patients had tamponade due to myocardial rupture prior to PCI that was revealed at the start of the PCI, and all five died. Of the remaining 38 patients, 1 patient underwent a successful pericardiocentesis and 36 were treated with PCI. Eleven of these patients were discharged alive in good neurological condition.
Conclusion: The use of mechanical chest compressions in the catheterisation laboratory allows for continued PCI or pericardiocentesis despite ongoing cardiac or circulatory arrest with artificially sustained circulation. It is unlikely that few, if any, of the patients would have survived without the use of mechanical chest compressions in the catheterisation laboratory.

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Cardiac arrest in the catheterisation laboratory during percutaneous coronary interventions (PCIs), although a rare event, is often treated rapidly and successfully with cardiopulmonary resuscitation (CPR) and DC conversions.[1] In a minority of these patients, the initial resuscitation efforts are not immediately successful, and extended periods of manual chest compressions are needed to maintain coronary and cerebral circulation. In patients who require prolonged CPR, mortality rates are very high.[2] Frequently, a continued uninterrupted PCI procedure of, for example, a suddenly occluded left main artery is often the best option for attaining return of spontaneous circulation (ROSC). However, continued cardiac compressions with simultaneous PCI, which requires fluoroscopy, is exceedingly difficult to perform effectively.

A novel mechanical chest compression device, LUCAS™ (Jolife AB, Lund, Sweden), (Fig. 1), has been shown to sustain both coronary and cerebral circulation despite cardiac arrest.[3,4] The device is mostly radio translucent, enabling continued PCI with maintained circulation despite ongoing cardiac arrest, which has been documented in several reports.[5–9] Although LUCAS™ has been shown to be successfully used in the catheterisation laboratory to maintain circulation,[5–9] a recent report found abysmal survival rates in patients who were brought to the catheterisation laboratory

Fig. 1. Image of LUCAS™, Jolife AB, Lund, Sweden.

in cardiac arrest but with circulation maintained with mechanical chest compressions.[8] Our experience since 2004 with the chest compression device LUCAS™ is similar. Essentially, all patients admitted to our catheterisation laboratory already in cardiac arrest, but with circulation maintained through mechanical chest compressions, do not survive. However, patients who arrive at the catheterisation laboratory with intact circulation and who then suf-

fer cardiac arrest in the catheterisation laboratory, often during the procedure of angiography or PCI, may have a benefit of LUCAS™, especially if there is concomitant PCI performed.

1. Methods

The study is a retrospective registry analysis of all patients who suffered a prolonged resuscitation episode while scheduled for any procedure in the coronary catheterisation laboratory at the Lund University Hospital during 2004–2008, to which the hospital's cardiac arrest team was alerted. The database of the cardiac arrest team was used to find the patients in the study.

Prolonged resuscitation was defined as an episode of cardiac arrest necessitating a period of several minutes of manual chest compressions, followed by the use of a mechanical chest compressions and then tracheal intubation. The other selection criterion was that the patients had to arrive alive to the catheterisation laboratory before the episode of cardiac arrest. We also evaluated similar patients (requiring >1 min of manual chest compressions and requiring tracheal intubation) in which no mechanical chest compression device was used in the same time span.

During the period 1 January 2004 to 31 December 2007, the mechanical chest compression device used was LUCAS V1 (European version).[3] During the period 1 January 2008 to 31 December 2008, the mechanical chest compression device used was LUCAS V2 (US version), which has the same operating parameters as LUCAS V1 except for the decompression force which is set to a maximum of 13 N.

All charts and autopsy reports of our cohort of 43 patients were examined. The predefined endpoints were mortality status on departure from the catheterisation laboratory, successful PCI and discharge from hospital in the Cerebral Performance Categories (CPCs) 1 or 2,[10] representing a good neurological outcome.

The use of LUCAS™ was stopped at the discretion of the attending physician either because the patient achieved ROSC or because further treatment with LUCAS™ was deemed futile.

Table 1
Patient characteristics and outcomes.

	n (%)	In hospital death	Discharged alive
Patient history (n = 43)			
Hypertension	24 (56%)	16	8
Diabetes	11 (25.5%)	10	4
Hyperlipidemia	15 (35%)	10	7
Smoking/X-smoke	22 (51%)	16	3
Previous MI	12 (28%)	8	4
Previous PCI	5 (11.5%)	5	0
Previous CABG	6 (14%)	5	1
Indication for cath lab procedure (n = 43)			
STEMI	33 (77%)	27	6
NSTEMI	7 (16.1%)	3	4
Elective PCI	2 (4.6%)	0	2
Tamponade	1 (2.3%)	1	0
Culprit lesion in coronary patients (n = 42)			
LM	9 (21%)	6	3
LAD	25 (60%)	20	5
LCx	2 (4.7%)	0	2
RCA	6 (14.3%)	5	1
Initial rhythm at cardiac arrest (n = 43)			
VF/VT	6 (14%)	2	4
PEA	28 (65%)	25	3
Asystole	9 (21%)	4	5

Background information of the 43 patients, the indication for the procedure in the cath lab, the culprit coronary artery and the initial rhythm at cardiac arrest. AMI: acute myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, STEMI: ST elevation myocardial infarction, NSTEMI: non-ST elevation myocardial infarction, LM: left main artery, LAD: left anterior descending artery, Cx: left circumflex artery, RCA: right coronary artery, VT: ventricular tachycardia, VF: ventricular fibrillation, PEA: pulseless electrical activity.

Table 2
Procedural data of the 42 coronary patients.

Procedural data	n (%)	In hospital death	Discharged alive
Angiography only	6 (15%)	5	1
PCI successful	27 (76%)	16	11
PCI Unsuccessful	8 (24%)	8	0
Use of IABP	19 (43%)	9	10

The procedural data in the cath lab a technically successful PCI was defined as achieving a residual stenosis in the coronary artery of <50% with TIMI 2 or 3 blood flow. PCI: percutaneous coronary intervention, IABP: intraaortic balloon pump, TIMI blood flow: a grading scale developed by the Thrombolysis in Myocardial Infarction study group in which TIMI 2 or 3 indicates successful reperfusion.

2. Results

During the study period, a total of 6350 PCIs were performed of which 3058 patients were treated for acute ST-elevation myocardial infarctions (STEMI). A total of 118 patients were in cardiogenic shock and 81 required defibrillations due to VF or ventricular tachycardia (VT).

Mechanical chest compressions were used in 43 patients of which 31 (72%) were males. Patients were between ages 31 and 86 years (mean age: 73.3 years). The patients were admitted for STEMI, non-ST-elevation myocardial infarct (NSTEMI), elective PCI and pericardiocentesis (Table 1). The culprit artery was the left anterior descending artery (LAD) or the left main in 81% of the cases and 65% of the patients had PEA as the initial rhythm during cardiac arrest (Table 1).

A total of 36 PCIs were attempted in the 42 patients with coronary disease, of which 27 PCIs were considered 'technically successful' procedures defined as a residual stenosis <50% at the site of the target lesion and achieving TIMI 2 or TIMI 3 blood flow with ongoing mechanical chest compressions (Table 2).[11] Reasons for unsuccessful PCIs were primarily complex lesions, distal embolisation or no reflow in the coronary arteries and not primarily due to the use of LUCAS™. A total of 39 were treated with LUCAS™, and mean treatment time was 28.15 min (SEM ± 3.4, range: 1–90 min). Seventeen patients were discharged from the catheterisation laboratory, one with ongoing treatment with mechanical chest compressions and 16 with ROSC. Twenty-six patients were declared dead in the catheterisation laboratory (Fig. 2). In six of the coronary patients, no PCI was performed; in five cases, the reason was undiagnosed subacute myocardial rupture that suddenly became a fulminate rupture in the catheterisation laboratory and in one case, it was global ischaemia without any

obvious culprit lesion. All five patients with myocardial rupture and tamponade died. Three patients were referred for emergency cardiac surgery, of which two died during surgery and one postoperatively. In 31 patients, the PCI procedures were performed with ongoing mechanical chest compressions and in four patients, only an angiogram was performed during mechanical chest compressions. Of the 17 patients who were discharged from the catheterisation laboratory, 12 were eventually discharged from the hospital with 11 of them in CPC 1 (Fig. 2). The initial rhythm in the 12 patients discharged alive was VF in four patients, PEA in three patients and asystole in five patients. One of the discharged patients had incurred a serious hypoxic brain injury and later died at the referral hospital. One patient, who was successfully treated for cardiac tamponade, died at the oncology ward due to cancer, and one patient died in the ward due to therapy-resistant VF.

Of the 11 patients who were discharged in good condition, all underwent successful PCIs, and in eight of the cases the PCI was performed with ongoing LUCAS™, while in two cases, LUCAS™ was used during the angiography. The mean treatment time of LUCAS™ for the 11 survivors was 16.5 min (SEM ± 3.8, range: 1–50 min).

All 12 patients, who were discharged from hospital, suffered rib fractures and, possibly, sternal fractures. One of the survivors suffered a ruptured spleen and gastric ventricle due to user error. Six autopsies were performed on the remaining thirty-one patients who died, and rib fractures were seen in all six patients and sternal fractures in five patients. One autopsy showed a small bleeding around the aortic arch. No other potential injuries of consequence due to mechanical chest compressions were found.

During the study period, only four patients with a lengthy cardiac arrest were treated with manual chest compressions alone and all four patients died.

3. Discussion

We have retrospectively analysed the effect of using a mechanical chest compression device as an adjunctive treatment for patients who suffer extended periods of cardiac arrest following arrival in the catheterisation laboratory and found that >25% of the patients could eventually be discharged to their homes in good neurological condition (CPC 1).

Although approximately 2,000,000 patients undergo PCI yearly worldwide, during the procedure, only a very small minority of patients will suffer a protracted cardiac arrest episode that results in death.[1] However, performing effective manual chest compressions during a PCI in the catheterisation laboratory is linked with
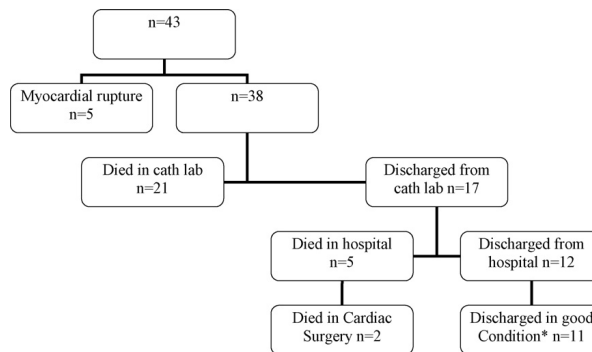
Fig. 2. Flow chart of the treatment and outcomes. Flow chart illustrating the treatment and outcomes of the patients in the study. *Cerebral Performance Categories, CPC 1.

extreme difficulties. Thus, it would be attractive to have a chest compression device that could deliver effective compressions while still allowing for continued PCI due to its radio-translucent design. LUCAS™ is one of two available mechanical chest compressions devices, the other being Autopulse™ (Zoll Medical Corporation, Chelmsford, MA, USA), which has been used in the catheterisation laboratory. With LUCAS™, due to the anterior–posterior (AP) design of the piston, essentially all views (such as cranial, caudal, RAO and LAO) except the straight AP are available during the time LUCAS™ is in place. Fortunately, the available views are almost always the preferred angiographic views during PCIs even without LUCAS™. Manoeuvring the X-ray detector around LUCAS™ is easily performed with a monoplane catheterisation laboratory and with more difficulty in a biplane laboratory. Although LUCAS™ produces an excessive movement of the chest and is somewhat bulky, it should still always be feasible, although not always easy, to perform a PCI. But if a high-precision manoeuvre is required, such as positioning a coronary stent, LUCAS™ can be temporarily paused for a few seconds, which remedies the situation of excessive chest movement during stenting.

How well does LUCAS™ work? From animal data, LUCAS™ been shown to maintain a positive coronary perfusion pressure and restore at least 60% of the cerebral blood flow in pigs.[3,4] In one particular patient, LUCAS™ maintained circulation for 25 min, during which time the patient was in VF. Following PCI and defibrillation, the patient regained consciousness in the catheterisation laboratory and was later discharged in CPC 1.[12] In patients with cardiac arrest and ongoing treatment with LUCAS™, Larsen et al. found that a mean systolic blood pressure of 70 mmHg (range: 60–110 mmHg, $n = 11$) could be attained,[8] which mirrors our own experience.

However, all of the patients in the study by Larsen et al. were already in cardiac arrest before arrival to the catheterisation laboratory and all these patients died. On the contrary, all the patients in our study arrived to the catheterisation laboratory with intact circulation and of these, 11 of 43 patients survived to discharge.

The main issue for patients in cardiac arrest is to restore circulation to the brain and only thereafter to attempt to remedy the cause of the cardiac arrest. Other means to solve restoration of blood flow in cardiac arrest in the catheterisation laboratory has been through percutaneous cardiopulmonary bypass (PCPB) or percutaneous left ventricular assist devices (PLVADs) such as Impella™ (Abiomed Inc., Danvers, MA, USA) or Tandem Heart™ (CardiacAssist Inc., Pittsburgh, PA, USA). Several small studies using PCPB in intractable cardiac arrest have been reported with good results.[13–15] PCPB and PLVADs seem to be effective but are usually take longer to initiate and can require extra staff with special skills, such as a cardiovascular surgeon and a perfusionist. LUCAS™ may, on the other hand, be applied quickly (<1 min) and may also be used as a bridge to a PLVAD or PCPB.

There are several limitations to our study. First, we were unable to find any remaining recordings of continuous blood pressure measurements or coronary perfusion pressures during the periods of mechanical chest compressions, but in our experience, the circulation attained mirrors that found by Larsen et al. Second, two surviving patients had use of mechanical chest compressions for a limited time, less than 5 min. However, both patients had undergone treatment with CPR and manual compressions for several minutes prior to the application of LUCAS™. Third, this is a retrospective registry study and is limited in size. Still, our centre is the first one to ever use LUCAS™ during PCI in the catheterisation laboratory and we have collected a large cohort of patients, mainly from our STEMI population.

During the analysed period, mechanical chest compressions during prolonged CPR were not used in four patients who were either very old or suffering from severe co-morbidities.

Another issue of importance is if mechanical chest compressions cause more injuries to patients than manually performed chest compressions. Manual chest compressions are well known to cause traumatic complications[16,17] and this is also likely to occur with mechanical chest compression devices to at least a similar degree.[18] Reports of injuries caused by manual chest compressions are, however, difficult to compare due to different methodologies used,[19] but a large ongoing randomised trial comparing manual chest compressions to mechanical chest compressions in out-of-hospital cardiac arrest will address this issue (the LINC study, see www.clinicaltrials.gov).

Among our patients, only one patient suffered severe injuries due to treatment with LUCAS™, but this was due to misapplication, as the LUCAS™ device was placed too low and started performing compressions in the upper abdomen, which caused traumatic rupture of both the gastric ventricle and the spleen. Both the gastric bleeding as well as the ruptured spleen was revealed and successfully treated during abdominal surgery following PCI. All survivors showed evidence of likely suffering from non-debilitating rib fractures and possibly sternal fractures. Similar injuries were seen in the limited number of autopsies performed on the deceased patients.

One patient suffered an anoxic brain injury. It is unclear why this occurred, but it is likely due to a delay in applying LUCAS™, as this was one of the early patients that LUCAS™ was used in, and this delay caused an insufficient cerebral perfusion leading to the injury.

Finally, one great advantage of mechanical chest compressions during cardiac arrest emergencies in the catheterisation laboratory is the ability to provide continuous chest compressions. Any interruption of chest compressions compromises both heart and brain blood flow. Such interruptions are a leading cause of poor outcome from cardiac arrest wherever it occurs. In circumstances where PCI or pericardiocentesis can correct the underlying cause of cardiac arrest, the provision of continued perfusion during such emergent procedures can result in not only lives being saved, but normal functioning neurological outcomes being achieved as well.[20]

4. Conclusions

Mechanical chest compressions devices enable continued chest compressions during PCI with maintained circulation, which may reduce mortality in patients with cardiac arrest, requiring lengthy CPR, in the catheterisation laboratory, especially in patients with an initial rhythm of VF.

Conflict of interest statement

Acknowledgments

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Paper II

Mechanical Chest Compressions in the Coronary Catheterization Laboratory to Facilitate Coronary Intervention and Survival in Patients Requiring Prolonged Resuscitation Efforts

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Abstract

Background
Resuscitation after cardiac arrest (CA) in the catheterization laboratory (cath-lab) using mechanical chest compressions (CC) during simultaneous percutaneous coronary intervention (PCI) is a class IIa recommendation in the 2010 AHA guidelines. This study aimed to re-evaluate survival to hospital discharge and assess 6-month outcomes in this patient population.

Methods
Patients presenting at the cath lab with spontaneous circulation, suffering CA, requiring prolonged mechanical CC during procedures from 2009-2013 were included. Circumstances leading to CA, resuscitation parameters and outcomes were evaluated within this cohort. For comparison, patients needing prolonged manual CC in the cath lab in the pre-mechanical CC era were evaluated. Six-month survival with a mechanical CC treatment strategy from 2004-2013 was evaluated.

Results
Thirty-two patients were included between 2009-2013 (24 ST-elevation myocardial infarction (STEMI), 4 non-STEMI, 2 planned PCI, 1 angiogram and 1 intra-aortic counter pulsation balloon pump insertion). Twenty were in cardiogenic shock prior to inclusion. Twenty-five were successfully treated with PCI. Median mechanical CC duration for the total cohort (n=32) was 34 min (range 5-90), for the 15 patients with circulation discharged from the cath-lab, 15 min (range 5-90), and for the eight discharged alive from hospital, 10 min (range 5-52). Twenty-five percent survived with good neurological outcome at hospital discharge. Ten patients treated with manual CC were included with one survivor.

Conclusions
Among patients suffering CA treated with mechanical CC in the cath-lab, 25% had a good neurological outcome at hospital discharge compared to 10% treated with manual CC. Six-month survival in patients discharged from hospital was 84%.

Introduction

Since 2004, we have routinely used a mechanical chest compression (CC) device in cardiac arrest (CA) situations in the coronary catheterization laboratory (cath-lab) when initial advanced resuscitation efforts have failed to obtain return of spontaneous circulation. A mechanical CC device can successfully be used to overcome the difficulties of performing manual CC during simultaneous percutaneous coronary intervention (PCI) [1]. There have been an increasing number of publications describing favorable outcomes with this treatment option, mostly small cohort studies and case reports [2-7]. We have previously documented a 25% survival rate in cerebral performance category 1 or 2 at hospital discharge using this treatment strategy [8]. Since 2010, the use of mechanical CC in CA situations in the cath-lab during simultaneous PCI has been incorporated into the American Heart Association's guidelines with a class-IIa level of evidence C [9].

When implementing a new treatment strategy, it is important to evaluate the results over a long period of time. One of the difficulties with new treatment options is that they are often introduced without critical evaluation such as a randomized trial and without an organized implementation [10]. Over the years of using mechanical CC in the cath-lab in resuscitation efforts in combination with simultaneous PCI, we have noted several practical short-comings. This has led to the development of a more structured and more tightly conducted approach, which has been described in detail elsewhere [11]. We have therefore continued to evaluate both short and long term outcomes in patients suffering CA and treated with mechanical CC during an invasive cardiac/coronary procedure.

However, little is known about survival to hospital discharge and long term survival after CA in the cath-lab when the patient is in the need of prolonged advanced resuscitation efforts during an invasive cardiac/coronary procedure. Ehlenbach et al. analyzed the outcomes of CA, in individuals >65 years of age suffering in-hospital CA, where the survival to discharge was 18.3% [12]. Girotra et al. studied in-hospital CA with an overall survival rate of 17% to discharge from hospital, with survival rates increasing from 13.7% to 22.3% at the end of the study [13]. However, CA cases occurring during a procedure in the operating room, in procedural suites or in the emergency department,

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were excluded [13]. A recently published study on in-hospital CA found a survival rate to discharge from hospital of 18.4% [14]. Further, in a Swedish study, the survival rate to discharge in in-hospital CA was found to be 37% and one-year survival among discharged patients was 84% [15]. Another study focusing on in-hospital CA, in an elderly cohort >65 years of age, concluded that among the patients discharged from hospital, 59% of were alive 1 year after discharge [16].

Therefore the aim of this prospective study was to analyze circumstances leading to CA and resuscitation parameters, to re-evaluate survival to hospital discharge and to assess 6-month outcomes in this patient population who suffer CA and require prolonged resuscitation with mechanical CC in combination with an invasive cardiac/coronary procedure.

Material and methods

This prospective study was performed between 9 April 2009 and 9 April 2013 at the cath-lab at Skane University Hospital, Lund, Sweden. This is a tertiary center in southern Sweden that performs PCIs 24 hours a day, 7 days a week, and serves a population of 1.2 million. The study was approved by the local ethics review board (667/2009). Informed consent was obtained from survivors or from family members.

Among those who suffered a CA in the cath-lab, patients were included if immediate resuscitation efforts failed and there was consensus among the attending cardiologist, anesthesiologist and the interventionist that mechanical CC was indicated. The reason for referral to the cath-lab for those who were included in the study was either a diagnostic coronary angiogram in a coronary stable state, non-ST-elevation myocardial infarction (non-STEMI), elective planned PCI, insertion of an intra-aortic balloon counter pulsation device and for primary PCI in patients suffering a STEMI.

Cardiac arrest treatment was performed according to the structural approach described elsewhere [11]. For mechanical CC, the LUCAS™2 chest compression system (Physio-Control/Jolife AB, Lund, Sweden) was used. The patient cohort was evaluated in four outcome groups: patient characteristics for the whole group, for patients who expired in the cath-lab, for patients discharged from the cath-lab and for patients discharged from hospital. The predefined endpoints were spontaneous circulation when leaving the cath-lab, and hospital discharge in cerebral performance category 1 or 2 [17]. The cause of the referral to the cath-lab, culprit lesion, circulatory state at the time of arrival to the cath-lab and rhythm at the time of the occurrence of the CA, were assessed in the 4 outcome groups. The number of PCIs during mechanical CC was assessed and successful PCI was defined according to the thrombolysis in myocardial infarction (TIMI) flow [18]. Treatment times with mechanical CC were calculated for all groups and compared across the four outcome groups. The use of vasoactive drugs was assessed.

As a comparison outcomes for 10 consecutive patients suffering CA who needed prolonged

resuscitation with manual CC in the cath lab (from 1999 – 2003) (the time period prior to the start of

using mechanical CC in our lab) were analyzed using the local hospital CA registry and medical files.

Inclusion criteria were the same as for those treated with mechanical CC (i.e. patients suffering CA

where initial resuscitation efforts failed).

The 6-month survival rate was analyzed in a merged group that consisted of 11 patients discharged

from hospital in cerebral performance category 1 – 2 from a previous retrospective registry (1

January 2004 to 31 December 2008) [8] and the eight patients discharged from hospital in the

current study.

Statistical methods
Continuous data are presented as mean ±SD and median and range as appropriate. Categorical

variables are presented as numbers or percentages. For non-parametric statistics, the Mann-Whitney

U-test was used for calculating differences between the outcome groups, in age and mechanical CC

time. A p-value < 0.05 was considered significant.

Results

Thirty-two patients were included during the study period. For patient demographics see Table 1.

Patient characteristics such as the indications for cath-lab procedure, culprit lesion, circulatory state

upon arrival at the cath-lab, and rhythm when the CA occurred, are presented in Table 2.

Table 1

Patient demographics, concomitant diseases, smoking habits and previous coronary interventions in

included patients.

Patient History	All patients n=32 (%)	Expired Cath-lab 17 (53)	Discharged Cath-lab 15 (47)	Discharged Hospital 8 (25)
Age	70.9±12.9	73±10	68.3±15.2	68.1±18.8
Gender (male)	20 (63)	11(65)	9 (60)	4 (50)
Hypertension	18 (56%)	9 (53)	9 (60)	7 (86)
Diabetes	8 (25%)	6 (35)	2 (13)	2 (25)
Hyperlipidemia	9 (28 %)	7 (41)	2 (13)	2 (25)
Smoking/X-smoker	14 (44%)	7 (41)	7 (47)	4 (50)
Previous MI	9 (28%)	4 (24)	5 (33)	4 (50)
Previous PCI	3 (9%)	1 (6)	2 (13)	2 (25)
Previous CABG	4 (13%)	3 (18)	1 (7)	1 (13)

Cath-lab = coronary catheterization laboratory, MI = myocardial infarction, PCI = percutaneous

coronary intervention, CABG = coronary artery by-pass grafting.

In one specific patient, the reason for referral for the intra-aortic balloon counter pulsation insertion

was therapy-resistant ventricular tachycardia with cardiogenic shock. In the patients referred for

planned PCI and non-STEMI, complications such as, for example, thrombus formation, vessel rupture

and dissection caused the CA. One of the patients with non-STEMI was in cardiogenic shock at the

time of arrival at the cath-lab. The patient, who was referred for an elective pre-operative coronary

angiogram for surgery on the aortic valve, deteriorated into pulseless electrical activity due to aortic

stenosis and reduced systolic left ventricular function.

Seventeen patients expired in the cath-lab. Fifteen left the cath-lab with circulation, of whom eight were discharged from hospital in cerebral performance category 1 - 2. During the study period (9 April 2009 – 9 April 2013), 8738 patients were admitted to the cath-lab for an invasive cardiac/coronary procedure. In total, 3368 patients were evaluated with a coronary angiogram only and 5370 patents were treated with PCI (acute or elective) whereof 2728 were treated for STEMI. Of these, 116 patients were in cardiogenic shock when admitted to the cath-lab. There was no statistical age difference between the patients who expired in the cath-lab and those who were discharged from the cath-lab with circulation (p = 0.37) and those discharged from hospital (p = 0.64). Successful PCI defined as TIMI-II-III or <50% residual stenosis, PCI during mechanical CC, and treatment time with mechanical CC are presented in Table 3. There was a statistically significant difference in time with mechanical CC when comparing patients who expired in the cath-lab to those discharged from the cath-lab with circulation (p = 0.02) and to those discharged from hospital (p = 0.004). At least one vasoactive drug (norepinephrine, epinephrine or dobutamine) was administered either intermittently or as a continuous infusion) to 29 patients, and the majority received a combination of these drugs during the procedure.

Table 2

Indication for referral to the coronary catheterization laboratory, culprit lesion, circulatory state at arrival in the coronary catheterization laboratory, rhythm at the time of the cardiac arrest.

	All patients n = 32 (%)	Expired Cath-lab 17 (53)	Discharged Cath-lab 15 (47)	Discharged Hospital 8 (25)
Indication for cath-lab procedure				
STEMI	24 (75)	15 (88)	9 (60)	4 (50)
non-STEMI	4 (13)	1 (6)	3 (20)	2 (25)
Elective PCI	2 (6)	1 (6)	1 (7)	1 (13)
Other	1 (3)	0	1 (7)	1 (13)
Angiogram	1 (3)	0	1 (7)	0 (0)
Culprit lesion in coronary patients				
LM	10 (31)	6 (35)	4 (27)	2 (25)
LAD	12 (38)	7 (41)	4 (27)	2 (25)

LCx	2 (6)	0	3 (20)	2 (25)
RCA	6 (19)	4 (24)	2 (13)	1 (13)
Other	2 (6)	0	2 (13)	1 (13)
Circulatory state at the arrival to the cath-lab				
Cardiogenic shock	20 (62)	12 (71)	8 (53)	2 (25)
Initial rhythm at cardiac arrest				
VT/VF	5 (16)	1 (6)	4 (27)	2 (25)
PEA	22 (69)	14 (82)	8 (53)	4 (50)
Asystole	5 (16)	2 (12)	3 (20)	2 (25)

Cath-lab = coronary catheterization laboratory, STEMI = ST-elevation myocardial infarction, non-STEMI-non-ST-elevation myocardial infarction, PCI = percutaneous coronary intervention, LM = left main coronary artery, LAD = left anterior descendent coronary artery, LCx = left circumflex coronary artery, RCA = right coronary artery, VT = ventricular tachycardia, VF = ventricular fibrillation, PEA = pulseless electrical activity.

Table 3

Coronary catheterization laboratory procedural data.

Procedural data	All patients n=32 (%)	Expired Cath-lab 17 (53)	Discharged Cath-lab 15 (47)	Discharged Hospital 8 (25)
Angiography during MCC	5 (16)	2 (12)	3 (20)	2 (25)
PCI during MCC	27 (87)	16 (94)	11 (73)	6 (75)
PCI successful	25 (81)	12 (71)	13 (87)	6 (75)
PCI unsuccessful	6 (20)	5 (29)	1 (7)	1 (12.5)
Use of concomitant IABP	12 (38)	3 (18)	9 (60)	4 (50)
CC- time	34 (5-90)	42 (10-75)	15 (5-90)	10 (5-52)
Thoracic surgery	4 (13)	0	4 (27)	2 (25)

Cath-lab = coronary catheterization laboratory, PCI = percutaneous coronary intervention, MCC = mechanical chest compression, IABP = intra-aortic counter pulsation pump, CC = chest compression times are presented as median minutes (range).

The manual CC treated group

Ten patients (eight men) with a mean age of 67.9 ±6.3 years suffered CA and required prolonged advanced resuscitation efforts with manual CC in the cath-lab between 1 January 1999 and 31

December 2003. Eight of these were referred due to a STEMI; one patient had a non-STEMI, and one patient had developed a ventricular septum defect due to a STEMI a few days earlier. Seven patients were in cardiogenic shock when admitted to the cath-lab. Two patients had a shockable rhythm at the time of the CA. Six patients were treated with PCI during manual CC, with 50% PCI success rate. The median time with manual CC for the whole group (n = 10) was 20 min (range 15 – 75min), 20 min (range 15 – 75) for those who expired in the cath-lab (n = 6), 25 min (range 15 – 60) for those discharged from the cath-lab (n = 4), and 15 min for the patient discharged from hospital in cerebral performance category 1 (n = 1).

6-month survival rate

In the merged group with survivors discharged from hospital in cerebral performance category 1 – 2 from the previous study (n = 11) [8] and current study (n= 8) there was an 84% survival rate at six months (n = 16) (Figure 1).
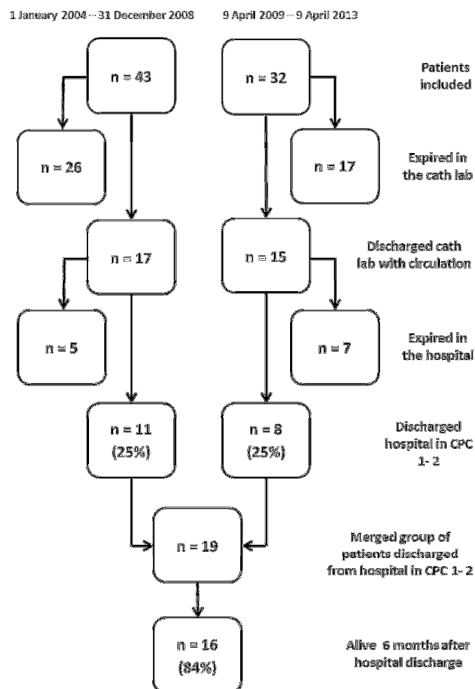
Figure 1.

Flow-chart showing the included patients requiring prolonged advanced resuscitation including

mechanical chest compressions during percutaneous coronary/cardiac interventions (Cath-lab =

coronary catheterization laboratory, CPC = cerebral performance category)

Discussion

In this prospective study evaluating the outcomes of patients treated with mechanical CC during a simultaneous cardiac/coronary procedure due to CA where normal advanced resuscitation efforts had failed, we found a 25% survival rate in cerebral performance category 1 or 2 at hospital discharge. These results verify our previous retrospective study [8] and lend further support to the current AHA guideline [9].

In-hospital CA could depend on a broad range of underlying conditions [12-15, 19, 20]. Reported survival rates to discharge from hospital after in-hospital CA vary widely, from 17 to 36% [12-15, 19, 20] and differences in inclusion and exclusion criteria are important when interpreting the results. In some studies, subgroups such as patients suffering a CA during a medical procedure or in the emergency department [13], or patients <65 years of age, have been excluded [12]. There are also important differences in background factors such as a high rate of initial shockable rhythm (49% and 39%) [15, 20]. As a comparison, the study presented here included patients without age restriction suffering CA in the cath lab, who required prolonged advanced resuscitation efforts including mechanical CC during an intervention, and only 16% had an initial shockable rhythm. Thus, comparisons with the referred studies are delicate because of the important population differences.

In one registry report covering survival to hospital discharge after a CA in the cath lab, survival was as high as 65% [19]. The survival difference compared to our study may be caused by different inclusion criteria. In the report by Herlitz et al. [19], a large proportion of patients suffering a CA may have received one or two defibrillations and/or a few moments of manual CC. The incidence of reperfusion ventricular fibrillation in patients with STEMI treated by primary PCI in the cath-lab in our institution is 1.9% annually, with a survival rate of 81.7% at discharge from hospital when defibrillated early [21]. In the current study we have excluded these specific patients: hence making direct comparisons with the study by Herlitz et al. [19] and the study by Demidova et al. [21] in terms of survival are difficult.

In the current study, 27 patients (84%) had a non-shockable rhythm at the time of the CA. This indicates that coronary ischemic-driven CA in this setting has a large proportion of patients presenting with a rhythm not treatable with defibrillation. A similar percentage was seen in our previous study [8] and in our historical group treated with manual CC. However, these percentages differ from other in-hospital studies, where 51% and 61% had an initial non-shockable rhythm [15, 20]. Again the cohorts studied in these papers differ, because all patients suffering a CA by any cause are included [15, 20] compared to the highly selected cohort in our current study. However, in the study by Nolan et al. there was a high amount of non-shockable rhythm (72.9%) and only 16.9% had an initial shockable rhythm [14]. The cause is unclear, but one explanation might be that 56.6% of the CAs occurred in a general ward, likely without monitoring [14]. Thus the occurrence of the CA may not be instantly noticed, which may lead to the conversion of an initial ventricular fibrillation or a pulseless ventricular tachycardia to a non-shockable rhythm, but this remains speculative.

Twenty-five out of 31 (80%) interventions were successful. Considering that 87% of the interventions were performed during mechanical CC, an 80% success rate is reasonable compared to the expected 90% success rate in primary PCI for STEMI [22]. In the previous study, there was a 76% PCI success rate [8]. Thus, the use of mechanical CC during simultaneous PCI does not appear to reduce PCI results substantially compared to primary PCI for STEMI.

In the 10 patients from the pre-mechanical CC era treated with manual CC, 10% survived to hospital discharge. One problem comparing historical data is that indications for referral to the cath-lab may have changed over time. This may be reflected by the fact that only 10 patients in four years needed prolonged resuscitation. The DANAMI-2 trial in 2003 showed superiority for primary PCI compared to fibrinolytic therapy in STEMI-patients [23], and Hochman et al. showed a survival benefit in patients in cardiogenic shock treated with early invasive strategy both in the short and long term perspective [24, 25]. The results of these studies may have increased referrals to the cath-lab of patients in a more severe cardio-vascular circulatory condition at greater risk of developing CA.

In the group treated with mechanical CC, only two (25%) of the patients discharged alive from hospital were in cardiogenic shock compared to 12 (60%) who expired in the cath-lab. This mortality rate is higher compared to what was reported by Minha et al. where 29% with cardiogenic shock expired in the cath-lab [26]. In another large registry (patients suffering CA and resuscitated prior to PCI), CA was more common in patients with cardiogenic shock presenting with and without STEMI, where 82% of the deceased patients in the STEMI-group and 78% in the non-STEMI group were in cardiogenic shock [27]. One explanation for the high mortality rate in the group with cardiogenic shock might be that when a CA has occurred, the hemodynamic status prior to the CA reflects the severity of the disease, which may be important for achieving the return of spontaneous circulation.

In the merged group (2004–2013), the 6-month survival rate for patients discharged from the hospital in cerebral performance category 1 – 2 was 84%. This is higher in comparison to a large retrospective study of elderly patients where the survival rate after in-hospital CA was found to be 58% at one year [16] but similar to the study from Fredriksson et al. [15]. However, these studies included different causes of CA and survival was analyzed at different time points, which makes comparison difficult.

When implementing new technologies in medical settings, it is important that this be done methodologically and with thorough follow-up [10]. In the case of the implementation of mechanical CC in the cath-lab, there have been no randomized trials. Over the past ten years, we have included 75 patients and show a survival rate of 25% at discharge from hospital. With this number of patients and reproducible findings of successful interventions, we find the use of mechanical CC devices in the cath lab to be a reliable, safe and a valuable tool in the treatment of CA during PCI.

In an effort to further increase the survival rate for these patients, extracorporeal membranous oxygenation has been used in CA treatment situations with some success [28-30]. If implementing this strategy, the challenge will be to choose the "right" patients. In a Japanese study, the authors found that patients with refractory ventricular fibrillation and pulseless ventricular tachycardia

without any evidence of developing signs of multi-organ dysfunction had a favorable outcome when treated with extracorporeal membranous oxygenation [31]. Most of those who died in our current study were in cardiogenic shock at the time of admission to the cath-lab. A reasonable thought is that the patients with cardiogenic shock should be selected for extracorporeal membranous oxygenation or Impella®, perhaps prior to the occurrence of the CA. Both the strategy with Impella® as well with extracorporeal membranous oxygenation for prolonged resuscitation efforts are currently under evaluation in two randomized studies [32, 33].

Limitations

The study has some limitations. Firstly, it was not a randomized, controlled study. However, performing a randomized study in this setting and comparing mechanical CC to manual CC during simultaneous PCI might be controversial, since it is exceedingly difficult to perform manual CC during simultaneous PCI and the CC provider would be exposed to unacceptably high amounts of X-ray radiation. The numbers of patients treated with manual CC during prolonged CA in the cath-lab are small, which make comparison difficult. The time period covering the period prior to the start of using mechanical CC could not be extended since registration started in 1999 and treatment recommendations differ in the two time periods. Despite the limitation of being a small study (only 0.09% of the patients who were referred for primary PCI suffered CA and required prolonged resuscitation including mechanical CC), this is the second-largest prospective single-center case series (n = 32) describing the use of mechanical CC devices in the cath-lab.

Conclusion

This study confirms the results of our earlier study, which showed a survival rate at hospital discharge of 25% in patients treated with mechanical CC during PCI and who arrived at the cath-lab with spontaneous circulation. Furthermore, there was an 84% 6-month survival rate with good neurological outcome among patients discharged from the hospital.

Contributions

HW has drafted the concept and design of the study, acquisition and evaluation of data, drafted the manuscript and was the main writer and has participated in the treatment of the patients.

BMH participated in the concept and design of the study, statistical analysis, of data as well as critical evaluation of the manuscript.

MR has participated in the treatment of the patients, critical evaluated the manuscript.

MG has participated in the treatment of the patients and critically evaluated the manuscript.

DZ has participated in the treatment of the patients and critically evaluated the manuscript.

JH has participated in the treatment of the patients and critically evaluated the manuscript.

GOA has drafted the concept and design of the study and has participated in the treatment of the patients and critically evaluated the manuscript.

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Paper III

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A Structured Approach for Treatment of Prolonged Cardiac Arrest Cases in the Coronary Catheterization Laboratory Using Mechanical Chest Compressions

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Abstract

Background: This article aims at describing a logistic approach for prolonged resuscitation efforts in the cath-lab using mechanical chest compressions (MCC) during simultaneous percutaneous coronary intervention (PCI).

Methods: When analysing physiological measurements and logistics in 10 patients experiencing prolonged CA in the coronary intervention laboratory (cath-lab), critical areas for improvement were identified. 1. Understanding and commitment to team work with designated individual roles. 2. Practical simulations within the cath-lab setting. 3. Knowledge of the physiological parameters limitations for successful restoration of spontaneous circulation (ROSC). 4. Familiarity with the advanced technology needed.

Results: The medical emergency team and the cath-lab team were trained as one team. A structured approach was developed: In patients not obtaining ROSC following a few minutes of advanced life support according to guidelines, perform MCC during simultaneous PCI and optimize physiological parameters; arterial blood pressure ≥70/40 mmHg, end-tidal carbon dioxide ≥15 mmHg/2.0 kPa, pulse oximetry >80%, thrombolysis in myocardial infarction-3-flow in open vessels and cerebral oximetry ~45%. Optimization can be done by repositioning the MCC-device, changing the ventilation rate, by use of vasoactive drugs and correction of acidosis. In shock resistant ventricular fibrillation, maintain circulation by MCC until restoration of coronary flow prior to further defibrillation attempts. Consider therapeutic hypothermia.

Conclusion: Implementing a structured resuscitation approach during prolonged resuscitation efforts in the cath-lab, might improve team work and physiological parameters, which may result in a more calm and success-oriented setting.

Keywords

Resuscitation; CPR; Mechanical chest compressions; PCI; Cardiac arrest

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Introduction

Cardiac arrest (CA) in the coronary intervention laboratory (cath-lab) is commonly resolved with defibrillation and a short period of chest compressions (CC). However, in some cases, the patient is in need of prolonged resuscitation efforts and does not obtain return to spontaneous circulation (ROSC) by advanced life support (ALS) according to current guidelines. In a previously study, we have shown a 25% survival rate among patients needing prolonged resuscitation efforts after suffering CA in the cath-lab [1,2]. This was achieved using mechanical chest compressions (MCC) provided by the LUCAS–device (Physio-Control Sweden/Jolife AB, Lund, Sweden) and simultaneously performing emergent percutaneous coronary intervention (PCI). The use of MCC has since been elevated to Class IIa in the AHA guidelines for use during CA in the cath-lab with simultaneous PCI [3].

Through our early experience we identified several points that were complex in this resuscitation situation: Familiarity with the working environment in the cath-lab, team work among the multiple staff involved, recognising the cause of the CA (typically a catastrophic acute closure of a coronary artery), and the opportunity for continuous monitoring of vital physiological parameters during the resuscitation effort. Available physiological parameters in most cath-labs include ECG, arterial blood pressure (ABP), end tidal carbon dioxide ($ETCO_2$) and pulse oximetry (SpO_2). These parameters have previously been correlated with successful return of spontaneous circulation (ROSC) in several studies [4-11]. This approach to monitor resuscitation efforts by physiology in cath-lab has to some extent already been described by Kern and co-workers [12], but has not been clinically tested or refined. Furthermore, our cath-lab setting (one interventionist, two registered nurses and one assistant nurse) and the staffing for medical emergencies such as CA (one anaesthesiologist, one registered anaesthetic nurse, one assistant nurse and one cardiologist) differ from day to day, which makes this approach challenging. Since the resuscitation situation is different in the cath-lab compared to a CA in an ordinary hospital ward, the demands for highly regimented team work, with specific assignments for individual personnel are important.

This article aims therefore to describe important changes in the standard advanced life support algorithm when implementing prolonged resuscitation efforts in the cath-lab combining MCC and PCI.

Material and Methods

Mechanical chest compressions were performed using a LUCAS™2 device. Parameters of ECG, ABP, central venous pressure (CVP), SpO_2 and $ETCO_2$ were monitored on an IntelliVue MP90 monitoring system (Philips, Eindhoven, The Netherlands), and cerebral oximetry ($SctO_2$) was monitored using the FORE-SIGHT (CAS Medical Systems, Inc. Branford, CT, US) monitoring system. Thrombolysis in myocardial infarction (TIMI) flow in non-occluded vessels was assessed as done routinely during PCI [13]. The hemodynamic parameters were recorded every 2nd to 5th ms on an external PC-computer using custom made software and evaluated using Lab Chart 7 (AD Instruments Corp., Colorado Springs, CO,

US). Coronary perfusion pressure (CPP) was calculated as described earlier [13]. Hemodynamic parameters collected are presented as mean ±SD of different time intervals of the MCC period for each patient.

Deficiencies found in the early experience

When analysing the physiologic parameters in the first 10 patients with prolonged CA in the cath lab [2] we noticed several deficiencies regarding monitoring and team work. Individual hemodynamic data, treatment and outcome for each patient are shown in Table 1. Four areas needing improvement were identified from this data. First, an understanding of the importance of team work within the unique circumstances of a prolonged resuscitation effort in the cath-lab. Second, the importance of practical simulations within the cath- lab setting. Third, an understanding of the vital physiological parameters for the successful restoration of spontaneous circulation. Fourth, familiarity with the advanced technology needed to succeed during such emergent and stressful circumstances.

Specific problems addressed following the initial evaluation

1. The complex collaboration required during resuscitation in the cath-lab between different categories of personnel was not fully appreciated in the beginning. This resulted in suboptimal team work.

2. Only two patients had all physiological parameters collected; we found long periods without recording of ABP data in all patients. In one patient three vital parameters were at suboptimal levels without any corrective action to optimize these parameters (Figure 1). The recommended ventilation rate [14] during resuscitation was not often followed (hyperventilation). We also found numerous variations in artefacts on the recorded $ETCO_2$ curve (Figure 2), ECG-leads and the SpO_2 probes fell off frequently and were not always placed on the patient again.

3. The monitor in the cath-lab was optimized for ischemic monitoring (Figure 3a).

4. The resuscitation algorithm was practiced in a separate training area, but not specifically in the cath-lab procedure room, thereby not experiencing the real life space and other limitations in these situations.

5. The extra equipment needed for resuscitation efforts blocked the movement of people in the room as wells as the movements of the fluoroscopy equipment.

6. Individual persons in the team were not trained to react in response to the measured physiological parameters, partly due to lack of knowledge of important minimally acceptable levels needed to secure return of spontaneous circulation.

Results

Training and teamwork

When launching the new approach, several lectures for cardiologists, anaesthesiologists, interventionists, nurses and assistant nurses, were held with focus on training CA-scenarios, team-work and the knowledge of minimally acceptable levels of vital parameters needed for successful resuscitation.

Monitoring equipment

In the cath-lab there are two web cameras, these are turned-on at the beginning of any CA situation which gives the possibility to record the resuscitation situation and serve as feedback and debriefing instrument. All hemodynamic measurements important for resuscitation should be recorded on the monitoring equipment in the cath-lab to simplify an instant overview of the vital parameters.
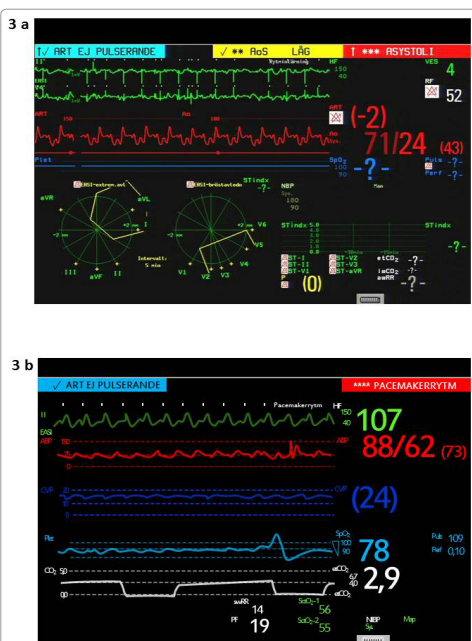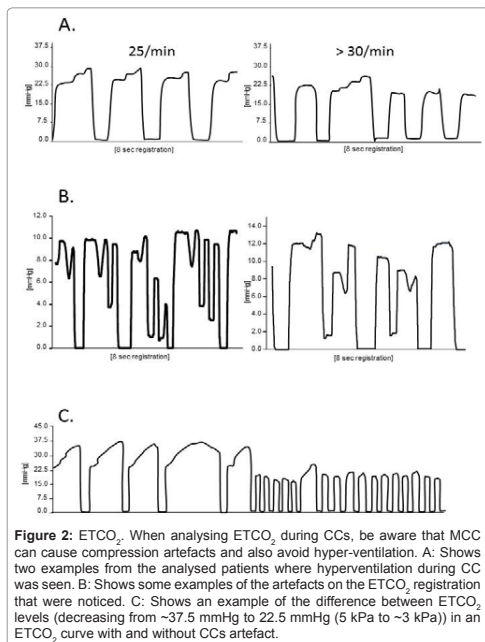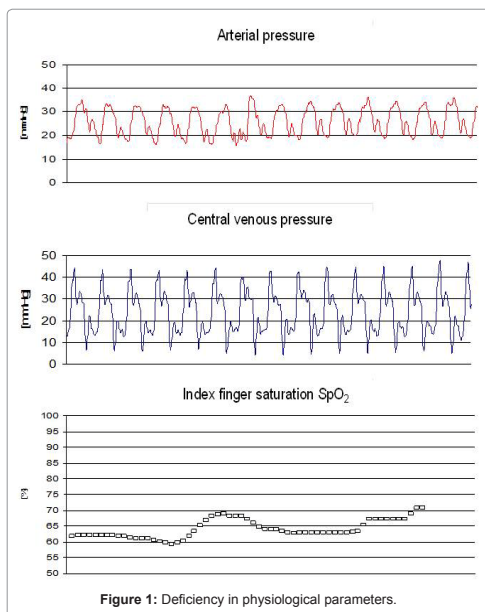
Other specific recommendations

- SpO_2, ECG and ABP should be measured from the start of all interventions in the cath-lab.

- In case of a CA, defibrillate as early as possible if indicated by rhythm. All these cases are witnessed and do not have a high volume load on the venous side [12,15]. After defibrillation, start immediately CC if the patient does not obtain instantaneous ROSC.

Table 1: Physiologic parameters, CPR time, outcome and drug treatments data in the 10 first patients evaluated, data is presented as Mean ± SD.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
ABP Systolic [mmHg]	114 ± 18	133 ± 4	63 ± 2	50 ± 18	87 ± 7	85 ± 6	34 ± 3	139 ± 19	117 ± 15	81 ± 10
ABP Diastolic [mmHg]	2 ± 12	10 ± 4	39 ± 3	22 ± 8	59 ± 4	7 ± 6	20 ± 2	nd	31 ± 18	12 ± 10
ABP Mean [mmHg]	40 ± 4	51 ± 3	46 ± 4	31 ± 10	68 ± 7	33 ± 6	25 ± 2	43 ± 9	60 ± 16	35 ± 9
CVP Systolic [mmHg]	123 ± 10	95 ± 4	nr	nr	nr	nr	46 ± 2	169 ± 17	70 ± 10	nr
CVP Diastolic [mmHg]	15± 11	-12 ± 3	nr	nr	nr	nr	6 ± 9	nd	13 ± 6	nr
CVP Mean [mmHg]	52 ± 13	24 ± 3	nr	nr	nr	nr	19 ± 1	36 ± 8	32 ± 7	nr
SpO_2 [%]	82 ± 8	81 ± 0	95 ± 0	77 ± 6	78 ± 4	nr	64 ± 3	nr	nr	nr
$ETCO_2$ [mmHg]	18 ± 3	26 ± 2	21 ± 4	nr	nr	nr	nr	nr	23 ± 5	nr
Outcome	ROSC (312 h)	Dead in lab	ROSC (216h)	Dead in lab	ROSC (13 h)	CPC 1	Dead in lab	Dead in lab	CPC 1	Dead in lab
CPR time (min)	45	50	15	75	35	10	50	30	45	70
Nor-ephinephrine	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Epinephrine	YES	NO	No	YES	YES	NO	YES	YES	No	YES
Dobutamin	YES	YES	YES	YES	YES	NO	NO	NO	NO	NO

ABP = Arterial Blood pressure, CVP = Central Venous Pressure, SpO_2 = Index finger saturation, $ETCO_2$ = End Tidal carbon Dioxid, nd = not determint due to artifacts, nr = not registered or lost during procedure. ROSC = Return Of Spontaneous Circulation, CPC = Cerebral Performance Category

Figure 1: Deficiency in physiological parameters.

Figure 2: ETCO₂. When analysing ETCO₂ during CCs, be aware that MCC can cause compression artefacts and also avoid hyper-ventilation. A: Shows two examples from the analysed patients where hyperventilation during CC was seen. B: Shows some examples of the artefacts on the ETCO₂ registration that were noticed. C: Shows an example of the difference between ETCO₂ levels (decreasing from ~37.5 mmHg to 22.5 mmHg (5 kPa to ~3 kPa)) in an ETCO₂ curve with and without CCs artefact.

Figure 3: Monitoring settings. 3a shows the monitoring screen equipment optimized for ischemic monitoring normally used during cardiac interventions. 3b shows the monitoring screen equipment optimized for physiologic monitoring during resuscitation efforts.
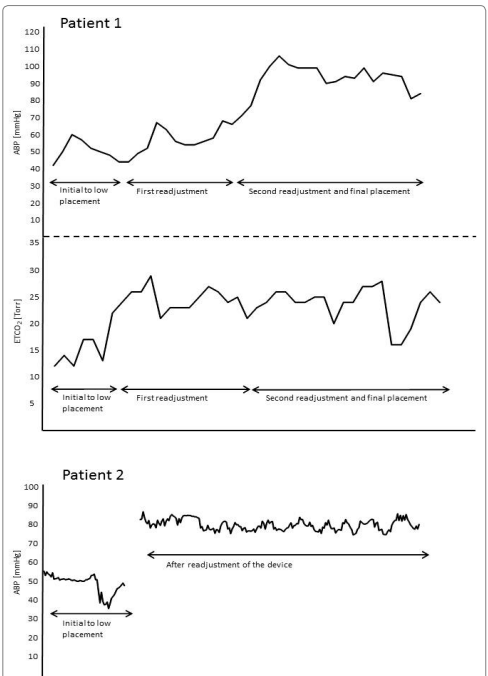
- If the CA situation has not been solved in a few minutes with manual CC and defibrillations, apply the MCC-device and start CC's in 30:2 mode (30 CC followed by two ventilations) for patients not intubated. The MCC-device should be placed in the cath-lab for quick access and deployment (Figure 5).

- When the patient is intubated, switch to continuous MCCs and a ventilation rate of 10/min, ventilation has to be modified to avoid high intra-thoracic pressures. Intermittent manual ventilation "between compressions" is usually possible. When blood gases are available, ventilation should aim at normo ventilation. Blood gases should also be used for adjustment of acidosis if needed.

- Alert the medical emergency team whose swift arrival should be in 60-90 seconds.

- Select a team leader (most often the cardiologist).

- If the patient has a shock resistant VF, continue MCC and precede with PCI in order to open the occlusion, rather than continue with further defibrillation attempts while the culprit coronary vessel remains occluded.

- Place the equipment brought by the medical emergency team in dedicated zones marked on the floor, so as not to interfere with the needed fluoroscopic projections; Left anterior

oblique (LAO) Cranial/Caudal Oblique, RAO Cranial/Caudal Oblique, Straight Caudal, Straight Lateral and Straight Cranial in monoplane (Figure 6).

- As soon as the patient is intubated start monitoring $ETCO_2$.

- To simplify an instant overview of the vital parameters, use a special designed monitor-screen showing one continuous ECG-lead, two ABP-curves, one CVP-curve (optional), one $ETCO_2$-curve, one SpO_2-curve and values for $SctO_2$ (Figure 3b).

- Optimize physiological parameters according to Table 2. Since coronary perfusion pressure (CPP) cannot be calculated instantaneously, TIMI might be used as a surrogate marker since it has been shown to correlate to CPP [16,17].

- If systolic ABP is below 70 mmHg, rule out cardiac tamponade, reposition the LUCAS-device (Figure 4), consider change in ventilation rate, or administer inotropic/vasoactive medications. Be careful with the latter to avoid high dose adrenaline (ADR).

- Apply the electrodes of $SctO_2$ on the fore head of the patient as soon as possible if available.

- On the interventionist´s discretion, an introducer in the femoral vein could be inserted, both in order to place a pig tail catheter in the right atria for measuring CVP and to serve as a central venous line for infusions and drug administration.

- Collaboration between the anaesthesiologist and cardiologist is key in all efforts to optimize vital parameters.

- In the relatively rare cases of pulmonary oedema, an adjustable PEEP-valve could be tried. When ROSC has been attained, intermittent positive pressure ventilation using a conventional ICU ventilator can be started.

- Record physiology parameters and communicate to the team leader and anaesthesiologist repeatedly or when dramatic changes occurs, each and every one in the cath-lab has the responsibility to react on unsatisfactory physiology parameters.

- Consider initiation of therapeutic hypothermia as soon as possible.

- If successful PCI is accomplished and the patient has a

Figure 4: Chest compressions point. Shows the increase in systolic blood pressure and $ETCO_2$ due to change of compression point for the MCC device since low blood pressure registrations were noted (in two patients). During the same period we also noted changes in the systolic and mean arterial pressure.
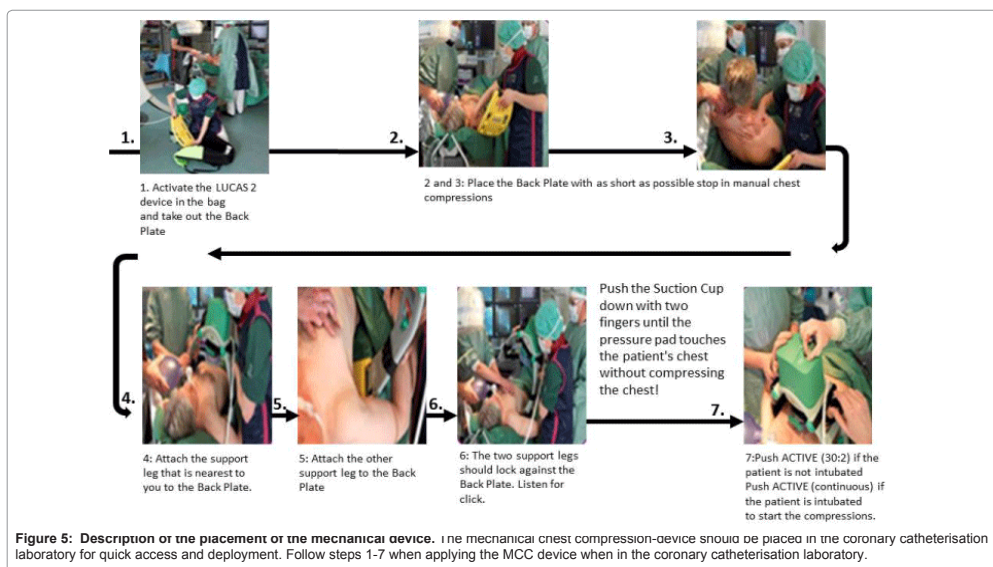
shockable rhythm, defibrillate during MCC, if no success, consider one bolus injection of ADR (1 mg) followed by defibrillation.

- If successful PCI and the patient has pulseless electrical activity (PEA) or a systole, continue MCC for 15-20 minutes followed by an infusion of ADR for approximately 2-3 minutes, then administering a bolus dose of 1 mg of ADR. Continue MCC for at least 10 minutes after last drug delivery before termination of resuscitation efforts.

- If successful PCI and the patient has obtained ROSC, deploy a left ventricular assist device if needed. Prepare for further post resuscitation treatment in the intensive care unit according to recommendation by guidelines [18] or local directive.

Discussion

In the cath-lab setting of prolonged resuscitation efforts, it is possible to monitor a number of important physiological parameters that has been predictive of resuscitation success in earlier studies [4-10]. On-going responses during the resuscitation to optimize such parameters might improve outcome, but this could probably only be accomplished when specific roles are assigned in the crucial team work dynamics.

Table 2: Target values for vital physiological parameters during the resuscitation in the cath-lab setting. Aortic diastolic pressure (AoD), Right atrial diastolic pressure (RaD), Thrombolysis in myocardial infarction (TIMI).

Parameter		Target value
Arterial blood pressure (ABP)	Systolic	>70 mmHg
	Diastolic	>40 mmHg
Central venous pressure (CVP)	Diastolic	<25 mmHg
Coronary perfusion pressure (CPP)	(AoD-RaD)	>15 mmHg
End Tidal Carbon Dioxide (ETCO$_2$)	Mean	>10 mmHg or >2 kPa
Pulse oximetry (SpO$_2$)		>80 %
Cerebral oximetry (SctO$_2$)		>45 %
Coronary flow		TIMI-3

Figure 5: Description of the placement of the mechanical device. The mechanical chest compression-device should be placed in the coronary catheterisation laboratory for quick access and deployment. Follow steps 1-7 when applying the MCC device when in the coronary catheterisation laboratory.
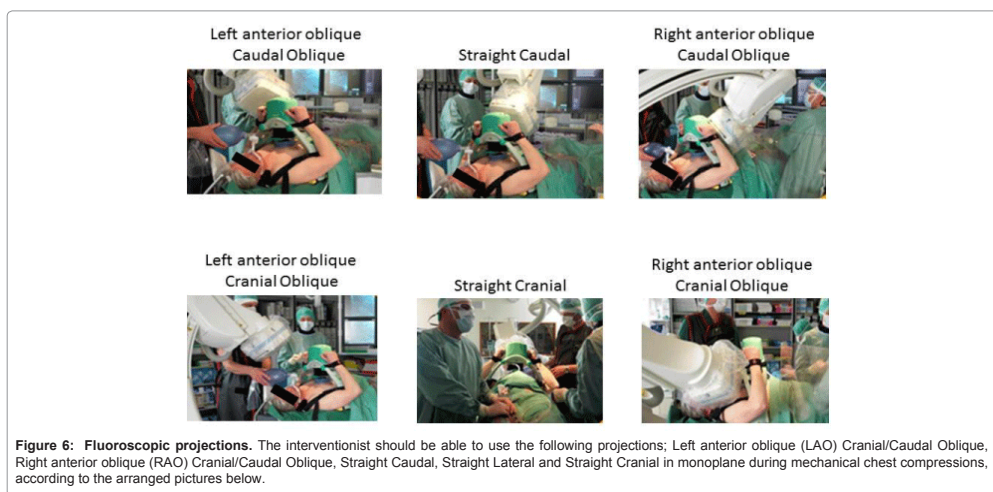
Figure 6: Fluoroscopic projections. The interventionist should be able to use the following projections; Left anterior oblique (LAO) Cranial/Caudal Oblique, Right anterior oblique (RAO) Cranial/Caudal Oblique, Straight Caudal, Straight Lateral and Straight Cranial in monoplane during mechanical chest compressions, according to the arranged pictures below.

Physiologic parameters

The cath-lab environment offers a unique opportunity to treat prolonged CA since one can immediately react to changes in parameters and evaluate given therapy while the interventionist is attempting revascularisation with PCI. Though the absolute minimal requirements for resuscitation physiological parameters are not known, some reasonable recommendations are possible. Pre-clinical translational studies has suggested a Systolic ABPof at least 70-80 mmHg, a Diastolic ABP> 40 mmHg, a Mean ABP > 40 mmHg [4,9] and other vital parameters as shown in Table 2 are needed to obtain ROSC [5-8,10,11].The position over the heart of the MCC pressure point might be important to achieve this ABP values [19-21]. If the compression point is inappropriate it can impair circulation, as well as cause injury [21,22]. It is important to assess the quality of ventilation and ventilation rate, since it is well known that hyperventilation has

a negative influence on chest compression generated blood pressure [14]. When analysing $ETCO_2$ during CCs, be aware that MCC can cause compression artefacts (Figure 2). Providing positive pressure ventilation during MCC can result in barotrauma, hence if possible, experienced personnel should be assigned this task.

Vasoactive drugs

The use of bolus doses of ADR recommended in current guidelines for CPR [23] is not used routinely in our CPR approach for prolonged CA in the cath-lab. Though the general use of ADR during resuscitation efforts remains controversial, it has been shown that high doses of ADR are detrimental [24,25]. In an effort to avoid cumulative high doses of ADR during these prolonged resuscitations using MCC and concurrent PCI, all efforts are made to improve hemodynamic support without repeated dosing with ADR. Noradrenaline (NA) might be a substitute, but it has the same potential for producing "stone heart" in prolonged resuscitations. If the MCC-generated blood pressure is still considered to be insufficient despite changes in placement of the MCC-device, changes in ventilation and rule out cardiac tamponade, we start with an infusion of NA which does not constrict cerebral vessels to the same extent as ADR and provides a higher cerebral oxygen consumption compared to ADR [26]. In an open chest model in cardiopulmonary resuscitation NA improves the 0_2-extraction ratio and eases defibrillation in obtaining ROSC compared to ADR [27]. In another study, Brown et al showed significantly higher cerebral blood flow with NA compared to ADR [28]. Thus in our approach we try to preserve acceptable physiology but avoid peak levels with ADR which appear to be harmful.

Treatment perspective

A major difference in this treatment approach proposed for refractory VF in the cath-lab is delaying defibrillation until the culprit coronary artery has been re-perfused. The rationale behind this decision once initial defibrillation proves ineffective is that reperfusion of the myocardium is required for successful restoration of spontaneous circulation. Indeed, the cause of such shock resistant ventricular fibrillation is almost certainly the acutely occluded vessel. Once the vessel is re-opened, defibrillation is usually easily accomplished. Systemic blood pressure and organ perfusion is provided by MCC and followed carefully to ensure adequacy. Our experience has shown that this approach, previously suggested by Kern et al. [12] indeed works. If the patient is in PEA/asystole we continue with PCI during MCC. During the PCI procedure, focus for the non-interventional staff is on optimizing each vital physiological parameter to levels that are predictive of attaining ROSC. When successful reperfusion with PCI is accomplished, additional resuscitation efforts are continued including defibrillation attempts if needed, as well as ADR. We have experienced success in beginning a low dose infusion of ADR to increase ABP 20-40 mmHg or administering a bolus of ADR into the right atria as was done in the early studies [29]. We recommend that resuscitation efforts with MCC, including the use of ADR, continue for at least an additional 20-30 minutes after the termination of the intervention.

Training and team work

An essential part of this modified ALS approach for prolonged CA during PCI is coordinated team work. Due to the large number of different individuals who could be responding with the CA emergency response team, continuous education and practical simulations are performed in the cath-lab with personnel from the CA team as well as from the cath-lab staff. Similar training has been shown to be beneficial in other studies with respect to retain and improve psychomotor skills [30]. The cardiologist and anaesthesiologist have clearly defined roles in the team dynamics. Multiple studies have shown that teamwork and leadership are an important issue in all CPR - performance [31-35]. Studies have shown that deviation from treatment algorithms can result in poorer outcomes [36-38]. This is the reason why the implementation of customized approaches suitable for the cath-lab must be followed with extensive education and practice. Since we have the opportunity to observe all CAs in the cath-lab, all personnel involved in these CA-situations can be debriefed after every case which has been shown beneficial for quality improvement in these critical clinical events [39,40].

Conclusion

When implementing a structured resuscitation approach during prolonged resuscitation efforts in the cath-lab, the improvement in team work and physiological parameters may result in a more calm and success-oriented setting.

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Paper IV

BMC
Cardiovascular Disorders

Evaluation of coronary blood flow velocity during cardiac arrest with circulation maintained through mechanical chest compressions in a porcine model

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Abstract

Background: Mechanical chest compressions (CCs) have been shown capable of maintaining circulation in humans suffering cardiac arrest for extensive periods of time. Reports have documented a visually normalized coronary blood flow during angiography in such cases (TIMI III flow), but it has never been actually measured. Only indirect measurements of the coronary circulation during cardiac arrest with on-going mechanical CCs have been performed previously through measurement of the coronary perfusion pressure (CPP). In this study our aim was to correlate average peak coronary flow velocity (APV) to CPP during mechanical CCs.

Methods: In a closed chest porcine model, cardiac arrest was established through electrically induced ventricular fibrillation (VF) in eleven pigs. After one minute, mechanical chest compressions were initiated and then maintained for 10 minutes upon which the pigs were defibrillated. Measurements of coronary blood flow in the left anterior descending artery were made at baseline and during VF with a catheter based Doppler flow fire measuring APV. Furthermore measurements of central (thoracic) venous and arterial pressures were also made in order to calculate the theoretical CPP.

Results: Average peak coronary flow velocity was significantly higher compared to baseline during mechanical chests compressions and this was observed during the entire period of mechanical chest compressions (12 - 39% above baseline). The APV slowly declined during the 10 min period of mechanical chest compressions, but was still higher than baseline at the end of mechanical chest compressions. CPP was simultaneously maintained at > 20 mmHg during the 10 minute episode of cardiac arrest.

Conclusion: Our study showed good correlation between CPP and APV which was highly significant, during cardiac arrest with on-going mechanical CCs in a closed chest porcine model. In addition APV was even higher during mechanical CCs compared to baseline. Mechanical CCs can, at minimum, re-establish coronary blood flow in non-diseased coronary arteries during cardiac arrest.

Background

Mechanical chest compression (CC) devices used during cardiac arrest in the cardiac catheterization laboratory (cath-lab) have been shown capable of producing adequate coronary perfusion pressures (CPP) which is well correlated to normal coronary blood flow, Thrombolysis In Myocardial Infarction-flow (TIMI-flow) III [1]. TIMI III flow in conjunction with mechanical CCs during cardiac arrest in patients has also been reported by Bonnemeier et al. [2,3]. TIMI-flow is commonly used in the cardiac cath-lab to evaluate coronary blood flow, however intracoronary Doppler blood flow measurements were not performed in these studies to correlate with the visual TIMI-flow [1-3]. Cardiac arrest (CA) due to ventricular fibrillation (VF) has frequently been used in animal cardiopulmonary resuscitation (CPR) models for measuring CPP, which is

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done by calculating the pressure gradient between the aorta and the right atrium during the end of the decompression phase [4-6]. Studies in animals and in humans have demonstrated a positive correlation between CPP and return of spontaneous circulation (ROSC) [5-9], however, little is known about the relationship between CPP and directly measured intracoronary blood flow velocity during mechanical CCs or manual CCs. Measurements of intracoronary blood flow is performed with a Doppler flow wire and the method has previously been used to measure coronary blood flow before and after percutaneous coronary intervention (PCI) in patients with stable circulation [10-12] or when correlating other modalities for measuring coronary blood flow [13,14]. One study used a cardio pulmonary bypass system to mimic a low flow state and an ultrasonic flow probe inserted in the left anterior descending artery (LAD) in a porcine open chest model [15], thus this method is well documented.

LUCAS™ (Jolife AB, Lund, Sweden) is a mechanical CCs device that delivers compressions according to international guidelines for resuscitation [16,17] and it has been shown to produce significantly higher mean arterial blood pressure, coronary perfusion pressure [9] and increases cerebral blood flow compared to manual CCs over extended periods of CA in pig models [18]. During cardiac/circulatory arrest in human as well as pig studies, using manual CCs over extended periods of time, blood pressure has been shown to successively decline and finally result in a low flow or no flow situation most often due to impaired manual CCs or development of stone heart [3,6]. This negative downward spiral will further reduce the possibility to obtain return of ROSC [8].

The aim of this study was to explore the correlation between CPP and Doppler blood flow in the LAD during mechanical CCs in an experimental animal model. To our knowledge this has not been done before.

Methods

Animal care

Eleven Swedish-bred specific (Swedish Landrace) pathogen free pigs with a mean weight of 31 kilo (range 28 - 31 kg) were used. Temperature of the pigs at VF was 37.9°C ± 0.7° C. The animals received humane care in compliance with *The Guide for the Care and Use of Laboratory Animals*, published by the national institute of health (NIH publication 85 - 23, revised 1985) and the European convention for the Protection of Vertebrate Animals used for experimental and Other Scientific Purposes (1986). The institutional Review Board for animal experimentation at Lund University, Sweden, approved the experimental protocols.

Anesthesia and preparation

The pigs had free access to water but were not allowed to eat on the day of experiment. They were anaesthetized with an induction dose of intramuscular ketamine (30 mg/kg). Sodium thiopental (5-8 mg/kg) and atropine (0.015 mg/kg) were given intravenously before tracheotomy. Anesthesia and muscular paralysis were maintained with continuous infusion of 10 ml/h of a 0.9% saline solution containing ketamine (16 mg/ml) and pancuronium (0.6 mg/ml).

Ventilator settings and instrumentation

A Boussignac ET tube, 7 mm internal diameter (Laboratories Pharamceutiques VYGON, Ecouen, France) was used as an ordinary endotracheal tube for ventilation. After tracheothomy it was connected to a Servo Ventilator 300 (Servo Ventilator 300, Siemens, Solna, Sweden) using pressure-regulated (max 30 cmH_2O = 23 mmHg) and volume controlled intermittent positive pressure ventilation (IPPV). Normo-ventilation (end-tidal CO_2 around 5.3 kPa = 40 mmHg) was obtained by using a tidal volume of 8 ml/kg body weight, 20 breaths/min, a PEEP of 5 cmH_2O (6 mmHg) and a FiO_2 of 0.21. End tidal CO_2 was measured by CO_2SMO Plus respiratory Profile Monitor (Model 8100; Novametrix Medical Systems Inc., Wallingsford, CT, USA) with a CO_2 sensor (REF 6719) connected to the proximal end of the Boussignac tube.

For monitoring of aortic pressure and central venous pressure, two catheters (Secalon-T-over-needle catheter, 16G/1.70/130 mm) were introduced via direct puncture of the right carotid artery and the right jugular vein respectively, in order to avoid ligation of the artery. The tip of the arterial catheter was inserted into the thoracic aorta and the central venous catheter was placed with the tip in the right atrium. The fluid filled catheters were connected via short tubes to pressure transducers.

A temperature probe was placed in the esophagus and electrocardiogram (ECG) was obtained by three electrodes glued to the chest. The following variables were continuously sampled (100 - 500 Hz) to a computer supplied with a data acquisition system (Testpoint, Capital Equipment Corporation, Billerica, Massachusetts): body temperature, ECG, intra thoracic arterial pressure (AP), right atrial pressure (CVP), CPP, End Tidal CO_2 ($ETCO_2$).

A 6 F introducer sheath (Boston Scientific Scimed, Maple Grove, MN, USA) was inserted into the surgically exposed left carotid artery and a 6F JL 3.5 Wiseguide™ (Boston Scientific Scimed, Maple Grove, MN, USA) catheter was then inserted through the introducer for placement of the tip in the left main coronary artery and 10,000 IU of Heparin was administered. The catheter was used to place a 0.014-inch, 12 MHz pulsed Doppler flow velocity transducer (FloWire® Volcano Inc., San Diego CA) into the mid-portion of the LAD. Continuous coronary velocity flow profiles were displayed and recorded using the Doppler flow wire connected to a FloMap monitor (Cardiometrics, Mountain View, CA). Coronary flow is in this

system measured as the average peak velocity (APV), in which APV is the time-averaged value of the instantaneous peak velocity samples over the last 2 cardiac cycles in centimeters per second. All radiological procedures were performed in an experimental catheterization laboratory, (GE Healthcare, Chalfont St Giles, UK).

Experimental protocol

After baseline when all parameters were stable, especially flow velocity in the LAD, VF was induced with a 5-20 mA, 6 Hz and 30 V alternating current delivered to the epicardial surface via a needle electrode. Circulatory arrest was confirmed by a fall in AP, fall in Doppler flow velocity and an ECG showing VF upon which ventilation was stopped (Figure 1, 2 and 3). Following 60 seconds of VF, CPR was started using the electrically driven mechanical chest compression/decompression device LUCAS™2 (Jolife AB, Lund, Sweden) and ventilation was initiated at a rate of 10 inflations per minute. Continuous measurements of ECG, body temperature, AP, CVP and CPP, were performed. APV was documented by both a VHS-recorder and by digital recording. After ten minutes of CPR the pigs were defibrillated. If return of spontaneous circulation (ROSC) was not obtained after the first defibrillation, epinephrine 0.01 mg/kg was given in the central venous catheter and another defibrillation attempt made after 2 minutes, if persistent VF. Repeat doses of adrenaline and defibrillation attempts were performed as needed for a total of 3 times, with 2-minute intervals of chest compressions between each dose. After the third dose of epinephrine, CPR was continued for 2 minutes and then terminated. When ROSC was obtained, measurements continued 15 minutes with a ventilation rate of 20 breaths per minute with 100% oxygen in the respirator setting described above.

Measurements

Arterial pressure and CVP were measured and the maximum, mean and minimum pressures were depicted. CPP was calculated as the difference between the thoracic intra-aortic pressure and the right atrial pressure in the end-decompression phase. The end of the decompression phase was defined between 0.1 - 0.05 seconds before the start of next compression [9,19]. Blood gases were drawn at baseline and after ten minutes of VF. APV, in the LAD was continuously measured and to evaluate the measurements, time periods which were visually free from noise and had a typical Doppler-curve like shape on the VHS-recording-tape where used for analysis (Figure 1) Time periods that were obviously artifacts were excluded. Arterial pressure, CVP and blood flow velocity signals were sampled 50 times/second and the mean value were recorded every 5 second during the whole experiment, using a computer supplied with a data acquisition system (Test Point, Capital Equipment Corporation, Bilerica,
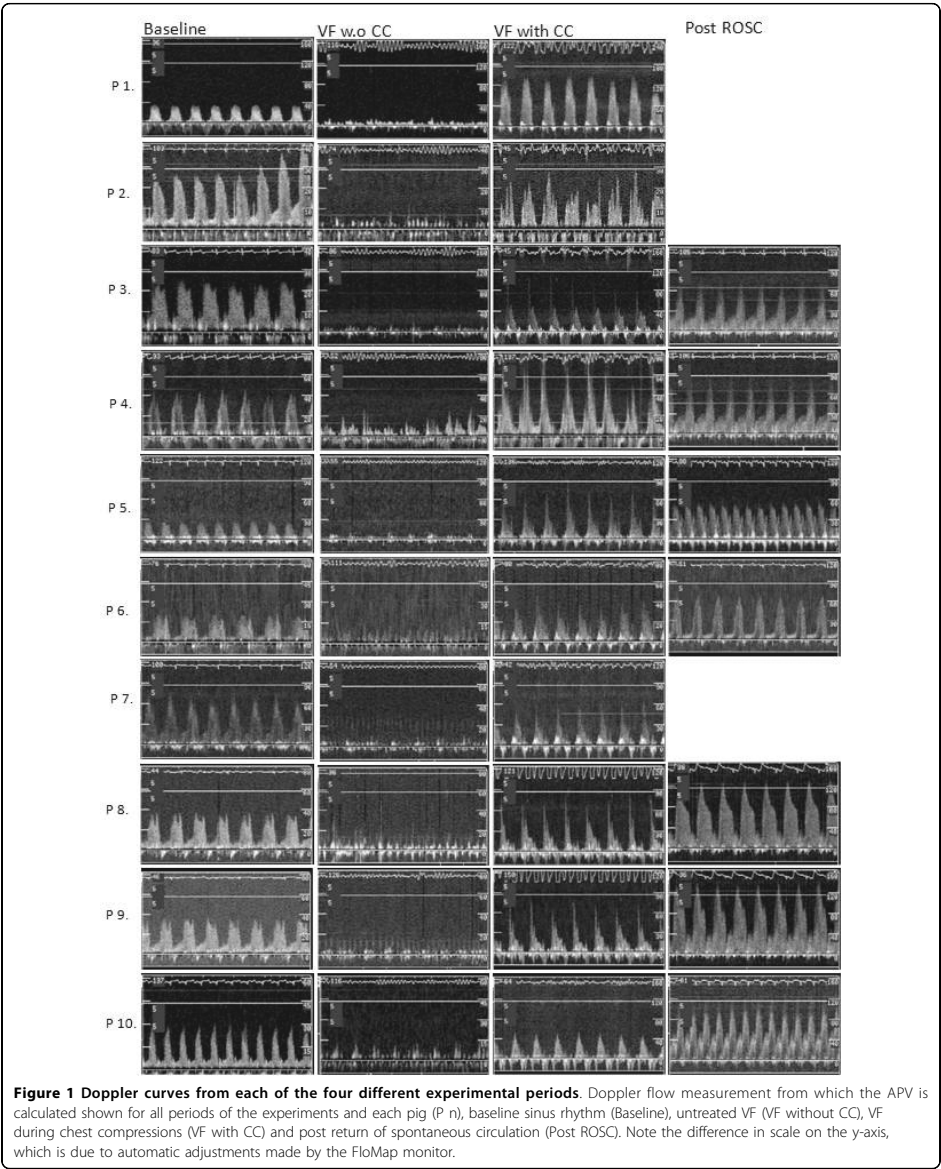
MA). Blood gas and electrolytes were analyzed directly after a sample had been obtained using a blood gas analyzer (ABL 505, Radiometer, Copenhagen, Denmark).
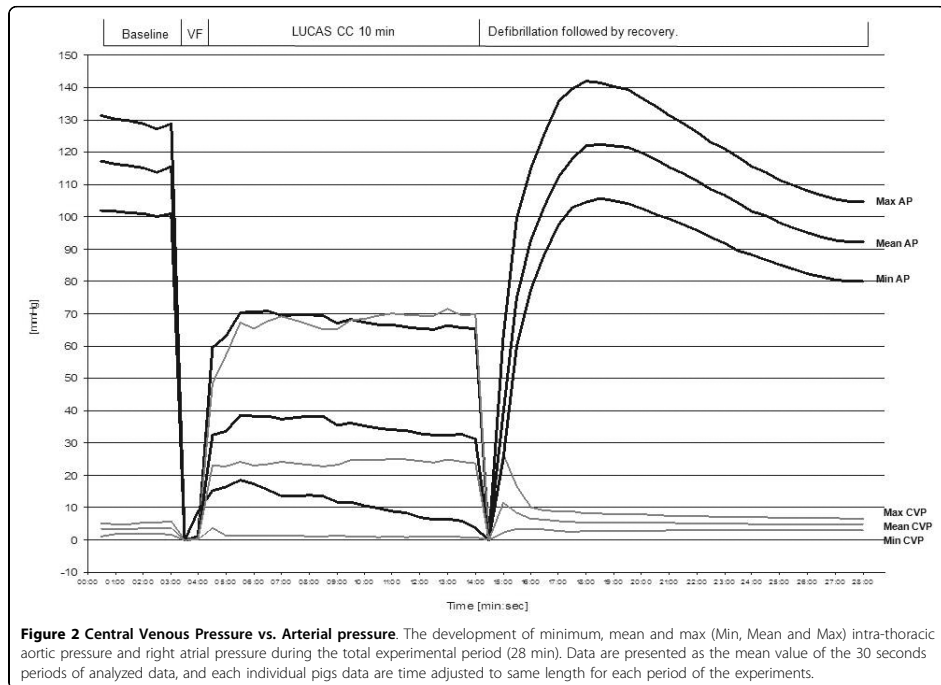
Statistics

All data are presented as Mean ± standard deviation (SD). When analyzing and calculating the blood pressure curves and APV curves, these were analyzed as Mean ± SD of 30 second registration periods which then was divided in to 2-minute-intervals (e.g. 0-2 min, 2-4 min, 4-6 min, 6-8 min, 8-10 min) and a mean value for each period was calculated for each animal during the mechanical CC period. The difference in pressure and blood flow curves between baseline measurements during the VF-period and measurements during mechanical CCs were analyzed. The Mann-Whitney U test was used to determine differences between baseline measurements of APV and APV during mechanical CCs as well as for analyzing differences between blood gases. To test the null-hypothesis for correlation between APV and CPP, correlation z-test was used. Multiple continuous statistical comparisons were made between base line APV in each two minute periods as well as in the blood gas analysis; therefore we used the Bonferroni correction on all p-values. All analyses were carried out using StatView for Windows, Version 5.01 (SAS Institute Inc., SAS Campus Drive, Cary, NC, USA). A p-value < 0.05 was considered significant.

Results

Seven animal regained ROSC following the first defibrillation attempt, two pigs required three defibrillation attempts to attain ROSC and two pigs did not obtain ROSC following defibrillation at the end of the 10 minute episode of VF of which one was excluded due to misplacement of the device before start of CCs. The baseline variables for the 10 pigs analyzed are shown in Table 1. The blood pressure and APV (APV noise free period was s: 0 - 2 min: 6 pigs = 66 ± 47 s, 2 - 4 min: 7 pigs = 114 ± 11 s, 4 - 6 min: 7 pigs = 99 ± 38 s, 6 - 8 min: 9 pigs = 68 ± 46 s, 8 - 10 min: 7 pigs = 84 ± 40 s) are shown in table 1, the statistical comparison revealed a significant (P < 0.0005) increase in coronary flow with mechanical CCs (CC-frequency 100 ± 1) compared to baseline (sinus rhythm, at a frequency of 97 ± 16) at each time interval, ranging between 12 and 39% increase (Table 1). Figure 1 shows the original Doppler curves from which APV was calculated during baseline, during the VF-period without CC, during the VF with mechanical CC and during the ROSC period indicating not only an instant increase in peak velocity but Doppler flow through the whole cyclic period of mechanical CCs. Arterial pressure and CVP during the total study period are presented in Figure 2. The progress of calculated CPP and the measured intracoronary APV is shown during the experimental period in Figure 3. Actual

Figure 1 Doppler curves from each of the four different experimental periods. Doppler flow measurement from which the APV is calculated shown for all periods of the experiments and each pig (P n), baseline sinus rhythm (Baseline), untreated VF (VF without CC), VF during chest compressions (VF with CC) and post return of spontaneous circulation (Post ROSC). Note the difference in scale on the y-axis, which is due to automatic adjustments made by the FloMap monitor.

Figure 2 Central Venous Pressure vs. Arterial pressure. The development of minimum, mean and max (Min, Mean and Max) intra-thoracic aortic pressure and right atrial pressure during the total experimental period (28 min). Data are presented as the mean value of the 30 seconds periods of analyzed data, and each individual pigs data are time adjusted to same length for each period of the experiments.

APV values from the velocity time integral could not be measured correctly during ROSC-period by the software in the Flomap machine which were likely caused by large repeated Doppler scale changes in response to a large reactive hyperemia combined with aliasing. However, there is a hyperemic period evident by increased APV and CPP that are shown in Figures 2 and 3 indicating that increased Doppler flow is evident (Figure 1).

Correlation analysis between calculated CPP and APV was performed for the entire 10 min period of mechanical CCs. A significant correlation (R = 0.761, R2 = 0.6 and P-value < 0.0001) between the calculated CPP and APV during mechanical CCs was seen (Figure 4). Arterial blood gas values are shown in Table 2. There was a significant fall between base line and after ten minutes of mechanical CC in pH and Base Excess (BE) but Lactate was significantly elevated as well as glucose. The significant difference in pH, Lactate and glucose was persisting also following 20 min of ROSC, but BE stabilized and PO_2 increased.
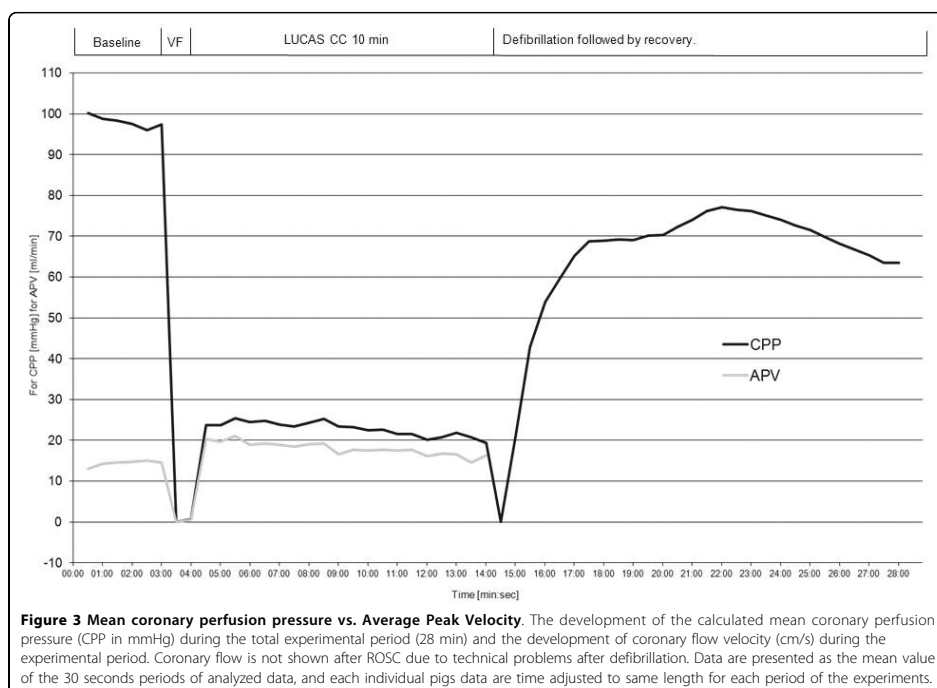
Discussion
We found a significant correlation between CPP and APV during VF with circulation dependent on mechanical CCs.

During ongoing mechanical CCs, APV was quantitatively equal or greater than baseline levels despite cardiac arrest, indicating that a mean CPP well above 20 mmHg might result in restored coronary blood flow.

Prolonged cardiac arrest in the cath-lab represents one of the biggest challenges to an interventional cardiologist. The recent introduction of mechanical chest compression devices may offer means of securing the initial circulation despite cardiac arrest. Several experiments have shown indirect evidence of good coronary circulation as measured by CPP and case studies have subjectively documented normalized coronary blood flow (TIMI III) during cardiac arrest during the use of mechanical chest compressions [1-3,20,21]. However, actual measurements of the coronary blood flow during cardiac arrest and ongoing mechanical chest compressions has been lacking. Reactive hyperemia may also play a role when assessing coronary blood flow with a Doppler flow wire, something which cannot be measured through evaluation TIMI flow during coronary angiograms or through CPP.

The initial measurements of APV and CPP at baseline were within the normal range for pigs. During VF without compressions both CPP and APV severely decreased.

Figure 3 Mean coronary perfusion pressure vs. Average Peak Velocity. The development of the calculated mean coronary perfusion pressure (CPP in mmHg) during the total experimental period (28 min) and the development of coronary flow velocity (cm/s) during the experimental period. Coronary flow is not shown after ROSC due to technical problems after defibrillation. Data are presented as the mean value of the 30 seconds periods of analyzed data, and each individual pigs data are time adjusted to same length for each period of the experiments.
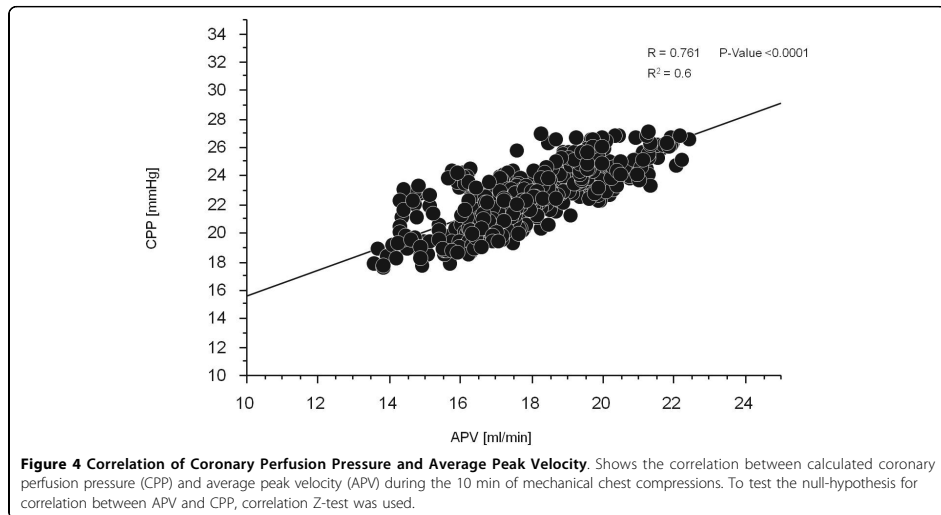
Then almost immediately following initiation of chest compressions both CPP and APV increased. APV increased to above baseline while CPP only increased to above 20 mmHg. Interestingly, APV and CPP correlate quite well during the VF phase although CPP is much lower than at baseline. During mechanical CCs arterial blood pressure was significantly lower than baseline resulting in an expected fall in CPP. However, APV was significantly higher compared to baseline during mechanical CCs and this was observed during the entire period of mechanical CCs. Following successful ROSC, CPP once again approaches baseline values while APV, after an initial increase, gradually decreases to return to the baseline values, but was still significantly higher than baseline at the end of mechanical CCs. This is a new finding as CPP has generally been assumed to correlate with coronary blood flow. How can APV be maintained close to baseline values while CPP remains significantly lower

Table 1 Measurements of central venous and arterial pressures, CPP and APV

Variable/time	Baseline	0-2 min	2-4 min	4-6 min	6-8 min	8-10 min
Min AP [mmHg]	101.1 ± 1.1	16.9 ± 2.3	14.1 ± 1.1	11.9 ± 1.2	8.5 ± 1.2	5.6 ± 1.3
Mean AP [mmHg]	115.7 ± 1.2	35.7 ± 3.3	38.0 ± 0.7	36.3 ± 1.4	33.8 ± 0.8	37.8 ± 1.3
Max AP [mmHg]	129.3 ± 1.5	65.9 ± 6.4	69.9 ± 0.8	68.0 ± 1.1	66.2 ± 0.9	65.6 ± 0.9
Min CVP [mmHg]	1.7 ± 0.5	1.9 ± 1.3	1.2 ± 0.2	1.1 ± 0.2	8.1 ± 0.2	1.0 ± 0.3
Mean CVP [mmHg]	3.5 ± 0.2	23.2 ± 1.7	23.7 ± 0.4	23.8 ± 0.8	24.8 ± 0.4	24.2 ± 0.6
Max CVP [mmHg]	5.2 ± 1.8	59.5 ± 8.4	67.9 ± 1.1	66.7 ± 1.7	69.7 ± 0.9	70.1 ± 1.2
CPP [mmHg]	98.0 ± 2.0	24.3 ± 1.4	24.1 ± 0.5	23.6 ± 1.3	21.5 ± 1.2	20.6 ± 1.5
APV [cm/s]	14.3 ± 1.0	20.0 ± 1.2	18.9 ± 0.5	17.8 ± 0.9	17.3 ± 0.9	16.0 ± 1.1

Baseline measurements and measurements during 0 - 2 min, 2 - 4 min, 4 - 6 min, 6 - 8 min and 8 - 10 min of mechanical chest compressions. AP = intrathoracic aortic pressure, CVP = Central Venous Pressure (right atrial pressure), CPP = calculated coronary perfusion pressure, APV = Average peak velocity. Data are presented as mean ± SD, n = 10.

Figure 4 Correlation of Coronary Perfusion Pressure and Average Peak Velocity. Shows the correlation between calculated coronary perfusion pressure (CPP) and average peak velocity (APV) during the 10 min of mechanical chest compressions. To test the null-hypothesis for correlation between APV and CPP, correlation Z-test was used.

compared to baseline until after ROSC? One can speculate that the APV value is primarily driven by hyperemia caused by a post ischemic state and probably a release of a number of endogenous substances such as ATP and catecholamine's which is known to be extremely high in this situation in humans and animal resuscitation [22-24]. CPP however only correlates with a theoretical calculation of the coronary perfusion pressure which does not take into account a dilatation or constriction of the capillary bed of the myocardium which is of course of great importance for the actual coronary flow when measuring APV. Measurements of the proximal diameter of coronary arteries during angiograms indicate that there is very little difference in diameter of the coronary vessels during baseline, VF and ROSC phases.

There was also an expected slight fall in pH as well as an increase in pCO_2 tension, Base Excess, and lactate, probably because of the impaired circulation after ten minutes with ongoing VF and mechanical CCs. The elevation of CO_2 may be the result of elevated CO_2 production during ischemia and/or lowered excretion from the lungs. The elevation of blood glucose could be the result of endogenous produced epinephrine. The slight elevation in K^+ could be due to metabolic acidosis; however this remains speculative and needs to be further evaluated in future studies.

Table 2 Arterial blood gas measurements

Variable	Baseline Arterial		10 min Arterial		P-value	ROSC 20 min Arterial		P-value
	Mean	± SD	Mean	± SD		Mean	± SD	
pH	7.350	± 0.026	7.257	± 0.060	0.012	7.287	± 0.050	0.014
PCO_2	5.8	± 0.63	6.5	± 1.30	ns	6.4	± 0.83	ns
PO_2	14.3	± 6.9	27.5	± 18.6	ns	48.75	± 17.7	0.042
ABE	-1.7	± 1.4	-6.0	± 1.4	0.002	-3.97	± 1.6	ns
Lactate	1.42	± 0.47	4.35	± 1.33	0.02	3.86	± 1.02	0.002
Hb	108	± 10	120	± 11	ns	114	± 10	ns
Na	137	± 2,1	136	± 2.7	ns	136	± 2.8	ns
K	3.96	± 0.24	4.59	± 0.89	ns	3.86	± 0.34	ns
Ca	1.33	± 0.04	1.35	± 0.06	ns	1.27	± 0.05	ns
Glucos	6.6	± 1.4	11.5	± 2.2	0.002	11.79	± 3.15	0.008

Measurements of blood gas, electrolytes, hemoglobin, hematocrit, lactate and glucose at base line and after ten minutes of mechanical chest compressions. Data are presented as Mean ± SD, n = 10. ns = not significant.

In this study we found CPP values and other physiological parameters that were comparable to earlier published data using a mechanical LUCAS device on pigs [6]. The CPP was high in this study as well. Judging from the visually observed TIMI-flow in the cath-lab, the mechanical chest compression device LUCAS seems capable of producing a TIMI-III flow in the cath-lab setting and corroborates earlier clinical findings [1-3,20,21].

Limitations

In this study there are some limitations. First of all we used healthy juvenile pigs. As in all animal studies it is difficult to extrapolate these findings into human medicine in which cardiac arrest is commonly caused by an underlying heart disease such as an acute myocardial infarction or heart failure.

The length of the period with circulation performed with mechanical CCs in our study was limited to ten minutes which might be a limitation compared to clinical cardiac arrest cases. However, in our recently published study on humans with prolonged cardiac arrest in the cath-lab treated with mechanical CCs, mean treatment time among the survivors was 16 minutes (range 1 - 50 minutes) and in all patients 28 minutes (range 1 - 90 minutes) [2]. This indicates that coronary flow velocity is sufficient for extended periods of time in humans, when circulated with mechanical CCs.

Thus, as a resuscitation model this study does not mirror the true life situation for out of hospital cardiac arrest since we have optimal conditions with anaesthetized, intubated and otherwise fully controlled pigs in which we induced VF. However, the model can be more readily applied to, and conclusions drawn from scenarios in which patients suffer cardiac arrest in the cath-lab.

During ongoing mechanical chest compressions when evaluating coronary flow with APV, the measured curves were prone to movement artifacts from the mechanical CCs and the curves had to a large part be manually validated frame by frame from VHS recordings. During the hyperemia phase in the ROSC-period, it was not possible to perform reliable calculations of APV due to technical disturbances but there was a clear elevation of Doppler flow (Figure 1) indicating that APV reacted on the hyperemic phase as well. Furthermore, during the mechanical CCs, the coronary catheter had a tendency to further intubate the Left Main and LAD something which we have not seen in real patients during mechanical CCs. This was probably due to the angle of the catheters entry to the circulation from the left carotid artery; however this complication was continuously checked for and avoided but caused disturbances in the measurements of the APV.

Conclusions

We conclude that there was a good correlation between CPP and APV which was highly significant, during mechanical CCs using an electrical driven LUCASTM2 device. In addition APV was even higher during mechanical CCs compared to baseline flow which also could be attributed to a combination of reactive hyperemia and endogenously produced epinephrine in the early phase of cardiac arrest. Thus, we have verified that mechanical CCs can, at minimum, re-establish coronary blood flow in non-diseased coronary arteries during cardiac arrest.

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Authors' contributions

HW drafted the manuscript and has partaken in the animal experiments as well as acquisition and evaluation of data. BMH has partaken in the animal experiments and acquisition of data as well as critical evaluation of the manuscript. SS has partaken in the animal experiments and critical analysis of the manuscript. TS has partaken in the animal experiments as well as acquisition and evaluation of data he has also made critical evaluation of the manuscript. JH has been essential for critical evaluation of the manuscript. GO is responsible for concept and design as well as critical evaluation of the manuscript.
All authors have read and approved the final version of the manuscript.

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HW is an interventional cardiologist and physician on staff at the Department of Cardiology, Skåne University Hospital-Lund at the time of the conduction of the study. BMH is a former RN and PhD at the Department of Cardiology, Skåne University Hospital-Lund who is now employed by Jolife AB, Lund. SS is the Professor at the Department of Thoracic Surgery, Lund University. TS is an Associate Professor at the Department of Thoracic Surgery, Lund University. JH is an interventional radiologist and Associate Professor at Lund University. He is also a Consultant at the Department of Cardiology, Skåne University Hospital-Lund. GO is an interventional cardiologist and a Consultant at the Department of Cardiology, Skåne University Hospital-Lund.

Competing interests

Göran Olivecrona has received honorariums from Jolife AB and Medtronic Inc. for presenting case based lectures. Henrik Wagner has received honorariums from Jolife AB for presenting case based lectures. Bjarne Madsen-Härdig is an Employee of the Jolife AB Company. Stig Steen has received economical support for the research in cardiopulmonary resuscitation from Jolife AB. There are no other competing financial or non-financial interests.

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Paper V

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Repeated epinephrine doses during prolonged cardiopulmonary resuscitation have limited effects on myocardial blood flow: a randomized porcine study

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Abstract

Background: In current guidelines, prolonged cardiopulmonary resuscitation (CPR) mandates administration of repeated intravenous epinephrine (EPI) doses. This porcine study simulating a prolonged CPR-situation in the coronary catheterisation laboratory, explores the effect of EPI-administrations on coronary perfusion pressure (CPP), continuous coronary artery flow average peak velocity (APV) and amplitude spectrum area (AMSA).

Methods: Thirty-six pigs were randomized 1:1:1 to EPI 0.02 mg/kg/dose, EPI 0.03 mg/kg/dose or saline (control) in an experimental cardiac arrest (CA) model. During 15 minutes of mechanical chest compressions, four EPI/saline-injections were administered, and the effect on CPP, APV and AMSA were recorded. Comparisons were performed between the control and the two EPI-groups and a combination of the two EPI-groups, EPI-all.

Result: Compared to the control group, maximum peak of CPP (P_{max}) after injection 1 and 2 was significantly increased in the EPI-all group (p = 0.022, p = 0.016), in EPI 0.02-group after injection 2 and 3 (p = 0.023, p = 0.027) and in EPI 0.03-group after injection 1 (p = 0.013). At P_{max}, APV increased only after first injection in both the EPI-all and the EPI 0.03-group compared with the control group (p = 0.011, p = 0.018). There was no statistical difference of AMSA at any P_{max}. Seven out of 12 animals (58%) in each EPI-group versus 10 out of 12 (83%) achieved spontaneous circulation after CA.

Conclusion: In an experimental CA-CPR pig model repeated doses of intravenous EPI results in a significant increase in APV only after the first injection despite increments in CPP also during the following 2 injections indicating inappropriate changes in coronary vascular resistance during subsequent EPI administration.

Keywords: Cardiac arrest, Mechanical chest compressions, Epinephrine

Background

Routine use of epinephrine (EPI) during cardiopulmonary resuscitation (CPR) was first described in the early 1960-ies [1] and has ever since been recommended in guidelines during advanced CPR. Current guidelines recommend administration of 1 mg of EPI given intravenously every 3 – 5 minute Class IIb (LOE A) [2,3]. Several clinical studies and randomized trials have reported an increased frequency of return of spontaneous circulation (ROSC) in

out-of-hospital cardiac arrest (OHCA) after various dosages of repeated EPI administrations [4-7]. However, the increased frequency of ROSC does not convey improvements in discharge from hospital in good neurological condition or long term survival [4,7,8].

Both experimental and clinical studies have shown a higher frequency of ROSC when the coronary perfusion pressure (CPP) can be brought to a level > 15 mmHg before defibrillation during CPR-treatment [9-13]. Both increments in CPP and myocardial creatine phosphate are associated with altered ventricular fibrillation (VF) wavelets that in turn increase the possibility of a successful CPR

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[14]. Amplitude spectrum area (AMSA) represents a quantitative combined measure of the electrical activity of VF wavelets, that seems to be a predictor of defibrillation success [15] and other experimental studies have shown a correlation between CPP, AMSA, and defibrillation success [13,16].

A Doppler flow wire can be used to measure coronary blood flow in patients with a stable circulation [17-19], and experimentally a good correlation has been demonstrated between CPP and the average blood flow (APV) in a coronary vessel assessed by a Doppler flow wire during mechanical chest compressions (MCC) [20].

Previous experimental studies have evaluated the effects of repeated doses of EPI on CPP [21,22], VF-amplitude [23] and myocardial blood flow [24] during CPR, but all these studies have been designed to reflect the OHCA situation. The aim of this study was to assess CPP, coronary artery APV reflecting myocardial pressure and perfusion in addition to AMSA (reflecting bioelectrical activity) during CA caused by VF in an experimental situation adopted to the catheterisation laboratory setting, which includes a shorter untreated VF time and prolonged need for CPR while performing PCI [25].

Methods

The study conformed to the guide for the care and use of laboratory animals, US National Institute of Health (NIH Publication No. 85-23, revised 1996) and was approved by the Malmö/Lund Committee for Animal Experiment Ethics, Dnr M 192-10.

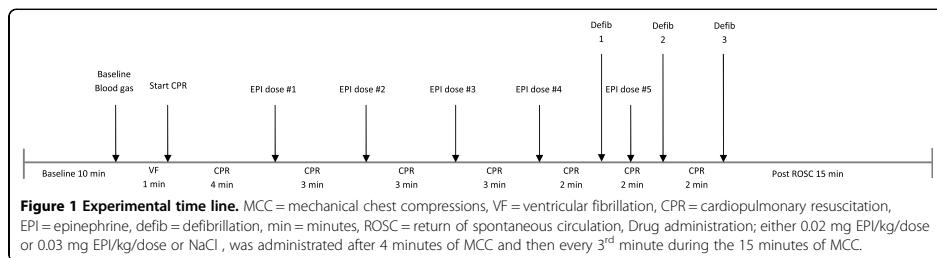### Animal preparation and monitoring

Thirty-six Swedish-bred (Swedish Landrace) pathogen free pigs with a mean weight of 38 kg (SD ± 4.1, range 32 - 46 kg) were included. The pigs were fasted overnight with free access to water. At the day of the experiment they were pre-medicated with Ketaminol 150 mg/10 kg (Ketamine 100 mg/ml, Intervet, Danderyd, Sweden) and Rompun 20 mg/10 kg intramuscularly (Xylazin 20 mg/ml, Bayer AG, Leverkusen, Germany). After induction of anaesthesia with thiopental 12.5 mg/kg/dose (Pentothal 100 mg/ml Abbott, Stockholm, Sweden) the animals were orally intubated with cuffed endotracheal tubes. To maintain anaesthesia, a slow infusion of (Fentanyl 1.25 µg/ml (Fentanyl Pharmalink AB, Stockholm, Sweden) in buffered glucose (25 mg/ml) was started at a rate of 2 ml/min and adjusted as needed. During the anaesthesia, meprobamat (Mebumal DAK Copenhagen Denmark) and/or thiopental was titrated if needed in small bolus doses. The animals were ventilated with a mixture of nitrous oxide (70%) and oxygen (30%) and normal air using a mechanical Siemens-Elema 900B ventilator (Siemens Elema Solna, Sweden) in the volume-controlled mode, adjusted in order to obtain normoventilation maintaining

end tidal carbon dioxide at 4.5 - 5.5 kPa. In addition, the animals were monitored with a three lead electrocardiogram using an IntelliVue MP90 monitoring system (Philips, Eindhoven, The Netherlands). A 6 F FL3.5 diagnostic catheter (Boston Scientific Scimed, Maple Grove, MN, USA) was introduced through the left carotid artery into the ostium of the left main coronary artery. This catheter was used to place a 0.014-inch, 12 MHz pulsed Doppler flow velocity transducer (FloWire® Volcano Inc., San Diego, CA, USA) into the mid-portion of the left anterior descending artery (LAD). A 7.5 F Continuous Cardiac Output Pulmonary Artery Catheter™ (Edwards Lifesciences, Irvine, CA, USA) was inserted through the surgically exposed right jugular vein. Central venous pressure (CVP) was measured in the right atria via a separate transducer. A 6 F pig-tail catheter was placed in the ascending aorta for arterial blood pressure (ABP) measurement. Ten-thousand units of un-fractioned heparin (LEO Pharma AB, Malmoe Sweden) was given intravenously at the start of the catheterisation. The procedures were performed in an experimental catheterization fluoroscopy laboratory (Shimadzu Corp., Kyoto, Japan).

Experimental protocol

A flow chart of the experiment is presented in Figure 1. Pigs were randomized using sealed envelopes. The person opening the envelope prepared the prescribed drug while the remainder of the researchers were blinded to the drug administered during the experiment. The animals received EPI 0.02 mg/kg/dose as previously described in a study by Pytte et al [26] or 0.03 mg/kg/dose as described in a study by Ristagno et al [27] or saline (control). Each syringe was diluted to a total of 10 ml. After preparation and a baseline period, VF was induced using a 9 V direct current (Duracell Battery, Procter & Gamble, Cincinnati OH, USA) between a skin electrode and an intracardiac needle inserted to the epicardium with a stimulation time between 5 – 10 seconds, resulting in an instant loss of ABP and LAD flow. After one minute of untreated VF, MCC and manual ventilation at a rate of 8 – 10 inflations/minute with 100% of oxygen was started and continued for 15 min prior to defibrillation. For standardized chest compressions an electrically driven MCC device was used (LUCAS™2, Physio-Control/Jolife AB, Lund, Sweden). At 5, 8, 11 and 14 minutes after VF-induction an injection of the allocated drug/saline was administered followed by a flush of 10 ml NaCl via a peripheral cannula in a vein in the ear. The rationale behind a 16 minute VF period (1 minute of untreated VF followed by 15 minutes of MCC) was an attempt to reflect a CA situation in the human cardiac catheterisation laboratory with prolonged advanced CPR in connection with PCI [25].

After 15 minutes of VF and MCC, the first defibrillation (LIFEPAK 12 Defibrillator/Monitor, Physio-Control,

Figure 1 Experimental time line. MCC = mechanical chest compressions, VF = ventricular fibrillation, CPR = cardiopulmonary resuscitation, EPI = epinephrine, defib = defibrillation, min = minutes, ROSC = return of spontaneous circulation, Drug administration; either 0.02 mg EPI/kg/dose or 0.03 mg EPI/kg/dose or NaCl , was administrated after 4 minutes of MCC and then every 3rd minute during the 15 minutes of MCC.

Redmond, Wa, USA) was attempted. If ROSC was not obtained, a fifth dose of EPI was given and repeated defibrillations were performed as needed for a total of 3 times, with 2-minute intervals during MCC. ROSC was defined as a stable circulation with an ABP > 60 mmHg for 15 minutes after defibrillation. After 15 minutes of ROSC the animals were euthanized with 40 mmol potassium injected into the pulmonary artery catheter.

Measurements and analysis

Arterial blood pressure and CVP were continuously measured using a sampling rate at 1000 Hz (AD Instruments Inc, Colorado Springs, CO, USA). Hemodynamic parameters were digitally recorded using Chart v4.2 (AD Instruments Inc, Colorado Springs, CO, USA). Coronary perfusion pressure was calculated as the difference between the arterial-end diastolic pressure and the venous right atrial-end diastolic pressure [28]. The maximum peak of CPP (P_{max}) was depicted at 20, 60, 120, 180 seconds after initiation of MCC, at the time of every EPI injection and when CPP reached the highest value after each injection. In the control group CPP was depicted 90 seconds after each saline injection. Continuous coronary APV were displayed and recorded using the Doppler flow wire connected to a FloMap monitor (Cardiometrics, Mountain View, CA). The APV was analysed in visual artefact free zones concomitantly with P_{max}.

Analog ECG signals were digitized and converted from a time to a frequency domain by fast Fourier transformation at a sampling rate of 250 Hz. Amplitude spectrum area was calculated as the sum of the products of individual frequencies between 8 and 48 Hz at P_{max}. The measurements were performed throughout the 16 minutes of VF as median values of every 10 second period. Time to P_{max} were analyzed in the EPI-groups. Survival was defined as stable ROSC for 15 min post successful defibrillation and assessed in each group.

All analyses of these parameters were performed on the three groups and on a merged group including the two EPI-groups (EPI-all).

Statistics

Analyses were performed comparing data in the control group with those of each EPI dose group and a combination of the 2 EPI-groups. Continuous variables are presented as their mean ± SD or median and 25th to 75th interquartile. Categorical values are presented as numbers and percentages. Fisher's exact test was used for comparing categorical variables. The Mann-Whitney U test was used for comparing unpaired continuous variables. The Kruskal – Wallis test was used to compare multiple median values when time to peak maximum was compared.

Results

No difference was seen during the baseline period regarding analysed measurements between any groups (Table 1).

CPP

During the first 4 minutes of MCC and at the time of the first EPI injection, there were no significant differences in CPP between the control group (n = 12), EPI-all group (n = 24), EPI 0.02 mg/kg/dose (n = 12) or EPI 0.03 mg/kg/dose (n = 12). During the following period of MCC there was a significant increase in CPP at P_{max} after EPI injection 1 and 2 in the EPI-all group (p = 0.022, p = 0.016), compared to the control group but not after injection 3 and 4. We found a significant increase in CPP after injection 2 and 3 in EPI 0.02 mg/kg/dose compared to the control group (p = 0.023, p = 0.027). When comparing EPI 0.03 mg/kg/dose to the control group there was a statistical significant difference at P_{max} following injection 1 (p = 0.013) but not at P_{max} following injection 2, 3 and 4 (Table 2, Figure 2a).

APV

During the first 4 minutes of VF there were no statistically significant differences in APV between any groups. During the following period of MCC there was a significant increase in APV after injection 1when comparing the control group to the EPI-groups except for EPI 0.02 mg/kg/dose group, in which the APV increase was only borderline (p = 0.056). We could not detect any

Table 1 Baseline parameters

	NaCl (n = 12)		EPI all (n = 24)		P-value	EPI 0.02 mg/kg/dose (n = 12)		P-value	EPI 0.03 mg/kg/dose (n = 12)		P-value
Syst ABP	152	(137 - 167)	151	(136 - 163)	0.5347	149	(136 - 172)	0.4357	152	(136 - 172)	0.7950
Diast ABP	96	(79 - 122)	96	(89 - 106)	0.6996	93	(89 - 99)	0.7075	100	(78 - 107)	0.7950
Mean ABP	115	(99 - 139)	114	(105 - 124)	0.5347	113	(105 - 118)	0.5067	116	(954 - 126)	0.7075
Max CVP	12	(10 - 13)	11	(10 -13)	0.6505	11	(10 - 13)	0.5444	11	(10 -13)	0.8852
Min CVP	8	(5 - 10)	7	(6 - 8)	0.4502	7	(4 - 8)	0.2855	7	(6 - 9)	0.8399
Mean CVP	10	(8 - 11)	9	(8 - 11)	0.7944	9	(8 - 11)	0.7350	9	(8 - 11)	0.9310
ETCO$_2$	4.9	(4.3 - 5.0)	4.5	(4.1 - 4.9)	0.5642	4.8	(4.4 - 5.0)	0.8691	4.3	(4.0 -4.7)	0.2727
APV	17	(12 - 28)	17	(12 - 24)	0.7677	20	(13 - 26)	0.8399	15	(11 - 21)	0.4417
Heart rate	88	(58 - 97)	75	(64 - 91)	0.7455	77	(71 - 93)	0.8955	71	(56 - 90)	0.4701
pH	7.473	(7.420-7.505)	7.484	(7.402-7.510)	0.9331	7.468	7.414-7.529)	0.7950	7.485	(7.3875-7.503)	0.6650
PCO$_2$	5.3	(5.0-6.5)	5.4	(5.1-5.9)	0.7246	5.5	(5.1-5.9)	0.9310	5.2	(4.9-5.9)	0.6236
PO$_2$	27.2	(16.6-37.1)	20.2	(17.2-33.9)	0.6030	23.0	(17.3-33.2)	0.8174	20.2	(16.4-33.9)	0.5254
ABE	6.0	(4.6-7.3)	5.9	(2.8-7.8)	0.9065	6.8	(3.2-8.7)	0.7075	5.5	(2.5-6.1)	0.2855

NaCl = Saline, EPI = epinephrine, Syst = Systolic, ABP = arterial blood pressure (mmHg), Diast = Diastolic, Max = maximum.
CVP = central venous pressure (mmHg), Min = minimum, ETCO$_2$ = end tidal carbon dioxide (kPa), APV = average peak velocity (cm/s).
Heart rate (beats/minute), PCO$_2$ = partial pressure carbon dioxide, (kPa), PO$_2$ = partial pressure oxygen (kPa).
ABE = arterial base excess (mmol/l). All values are expressed as median, 25th and 75th interquartile.

change in APV after the subsequent EPI injections (Table 3, Figure 2b).

AMSA
There were no statistical differences in AMSA, when comparing the control group to any of the EPI-groups. (Table 4, Figure 2c).

Time to maximum peak of CPP
The median time to P_{max} following the EPI injections was 50 (interquartile range 48 to 52) seconds (Table 5). There were no significant difference in time to P_{max}

between the EPI-groups following injection 1 to 4 (Table 5).

ROSC
Return of spontaneous circulation was achieved in 10/12 (84%) animals in the control group compared with 7/12 (58%) in each EPI-group (p = 0.37).
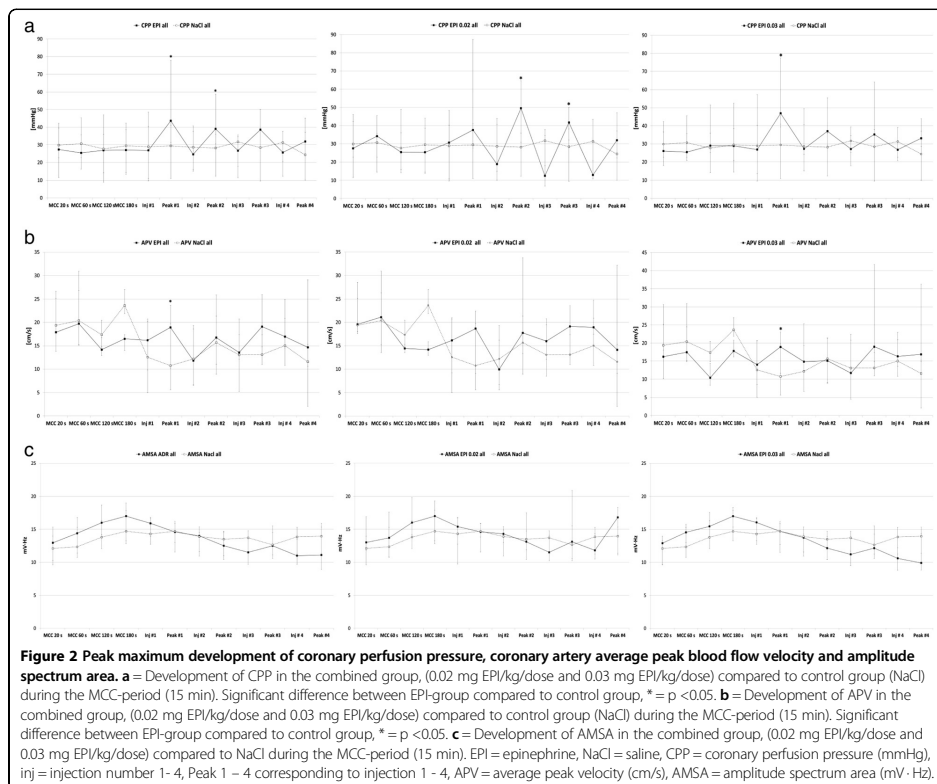
Discussion
This study shows that intravenous administration of recommended doses of EPI during prolonged advanced CPR with MCC increases the perfusion pressure in the

Table 2 Physiological values of CPP during 15 minutes of MCC-time

	CPP NaCl (n = 12)		CPP EPI all (n = 24)		P-value	CPP EPI 0.02 mg/kg/dose (n = 12)		P-value	CPP EPI 0.03 mg/dose (n = 12)		P-value
MCC 20 s	30	(23-42)[a]	27	(12-40)[e]	0.4141	28	(12-46)[b]	0.7818	26	(18-37)[a]	0.2855
MCC 60 s	31	(23-36)[a]	25	(16-45)[d]	0.9331	34	(14-46)[a]	0.6650	25	(21-46)[a]	0.7950
MCC 120 s	28	(14-36)[a]	27	(9-47)[e]	0.7152	25	(16-49)[b]	0.5588	29	(25-52)[b]	0.6891
MCC 180 s	29	(14-39)[a]	27	(13-42)[f]	0.8712	25	(14-44)[b]	1.0000	29	(21-53)[c]	0.9737
Inj #1	29	(10-40)[b]	27	(11-49)[n]	0.9368	31	(11-48)[b]	0.9476	27	(14-57)[c]	0.9719
Peak #1	29	(11-41)[c]	44	(31-78)[e]	0.0219	38	(28-78)[b]	0.1489	47	(39-77)[a]	0.0134
Inj #2	29	(15-41)[b]	25	(16-38)[e]	1.0000	19	(10-44)[a]	0.6009	27	(24-50)[b]	0.5545
Peak #2	28	(12-36)[c]	39	(31-59)[e]	0.0160	50	(31-65)[a]	0.0229	37	(29-56)[b]	0.0620
Inj #3	32	(18-35)[c]	27	(11-36)[d]	0.9849	12	(7-38)[a]	0.6209	27	(25-39)[a]	0.6682
Peak #3	28	(10-38)[c]	39	(29-50)[e]	0.1434	42	(32-50)[a]	0.0265	35	(28-64)[a]	0.1213
Inj # 4	31	(21-32)[b]	26	(12-38)[f]	0.9848	13	(11-43)[c]	0.5974	27	(23-39)[a]	0.6891
Peak #4	24	10-37)[c]	32	(24-45)[a]	0.1894	32	(22-47)[b]	0.2453	33	(29-44)[a]	0.2766

CPP = Coronary perfusion pressure (mmHg), NaCl = Saline, EPI = epinephrine, MCC = Mechanical chest compressions, Inj = injection, a: n = 12, b: n = 11, c: n = 10, d: n = 24, e: n = 23, f: n = 22, g: n = 21. Peak values at 20 , 60, 120, 180 seconds after start of MCC, at each time point of the 4 drug injections (4, 7, 10, 13 minutes after start of MCC) and the corresponding peak to each injection for NaCl compared to EPI. All values are expressed as median, 25th and 75th interquartile.

Figure 2 Peak maximum development of coronary perfusion pressure, coronary artery average peak blood flow velocity and amplitude spectrum area. a = Development of CPP in the combined group, (0.02 mg EPI/kg/dose and 0.03 mg EPI/kg/dose) compared to control group (NaCl) during the MCC-period (15 min). Significant difference between EPI-group compared to control group, * = p <0.05. **b** = Development of APV in the combined group, (0.02 mg EPI/kg/dose and 0.03 mg EPI/kg/dose) compared to control group (NaCl) during the MCC-period (15 min). Significant difference between EPI-group compared to control group, * = p <0.05. **c** = Development of AMSA in the combined group, (0.02 mg EPI/kg/dose and 0.03 mg EPI/kg/dose) compared to NaCl during the MCC-period (15 min). EPI = epinephrine, NaCl = saline, CPP = coronary perfusion pressure (mmHg), inj = injection number 1- 4, Peak 1 – 4 corresponding to injection 1 - 4, APV = average peak velocity (cm/s), AMSA = amplitude spectrum area (mV·Hz).

coronary vessel as expected. However, the effect of EPI seems to be weakened after three out of four injections when compared to controls. We also found, that the increase in CPP only transfers into an increase in APV after the first injection of EPI and no effect could be detected in AMSA. Human studies have shown that administration of EPI according to guidelines recommendations has a positive effect to attain ROSC but a worse neurological/survival outcome at discharge from hospital [8,29]. This has also been observed when using higher cumulative doses of EPI [4]. In the present study, numerically fewer animals receiving EPI obtained ROSC compared to the control group, although the difference was not significant. Larger studies are needed to demonstrate a possible negative effect on survival of repeated intravenous EPI-doses during CPR.

In this study median time to P_{max} was 50 (48 – 52) seconds. Pytte et al showed a median time to peak after

53 seconds with MCC with a CC-depth at 45 mm and after 83 seconds with manual CC according to guidelines from 2005 [26]. Thus both studies support a better circulation in terms of time to peak of CPP created by MCC.

In addition to an adequate CPP, myocardial perfusion is dependent on coronary artery flow velocity. In a previous study it was shown that APV was highly correlated to CPP during prolonged CPR with MCC [20], a study that was conducted without administration of EPI. In another study Mayr et al demonstrated that repeated injections of vasopressin resulted in an increased coronary blood flow in pigs with induced VF circulated with a cardio-pulmonary bypass technique in a low flow state [30]. Brown et al showed that high doses of EPI elevated myocardial blood flow to a higher extent compared with standard doses [24]. In our study we could only detect a significant rise in APV after the first EPI injection. Thus, the increase in CPP after EPI-injection 2 and 3 was not

Table 3 Physiological values of APV during 15 minutes of MCC-time

	APV NaCl (n = 12)		APV EPI all (n = 24)		P-value	APV EPI 0.02 mg/kg/dose (n = 12)		P-value	APV EPI 0.03 mg/kg/EPI (n = 12)		P-value
MCC 20 s	19	(12-28)[a]	18	(12-22)[h]	0.3571	20	(13-24)[a]	0.5444	16	(11-32)[b]	0.3401
MCC 60 s	20	(15-29)[a]	20	(11-24)[h]	0.4141	21	(12-25)[a]	0.8399	17	(10-22)[b]	0.2071
MCC 120 s	17	(12-25)[a]	14	(9-21)[h]	0.3220	14	(10-21)[a]	0.4025	10	(8-21)[b]	0.3401
MCC 180 s	24	(17-29)[a]	17	(11-26)[g]	0.0901	14	(10-30)[a]	0.0606	18	(12-24)[b]	0.1316
Inj #1	13	(12-20)[c]	16	(8-20)[m]	0.8536	16	(9-20)[e]	0.9646	14	(7-25)[e]	0.6893
Peak #1	11	(9-15)[c]	19	(15-26)[j]	0.0109	19	(12-23)[e]	0.0561	19	(15-42)[b]	0.0183
Inj #2	12	(8-18)[e]	12	(9-20)[i]	0.8262	10	(8-16)[b]	0.5915	15	(12-21)[b]	0.2303
Peak #2	16	(6-19)[e]	17	(13-31)[l]	0.1899	18	(13-36)[d]	0.1629	15	(13-35)[e]	0.4309
Inj #3	13	(11-20)[d]	14	(7-22)[k]	0.5892	16	(9-26)[c]	0.9674	12	(7-18)[e]	0.3606
Peak #3	13	(9-22)[b]	19	(14-31)[j]	0.5892	19	(15-29)[a]	0.1661	19	(14-33)[f]	0.3191
Inj # 4	15	(9-20)[b]	17	(9-21)[j]	0.9314	19	(8-29)[d]	0.8792	16	(10-21)[c]	1.0
Peak #4	12	(8-21)[b]	15	(10-29)[m]	0.6749	14	(12-22)[e]	0.6497	17	(8-37)[e]	0.8365

APV = Average peak velocity (cm/s), NaCl = Saline, EPI = epinephrine, MCC = mechanical chest compressions, Inj = injection, a: n = 12, b: n = 11, c: n = 10, d: n = 9, e: = 8, f: n = 7, g: n = 24, h: n = 23, i: n = 21, j: n = 19, k: n = 18, l: n = 17, m: n = 16. Peak values at 20 , 60, 120, 180 seconds after start of MCC, at each time point of the 4 drug injections (4, 7, 10, 13 minutes after start of MCC) and the corresponding peak to each injection for NaCl compared to EPI. All values are expressed as median, 25th and 75th interquartile.

accompanied by a concomitant elevation in APV indicating a rise in local vascular resistance and a lesser amount of oxygenated blood reaching the myocardium, corresponding to the findings of Brown et al using standard doses of EPI. The different circulation techniques and ventilation rates used in these studies may have significant impact on differences in their results. Still, the importance to keep CPP at a high level may be questioned, since the elevated pressure values caused by EPI in 3 out of 4 injections was not accompanied by an increase in APV.

Amplitude spectrum area has been associated with a high positive and negative predictive value to obtain a successful defibrillation in both experimental and human studies [31,32]. In one study the analyses were performed only on data from defibrillators used in CA-cases, no other information about CPR-time or administered EPI during the resuscitation were recorded [32], rendering further comparisons difficult to our experimental study.

Furthermore, human and experimental studies have shown that a CPP above 15 mmHg markedly increases the possibility to attain ROSC following defibrillation [9,10]. Hence, to strive towards a CPP above 15 mmHg during CPR in order to attain ROSC seems logical. Several experimental studies have shown that an EPI-induced elevation of CPP leads to a higher probability of subsequent

Table 4 Physiological values of AMSA during 15 minutes of MCC-time

	AMSA NaCl		AMSA EPI All		P-value	AMSA EPI 0.02 mg/kg/dose		P-value	AMSA EPI 0.03 mg/kg/dose		P-value
MCC 20 s	12.1	(9.6-14.0)[b]	13.0	(10.9-16.0)[d]	0.4099	13.0	(11.8-13.0)[c]	0.3913	13.1	(10.6-15.0)[a]	0.5752
MCC 60 s	12.4	(10.8-15.3)[b]	14.4	(11.4-16.8)[d]	0.4990	13.7	(10.8-17.6)[c]	0.7751	14.6	(13.0-15.8)[a]	0.4288
MCC 120 s	13.8	(12.1-16.3)[b]	16.0	(14.2-18.7)[d]	0.1974	16.0	(14.2-19.8)[c]	0.1779	15.5	(13.8-17.6)[a]	0.3734
MCC 180 s	14.7	(13.3-17.9)[b]	17.0	(12.8-19.0)[d]	0.3749	17.0	(12.8-19.3)[c]	0.4877	17.0	(15.3-18.3)[a]	0.4288
Inj #1	14.3	(12.7-16.8)[b]	15.9	(13.9-16.7)[d]	0.4725	15.4	(9.7-16.7)[c]	0.4142	16.1	(13.3-16.7)[a]	0.6682
Peak #1	14.7	(11.5-15.9)[b]	14.6	(13.0-16.2)[d]	0.6121	14.6	(13.8-15.9)[c]	0.7133	14.7	(12.7-16.2)[a]	0.6444
Inj #2	13.9	(11.0-15.4)[b]	14.0	(11.6-14.5)[d]	0.8824	14.3	(13.0-14.9)[c]	0.7751	13.8	(11.6-14.3)[a]	0.6209
Peak #2	13.5	(10.4-14.7)[b]	12.5	(11.0-14.6)[d]	1.0000	13.1	(11.9-17.5)[c]	0.5956	12.2	(10.4-13.9)[a]	0.6682
Inj #3	13.7	(11.4-14.8)[b]	11.5	(9.7-13.8)[d]	0.2285	11.5	(10.2-20.9)[c]	0.5676	11.2	(9.5-11.7)[a]	0.1616
Peak #3	12.7	(10.6-15.5)[b]	12.5	(11.1-14.5)[d]	0.9831	13.1	(10.2-20.9)[c]	0.5954	12.2	(11.3-14.3)[a]	0.7169
Inj # 4	13.9	(11.3-15.3)[b]	11.0	(9.7-13.5)[d]	0.1696	11.8	(10.5-14.3)[c]	0.6534	10.6	(8.8-12.2)[a]	0.0806
Peak #4	14.0	(11.4-15.3)[e]	11.0	(8.9-15.9)[d]	0.8841	16.8	(9.9-11.1)[c]	0.3165	9.9	(8.8-14.3)[a]	0.2814

AMSA = amplitude spectral area (mV · Hz), NaCl = saline, EPI = epinephrine, MCC = Mechanical chest compressions, Inj = injection, a: n = 12, b: n = 10, c: n = 9, d: n = 21, e: n = 6. Peak values at 20 , 60, 120, 180 seconds after start of MCC, at each time point of the 4 drug injections (4, 7, 10, 13 minutes after start of MCC) and the corresponding peak to each injection for NaCl compared to EPI. All values are expressed as median, 25th and 75th interquartile.

Table 5 Time to peak

	Inj #1		Inj #2		Inj #3		Inj #4		P-value
Epinephrine all	51	(32-66)[c]	53	(41-58)[c]	49	(41-70)[c]	56	(44-78)[c]	0.392
Epinephrine 0.02 mg/kg/dose	48	(39-49)[b]	48	(40-52)[a]	52	(50-60)[a]	47	(43-59)[b]	0.440
Epinephrine 0.03 mg/kg/dose	48	(38-60)[a]	51	(40-56)[b]	51	(46-62)[b]	49	(44-65)[a]	0.440

Time duration from drug administration to peak time (seconds) /P_{max} of CPP for the 4 different drug injections. Inj = Injection, mg = milligram, kg = kilogram, a; n = 12, b; n = 11, c; n = 23. All Values are expressed as median, 25th and 75th interquartile.

ROSC [11,12,33]. It is important to stress, that in these studies only one injection of EPI was administered.

In studies investigating repeated injections of EPI, Bar-Joseph et al showed a significant increase in CPP only after the first injection of repeated doses of high dose EPI (0.1 mg/kg) [22], and Cairns et al showed a significant increase in CPP only in the animals who attained ROSC after first EPI injection followed by defibrillation [21]. We found a significant increase of CPP in 3 out of 4 injections, however less pronounced after injection 2 and 3. The studies by Bar-Joseph et al and Cairns et al used longer periods of untreated VF-period simulating OHCA, higher doses of EPI and defibrillation attempts after each injection of EPI [21,22]. Our goal was to simulate a frequently occurring situation in the coronary catheterisation laboratory, with a short period of untreated VF, followed by repeated administrations of EPI in conjunction with defibrillation and resistant VF. As opposed to the previous studies we administrated doses of EPI which were closer to those recommended in the guidelines. In addition, the different periods of untreated VF time in, previous experimental settings may influence the metabolic status and consumption of endogenously produced EPI in the animals at the initiation of CPR, which in turn may affect the response to EPI. We also used slightly different CC-techniques and ventilation rates [21,22], which also may affect the distribution and effect of administered drugs.

In regards to cardiac pressure and their influence on the bioelectrical activity during VF a high CPP correlates to a high AMSA in some studies [13,16]. Similar to our study, Achleitner et al showed an elevated mean fibrillation frequency and VF mean amplitude, during basic life support [23]. On the contrary, AMSA showed an insignificant tendency to decline in the EPI-groups in our study despite an increase in CPP, similar to previous findings [23]. Despite different CPR models and EPI dosages, the results in AMSA were similar in previous study [23] compared to current study. In the present study EPI was unable to induce a rise in AMSA, despite increased CPP and therefore it contributed to a successful defibrillation in only 7 out of 12 animals in each EPI-group. A possible explanation for this result may be an increased resistance resulting in a decreased myocardial microcirculatory blood flow induced by EPI, which has also been described in capillaries of the brain [34]. The lack of effects on AMSA following the repeated doses of EPI may accordingly be a result of a successively diminished myocardial tissue perfusion caused by EPI throughout the experiment. Thus, the initial injections of EPI may serve a purpose, but repeated injections may not be beneficial and may in fact be detrimental in subjects with VF who are reasonably circulated with manual CC or MCC. Further research is needed to determine the optimal dosages and frequency of EPI-injections during CPR.

Limitations

The experimental set up primarily reflects a very specific in-hospital CA scenario including a prompt response to a CA with CC followed by a prolonged CPR situation, for instance in the catheterisation laboratory with a therapy resistant VF and MCC. Since the animals were young, healthy and without coronary artery disease, it may be difficult to extrapolate our findings into an unselected patient category suffering CA. The study was not powered to evaluate differences in survival. EPI was administered according to guidelines, and the results should be interpreted accordingly. Different regimens of dosage and time intervals might give different results.

Conclusion

We conclude that repeated intravenous injections of EPI administered according to resuscitation guidelines during CA, increases APV after the first injection only despite an increase in CPP after 3 out of 4 EPI injections. We found no difference in AMSA values at any measuring point.

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