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Gunnar Waage Skjeflo

Doctoral thesis

Development of Electrocardiographic Characteristics During Resuscitation from Pulseless Electrical Activity

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NTNU
Norwegian University of Science and Technology
Thesis for the Degree of
Philosophiae Doctor
Faculty of Medicine and Health Sciences
Department of Circulation and Medical Imaging

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Avhandling for graden philosophiae doctor

Trondheim, mai 2019

Norges teknisk-naturvitenskapelige universitet
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Endringer i elektrokardiogrammet under gjenopplivingsforsøk ved hjertestans med pulsløs elektrisk aktivitet

Pulsløs elektrisk aktivitet (PEA) er en form for hjertestans hvor elektrokardiogrammet (EKG) viser elektrisk aktivitet som kan ligne på den i et normalt hjerte. Om lag 40% av hjertestans i sykehus og 20% av hjertestans utenfor sykehus har PEA som første rytme. PEA kan ikke behandles med elektrisk støt fra en hjertestarter. Overlevelsen er mye dårligere enn ved hjertestans som kan behandles med et slikt støt. Norske og internasjonale behandlingsanbefalinger vektlegger forsøk på å finne og behandle årsaken til hjertestans med PEA.

Siden det er elektrisk aktivitet i hjertet ville vi undersøke om endringer i EKG-signalet under pågående gjenopplivingsforsøk kunne gi noen informasjon om utfall og årsaken til hjertestansen. Vi ville også undersøke om medikamentell behandling med intravenøst adrenalin påvirket utviklingen av EKG-signalet. Vi undersøkte bredden på den delen av EKG signalet som representerer aktivering av hjertets hovedkamre (QRS-komplekset), samt raten av slike komplekser (hjerterate), under alle pauser i hjertekompresjoner. Vi analyserte data fra hjertestartere brukt under gjenopplivingsforsøk både på og utenfor sykehus, ved henholdsvis St. Olavs Hospital i Trondheim og utenfor sykehus i Oslo. Datamaterialet fra Oslo kom fra en tidligere randomisert studie av intravenøs tilgang under hjerte-lungeredning, der noen av pasientene ikke hadde fått intravenøst adrenalin.

Vi fant at utviklingen av QRS-kompleksets bredde og hjerterate var forskjellig hos pasienter der hjertet kom i gang igjen sammenlignet med pasienter der gjenopplivingsforsøket mislyktes. Denne utviklingen var svært lik både i og utenfor sykehus. Hos pasienter som fikk adrenalin under gjenopplivingsforsøk utenfor sykehus var utviklingen av hjerterate forskjellig sammenlignet med pasienter som ikke fikk adrenalin. Hos pasienter med hjertestans i sykehus var utviklingen av QRS-bredde forskjellig hos pasienter der hjertestansen skyldtes hjertesykdom, sammenlignet med pasienter der hjertestansen hadde andre årsaker. QRS-bredde og hjerterate hadde negativ samvariasjon, men utviklingen over tid var ulik.

Endring i QRS-bredde og hjerterate over tid kan gi informasjon om umiddelbar prognose, effekt av behandling, og underliggende årsak til hjertestans med PEA. Gjennom ytterligere studier kan denne informasjonen bidra til at behandlingen av pasienter med PEA bedre kan tilpasses den enkelte pasient, og dermed kanskje føre til økt overlevelse.

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Table of Contents

Original Papers

The current Thesis is based on the following papers:

Paper I:

Skjeflo GW, Nordseth T, Loennechen JP, Bergum D, Skogvoll E.
ECG changes during resuscitation of patients with initial pulseless electrical activity are associated with return of spontaneous circulation.
Resuscitation 2018 Jun; 127:31-36.

Paper II:

Skjeflo GW, Skogvoll E, Loennechen JP, Olasveengen TM, Wik L, Nordseth T.
The effect of intravenous adrenaline on electrocardiographic changes during resuscitation in patients with initial pulseless electrical activity in out of hospital cardiac arrest.
Resuscitation 2019 Mar; 136:119–25.

Paper III:

Skjeflo GW, Bergum D, Loennechen JP, Nordseth T, Skogvoll E.
Changes in QRS Complex Width during Resuscitation Depend on Aetiology in Patients with Pulseless Electrical Activity
Manuscript submitted to Resuscitation

English Summary

Background

Pulseless electrical activity (PEA) refers to patients in cardiac arrest in whom the electrocardiogram (ECG) shows organized electrical activity. In cardiac arrest in-hospital, PEA is the presenting rhythm in around 40% of cases. In the out-of-hospital setting, PEA is the presenting rhythm in about 20% of cardiac arrests. The ECG is a recording of the electrical activity of the heart, and is widely used in diagnosis of heart disease and monitoring of heart function. The presence of ECG complexes represents a possible source of information during PEA. The development of ECG characteristics during the provision of advanced life support (ALS) for cardiac arrest with PEA has not been investigated previously.

Aims of the Thesis

1. To describe the development of ECG characteristics during ALS in patients with and without return of spontaneous circulation (ROSC).
2. To explore the effect of intravenous adrenaline on the development of the ECG characteristics during ALS.
3. To investigate the development of ECG characteristics based on the cause of cardiac arrest.

Methods

We measured QRS complex width (the duration of ventricular depolarization) and QRS complex rate (heart rate) at all pauses in compression during the provision of ALS. Studies I and III included patients with cardiac arrest at St. Olav University Hospital, Trondheim, Norway. Study II included patients with cardiac arrest out-of-hospital in the city of Oslo, Norway, that were originally part of a randomized controlled trial of intravenous access during ALS. We examined whether QRS complex width and heart rate during ALS were related to whether ROSC was obtained or not (all three studies), whether adrenaline was administered (study II), and whether there was a cardiac or other,

non-cardiac etiology of arrest (study III). Statistical methods included correlation analysis, multivariate analysis of variance, analysis of covariance, and various mixed model methods.

Results

In studies I and II, we found that the pattern of change in QRS width and heart rate differed between patients who obtained and did not obtain ROSC. More specifically, QRS width decreased and heart rate increased in patients who obtained ROSC. This difference was consistent in the in- and out-of-hospital populations. In study II, we found that heart rate increased in patients who received adrenaline during ALS, more in patients who obtained ROSC, but also in patients who did not obtain ROSC. Study III showed that the development in QRS width differed between patients with a cardiac etiology of arrest compared to patients with other etiologies; QRS was wider in the cardiac etiology patients, but narrowed in those that did obtain ROSC. In the other etiology groups, QRS width was narrower throughout ALS.

Conclusion

QRS narrowed and heart rate rose during the provision of ALS for cardiac arrest with PEA in patients who did obtain ROSC, but not in those who died. The same pattern of change in QRS width and heart rate was seen in the in-hospital and out-of-hospital populations studied. Heart rate increased in patients who did get adrenaline during ALS out-of-hospital, even if they did not obtain ROSC. QRS width was wider in patients with cardiac etiology of in-hospital cardiac arrest, but narrowed in those who obtained ROSC. Patients with other, non-cardiac, etiologies had narrower QRS widths that did not change during ALS.

Abbreviations

ALS	Advanced life support
BLS	Basic life support
bpm	beats per minute
CCU	Coronary care unit
CI	Confidence interval
CPC	Cerebral performance category
CPR	Cardiopulmonary resuscitation
ECG	Electrocardiogram
ED	Emergency department
e.g.	exempli gratia (Latin: for example)
EMD	Electromechanical dissociation
Et al.	et alia (Latin: and others, co-workers)
EU	European Union
GAMM	Generalized additive mixed effects model
i.e.	id est (Latin: in other words)
ICD	Implantable cardioverter defibrillator
ICU	Intensive care unit
IHCA	In-hospital cardiac arrest
IQ range	Interquartile range
IV	Intravenous
LME	Linear mixed effects model
MANOVA	Multivariate analysis of variance
mg	milligram
min	minute
/min	per minute
mRS	modified Rankin Scale
ms	millisecond
n	Number (of patients)
OHCA	Out of hospital cardiac arrest

PEA	Pulseless electrical activity
ROSC	Return of spontaneous circulation
SE	Standard Error
UK	United Kingdom of Great Britain and Northern Ireland
U.S.	United States (of America)
USA	United States of America
VF	Ventricular fibrillation
VF/VT	Ventricular fibrillation / (pulseless) ventricular tachycardia
VT	Ventricular tachycardia
yrs	Years

Figures and Tables

Figures

Tables

1 Introduction

Cardiac arrest is the cessation or abrupt reduction of cardiac output to levels insufficient for the perfusion of the brain and other vital organs. The clinical definition utilized by both the European and Norwegian Resuscitation councils follows from this pathophysiology (1,2). The patient is quickly rendered "unresponsive and not breathing normally" (1). If this condition cannot be reversed within a short time span, death ensues. Cardiac arrest out-of-hospital (OHCA) has a reported incidence of about 38 per 100,000 person years in Europe according to a review (3), with great variation. The lowest incidence rate was 5.45/100,000-person years, while the highest was found to be nearly 120/100,000-person years. In the Norwegian Cardiac Arrest Registry the incidence was 60 per 100,000-person years in 2017 (4).

In-hospital cardiac arrest (IHCA) in Europe has an estimated incidence of about 1.5 per 1000 hospital admissions (5), and between 1.3 and 2.1 per 1000 hospital admissions in Norway (6,7). These incidence rates are not easily comparable, but the incidence of in-hospital cardiac arrest is, perhaps not surprisingly, much higher than the rate out-of-hospital.

Many conditions can lead to cardiac arrest, and it can be viewed as a symptom or manifestation of a disease process, more than a disease entity on its own. In some cases, cardiac arrest is merely the expected end of the dying process. But it can also be abrupt and acute, unwanted and dramatic, warranting extensive efforts to restore life.

The subject of the present Thesis is cardiac arrest in which the initial rhythm is pulseless electrical activity, henceforth called PEA. The presence of an electrocardiographic (ECG) signal, with discernible QRS complexes (the electrical activity representing ventricular activation) reminiscent of that of the normally beating heart makes this entity unique. In these studies, we measured the rate and width of the QRS complexes in recordings from the defibrillators, for the duration of advanced life support (ALS). Measurements were made at all pauses in compressions as long as there were discernible QRS complexes in the ECG, and the change in these parameters over time was compared with respect to outcome, adrenaline administration and the etiology underlying the cardiac arrest.

Data were collected by the emergency teams of St. Olav University Hospital, Trondheim, Norway between January 2009 and January 2012 (Studies I and III), and provided from a randomized study of intravenous access in out-of-hospital cardiac arrest that took place in Oslo, Norway between 2003 and 2008 (Study II).

2 Background

2.1 Definitions

Resuscitation is from the Latin "*resuscitatus"*, meaning to reawaken (8). Today this is often taken to refer to the restoration of a patient from an acutely life-threatening state. Cardiopulmonary resuscitation (CPR), comprising external chest compressions and ventilations, is more specifically directed at cardiac arrest. Further, Basic Life Support (BLS), consists of CPR with the aid of an automatic defibrillator (1). ALS is performed by healthcare professionals or other specially trained personnel. It consists of CPR, the use of manual defibrillators, advanced airway management and intravenous medications. The cause of arrest is sought and treatment attempted if possible (9).

A distinction between different *electrocardiographic rhythms* of cardiac arrest is made based on the ECG patterns seen when the defibrillator pads are attached to the

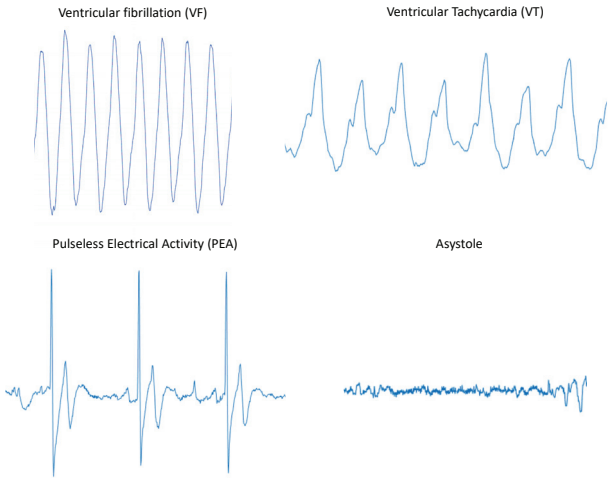

Figure 2.1 Examples of the four possible electrocardiographic rhythms in cardiac arrest.

patient. These are ventricular fibrillation (VF) and (pulseless) ventricular tachycardia (VT), PEA and asystole. The different ECG patterns are illustrated with examples from study I in Figure 2.1. For simplicity, the term "rhythm" will be used throughout this Thesis. VF is characterized by coarse and unorganized activity, while VT is a fast, wide complex rhythm. In asystole, there is no or very little electrical activity. PEA is

characterized by organized electrical activity, as in the beating heart, but with no or very little cardiac output (10).

The waves seen on the ECG tracing both in normally beating hearts, and during PEA, are named by letters in the alphabet, as illustrated in Figure 2.2. As stated earlier, the QRS complex represents ventricular electrical activation or more precisely ventricular depolarization (11). The term QRS width will be used in this Thesis, though width in reality refers to the duration of ventricular myocardial depolarization, and is measured in units of time (milliseconds, in this Thesis).

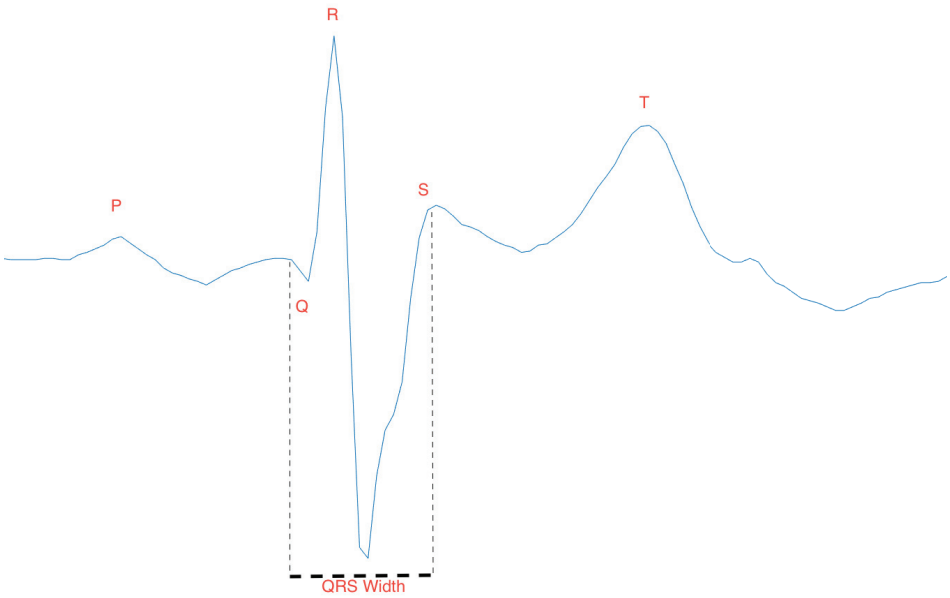

Figure 2.2 Example ECG complex from study II, waves named as by convention.

In addition to the rhythm, it is possible to differentiate between different clinical states. These include the four cardiac arrest rhythms, but also return of spontaneous circulation (ROSC), which is the immediate goal of all resuscitation from cardiac arrest. This can be temporary, with relapse to one of the four cardiac arrest rhythms, or sustained. Death is another clinical state, which in practice is usually declared by the ALS team when ALS is terminated, and at which point the patient's rhythm may be any of the four cardiac arrest rhythms.

Defibrillation is the delivery of an electric shock to the heart either through paddles or pads placed on the skin of the chest, or to the heart directly during open chest surgery or by an implantable cardioverter defibrillator (ICD). The electric current depolarizes most of the heart simultaneously, which allows the heart to “restart” in a synchronized rhythm. This is only effective against VF and VT, and the initial treatment of PEA and asystole is limited to chest compressions, ventilation and intravenous or intraosseous adrenaline (epinephrine) (9).

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2.2 The ECG

Electrical activity in the skeletal muscles were first demonstrated by dr. Luigi Galvani in 1781, when contact between a lancet and nervous tissue simultaneously as an electrical spark was produced, caused a twitch in a preparation of a frog's thigh (12). Dr. Carlo Matteucci found that electrical current accompanied the heart beat in frogs in 1842 (13,14). In 1887, Waller demonstrated the first external recording of the electrical activity of the human heart – an ECG recording. At the same time, he also demonstrated that the electrical activity preceded movement of the heart (15). The development of the modern ECG is credited to Willem Einthoven, for his design of the string galvanometer, the standardization of ECG recordings using the extremity leads and the use of the ECG in the diagnosis of disease. He received the Nobel Prize in Physiology or Medicine in 1924 (16).

Today, the ECG is an integral part of the evaluation and diagnosis of both cardiac and, in some cases, extracardiac disease (17). Of specific interest to the current Thesis, QRS width depends on conduction velocity. QRS width is the time taken from start of depolarization to all parts of the ventricles are depolarized. Reduced conduction velocity or blocks in the ventricular conduction system, or electrical activation outside the ventricular activation system will prolong the QRS. Increased QRS width is mandatory in bundle branch block and ventricular tachycardias and has been shown to be a marker of myocardial ischemia (18,19). Heart rate has been shown to influence myocardial perfusion and risk of ischemia through effects on both myocardial oxygen demand and perfusion (20).

2.3 The ECG in Cardiac Arrest

As stated above, the different rhythms in cardiac arrest are diagnosed by examining the ECG. Figure 2.1 contains illustrations of the different rhythms. The distinction between the four different rhythms is important, as the immediate treatment differs: Defibrillation is only effective in VF/VT, the so-called shockable rhythms(9).

Usually, the ECG displayed by most modern defibrillators is recorded though the defibrillation pads, producing a single lead ECG (often close to a lead II recording), but, with advanced defibrillators, three-, five- or even 12-lead ECG monitoring is often possible using separate ECG electrodes. For the determination of cardiac arrest rhythm, a single lead ECG from the defibrillation pads is recommended in the current guidelines from the European Resuscitation Council (1,9). Automatic rhythm analysis has also been incorporated in fully- or semi-automated defibrillators for over 30 years (21–25).

2.4 PEA

The European Resuscitation Council has defined PEA "as cardiac arrest in the presence of electrical activity (other than ventricular tachyarrhythmia) that would normally be associated with a palpable pulse", a definition which has been adopted from an American National Heart, Lung and Blood Institute workshop on PEA (10,26). PEA was earlier known as electromechanical dissociation (EMD). This term is rarely used anymore, perhaps due to the realization that true myocardial stand-still in the presence of discernible ECG signals was rare in perceived EMD (27,28). PEA was considered a more accurate term.

2.4.1 Epidemiology

A number of papers describe a reduction in the incidence of OHCA from the 1980s onwards (29–33). The papers that report the change in the percentage with initial PEA all find this to be increasing with time to between 21 and 28% (29,31,32).

Figure 2.3 illustrates the change in in the incidence of OHCA, and OHCA with initial PEA, and is based on data from the studies referred to above. The data from Norway are from a study of OHCA published in 1999, and from the Norwegian Cardiac Arrest Registry's annual report for 2017(4,34).

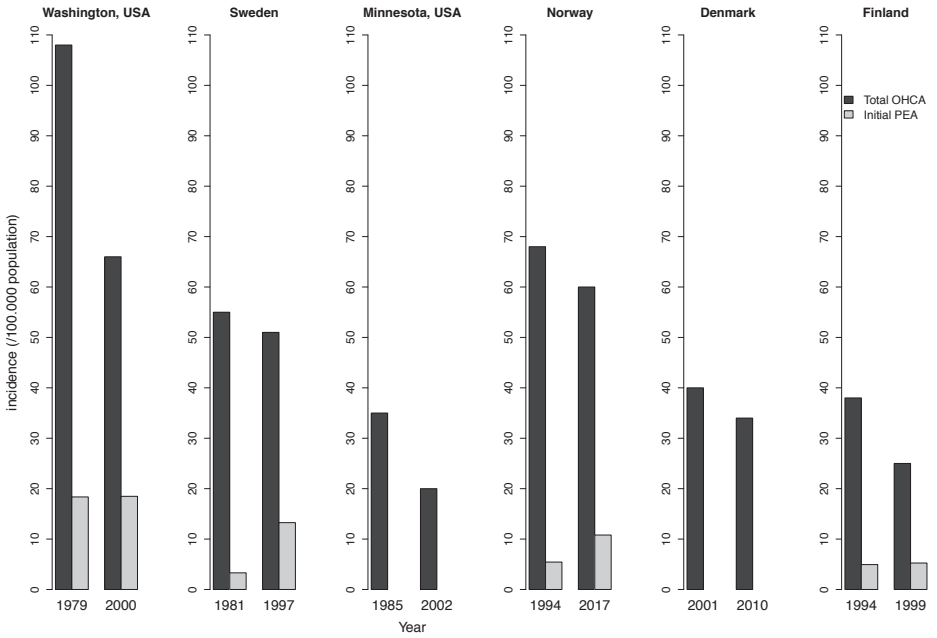

Figure 2.3 Changing incidence of OHCA and initial PEA (Black bars represent incidence of OHCA per 100,000 population, while the grey bars represent the incidence of OHCA with initial PEA, also per 100,000 population) *(4,29–34)*).

In the in-hospital setting, Girotra et al. reports a rise in the share of IHCA with initial PEA from the years 2000-2003 to 2007-2009 (36.7% to 46.5%), and a decrease in the percentage with initial VF simultaneously (16.9% to 9.4%) (35). In Vienna, Austria, 41% of patients with IHCA treated in a university clinic over a 17.5 year period had initial PEA (36).

The prevalence of PEA is generally higher in-hospital than out-of-hospital. Figure 2.4 shows the percentage with initial PEA in the OHCA and IHCA setting in comparable populations (geographically and temporally). This is based on data from Trondheim, Norway; Gothenburg, Sweden; Bergen, Norway; two registry based publications from the U.S., two publications from the UK, and the national cardiac arrest registry of Norway (4–7,34,37–40). It must be noted that the reporting of IHCA to the Norwegian cardiac arrest registry was incomplete in 2017, with only 18 of the 52 eligible hospitals in the country participating. All ambulance services participated in the reporting of OHCA (4).

As can be seen, the percentage of initial PEA was higher in IHCA in all locations, except in Gothenburg, Sweden.

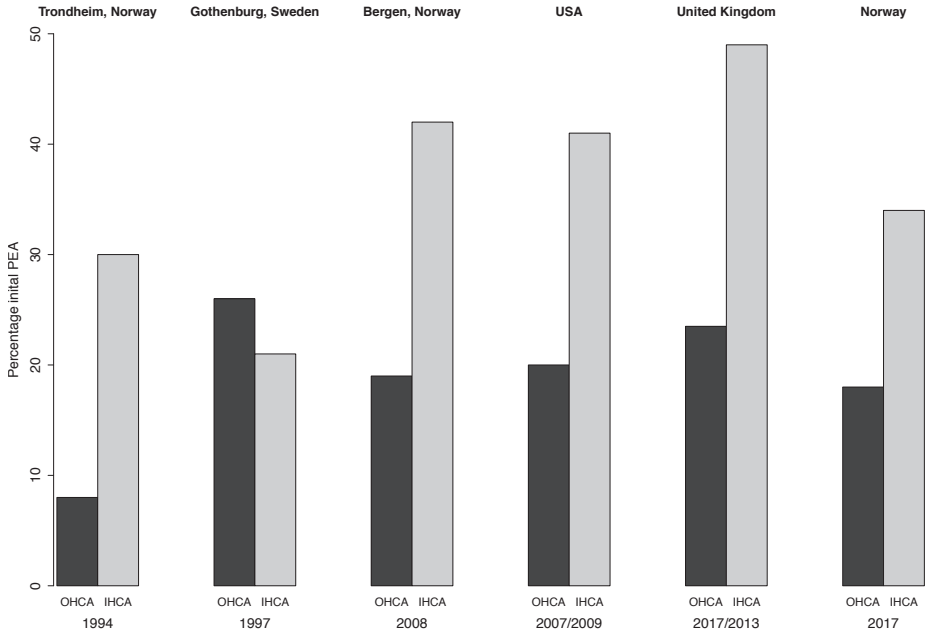

Figure 2.4 Comparison of the percentage with initial PEA in out-of-hospital cardiac arrest (OHCA) versus in-hospital cardiac arrest (IHCA) The labels on the x-axis are the last year(s) of data collection, for the OHCA and IHCA data respectively (if not collected entirely simultaneously) *(4–7,34,37–40)*.

It seems reasonable to believe that the prevalence of initial PEA is higher in hospital, though the exact magnitude of both the difference and the actual incidence is less certain.

There are several reasons why comparing in-hospital and out-of-hospital cardiac arrest occurrence and characteristics is difficult. The underlying population differs widely in health status and geographical location. Inclusion criteria in most studies of cardiac arrest are often that some kind of resuscitative efforts have been commenced. Out-of-hospital, where and when BLS or ALS is started is perhaps more random than in the in-hospital setting, but patients for whom ALS would not have been started in the IHCA setting because of known comorbidities or do not resuscitate orders, could have been

included in the OHCA setting. Differences in response times may influence the observed initial rhythms, as all cardiac arrest rhythms degenerate into asystole eventually. Also, comparing both in-hospital and out-of-hospital data from different countries and parts of the world is difficult. The incidence and survival from OHCA varies (41). With respect to IHCA, especially US hospitals seem to have a much less selective use of intensive care unit (ICU) beds and more liberal use of advanced treatment and monitoring (35), than the Scandinavian countries (42,43) and the UK (5). It may also be that cardiac arrests in these locations are missed because such units may treat cardiac arrest without calling an emergency team.

2.4.2 The ECG in PEA

As the ECG is a valuable and accurate diagnostic tool in the evaluation of heart disease outside the setting of cardiac arrest (44), it seems reasonable that the ECG could contain information also during PEA.

The first observation of ECG changes in readings from dying human hearts was reported by Rohmer in 1911 at a meeting of the section of pediatrics in the German association of nature scientists and doctors. Three pediatric patients that had died from diphtheria were the subjects. The ECGs showed abnormal QRS complexes and complete atrio-ventricular disjunction (45). In 1912 this was followed by a paper describing the ECG changes upon death of 7 patients dying from poliomyelitis, pneumococcal meningitis and pneumonia. “Marked slowing of the rate of cardiac activity always occurred, and there was usually a distinct delay in the conduction time between auricles [atria] and ventricles.” Fusion of the R and T waves was also described, as well as occurrence of VF in two cases (46).

Further reports of changes in the ECG during death up to 1931 was summed up and expanded upon by Turner. He found that regardless of cause, slowing of the heart rate was the most consistent ECG finding in ECGs from dying human hearts, occurring in over 70% of the episodes examined. Second, atrio-ventricular conduction changes, and junctional and nodal rhythms, were common. He concluded that this was of mere academic interest as these changes occur only minutes before death. “Significant changes of the electrocardiogram appear so little ahead of death that the patient is usually dead before the film is developed” (45).

In an experimental study using anaesthetized dogs (of unreported number), Kountz and Gruber demonstrated changes in the T-wave morphology as hypoxemia progressed, until fusion with the QRS complex occurred. This was reversible by the administration of oxygen (47).

Attin et al. demonstrated that especially heart rate declined and QRS width increased in the hour before cardiac arrest with initial PEA or asystole in hospitalized patients (48). It seems that the ECG characteristics in PEA deteriorate with time, both up to the point of arrest, and as a function of time after arrest. Importantly, PEA can also be seen as a stage between a rhythm that generates perfusion and asystole. Paradis and co-workers hypothesized that PEA in which the heart moves, but does not produce an adequate cardiac output, is a precursor to PEA with mechanical stand-still of the heart, and subsequently asystole (28).

A few studies have examined the relationship between the morphology of the electrical complexes in PEA and outcome. Stueven and Aufderheide published two papers on the subject, in an OHCA population, in 1989 (49,50). They found that in patients without evidence of atrial activity or with monophasic QRST complexes, none survived. Further, in patients who were admitted to hospital alive (i.e. had ROSC), they found higher heart rates, narrower QT and QRS complexes initially, and at admission to hospital. Patients who survived to hospital discharge differed from those who died in-hospital by not remaining tachycardic after ROSC.

Recently, Weiser et al. published a study of OHCA with initial PEA from Austria (51). They examined QRS width and heart rate during the initial 60 seconds of ALS, and found that patients with an initial heart rate above 60/min were more likely to survive to 30 days and with a favorable Cerebral Performance Category (CPC) (52) compared to patients with lower initial rates. QRS width did not affect outcome.

2.4.3 Pulselessness and Cardiac Activity

PEA is a descriptively accurate term, but it encompasses a range of clinical states, with a number of underlying etiologies. Bocka and co-workers examined 22 patients with PEA in the emergency department, using echocardiography with a sub costal view, and found ventricular wall motion and change in the dimensions of the heart chambers in 86% of patients (27). They could see valve motion in 15 of these patients (62.5%), but could only

ascertain valve closure in four patients (18%). Expanding on this, Paradis et al. measured aortic root pressures during PEA via an arterial catheter (28). The 94 patients in that study were victims of OHCA who were transported to hospital under CPR and then had the catheter placed a median of 26 minutes after arrest. Thirty-nine (41%) of the patients had an aortic pulse pressure above 60mmHg, which was defined as "pseudo-EMD".

The distinction between PEA with and without cardiac wall motion may be important. In a large multi-center study of cardiac arrest victims transported to emergency departments or who arrested in the emergency department, Gaspari and co-workers found that lack of cardiac movement as assessed by echocardiography was a strong predictor of unsuccessful resuscitation, in patients with both PEA and Asystole (53). Breitkreutz and co-workers found that OHCA patients who had visible cardiac wall motion when examined by ultrasound had better survival to hospital admission than patients without evidence of such motion both in PEA and asystole (54). That both laypersons and health-care professionals have difficulties determining the presence of a palpable arterial pulse has been demonstrated (55,56). Thus, in the clinical setting, unconscious patients with abnormal respirations but perhaps only a lowered blood pressure, as well as patients with no cardiac movement and no perfusion all could be registered with initial rhythm PEA on Utstein style cardiac arrest forms. That the prognosis can vary greatly within such a population is hardly surprising.

2.4.4 The Etiology of PEA

The current European guidelines for adult advanced life support states: "Potential causes or aggravating factors for which specific treatment exists must be considered during any cardiac arrest. For ease of memory, these are divided into two groups of four, based upon their initial letter: either H or T" (9). The American Adult Advanced Cardiovascular Life Support guidelines include a similar statement: "PEA is often caused by reversible conditions and can be treated successfully if those conditions are identified and corrected. During each 2-minute period of CPR the provider should recall the H's and T's to identify factors that may have caused the arrest or may be complicating the resuscitative effort" (57). In the latter guidelines, there are 5 each of H´s and T´s. Both guidelines include the same diagnoses however, and for simplicity the European version is presented in table 7-1 below (9).

Table 2-1 Reversible causes of cardiac arrest. The 4H´s & 4T´s mnemonic.

The 4 H´s and 4T´s	
Hypoxia	Thrombosis, Coronary or Pulmonary
Hypovolemia	Tension Pneumothorax
Hyperkalemia, hypokalemia, hypocalcemia, acidosis and other metabolic disorders	Tamponade, cardiac
Hypothermia	Toxins

An alternative view of different etiologies of PEA is to distinguish between mechanical and metabolic causes. For instance, cardiac tamponade may be a mechanical cause of PEA, while ischemia is a metabolic cause (58).

Few authors have addressed the causes of cardiac arrest, either generally or in the special case of PEA. Wallmuller and co-workers found cardiac causes (coronary artery disease, arrhythmia, structural heart disease, hypertension) in 63% of patients in a retrospective review of 1041 IHCA (36). PEA was the initial rhythm in 29% of arrests with a cardiac cause, where ST-elevation myocardial infarction was found to be most frequent immediate cause. The initial rhythm in 62% of arrest with a non-cardiac cause was PEA; in this group, pulmonary causes (including pulmonary embolism) dominated.

Bergum and co-workers found similar numbers in a prospective Norwegian study of IHCA which included 258 patients (43). PEA was the initial rhythm in about 28% of arrests with a cardiac cause, and as in Wallmuller and co-workers' study (36) myocardial infarction was the largest cause in this group. Hypoxia was the most frequent non-cardiac cause, about twice as prevalent as in Wallmuller et al's study (36). PEA was the initial rhythm in approximately 70% of these (43).

Researchers in Finland and Sweden examined 104 patients with IHCA with initial PEA retrospectively, in a paper by Saarinen et al., and found hypoxia and myocardial infarction as the most prevalent immediate causes (59). They also found pulmonary embolism to be relatively common (43% of cases). These researchers also reported results from autopsies performed in 44 of the patients included in the study: Cardiac causes (myocardial infarction or heart failure) was found as the cause of PEA in 48%, pulmonary embolism in 17%, pneumonia in 12% and aortic dissection or aortic rupture in 12%.

Both Wallmuller et al. (36), Bergum et al. (43) and Saarinen et al. (59) found that except for coronary thrombosis, and hypoxia/pulmonary causes, the other H´s and T´s are relatively rare causes of cardiac arrest. Hypovolemia, of the 4H´s and 4T´s, was found to be responsible for 8% of cardiac arrests in the study by Bergum et al. (43), while pulmonary embolism was very prevalent in Saarinen et al's (59) study when determined clinically, less so in the autopsy material. Still, when added up, the 4H´s and 4T´s together were the cause in about 28% of non-cardiac IHCA in Wallmullers et al's (36) study (authors own calculation); in 48% of the non-cardiac PEA with autopsy data in the study by Saarinen et al. (59) (authors own calculation); and 42% of non-cardiac IHCA in the study of Bergum et al. (43). (The etiologies based on clinical judgement in Saarinen et al's (59) study are not reported as mutually exclusive, consequently it is difficult to calculate the percentage of arrests with a single cause in this material.)

Saarinen et al. found statistically significant increased 30-day survival by univariate analysis in a small subgroup of patients (n=19), who were given what was deemed "appropriate treatment" during CPR (36% vs 11%) (59). However, by multivariate logistic regression – controlling for other variables – this association did not reach statistical significance. Another study by Bergum et al. reported increased survival at 1 hour and to hospital discharge in patients with IHCA where the cause of arrest was found by the ALS providers (60). This effect was strongest in patients where the initial rhythm was PEA or asystole or the cause was non-cardiac.

In OHCA cardiac causes dominate the etiology spectrum. Pell et al. reported that more than 82% of OHCA in Scotland over a 7 year period were of cardiac etiology, but this was based on data recorded by prehospital services on Utstein style cardiac arrest forms (61). Kuisma et al. found that out of a total of 809 OHCA, 34.1% had a verifiable non-cardiac etiology of arrest, about 12% of these were first erroneously classified as cardiac and later reclassified based on further examinations (62–64)(62). In a large Japanese study, that even employed what they called "peri-mortem computed tomography scanning" to find the cause of arrest, only 37.5% of cases were classified as Cardiac (63), but the report is unclear as to the criteria for inclusion of patients: Patients with shockable rhythms may have been excluded. Cardiac causes of arrest were apparently more prevalent when the initial rhythm was shockable (VF/VT), and other causes more prevalent in cases with initial PEA or asystole both in the study by Pell et al. (61) and that by Kuisma et al. (62).

Echocardiography during ALS is mentioned in the latest European Resuscitation Council guidelines as a tool to diagnose the cause of arrest. So far no studies have demonstrated a survival benefit, though both Gaspari et al. (53) and Breitkreuz et al. (54) reported that a number of patients with diagnoses treatable by specific interventions were found by echocardiography (pericardial effusions were the most prevalent of these). Unfortunately, echocardiography during ALS may increase hands-off time (64), which has been shown to worsen prognosis (65). It has been suggested that the diagnosis of the etiology of PEA may be reached quicker by examination of QRS complex width, and selective use of echocardiography (58).

2.5 The Use of Adrenaline in Cardiac Arrest

Pearson and Redding described the experimental and clinical use of adrenaline (epinephrine) in cardiac arrest in the 1960´s. They used 1 mg of adrenaline either intravenously or directly intracardiac (66,67). Crile and Dolley first described the use of adrenaline to resuscitate dogs in 1906 (68), but the nearly uniform use in ALS came first after the aforementioned work by Pearson and Redding. Today the European guidelines for ALS recommend giving 1mg of adrenaline intravenously after the third failed shock and then every alternate 2 minute cycle (every 3-5 min), or as soon as possible if the initial rhythm is non-shockable (9). The Norwegian guidelines differ slightly, recommending adrenaline after the second failed shock or as soon as possible in non-shockable rhythms, and then 1 minute after each failed shock, or 1 minute into each 3 minute cycle if the rhythm is non shockable (69).

The desired effect of adrenaline during cardiac arrest is mediated through alpha-adrenergic receptors in the vasculature, notably by increasing vascular tone which in turn increases the aortic pressure and the cerebral and coronary perfusion pressure (70). On the other hand, adrenaline has notable beta-adrenergic effects, both inotropic and chronotropic which may be detrimental in the setting of cardiac arrest or post-ROSC (71–74). A study of the cerebral microcirculation in pigs also suggests that adrenaline may impair cerebral microcirculatory blood flow (71), though a small study using cerebral oximetry during cardiac arrest in humans found a “small but clinically insignificant” rise in cerebral oxygen saturation following 1 mg adrenaline intravenously (75).

Neither of three often cited observational studies of adrenaline use in OHCA, one from Japan (76), one from Singapore (76) and one from Sweden (77) found any beneficial effect of adrenaline on long term survival or neurological outcome. The large Japanese study, by Hagihara et al. even found less survival with a favorable neurological outcome in patients who had been given adrenaline (76). In a study from Paris, France, that only included patients with ROSC at hospital admission, Dumas et al. found that use of adrenaline during ALS was associated with decreased neurologically intact survival. This effect increased with increased dose of adrenaline, delayed administration and was the same also when controlling for duration of resuscitation (78).

Three randomized trials have studied the effect of adrenaline in cardiac arrest. In the first, a study conducted from 2003 to 2008 in Oslo, Norway (79), paramedics opened

sealed envelopes when cardiac arrest had been ascertained to discover if their particular patient were to have ALS with access to intravenous medication or not. The authors published two reports based on this study. In the first, based on randomization status, where 418 patients were included in the intravenous group and 433 in the no-intravenous group, more patients in the intravenous group had ROSC and were admitted to hospital and to ICUs. But there was no difference in survival to hospital discharge or with a favorable neurologic outcome (defined as Cerebral Performance Category (CPC) 1 or 2) (79). Interestingly, when the data was broken down by initial rhythm (VF/VT or PEA/asystole), the increased short-term survival seen in the intravenous group seemed to be almost entirely found in the PEA/asystole group. In a post-hoc analysis where patients were stratified on whether adrenaline had been given or not, Olasveengen et al. found that adrenaline had been given to 367 of 842 patients. The results were in line with the original study in that the short-term survival was higher in the adrenaline group. However more than twice as many in the no adrenaline group were discharged alive (13% versus 7%) and with a favorable neurological outcome (11% versus 5%). Both differences were statistically significant (80).

The second was carried out in Perth, Australia by Jacobs et al: A double blind randomized clinical trial on the effect of adrenaline in OHCA (81). Randomization took place when the paramedics selected a vial that contained either adrenaline or saline, but which was indistinguishable to the paramedics. Unfortunately, though the authors had calculated that they needed more than 2200 patients in each arm of the study, only 534 patients were included in the final analyses, partly due to criticism in media and non-compliance by ambulance services during inclusion. Similar to Olasveengen et al. (79,80), short term survival was higher in the adrenaline group, with no difference in the proportion that survived to hospital discharge or with a favorable outcome (81). In this study, there was no difference in short term survival based on whether the initial rhythm was shockable or not.

The third, a large, double blinded randomized clinical trial was recently carried out in the UK. Patients were randomized when paramedics opened sealed envelopes containing identical looking prefilled syringes that contained either adrenaline or saline. The adrenaline arm of the study comprised 4015 patients, the placebo arm 3999 patients. There was a statistically significant difference between the groups in the primary outcome

of the study: Survival to 30 days (3.2% versus 2.4% in the adrenaline and placebo groups respectively, adjusted odds ratio 1.47 ($CI_{95\%}$: 1.09-1.97) (40). As in the previous studies, the short-term survival was larger in the adrenaline group (23.8% versus 8%), but there was also a difference in survival to hospital discharge (3.2% versus 2.3%). There was however no difference in survival with a favorable neurological outcome (2.2% versus 1.9%). This study used the modified Rankin scale (mRS) as the parameter of neurological outcome (82). Though this was not the primary outcome of the study, the authors underline that the survival with neurological disability (mRS $\geq$4) at discharge and at 3 months was more frequent in the adrenaline group. In the supplementary appendices to this paper, the difference at three months appears to be small (40).

In the studies by Jacobs et al. (81) and Perkins (40) et al., patients that responded to early CPR were excluded by the process of randomization. Olasveengen (79,80) et al. included these patients, which could potentially bias this study towards more positive results for the no adrenaline group, especially in the post-hoc analyses (80).

Nordseth and co-workers studied the effect of adrenaline on transitions from PEA to the other cardiac arrest rhytms in a subset of 173 patients with initial PEA in Olasveengen et al's study (79,83). They found increased transitions from PEA to ROSC in patients who received adrenaline during ALS, and an increased time window for this to happen. However, increased transitions from ROSC and PEA to VF/VT were also found (83).

Given the current controversy regarding adrenaline in ALS, it is natural and reasonable to investigate its effect more closely with respect to the immediate cardiac consequences. Olasveengen's study was the only one of the three studies that collected defibrillator files during study conduct. Thus, the material analyzed in this Thesis provided a unique opportunity to investigate the effects of adrenaline on ECG-changes during ALS.

2.6 Prelude to This Thesis

In addition to the studies mentioned in Section 2.4.4, Bergum et al. (including the author of the current Thesis) examined the ECG characteristics (initial QRS width, corrected QT time and heart rate) in 51 patients with IHCA and initial PEA (84). These were related to 1-hour survival, and the etiology of arrest. The etiologies of arrest were categorized as cardiac; either of the 4H/4T (see Section 2.4.4), or other, neither cardiac nor 4H/4T etiologies. Etiologies were also classified as mechanical or metabolic (Section 2.4.4). The results with respect to QRS width and heart rate are presented in the following bivariate scatterplots (Figures 2.5 to 2.7), which are reproductions from Bergum et al's original paper, with permissions from the first author. QRS widths above 120ms were considered wide, heart rates between 60 and 100 beats per minute were considered normal, otherwise slow (<60/min) or fast (>100/min). The majority of patients presented with bradycardia and wide QRS complexes, but no association between these ECG characteristics and either outcome or etiology was found.

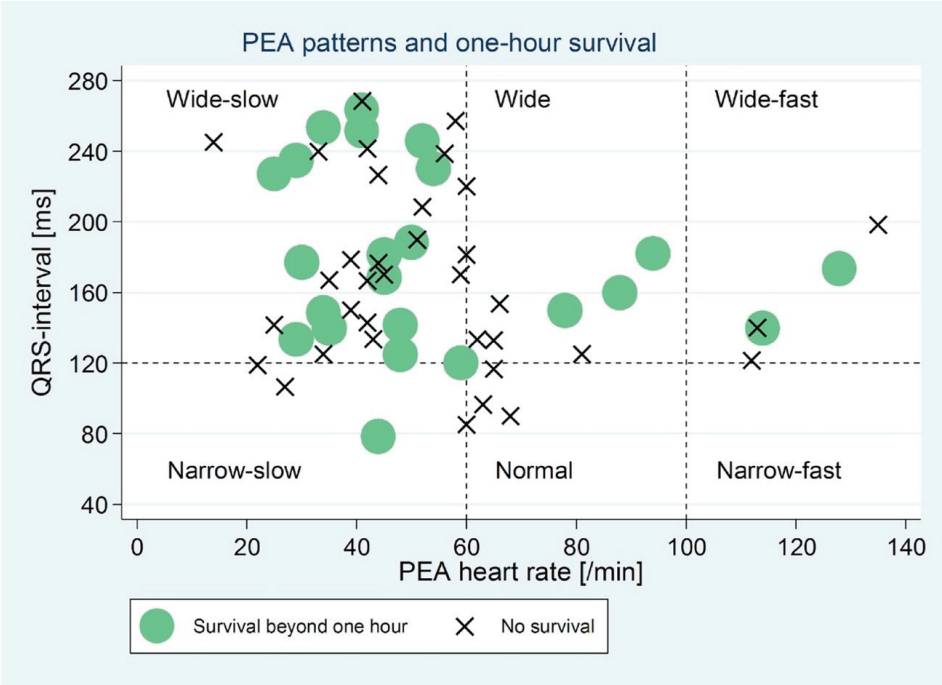

Figure 2.5 Initial QRS width and heart rate, Surivival 1 hour and no survival.

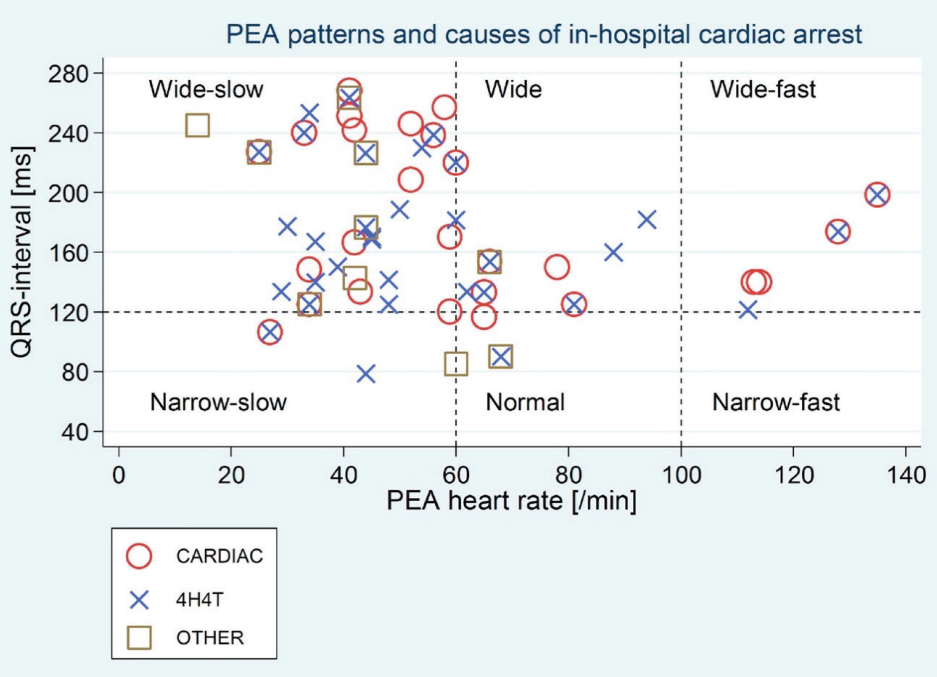

Figure 2.6 Initial QRS width and heart rate, Cardiac, 4H4T and other causes.

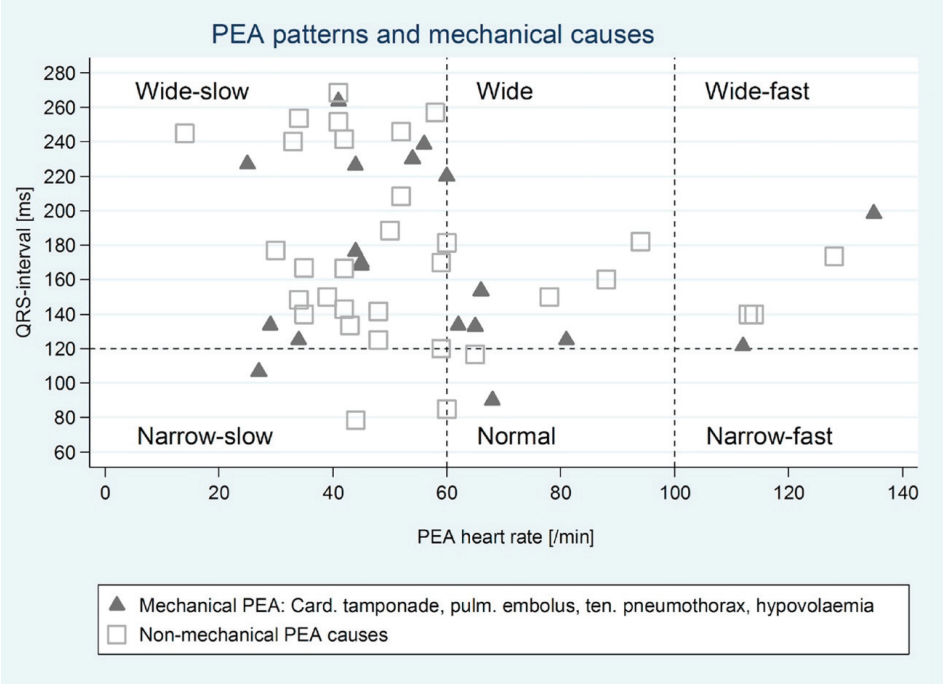

Figure 2.7 Initial QRS width and heart rate, mechanical and metabolic causes.

Though no distinct pattern of these initial ECG characteristics were associated with either survival or etiology, the dominance of abnormally wide QRS complexes and slow heart rates suggest that there may be a potential for improvement in these characteristics during ALS. A very natural way forward was thus to investigate whether there was information in the continuous development of the ECG characteristics during ALS in cardiac arrest with PEA.

3 Motivation and Aims

The preceding pages summarizes the background for the current Thesis. The ECG is important in cardiac arrest as the treatment algorithm differs based on the ECG rhythm. PEA is increasingly prevalent, concerns more and more patients, and the prognosis for survival is grave. It has been the focus of less research than the shockable rhythms.

In PEA, some mechanical activity seems to be better than none, and treatment of the specific cause of arrest may improve survival. The QRS complex, as seen on an ECG recording, is a recording of the electrical depolarization of the cardiac ventricles, which in turn depends on the metabolic state of the myocardium. In the study of initial ECG characteristics in IHCA with initial PEA discussed in Section 2.6, our research group found that broad QRS complexes and low heart rates dominated (84). We hypothesized that changes in ECG characteristics during the provision of ALS in cardiac arrest with initial PEA might reflect prognosis, and that certain ALS interventions could influence these changes. We also hypothesized that different etiologies of cardiac arrest could give rise to different patterns of change in the ECG characteristics.

The main aims for this Thesis were:

1. To describe the development of ECG characteristics during ALS in patients with and without return of spontaneous circulation.
2. To explore the effect of intravenous adrenaline on the development of the ECG characteristics during ALS.
3. To investigate the development of ECG characteristics according to the cause of cardiac arrest.

4 Material and Methods

4.1 Inclusion of Patients

Studies I and III examined electrocardiographic and clinical data collected prospectively from cardiac arrests that occurred at St. Olav University Hospital, Trondheim, Norway, between January 2009 and January 2012 (clinicaltrials.gov id: NCT00920244). St. Olav Hospital, Trondheim University Hospital, has about 740 somatic beds, and is the regional central hospital for the counties of Trøndelag and Møre and Romsdal, serving 7 local hospitals and approximately 725,000 people in 2018. It also hosts some national functions (85).

Five previous papers have been published based on data included in Papers I and III. Two by Nordseth and co-workers on clinical state transitions during ALS in IHCA (86), and on the duration of ALS loops for patients with non-shockable rhythms (87). Bergum and co-workers (with additional data) examined causes of IHCA (43), the importance of diagnosing these causes during ALS (60) and the association between initial ECG characteristics, etiology and outcome in IHCA with initial PEA (84). Figure 5.1 shows a flow chart illustrating the inclusion of patients and the path to the resulting data material for papers I and III. For paper III, a certain or reliable etiology was also required. The etiology was uncertain or unknown in 11 of the 74 patients included in study I, thus data from 63 patients were analyzed in study III (Figure 5.1).

Study II included ECG and clinical data collected from patients with OHCA in Oslo, Norway between May 1.st 2003 and April 28.th 2008. These patients were part of a randomized trial of ALS with and without access to intravenous medication (clinical-trials.gov id: NCT00121524) (79), also discussed in section 2.5. Patients with initial PEA and a defibrillator file available for analysis were included in study II, see Figure 5.2. The city of Oslo has a single tiered ambulance system organized under Oslo University Hospital(88), serving an urban population of approximately 540 000 people at the time of data collection for study II (89).

4.2 Electrocardiographic Characteristics

ECG and impedance signal data were collected from LIFEPAK 20 and LIFEPAK 1000 defibrillators (Physio-Control, Redmond, USA) as well as Zoll M-series defibrillators (Zoll Corporation, Chelmsford, MA, USA) for studies I and III. In study II, LIFEPAK 12 (Physio Control, Medtronic, Redmond, WA, USA) defibrillators were used.

The most common reason for exclusion from the analyses for patients with initial PEA was missing or illegible defibrillator recording. In the case of studies I and III, the defibrillator recording was stored on solid state memory cards in the defibrillators. These had to be collected manually, and the contents transferred to a separate computer. The limited memory on these cards caused some episodes to be overwritten before the recording could be secured, while in other cases there appeared to be a malfunction in the transfer of data to the cards. In the case of study II, the reasons for missing defibrillator files were technical difficulties and human error, but no systematic differences between patients with and without defibrillator files were identified (T. Olasveengen, personal communication).

4.2.1 Annotation of Clinical State

Annotations of clinical states were made by author T. Nordseth for study I and II and by authors T. Nordseth and T. Olasveengen for study II. The method has been described in two original papers (83,86), but a synopsis is included here for completeness. For studies I and III annotations were performed in MATLAB (The Mathworks, Natick, MA, USA). For study II, files were annotated using CODE-STAT 7.0 (Physio-Control Medtronic, Redmond, WA, USA). In all cases the state was determined during pauses in chest compressions, as determined from the impedance signal. Organized electrical rhythm with a frequency of 12, or more, per minute was defined as PEA. VF and VT were annotated based on the distinct features of these rhythms. Asystole was defined as either a flat or very low amplitude ECG signal, or where organized complexes occurred less than 12 times per minute. That is equals 5 seconds or more between complexes, or 12.5 cm on a standard monitor with a sweep speed of 25mm/s.

4.2.2 Measurements of QRS Complex Width and Heart Rate

The ECG and impedance signal data were analyzed using the software MATLAB (R2014b and R2017b, Math Works Inc., Natick, MA). The rhythm, QRS widths and heart rates (where applicable), were evaluated during pauses in chest compressions for any reason (including end of efforts), or when ROSC was obtained. Pauses in chest compressions were determined from the impedance signal.

The impedance signal is a tracing of trans-thoracic impedance to electrical current, measured by the defibrillator for a number of purposes. The impedance is affected by chest compressions, and can be utilized to determine where there were pauses in chest compressions in defibrillator files (90).

The definition of the QRS complex is a reproduction from paper I: "The QRS width was defined as the interval between the initial deflection from the baseline towards the Q- or R-wave and the beginning of the ST-interval on the ECG. The QRS end-point was marked off where a clear break from the high frequency changes of the QRS complex (depolarization), towards the lower frequency change of the ST-interval (repolarization) was observed. In cases with no obvious transition from the QRS to the ST-interval, the point where the ECG tracing crossed the baseline towards the T-wave was marked off as the QRS end-point" (91). Each point of measure – the beginning and end of each QRS complex – was marked by a red cross, for reproducibility and to enable consultation with cardiologist J.P. Loennechen in difficult cases. An example, reproduced from paper I, is shown in Figure 4.1. Two to three adjacent QRS complexes were measured at each pause in compressions. Complexes that had very deviant morphology compared to the neighboring complexes were omitted.

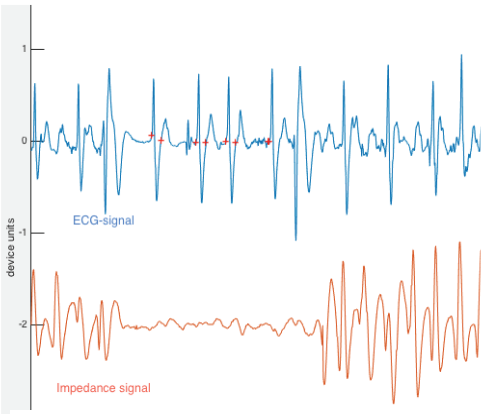

Figure 4.1 Example – QRS measurements.

QRS complex rates, which will be called *heart rates* for the remainder of this Thesis, were calculated from the intervals between the beginnings of the three measured

QRS complexes, with the addition of the distance from the beginning of last measured QRS complex to the beginning of a fourth QRS complex when this was possible.

4.2.3 Etiology

Author D. Bergum and co-workers determined the etiologies of the cardiac arrests for patients included in study III. The method has been described thoroughly in the original paper (43): Every IHCA was examined by an "etiology study group", which consisted of anesthesiologists, cardiologists and one pathologist. The relevant clinical and paraclinical data, sometimes including autopsy findings were reviewed. When a cause of arrest could be objectively ascertained, or the other possibilities ruled out, the cause was defined as "*certain"*. An intermediate category called "*probable"* was also included in the analyses in study III, the causes in this category were suspected on the basis of clinical or paraclinical data, but could not be ascertained with the level of confidence as those in the "certain" category.

The words etiology and cause are used interchangeably in this Thesis, though this may be imprecise. In this setting, they are taken to mean the clinical condition or disease that lead to cardiac arrest, or triggered the arrest (on top of other conditions and diseases).

4.3 Statistical Methods

The dynamics – changes over time – of QRS width and heart rate while resuscitation was ongoing was the focus of all three studies. The main aim was to establish whether a certain pattern of change was distinctive in different groups of patients; stratified by either outcome alone (study I), adrenaline administration and outcome (study II), or etiology and outcome (study III).

Because ALS by its nature is an extreme event, it is never fully organized even when performed by well trained and experienced teams. Although the guidelines emphasize hands on time, and (in Norway) the standard is three minute loops (69), pauses in compressions in the data analyzed in these studies were not evenly spaced or of even duration. Moreover, the duration of ALS differs from patient to patient. Some patients had numerous state changes during ALS, others remained in the same state for longer periods. Additionally, the number of QRS complexes available for measurement at each pause in compressions differed. The result was uneven, unbalanced data, with repeated measurements within each patient. To approach this statistically a number of methods were applied; to be described in the following sections.

The software R version 3.4.3 (92), running in RStudio version 1.1.419, with the packages *mcgv, nlme, lspline, aareg, BlandAltmanLeh, itsadug, data.table, car,* and *gmodels*, was utilized for the statistical analyses. A p value < 0.05 was considered to indicate statistical significance. The software Stata version 15.1 was also applied in Study II (93).

4.3.1 Visualization

Spaghetti plots are commonly used to visualize repeated measures data, but are often over-plotted, and important patterns may be difficult to distinguish (94). Spaghetti plots were made for each study in this Thesis, and illustrate the considerable spread in the

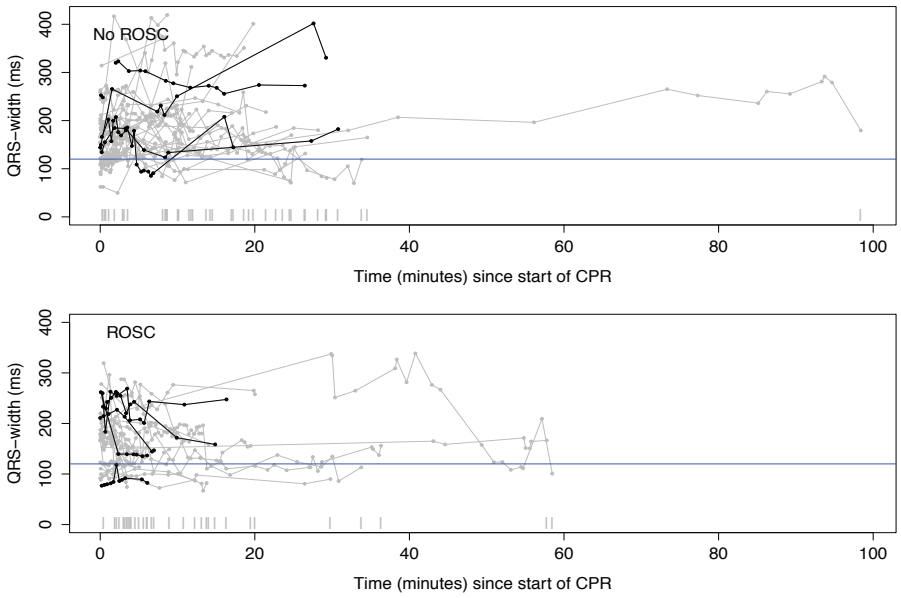

Figure 4.2 Spaghetti plot – QRS width in patients without and with ROSC. Dots represent mean QRS width at each pause in compressions. The five first patients are highlighted (black), blue line at 120ms, grey dashes along the x-axis represent end of ALS for individual patients (ms: milliseconds).

individual measurements, even within each patient. The spaghetti plot of QRS width measurements from study I is shown in Figure 4.2.

Examining repeated measures data for patterns, locally weighted regression (loess) can be used (95). This a technique that has been likened to using a flexible string that can form any pattern to fit a best-fit line through a scatterplot (96). This method does not account for the positive correlation between repeated measurements, however, which makes standard errors wrong (often too small). For this reason, additive mixed models are more appropriate, and were used rather than loess models. See Section 4.3.4

An example of loess and additive mixed models smoothing of data that is shown as spaghetti plots in Figure 4.2 is presented in Figure 4.3. As can be seen the smooths agree to a large degree, at least for the first 30 minutes. The confidence intervals (dashed lines) are wider with the additive mixed model.

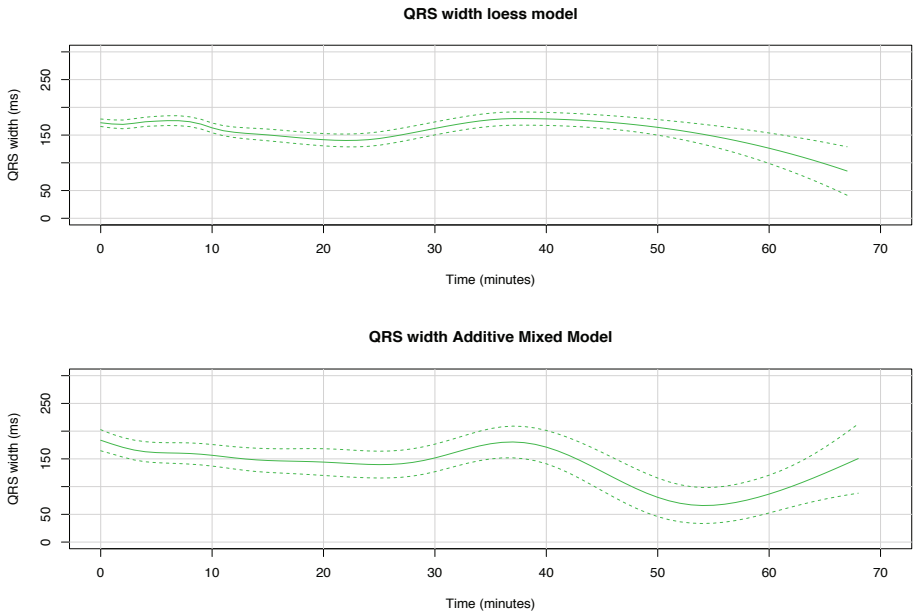

Figure 4.3 Comparison of smooths by loess and additive mixed model, QRS width in the group of patients with ROSC in study I (Solid line: estimate of the mean, dashed lines: upper and lower border of $CI^{95\%}$, ms: milliseconds).

To illustrate both the change in QRS width and heart rate from the start until the end of ALS (ROSC or termination of ALS efforts), as well as the individual measurements, bivariate scatterplots were made for all studies, with QRS width on the y-axis and heart rate on the x-axis. Without the time dimension, the scatterplot illustrates the spread in individual measurements well. We added mean vectors that illustrates the mean change in the two ECG parameters from start to end of ALS, as well as confidence areas for the individual end-points in the ROSC groups. This illustrates the mean change over time, and adds a representation of the time dimension to the plot.

4.3.2 Multivariate Analysis of Variance

Multivariate Analysis of Variance (MANOVA) can be used to compare two or more vectors of multivariate sample means, in the same way as ANOVA can be used to test for differences in (univariate) mean values between two or more groups (97). It allows differences in two, or more, dependent variables to be examined simultaneously (i.e. combined), and may reveal differences that are hard to establish by univariate methods. In studies I, II and III this method was applied to compare the mean QRS width and heart rate at the beginning and end of ALS, for groups of patients based on whether ROSC was obtained and the additional covariates of adrenaline administration (study II) and etiology group (study III). Stratification of patients to yield groups for comparisons is explained separately for each study in Section 5. To construct the start and end QRS width and heart rate for each episode, the average QRS width and heart rate during the first and last 15 seconds of ALS were calculated. We checked for any statistically significant interaction – that the effect of one covariate depends on the level of another – between the strata by including an interaction term.

To construct the start and end QRS width and heart rate for each episode, the average QRS width and heart rate during the first and last 15 seconds of ALS were calculated, and this then used as the basis of the sample mean vectors in the MANOVA.

The underlying assumptions of the MANOVA methodology are independence of observations, multivariate normality and equality of the variances. Assumptions of multivariate normality and equality of variances were checked graphically (normal Q-Q plots), and transformations were made where necessary.

As was discussed above, the structure of the data in these studies is less than ideal for statistical analysis, and the MANOVA methodology is one way of averaging our way out of the problem of repeated measures. The problem with this methodology is that even though change from start to end of ALS can be estimated, and groups compared statistically, the time course and pattern of change over time remains obscured.

4.3.3 Analysis of Covariance

Analysis of covariance is a regression method can be used to compare differences in the outcome variable based on levels of categorical predictors, with the addition of continuous covariates. A covariate is an independent, or predictor, variable which can be either continuous or categorical. In this way, differences between groups (by levels of the categorical predictor) in the covariate can be adjusted for statistically. The advantages of this over alternative methods of analysis, like the change in the dependent variables (as in the MANOVA method used in studies I and III); or ignoring the baseline values of the dependent variables, are statistical efficiency and accuracy. On the other hand, analysis of covariance should not be used to balance pre-existing differences in pure observational studies. Such adjustment may give rise to results that may be contradictory and unreliable, a phenomenon referred to as *Lord's paradox* or *the reversal paradox* (98,99).

The original study behind paper II was a randomized controlled trial. We modelled the average QRS width and heart rate during the last 15 seconds of ALS separately, conditional on the average QRS width and heart rate during the first 15 seconds of ALS, ROSC and adrenaline status, as proposed by Vickers and Altman (100). Thus, potential differences in initial values were controlled for. Interaction was checked by including an interaction term, to verify that the assumption of equality of slopes was not violated. The assumptions of normality and homoskedasticity of the residuals were checked graphically.

4.3.4 Additive Mixed Effects Models

To account for the repeated measures nature of the data, we used additive mixed models to visualize the trends in the data. In the R terminology this method is often referred to as *GAMM* (generalized additive mixed effects model), but as we have assumed that our dependent variables are distributed normally, the method will be called *additive mixed effects model* in this Thesis (92,101).

The smooths in additive mixed effects models are based on splines –separate regression lines in regions of the data – that are made continuous with adjacent regression lines to produce a smooth curve. The border of each regression line is called a knot. In additive mixed models these are usually numerous and evenly spaced within the data by

default. The result is a smooth line that represents the trend in the data well, and which has more correct standard errors than for example loess models, as mixed models methodology handles dependencies in the data, and more complex error structures (102). The p-values from this model addresses the null hypothesis that the smooth is actually zero – that there is no change in the dependent variables by the covariates (101). For all the studies in this Thesis a first order continuous autocorrelation structure was applied to the residuals, see Section 4.3.5 for further explanation. Figure 4.3 shows an example of a curve that was fitted using additive mixed models.

4.3.5 Linear Mixed Effects Models

Linear mixed effect models are an extension of ordinary linear regression that takes nesting or hierarchical data structure (repeated measurements within the same individual, in the case of this Thesis) into account. These models are suitable for the analysis of longitudinal data also because they can handle data with an unequal and unbalanced data structure, as in the studies discussed in this Thesis (103).

We only applied linear mixed effects models in study III. Here separate models were fit for the outcome variables QRS width and heart rate over time, with a random intercept (i.e. an individual "offset") for each patient. This decomposes the total variation in the response to that between and within subjects, so that meaningful inference between groups of subjects can be made, and correct standard errors constructed. To further increase model fit, a first order continuous autoregressive correlation structure for the residuals was used because measurements closer to each other in time would be expected to be more alike than those further apart. The first order continuous autoregressive correlation structure specified here assumes that the correlation between the residuals decrease exponentially with increasing time separation, and is not compromised by the unequal sampling in the underlying data (103). The assumptions of normality and homogeneity of variance were checked graphically using normal Q-Q plots and residual versus fitted values plots.

4.3.6 Aalen's Additive Model

Aalen's additive model was used to assess the impact of changes in QRS width and heart rate on the probability of a transitions from PEA to ROSC (104). The resulting coefficients represent cumulative transition ("hazard") intensities in the survival analysis sense, additive to the baseline transition intensity, that may vary with time. In Study I, this translates to the number of transitions from PEA to ROSC per unit time *and* per unit increase in heart rate or increase in inverse QRS width (i.e. decrease in actual QRS width). A positive value of the coefficient means that the number of transitions per unit time increases with increase in heart rate or increase in the inverse QRS width. An illustration is provided in Figure 4.4. In this figure, taken from study I, the impact of heart rate is on the left, the inverse QRS duration is on the right. In regions where the curve is steep, each unit change in the covariate (heart rate or inverse QRS width) leads to more transitions from PEA to ROSC in this period: the effects are "time varying". For heart rate, the effect appears to be almost linear for the first 15 minutes of ALS.

The slope (derivative) of the cumulative coefficient curve represents the instantaneous intensity. With small intensities, it is roughly equal to the probability of a transition. In this particular case (the 15 min linear phase), the intensity may be estimated as 0.00158 per minute and bpm (i.e. 0.09 per 3 minutes and 20 bpm); equivalent to a 9% increased probability of ROSC per 20 bpm increase in heart rate per 3 minutes.

We inverted the QRS width to model this process properly, which makes the zero point of inverse QRS width equal to a – nonsensical – infinite QRS width. The transformation also gives a non-linear relation between QRS width and the inverse QRS width. Thus, the cumulative coefficients on the y-axes of the two plots below are not readily comparable; however both show an almost linear positive effect of increase in either heart rate or decrease in QRS width on the transitions from PEA to ROSC.

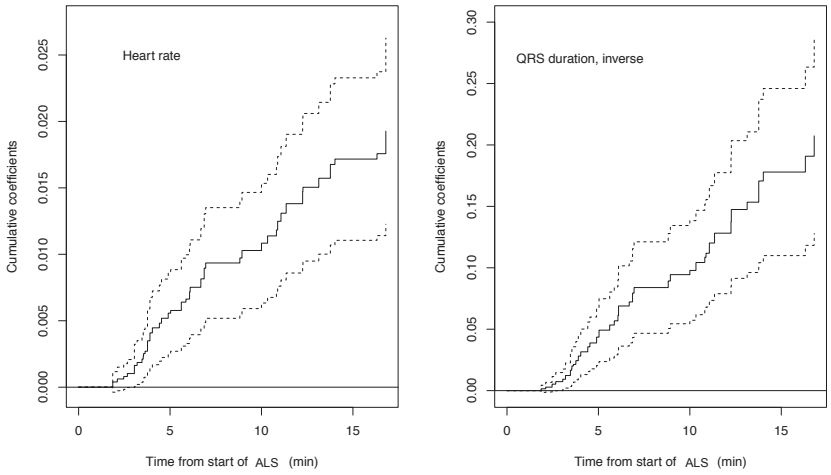

Figure 4.4. Aalen cumulative transition intensities, PEA to ROSC, Study I. Solid line: estimated cumulative coefficients, dashed lines: upper and lower border of the 95% confidence interval for this estimate. (min: minutes, ROSC: Return of Spontaneous Circulation, PEA: Pulseless Electrical Activity).

4.3.7 Reversing Time

Time is a very important variable in cardiac arrest, both clinically, and in the models used in in all three studies of this Thesis. In the data analyzed for these papers, time was recorded in seconds, and time zero was defined as the moment that the defibrillator pads were placed on the patients' chests, and recording of the ECG and impedance data commenced. In the bivariate plots, MANOVA and analysis of covariance models, we handled time from start to end of ALS in chronological order. However, the duration of ALS from the start of ALS to ROSC or termination of ALS efforts varied greatly between patients, as could be expected. This made modeling the mean responses (i.e. QRS width and heart rate) continuously over time difficult: as the number of patients still included in the analyses declined with time the estimates of the mean lost precision simultaneously.

Important developments in the patients who had ROSC at different time-points was also "obscured" by the ongoing development in patients with later ROSC.

To overcome this problem, we re-defined time zero to represent ROSC or termination of ALS efforts (death), thus counting backwards from this point. This ensured that all patients would contribute with as much data as possible close to the event of main interest, ROSC, and that estimates would increase in precision close to this point. This method comes with a price, however, as forward prediction is impossible when conditioning on an already observed event. Predictions in individual patients is a matter of further study.

4.3.8 Pearson`s Correlation Coefficient

Pearson`s correlation coefficient measures how one (normally distributed) random variable is related to another, in particular, it is possible to determine to which extent one variable can be predicted from the other. The values can be from -1 (perfectly negatively correlated) to +1 (perfectly positively correlated). Independent variables have a correlation coefficient of 0 (105). In all three studies, the correlation between QRS width and heart rate was assessed using Pearson's correlation coefficient.

4.4 Ethical Considerations

The Regional Committees for Medical and Health Research Ethics approved both the original studies on which studies I - III are based and the further processing of data, such as in the current studies. We obtained informed consent from surviving patients, otherwise from the next-of-kin. The study on which studies I and III are based is registered at clinicaltrials.gov: NCT00920244. The study on which study II is based is registered at clinical-trials.gov with ID: NCT00121524.

5 Results

5.1 Overview of Studies

The measurement of QRS width and rate at all pauses in chest compressions during ALS from cardiac arrest with initial PEA formed the basis of the three studies included in this Thesis, as described in 9.3.2, and illustrated in Figure 4.1. Study I focused on the development in these two variables in patients with and without ROSC in the in-hospital setting. Study II examined the same problem in the out-of-hospital setting, and also whether the ECG characteristics developed differently if patients had received intravenous adrenaline or not. Study III examined the same ECG characteristics according to ROSC status, but focused mainly the underlying etiology of the cardiac arrest in a subgroup of the patients examined in paper I.

5.2 Inclusion of Patients

A flow chart describing the inclusion of patients for studies I and III is shown in Figure 5.1 below.

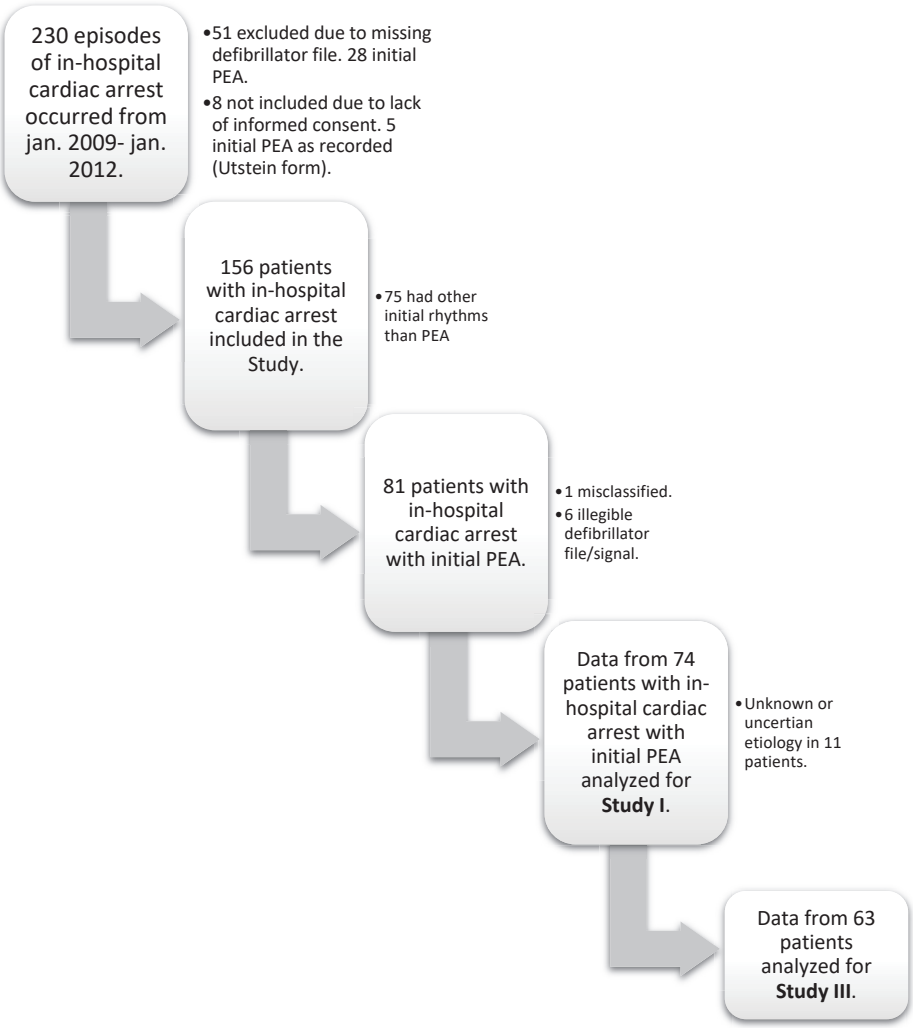

Figure 5.1. Inclusion of patients studies I and III.

Inclusion of Patients for Study II is illustrated in Figure 5.2

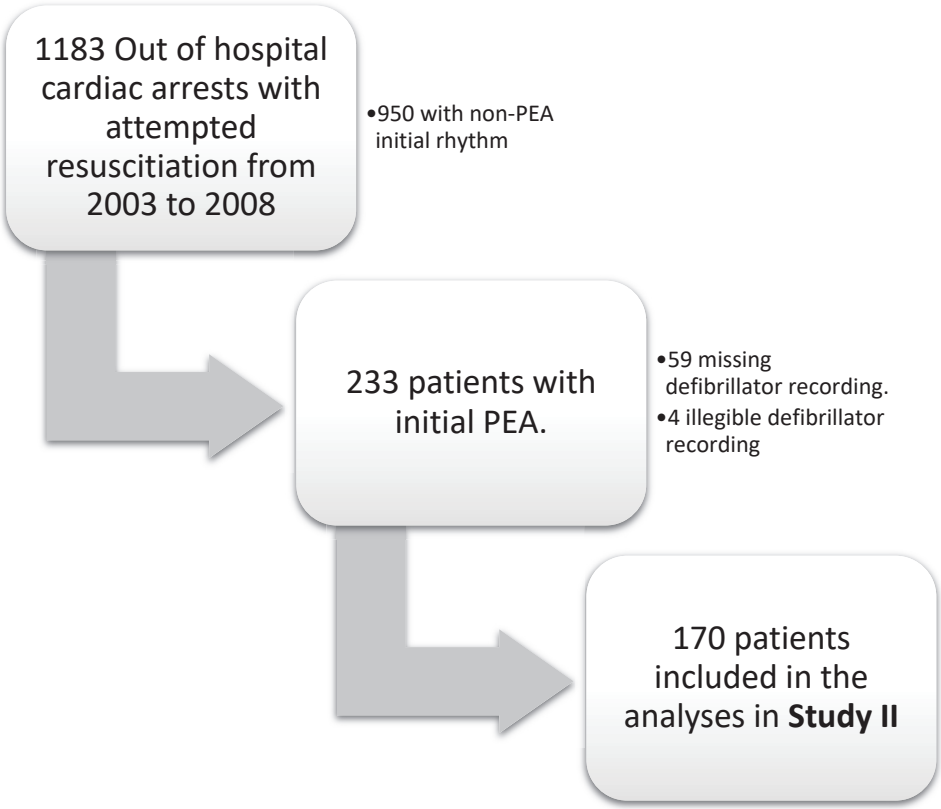

Figure 5.2 Inclusion of patients, Study II.

5.3 Study I

Data from 74 patients who suffered in-hospital cardiac arrest with initial PEA were analyzed, yielding a total of 2187 combined observations of QRS width and heart rate. Clinical and demographic data is presented in Table 5-1, corresponding to Table 1 from paper I.

Table 5-1 Demographic and clinical data, Study I.

	ROSC		No ROSC	
Age, median (IQ-range)	65	(60-80)	78	(68-84)
Males, n (%)	25	(76)	22	(54)
Department, n (%)				
Ward	12	(36)	28	(68)
CCU	13	(39)	9	(22)
ED	5	(15)	2	(5)
Other	1	(3)	2	(5)
ICU	2	(6)	0	(0)
Admission cause, n (%)				
Cardiac	12	(36)	15	(37)
Pulmonary	8	(24)	10	(24)
Surgical	7	(21)	5	(12)
Infectious diseases	2	(6)	5	(12)
Other Internal Medicine	0	(0)	3	(7)
Other	4	(12)	3	(7)
Arrest cause, n (%)				
Cardiac	11	(33)	15	(37)
Hypoxic	13	(39)	5	(12)
Pulmonary Embolism	4	(12)	4	(10)
Hypovolaemic	1	(3)	6	(15)
Sepsis	0	(0)	3	(7)
Other	3	(9)	4	(10)
Unkown	1	(3)	4	(10)

The main goal of this study was to examine any differences in the development of heart rate and QRS width during ALS in patients who did and did not obtain ROSC, and the patients were grouped accordingly. A table of demographic and clinical data comparing included patients with those that could not be included for various reasons (Figure 5.1) except those without consent, is presented in Table 5-2.

Table 5-2. Demographic and clinical data, patient included and not included, study I.

	Cases included (n=74)	Cases not Included (n=35)
ROSC no (%)	33 (45)	20 (57)
Survival to discharge, no (%)	9 (12)	6 (17)
Median age (IQ-range)	71 (63-82)	71 (63-81)
Males, no (%)	47 (64)	23 (66)
Department, no (%)		
Ward	40 (54)	22 (63)
CCU	22 (30)	6 (17)
ED	7 (9,5)	2 (6)
Other	3 (4)	5 (14)
ICU	2 (2.5)	0 (0)
Admission cause, no (%)		
Cardiac	27 (36.5)	14 (40)
Pulmonary	18 (24)	5 (14)
Surgical	8 (11)	4 (11)
Infectious diseases	7 (9.5)	1 (3)
Other Internal Medicine	3 (4)	3 (8.5)
Orthopedic surgery	3 (4)	6 (17)
Other	8 (11)	2 (6)
Arrest cause, no (%)		
Cardiac	26 (35)	17 (49)
Hypoxic	18 (24.5)	7 (20)
Pulmonary Embolism	8 (11)	2 (6)
Hypovolemic	7 (9.5)	2 (6)
Sepsis	4 (5.5)	0 (0)
Other	6 (8)	4 (11)
Unknown	5 (6.5)	3 (8.5)

Comparison of demographic data of cases that were included in the analyses, to those that could, for various reasons, not be included.

To illustrate the development of ECG characteristics in PEA over time, a prevalence plot with PEA subdivided into categories based on the QRS width (below or above 0.12ms) and heart rate (below 60/min, 60-100/minute and above 100/minute), as in the paper by Bergum et al. discussed in Section 2.6 (84), was produced. The PEA categories based on the described division were: NF – Narrow Fast, N – Narrow Normal, NS – Narrow Slow, WF – Wide Fast, W – Wide Normal and WS – Wide Slow. See Figure 5.3, where PEA is Yellow, the subdivisions named as described, ROSC is green, VF/VT red, asystole light grey, and the state of death dark grey (Figure 2 from paper I).

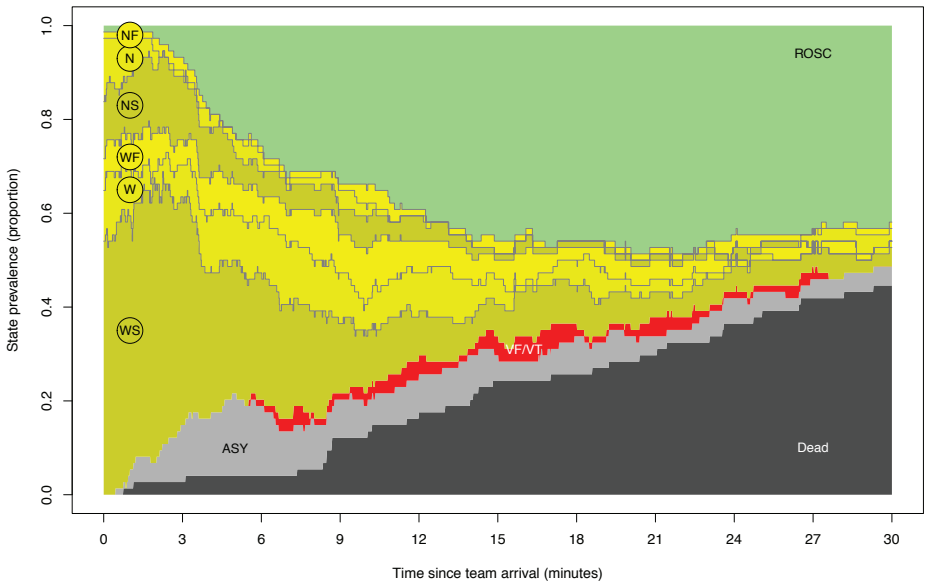

Figure 5.3. Prevalence plot of the different states during ALS (From top to bottom: Green: ROSC. Yellow: PEA, NF: Narrow-Fast, N: Narrow, NS: Narrow-Slow, WF: Wide-Fast, W: Wide, WS: Wide-Slow. Red: VF/VT, Light Grey: Asystole, Dark-Grey: Dead).

Besides illustrating the prevalence of the different states and the different sub-groups of PEA over time, it also shows that there was no increase in the proportion of patients with ROSC after roughly 15 to 18 minutes (though transitions between ROSC and all the other states may still have occurred).

Further results from the analysis of the data will be presented in a different order in this Thesis than in paper I, for reasons of coherence.

We found QRS width and heart rate to be negatively correlated (Pearson's r -0.37, p < 0.0001).

By bivariate Regression analysis (MANOVA), we found that there was a statistically significant difference in the development of heart rate and QRS width from the beginning to the end of ALS in patients who obtained ROSC compared to those who did not (P <0.001). The vectors of change are illustrated as arrows in Figure 5.4 (Figure 4 in paper I), and it can be seen that in the patients that obtained ROSC, heart rate increased while QRS width decreased, while in patients without ROSC, heart rate was unchanged and QRS width increased. The green ellipses are the 50%, 75% and 90% coverage areas for the individual end points in the ROSC group.

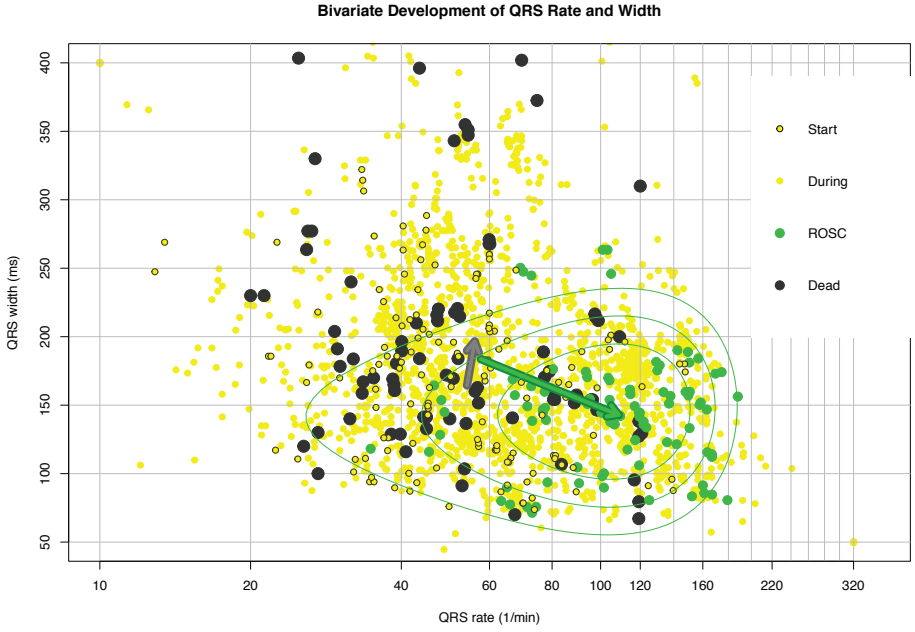

Figure 5.4 Bivariate scatterplot, paper I. The difference between the mean start and end values for QRS width and rate are illustrated as arrows. Green: ROSC, grey: no ROSC. The dots represent individual measurements at different times during ALS (legend), and the green ellipses are the 50, 75 and 90 percent coverage areas for the end estimate of individual QRS width and heart rate for the ROSC group (ROSC: return of spontaneous circulation, ms: milliseconds, 1/min: per minute).

Figure 5.4 also shows the considerable spread in the actual measurements at the beginning, during and at the end of ALS. Additionally, there was considerable spread in the duration of each episode, Figure 5.5 are spaghetti plots of QRS width and heart rate measurements from Study I, with time zero defined as the end of ALS. The considerable variation between and within episodes is evident, but a trend may nevertheless be discerned.

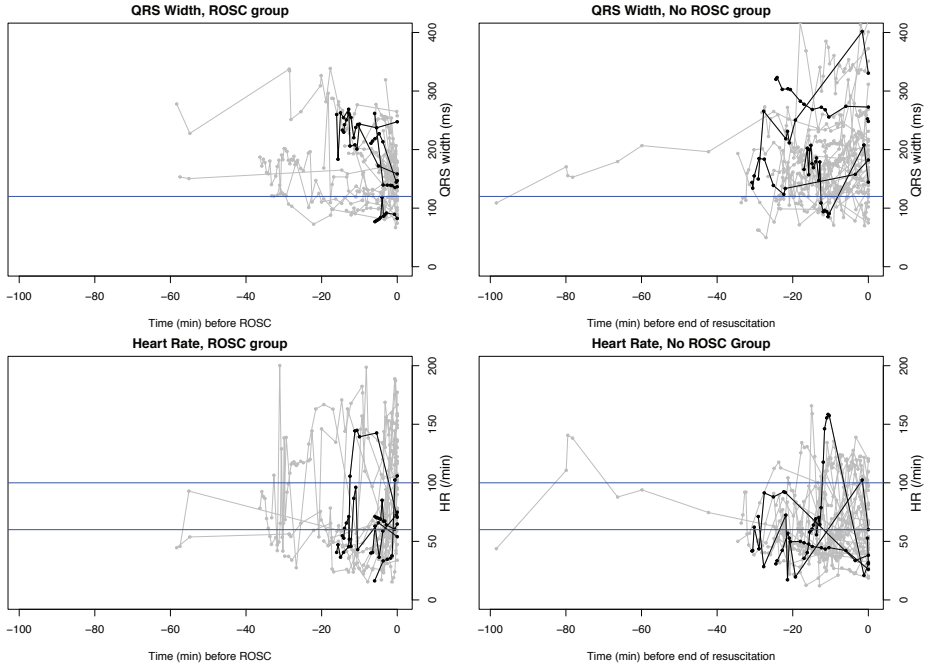

Figure 5.5 Spaghetti plots, reversed time axis – QRS Width and Heart Rate, study I. Dots represent mean QRS width (upper panels) and heart rate (lower panels) at each pause in compressions. Five patients are highlighted (black), blue line at 120ms in the upper panels, at 60 and 100/min in the lower panels (min: minute, ms: milliseconds, /min: per minute, ROSC: return of spontaneous circulation).

To model this properly, we applied additive mixed models to model the development of mean QRS width and heart rate during the last 12 minutes of ALS. As can be seen in Figure 5.6 (Figure 3 in paper I), there are clear differences in the development of these characteristics between patients with and without ROSC. The mean QRS width in the ROSC group decreased gradually towards ROSC, while it increased gradually in the no ROSC group. Mean heart rate increased sharply during the last 6

minutes before ROSC, but remained essentially unchanged in the no ROSC group until the end of ALS.

This difference in the temporal development of QRS width and heart rate suggests that there may be different mechanisms behind the change in these two variables, and that paying attention to each may be valuable.

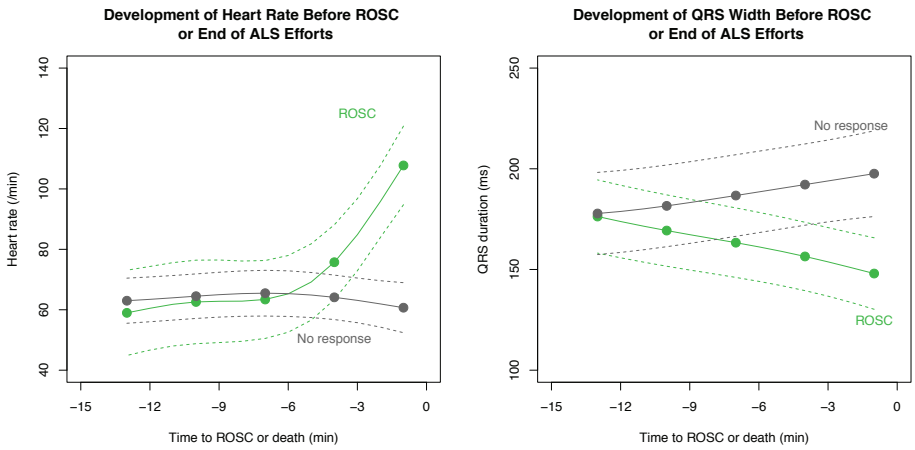

Figure 5.6 Mean heart rate (left) and QRS width (right), the last 12 minutes before sustained ROSC (solid green line) or before ALS efforts were stopped (solid grey line), according to the additive mixed effects model. Dots are placed every three minutes. Dashed lines: 95% confidence intervals. (/min: per minute, min: minutes, ms: milliseconds, ROSC: return of spontaneous circulation).

Additive mixed models of mean heart rate and QRS width from the start of ALS (i.e. with time zero at ALS start) were also fitted, and the figures provided as an online supplement to paper I. Figure 5.7 is a reproduction of this figure. The figure shows differences in development of mean heart rate and QRS width between the ROSC and no ROSC groups, at least for the first 20 to 30 minutes of ALS. After 30 minutes only 4 patients remained in each group, i.e. have not attained ROSC or been declared dead. The

widened confidence intervals reflect this, and the estimates are highly uncertain after about 25 minutes.

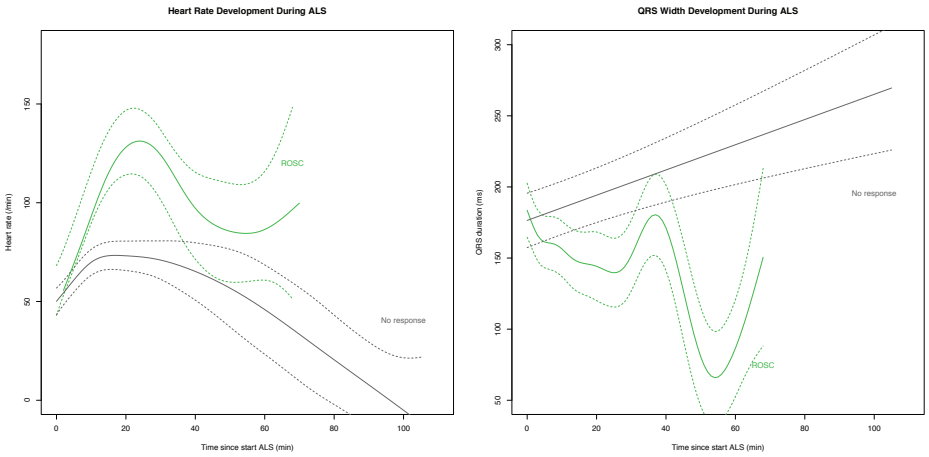

Figure 5.7 Mean heart rate and QRS width, from the beginning of ALS. Heart rate on the left, QRS width on the right. Solid line: estimated mean, dashed lines: 95% confidence interval. Green: ROSC group, Grey: No ROSC group. (/min: per minute, min: minute, ms: milliseconds, ROSC: return of spontaneous circulation).

By applying Aalens additive model, we found that both increased heart rate and decreased QRS width increased the intensity of transitions from PEA to ROSC during the first 18 minutes of ALS (both p´s <0.01). Figure 4.4 illustrates the impact of increased heart rate and decreased QRS width on the intensity of transition from PEA to ROSC graphically, a detailed explanation of this figure has been provided in Section 4.3.6

5.4 Study II

As presented in Figure 5.2, data from 170 episodes of OHCA were analyzed for this study. In all, 4840 combined observations of QRS width and heart rate were made. The individual measurements of QRS width and heart rate are presented separately in Figures 5.8 and 5.9 as spaghetti plots.

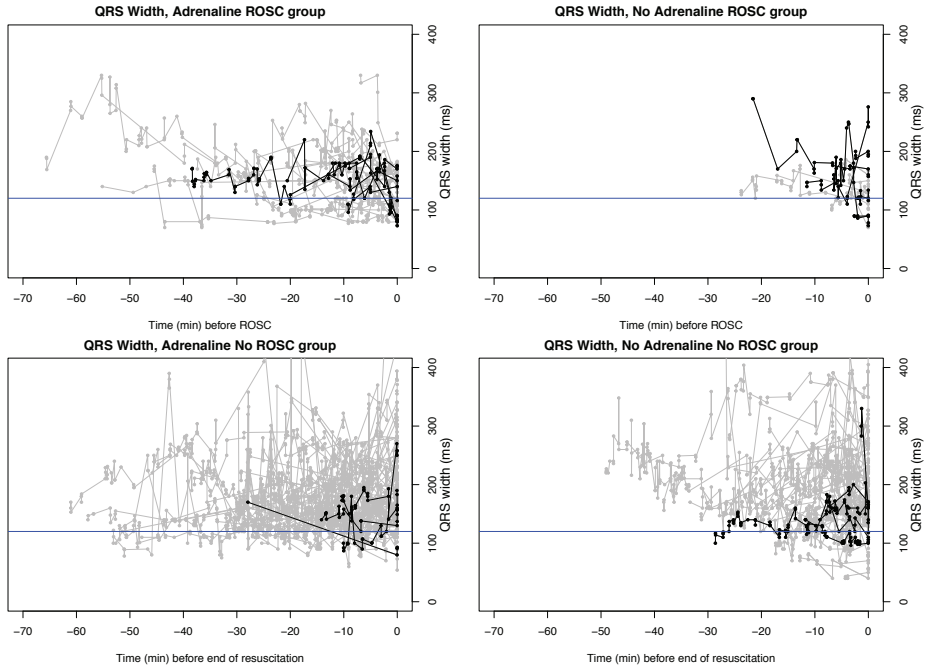

Figure 5.8 QRS width measurements, Study II. Reversed time axis. Dots represent individual QRS width measurements. Five patients are highlighted (black), blue line at 120ms (min: minute, ms: milliseconds, ROSC: return of spontaneous circulation).

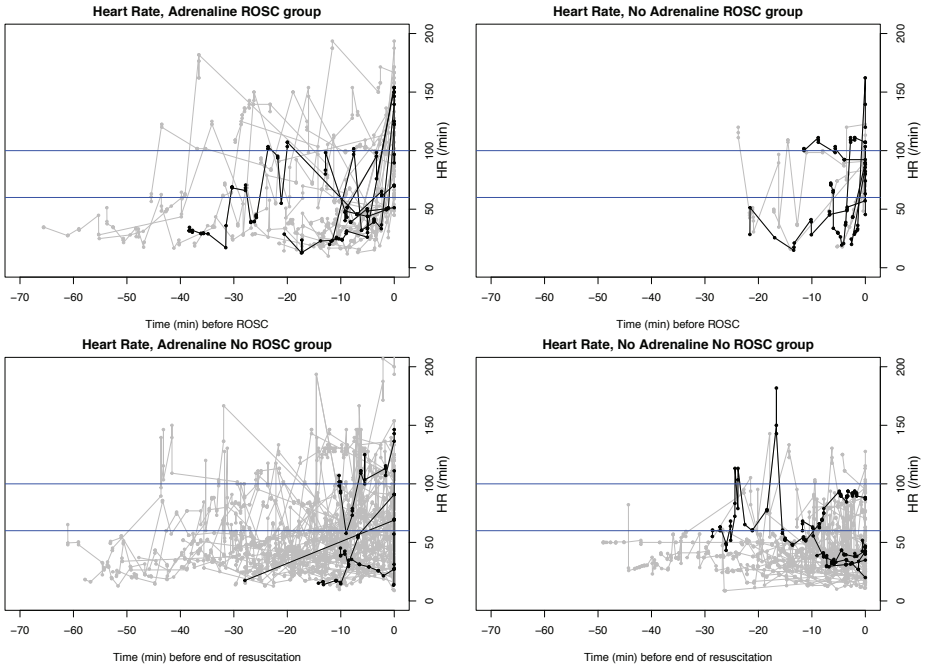

Figure 5.9 Heart rate measurements, Study III. Reversed time axis. Dots represent individual heart rate measurements. Five patients are highlighted (black), blue line at 60 and 100 beats per minute (min: minute, /min: per minute, ROSC: return of spontaneous circulation).

Table 5-3 contains clinical and demographic data (published as Table 1, Paper II). The purpose of this study was to examine the development of QRS width and heart rate during ALS for differences between groups of patients based on whether they had ROSC or not, and also investigate the impact of adrenaline on these developments. Thus, patients were grouped into four groups by ROSC status, and whether adrenaline had been administered or not. (Table 5-3).

Table 5-3 Demographic and clinical data, study II.

	Return of Spontaneous Circulation (n=41)		No Return of Spontaneous Circulation (n=129)	
	Adrenaline (n=29)	No Adrenaline (n=12)	Adrenaline (n=72)	No Adrenaline (n=57)
Age (yrs), median (IQ range)	61 (56 to 75)	65 (62 to 75)	78 (56 to 83)	77 (65 to 85)
Males, n (%)	15 (52)	11 (92)	47 (36)	34 (60)
Location				
Home, n (%)	20 (69)	5 (42)	41 (57)	41 (72)
Public, n (%)	5 (17)	5 (42)	20 (28)	11 (21)
Work, n (%)	0 (0)	1 (8)	1 (1)	0 (0)
Other, n (%)	4 (14)	1 (8)	10 (14)	5 (9)
Witnessed by layperson, n (%)	19 (66)	8 (67)	31 (43)	38 (67)
Witnessed by paramedic, n (%)	6 (21)	1 (8)	28 (38)	6 (11)
Bystander CPR, n (%)	12 (41)	3 (25)	26 (36)	27 (47)
Response time (min), median (IQ range)	7.9 (5.3-9.0)	10.6 (6.3-11.4)	6.1 (0-8.7)	9.6 (6.6-11.3)
Duration of ALS (min), median (IQ range)	20 (12.5-28.1)	6.7 (5.2-11.5)	26.5 (19.1-31.9)	21.4 (14.4-28.9)
Compression Rate (/min), median (IQ range)	117 (112-120)	115 (112-126)	119 (112-126)	112 (107 -120)
Hands Off Ratio, median (IQ range)	0.15 (0.1-0.26)	0.18 (0.12-0.28)	0.17 (0.12-0.25)	0.20 (0.13-0.29)
Defibrillation at least once, n (%)	4 (14)	0 (0)	24 (33)	7 (12)
Intubated, n (%)	27 (93)	9 (75)	62 (86)	45 (79)
Intravenous Access, n (%)	29 (100)	8 (67)	71 (99)	7 (12)
Adrenaline dose (mg), median (IQ range)	2 (1 to 3)	0 (0)	3 (2 to 5)	0 (0)
Atropine, n (%)	8 (28)	0 (0)	35 (49)	2 (4)
Amiodarone, n (%)	0 (0)	1 (8)	9 (13)	0 (0)
Admitted to hospital, n (%)	29 (100)	12 (100)	22 (30)	11 (19)
Discharged from hospital alive, n (%)	1 (3)	3 (25)	0 (0)	1 (2)*

Missing data: Witnessed (n=1), Age (n=1), Adrenaline dose (n=19), Duration of ALS (n=1), IV access (n=1).
* One patient without pre-hospital ROSC but admitted to hospital under ALS survived to hospital discharge.

QRS width and heart rate were found to be negatively correlated in the sample analyzed in this study (Pearson's r -0.35, p<0.001).

By bivariate analysis (MANOVA), we found that the combined change of heart rate and QRS width from the beginning and to the end of ALS was statistically significantly (p <0.001) associated with ROSC and adrenaline status (i.e. whether ROSC was attained or not, and whether adrenaline was administered or not). There was no evidence of interaction between ROSC and adrenaline status (p= 0.86). As in study 1, we found increased heart rates and decreased QRS widths were found in patients who attained ROSC. The magnitude of heart rate change was greater in the adrenaline ROSC group. The average development in the no-ROSC groups differed based on whether adrenaline had been given or not. In the adrenaline group, we found increased heart rate *and* increased QRS width, while in the no adrenaline group QRS width increased and heart rate declined. See Table 5-4 for detailed results.

Table 5-4 Mean change in heart rate and QRS width, study II.

Heart Rate	Mean Change (1/min)	95% Confidence Interval
Adrenaline-ROSC	63	51 - 74
No-Adrenaline-ROSC	38	25 - 52
Adrenaline-no-ROSC	22	14 - 30
No-Adrenaline-no-ROSC	-3	-11 - -6

QRS width	Mean Change (ms)	95% Confidence Interval
Adrenaline-ROSC	-34	-65 - -5
No-Adrenaline-ROSC	-33	-67 - 2
Adrenaline-no-ROSC	30	10 - 50
No-Adrenaline-no-ROSC	31	9 - 55

Univariate analysis of mean final heart rate or QRS width separately showed that the final mean heart rate was dependent on the mean initial heart rate (coefficient 0.28, p= 0.01), ROSC (46,6 bpm increase with ROSC, p<0.0001), and adrenaline (21.7 bpm increase with adrenaline, p< 0.0001). Final mean QRS width depended on mean initial QRS width (coefficient 0.45, p< 0.0001) and ROSC (62ms less with ROSC, p <0.0001), but not adrenaline (p=0.4). There was no evidence of interaction between ROSC and

adrenaline status in the univariate analyses (p= 0.8 and 0.72 for heart rate and QRS width respectively).

As in study I, we made bivariate scatterplots of the individual observations with superimposed arrows to show the change from beginning to end of ALS, shown below in Figure 5.10. The green ellipses are the 50%, 75% and 90% coverage areas for the individual end points in the ROSC groups. The coefficients from the univariate analyses were used to calculate the start and end values of QRS width and heart rate for each group, the resulting coordinates correspond well with the start and end points of the arrows shown in the figure.

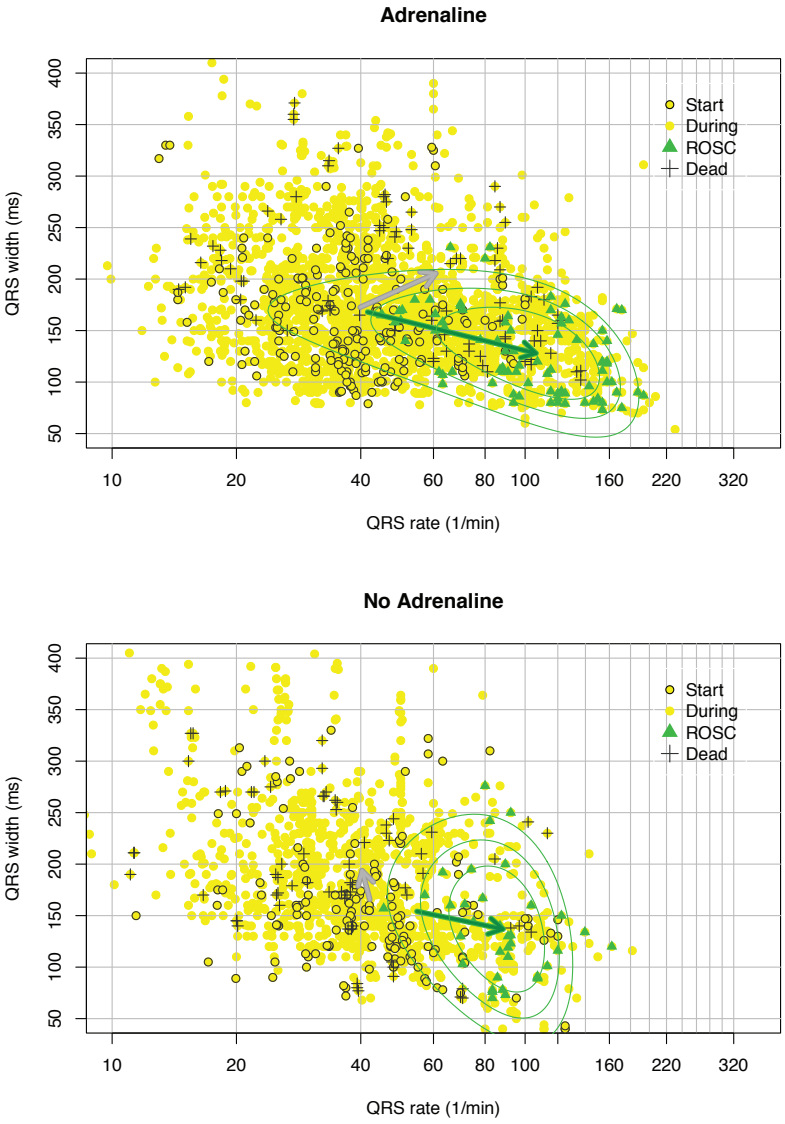

Figure 5.10 Bivariate scatterplots, study II. The difference between the mean start and end values for QRS width and rate are illustrated as arrows. Green: ROSC, grey: no ROSC. The dots represent individual measurements at different times during ALS (legend), and the green ellipses are the 50, 75 and 90 percent coverage areas for the individual end points for the ROSC group (ROSC: return of spontaneous circulation, ms: milliseconds, 1/min: per minute).

The development of mean heart rate and QRS width during the last 12 minutes of ALS were modeled using additive mixed models, see Figure 5.11. The development of heart rate was similar to that in study I, in that heart rate increased sharply form between 6 and 3 minutes before ROSC in all patients who obtained ROSC. We found a linear and slight increase in heart rate in the adrenaline no ROSC group, while heart rate remained unchanged in the no adrenaline no ROSC group. Mean QRS width developed in different directions in the ROSC and no ROSC groups, narrowing in the ROSC groups. The development in the adrenaline ROSC groups appeared less linear than in the no adrenaline ROSC group, with decline in QRS width beginning only at about 6 minutes before ROSC.

In the patients who did not get adrenaline, the temporal development of QRS width and heart rate was similar to that found in Study I, while the QRS width and heart rate was found to vary inversely in the adrenaline group.

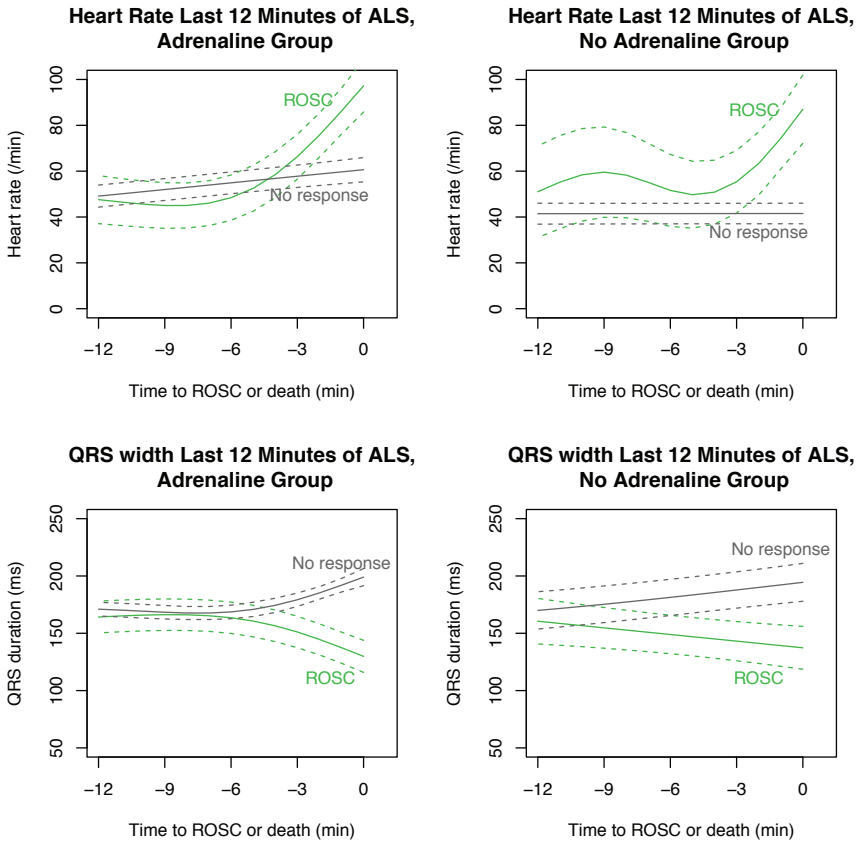

Figure 5.11 Mean heart rate (upper panels) and QRS width (lower panels) development, Study II. Last 12 minutes before sustained ROSC (solid green line) or before ALS efforts were stopped (solid grey line), according to the additive mixed effects model. Dashed lines: 95% confidence intervals. (/min: per minute, min: minutes, ms: milliseconds, ROSC: return of spontaneous circulation).

The figures and tables are presented in the same order as in Paper II, e.g. Figure 8.10 corresponds to Figure 1 in Paper II, Table 5-3 to Table 1 in the same paper. Figures 5.8, 5.9 and Table 5-4 were not included in the original paper.

5.5 Study III

Figure 5.1 shows that 63 patients from the population studied in paper I were included in the analyses for study III. There were 1844 observations of QRS width and heart rate. The objective of this study was to examine the development of the ECG parameters in patients with different etiologies of cardiac arrest, specifically comparing patients with cardiac etiologies of arrest to patients with other, non-cardiac, causes of arrest. Patients were stratified by whether they had ROSC or not, and the etiology of arrest. Demographic and clinical data is presented in Table 5-5 (Table 1, Paper III).

Table 5-5 Demographic and clinical data, study III.

	Cardiac Etiology (n=24)		**Other Etiology** (n=39)	
	ROSC (n=9)	No-ROSC (n=15)	ROSC (n=20)	No-ROSC (n=19)
Male sex, n (%)	7 (77)	8 (53)	15 (75)	9 (47)
Age, median (IQ-range)	64 (63-80)	78 (65-86)	65 (57-74)	75 (67-81)
Duration of ALS (min), median (IQ-range)	5 (3-26)	9 (2-16)	6 (2-12)	7 (2-14)
Location of arrest, n (%)				
Ward	2 (22)	10 (67)	8 (40)	12 (63)
Coronary Care Unit	3 (33)	4 (27)	8 (40)	5 (26)
Emergency department	2 (22)	1 (7)	3 (15)	—
Intensive care unit	1 (11)	—	1 (5)	—
Other	1 (11)	—	—	2 (11)
Admission Cause, n (%)				
Cardiac	8 (89)	10 (67)	2 (10)	4 (21)
Pulmonary	—	1 (7)	7 (35)	6 (32)
Surgical	1 (11)	2 (13)	6 (30)	3 (16)
Infectious disease	—	1 (7)	2 (10)	2 (11)
Other internal medicine	—	1 (7)	1 (5)	1 (5)
Other	—	—	2 (10)	3 (16)
Arrest Cause, n(%)				
Cardiac	9 (100)	15 (100)	—	—
Hypoxic	—	—	12 (60)	4 (21)
Pulmonary Embolism	—	—	4 (20)	4 (21)
Hypovolaemic	—	—	1 (5)	5 (26)
Sepsis	—	—	1 (5)	3 (16)
Other	—	—	2 (10)	3 (16)

Heart rate and QRS width were found to be negatively correlated (Pearson's r: -0,37, p <0.001).

By bivariate analysis, the change in QRS width and heart rate was only dependent on whether ROSC was achieved (p=0.001), but not on etiology (p=0.8). There was no significant interaction between ROSC and etiology in this analysis (p =0.1). The results are illustrated in Figure 5.12.

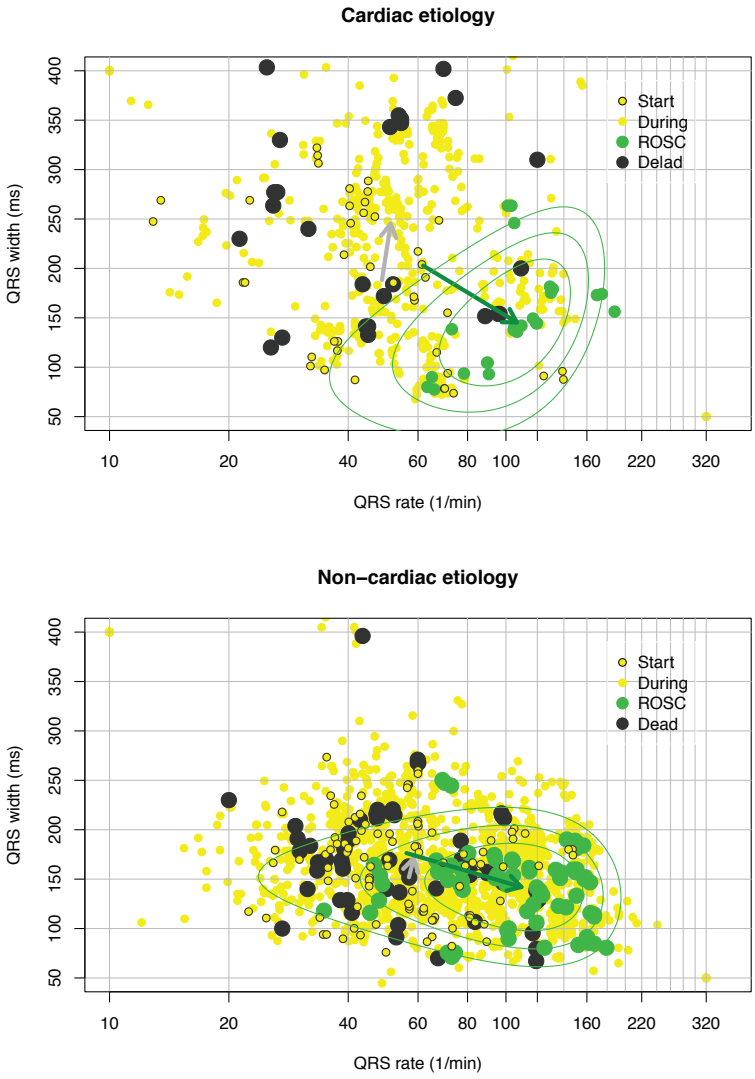

Figure 5.12 Bivariate plot, Study III. The difference between the mean start and end values for QRS width and rate are illustrated as arrows. Green: ROSC, grey: no ROSC. The dots represent individual measurements at different times during ALS (legend), and the green ellipses are the 50, 75 and 90 percent coverage areas for the individual end points for the ROSC group (ROSC: return of spontaneous circulation, ms: milliseconds, 1/min: per minute).

By the use of additive mixed models, we plotted the development of mean heart rate and QRS width during the last 18 minutes of ALS, shown here in Figure 5.13 with predictions from the linear mixed effects models superimposed.

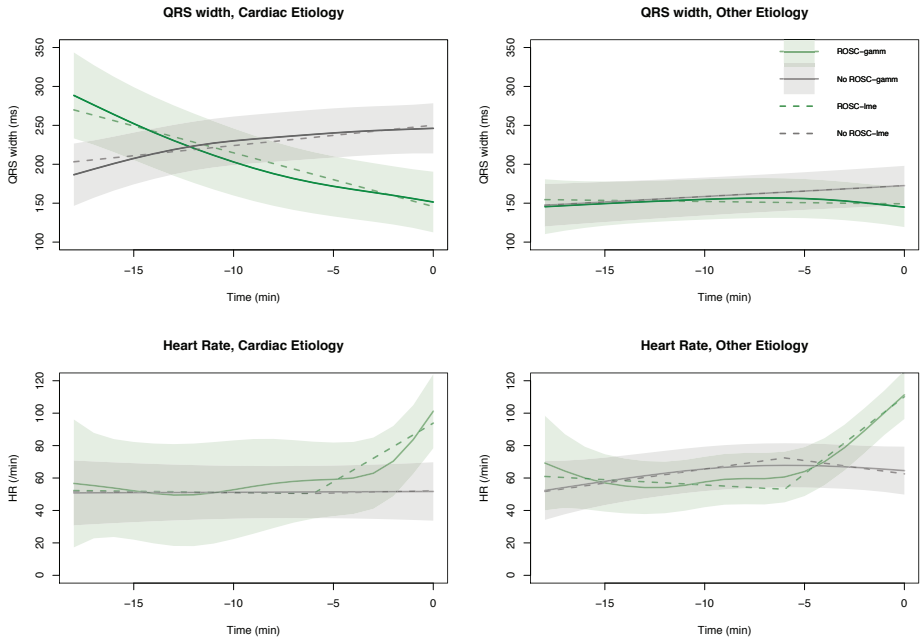

Figure 5.13 Mean heart rate and QRS width, last 18 minutes of ALS. Study III, by the additive mixed models (solid lines) with 95% CI (shaded area), and linear mixed model predictions (dashed lines) superimposed. (ms: milliseconds, min: minutes, /min: per minute, ROSC: return of spontaneous circulation, gamm: generalized additive mixed model, lme; linear mixed effects model).

The development of mean QRS width differed between the etiology groups. The cardiac etiology group had wider QRS complexes at 18 minutes before ROSC/end of ALS. This narrowed almost linearly towards ROSC in the ROSC group, and increased slightly in the no ROSC group. In the Other etiology group QRS width was narrower at 18 minutes before ROSC/end of ALS and equal in the ROSC/no ROSC groups, and then increased slightly until about 5 minutes before ROSC/end of ALS, when the ROSC group narrowed some compared to the no ROSC group. By the additive mixed effects model, we found evidence suggesting a trend in the development of QRS width in both the Cardiac ROSC group ($p<0.001$) and the Cardiac No ROSC group ($p<0.001$), but not in

the Other etiology ROSC group (p=0.6). In the Other etiology No ROSC group some evidence for a trend (p=0.04) was found. The development in QRS width was very close to linear in all groups and the linear mixed effects model of QRS width during the last 18 minutes of ALS give the same results as the additive mixed effects model: The model depended significantly on ROSC status (p= 0.02) and etiology group (p < 0.01).

By direct comparison, based on the linear mixed effects model, the change in QRS width in both other etiology groups and the cardiac no ROSC group differed significantly from the change in the cardiac ROSC group (all p values <0.001). The no-ROSC groups differed in the end QRS-estimate, the cardiac no ROSC group had wider mean QRS width than the Other etiology no ROSC group and both ROSC groups at end of ALS (all p values <0.001). The development over time, however, was not statistically significantly different in these two groups.

The development of heart rate was essentially the same in both etiology groups, but differed between the ROSC and no ROSC groups: In the ROSC groups, heart rate increased during the last 6 to 3 minutes before ROSC, while heart rate remained unchanged for the last 18 minutes of ALS in the no ROSC groups. By the additive mixed models, there was a trend in both ROSC groups (both p's <0.001), but not in either of the no ROSC groups (smallest p value =0.2). Linear mixed effects models with linear splines, showed that development of heart rate depended on ROSC status (p <0.001), but not on etiology group (p =0.3).

As we found in Studies I and II, the temporal development differed between QRS width and heart rate in the ROSC groups.

6 Discussion

6.1 Main Findings

The main findings of the three studies included in this Thesis are listed below:

1. The average development of QRS width and heart rate during ALS was different in patients who achieved ROSC compared to those who did not.
2. The overall pattern of development was very similar in the in- and out-of-hospital cardiac arrest populations studied.
3. In patients with OHCA, those who did get intravenous adrenaline had different developments of heart rate during ALS, while QRS width only differed between the ROSC and no ROSC strata. The difference between the adrenaline and no adrenaline groups was particularly pronounced in patients who did not achieve ROSC.
4. Average QRS width development during ALS in in-hospital cardiac arrest was different in patients with cardiac etiology compared to patients with a non-cardiac etiology, while the development of heart rate depended only on the immediate outcome.
5. Although correlated, QRS width and heart rate exhibited a different time-dependent pattern of development during ALS.

6.2 Interpretation of Main Findings

6.2.1 Differences in ECG Patterns and Prognosis

Decreased QRS width and increased heart rate in the ROSC groups but not in the no ROSC groups both in- and out-of-hospital, suggests that these ECG characteristics may be markers of biological processes common to cardiac arrest with PEA in general. The observed changes in the ROSC groups in study I and II, were changes from relatively wide QRS complexes and slow heart rates towards more normal values of both QRS width and heart rate.

The only other studies of changes in ECG parameters during resuscitation from cardiac arrest with initial PEA are those of Aufderheide and Stueven from 1989 (49,50). In these studies, patients who were successfully resuscitated (i.e. brought to the emergency department alive), either all had normal or near normal ECGs with respect to QRS width, QT time and presence of p-waves, or their ECGs changed towards normal during resuscitation. In the paper by Aufderheide (50), patients who were resuscitated successfully had higher heart rates at emergency department presentation than they had initially. These results support the findings in studies I and II, but the initial QRS widths in successfully resuscitated patients were narrower in Aufderheides paper (50) than in either of study I or II in this Thesis.

For study I, possible explanations for this are differences between the in- and out of- hospital populations, and differences in response times: Patients already admitted to hospital may have been older and sicker before arrest than patients out-of-hospital, which could have resulted in more pathologic ECGs at time of arrest. Also, the response time can be expected to be shorter in-hospital: the median response time was 1 minute from arrest to CPR was initiated at St. Olav University Hospital (43) and 5 minutes on average in the emergency medical services described in Aufderheide and Stuevens papers (49,50). Thus patients whose ECGs would otherwise quickly deteriorate into asystole could be caught while there was still electrical activity on their ECGs.

For study II these explanations do not hold, as obviously both populations studied were out-of-hospital populations. Additionally, the average response time by the paramedics in Oslo was 10 minutes in the study that contributed the data (79). From the 1980s onwards, a change in the spectrum of OHCA has been noted both in the USA and

in Europe. In Seattle, USA, the overall incidence of sudden cardiac arrest fell from 1980 to 2000, but the proportion of PEA and asystole increased. The authors attribute these changes to decreases in mortality from coronary artery diseases due to improvements in the treatment modalities available (31). In the Helsinki area, Finland, Kuisma et al. found a nearly 50% reduction in the incidence of primary VF from 1994 to 1999, a decrease in the incidence of witnessed cardiac arrest in general, but an increase in the proportion of cases with initial PEA and asystole (29). As in Seattle, this change was attributed to changes in cardiovascular health, with improved treatment and prevention of coronary artery disease in particular. In Gothenburg, Sweden, there was no decline in overall cardiac arrest incidence from 1981 to 1987, but the proportion with initial VF declined (32). Both in Seattle and Gothenburg the age of patients who suffered cardiac arrest had increased during the study periods, and the proportion of women increased.

It might be that both the causes of, and the patient population suffering, OHCA may have changed from the 1980s, and that this also could impact the ECG characteristics seen in PEA: Changes in the causes of cardiac arrest from the 1980´s to 2009-2013 may be a possible explanation for the differences in initial QRS widths between Aufderheide`s paper and our studies I and II.

The patterns of change in QRS width and heart rate as seen in Figures 5.6 and 5.11 towards ROSC were roughly similar in the ROSC group in study I and both the adrenaline and no adrenaline ROSC groups in study II. The decline in QRS width was more gradual, while the increase in heart rate occurred mainly during the last 3-6 minutes before ROSC with a sharp change in the development of this parameter. The similarity of the response in the in- and out-of-hospital populations supports the validity of the results in either study. The difference in the development over time in QRS width and heart rate suggests that different mechanisms may impact the change in each variable.

From a clinical point of view, noticing small changes in the width of the QRS complexes on defibrillator monitors seems less feasible than the ability to register a more abrupt change in heart rate, a number that is usually displayed on defibrillator monitors (as long as there are discernible complexes). However, the different patterns of change in the two parameters, as well as the calculated correlation coefficients suggest that there may well be information when considering both variables that is not discernible by examining only one or the other. Furthermore, it is not possible to say if these changes

in the ROSC groups are results of ALS interventions, or necessary precursors for ALS success resulting from underlying processes in these patients' hearts that sets them apart from the patients that did not have ROSC.

6.2.2 Impact of Adrenaline

In study I an increase in heart rate was observed before ROSC. The effects of Adrenaline are mediated through alpha- and beta- adrenergic receptors, and though the desired effect of adrenaline in the setting of cardiac arrest is an increase in coronary perfusion pressure, mediated mainly through alpha-adrenergic receptors in the vasculature (106), one of the beta-adrenergic effects of adrenaline is an increase in heart rate (107).

As was discussed in the preceding Section, the overall development in QRS width and heart rate before ROSC was very similar in the in- and out-of-hospital populations of studies I and II respectively. However, in study II a more pronounced increase in heart rate was found in the group of patients with ROSC who had been given intravenous adrenaline, than in the ROSC patients who had not. The average decrease in QRS width was the same in these two groups. Even more interesting: heart rate also increased, albeit less than in the ROSC groups, in patients who did not have ROSC but who had been given adrenaline. In this group, QRS width increased the same as in the group of patients without ROSC who did not get adrenaline. The univariate analyses of covariance also imply that adrenaline was associated with differences in heart rate, but not in QRS width. As stated earlier, QRS prolongation represents ventricular activation, and is influenced by ventricular conduction disturbances that can be caused by an impaired myocardial metabolic state (108–110).

Outside the setting of cardiac arrest, increased QRS width has been linked to decreased left ventricular function(111,112), and poorer prognosis after non- ST-elevation myocardial infarction (113). Narrowing of the QRS complex after fibrinolytic therapy for acute myocardial infarction has been found to be an independent predictor of reperfusion (114).

Adrenaline has been shown to impair the balance between myocardial oxygen consumption and delivery in an animal model of cardiac arrest (74). This is a possible mechanism behind the increased QRS widths seen in the patients without ROSC but who did get adrenaline, though without a demonstrated temporal relationship between

adrenaline administration this may be considered a speculation. The change in QRS width in the adrenaline no ROSC group in study II was the same as in the no adrenaline no ROSC group, and the results from the univariate analyses in study II indicates that adrenaline administration did not affect the QRS width in these patients. The increased heart rate found may be a beta-adrenergic effect of adrenaline. That the patients with ROSC had a different development of QRS width and heart rate may be due to many factors. For example, the effect of adrenaline on survival may be time dependent, with earlier administration associated with better prognosis in in-hospital cardiac arrest with non-shockable rhythms (115), but not with shockable rhythms(116). In OHCA, an association between early adrenaline and increased survival to hospital discharge has also been described (117). In an animal study cardiac function after ROSC was improved with prompt adrenaline administration and CPR, but impaired in rats that were given adrenaline when CPR was delayed (72). Unfortunately, we were unable to control for timing of adrenaline administration, as this was not recorded during the data collection.

As discussed in the introduction, Section 2.5 (The Use of Adrenaline), there has been some uncertainty regarding the efficacy of adrenaline in cardiac arrest. Clinically, it seems that adrenaline has a positive effect with regard to achieving ROSC, but that long term survival and neurologically intact survival is perhaps no or only marginally better in patients resuscitated with adrenaline than without (40,79,81). The mechanisms behind this may be related to neurological injury (118,119), but post-ROSC myocardial dysfunction (120,121), in which adrenaline has been implicated (72,74,122), may also be important.

6.2.3 Differences Due to Etiology

The observation of concomitant increase in QRS width and heart rate in patients who had been given adrenaline but did not get ROSC in study II led us to wonder if QRS width perhaps is a more sensitive marker of myocardial state than heart rate. By analyzing the development of ECG characteristics during ALS based on the etiology of the arrest, we found a marked difference in the development of QRS width before ROSC/ end of ALS. The heart rate development was similar in both etiology groups, and followed the same pattern, with respect to ROSC/no ROSC, as in studies I and II.

First, this underscores the point that change in QRS width and heart rate develop differently. Though they are not independent, some ongoing disease processes and therapeutic measures taken during ALS may produce change in one but not the other. The other important point is that there seemed to be a difference between the cardiac etiology group and the other etiology group regarding the development of QRS width. In the Other etiology group QRS width was largely unchanged during ALS, with a possible slight narrowing towards the end in the ROSC group. In the cardiac etiology group, not only did it appear that QRS widths were wider overall, but change towards ROSC was also large. So, if QRS width is a more sensitive marker of myocardial metabolic derangement; this could signify that patients' hearts in the cardiac etiology group were either more damaged before the arrest, were more susceptible to derangement during ALS than those in the Other etiology group, or that the etiology of arrest in some other way impacted the development of the QRS complex.

A study of etiologies of in-hospital cardiac arrest from Austria found a comparable proportion of cardiac and non-cardiac causes as in our study (36). Though a link between the width of QRS complexes and different etiologies of PEA has been suggested, the foundation of such a suggestion appears to be entirely theoretical (58). As far as we know, only one other study has examined the relationship between QRS width and etiology of PEA: Bergum et al. who examined the relationship between initial QRS width, heart rate and QT-times. The study concerned (partially) the same patient population as the present Study III is based on, the present author was a co-author (84). No association between any of the initial ECG characteristics etiologies, etiology groups ("mechanical vs. metabolic", "cardiac vs. 4H4T vs. other") or survival could be found. The patient population differs from that study to the present study III because of slightly less stringent requirements regarding the level of certainty with respect to etiology. Furthermore, the need for complete defibrillator files, some of the patients in Bergum et al's paper could not be included in the analyses for study III.

The ECG reflects the underlying electrophysiology of the heart, and also that the normal electrophysiological and mechanical function, as well as the mechanical function of the heart depends on metabolic homeostasis. In patients with a cardiac etiology of their cardiac arrest the development of QRS width from wide towards narrower in the ROSC group may represent effect of ALS, i.e. some reperfusion as coronary perfusion pressure

increases. It is more difficult to explain the lack of change in the non-cardiac etiology ROSC group. It is possible that this group includes patients that were in a state of severe cardiogenic shock, but not with complete cardiac stand-still, or that myocardial metabolic state, for some reason was never as severe as in the Cardiac group.

7 Methodological Considerations

Studies I and III of this dissertation were based on data collected as part of a prospective study of in-hospital cardiac arrest. Study II was based on data collected as part of a randomized controlled trial of intravenous medication in OHCA. Review of clinical data and measurements of QRS width and heart rate were done retrospectively – which limited the analyses to what could be found in the data already collected.

The measurements of the ECG characteristics during cardiac arrest resulted in longitudinal data that was unbalanced with respect to the number and timing of measurements per patient, as well as the duration of episodes. This is an inherent problem with collecting data during treatment of cardiac arrest, and not unique to the studies in this dissertation.

Particularly the varying duration of episodes constituted a problem in the modelling and visualizing change over time, as discussed in Section 4.3.7. The overall change in the ECG characteristics from start to end of ALS were modelled using MANOVA and analysis of covariance. Concerning patterns in the continuous change in the ECG characteristics in individual episodes, important aspects could still be obscured by longer lasting episodes, and this made us to also turn time around, and count time backwards from the point of ROSC or end of ALS efforts. Now the end of each episode was included in the models, but the cost is that changes and differences that occurred earlier during ALS now could remain unobserved. The defined end-points are also somewhat problematic. The transition from cardiac arrest to ROSC is not always clear, as this is based on a comprehensive clinical evaluation. The exact time of ROSC may therefore have occurred at some time before it was discovered by the ALS team, which can lead to some inaccuracy in the exact timing of this event. Still, because it is a transition from one state to another, ROSC is a better-defined end-point in clinical reality, and in our studies, compared to termination of ALS.

Termination of ALS is a more arbitrary end-point than ROSC, with respect to timing. It does not necessarily represent any change in the clinical state of the patient, only the cessation of ALS efforts. The reasons for giving up ALS efforts are many, and the exact timing is often discretionary. Thus, comparing development of mean QRS width and heart rates in the ROSC and no-ROSC groups may not be entirely straightforward.

The pattern of change in the no-ROSC groups could have been different if ALS had been continued longer or terminated earlier.

The goal of most scientific studies is to say something about some population as a whole through the study of a sample from that population, often called external validity. The external validity of a study pertains the degree to which study results can be generalized to the larger population, and depends on consideration of the impact of chance, bias and confounding on the study results (123).

7.1 Chance

To evaluate the role of chance in medical and scientific studies in general, statistical hypothesis tests are commonly employed. These compare a null hypothesis (e.g. that there is no association between exposure and disease, no difference in means between two groups, etc.) and an alternative hypothesis (that the null hypothesis is incorrect). The two most commonly reported results of such tests are the p-value and the (95%) confidence interval. The p value represents a conditional probability, specifically that one could get results as extreme as was observed in a study by chance, given that there really was no association between the outcome in question and the exposure (i.e. that the null hypothesis is true).

Common to all statistical tests are that they depend on both the magnitude of the difference between observed values and the values under the null hypothesis and the variability in the variables observed. The test statistic, which in turn is used to calculate the p value, is the result of a fraction with the observed difference in the numerator and the variability in the denominator (124). The p-value is inversely related to the test statistic. A large difference between observed and expected values results in a higher test statistic value and a lower p value. The variance or standard deviation are common measures of variability, and yield the standard error (SE) of the estimate (105). It follows that larger sample sizes result in lower standard errors. Thus, larger sample sizes give higher value of the test statistic (and the p value decreases). As is the convention in medical literature, a significance, or alpha level, of 5% was employed, and p values less than 0.05 were considered statistically significant. This means that the probability of rejecting the null hypothesis when it is really true – type I error– is 5%, or one in twenty.

The confidence interval – a 95% confidence interval when a significance level of 5% is used –gives information about both whether observed differences are statistically significant and the precision of the estimate. If the expected value under the null hypothesis is included in the confidence interval, the observed differences are not statistically significant. The precision of the estimate is reflected in the width of the confidence interval, and can be particularly informative when considering findings that are not statistically significant. Here, wide confidence intervals may indicate insufficient power to detect true differences, so that there is a risk that the alternative hypothesis is rejected when really true, so called type II error (124).

In the present studies, the same variables were measured repeatedly within each patient over time, and the development or change in these variables were treated as the dependent variables in all the statistical models used. In the case of the Multivariable Analysis of Variance models used in studies I, II and III, these compare the average change in two or more variables dependent on some factor, from one occasion to another. Only the average values at the beginning and end ALS were used in these analyses, so only the temporal order of the observations was important.

When dealing with longitudinal data as in these studies, it is important to consider both the temporal relationship and covariance between observations within each patient. The variance in the estimates are in part due to the variance within each patient, and part variance between patients (as well as random measurement error) (103). This is important when conducting statistical tests: variance is a key component in statistical hypothesis testing, as described above. Equally, the lack of independence between observations within the same patient violates a key assumption of most ordinary regression methods. The generalized additive mixed models (and linear mixed effects model in study III) used in all three studies are suitable for this kind of data (101,103). An illustration of this point can be seen in Figure 4.3, where the confidence intervals around the estimated mean in the curve from the *gamm* model are wider than in those in the *loess* model, because the latter treats all observations as independent.

The limited sample sizes in all three studies of this Thesis increase the risk of chance impacting the results. When relying on samples from a larger population to make inferences about the population as a whole, smaller samples can be less representative, lead to larger variance, but also increase the risk of studying a skewed sample, which could inflate the difference between the observed and expected values.

The variability in the observations was considerable both within and between patients, which impacts on the precision of the estimates.

7.2 Bias

Bias, in scientific studies, can be defined as "any systematic error that results in an incorrect estimate of the association between exposure and risk of disease" (124). There are two main classes of bias, selection and information bias. The possibility and impact of these will be discussed for the three studies of this Thesis together and separately.

Selection bias are errors that occur in the selection of the study population, or sample. The population of interest in the current Thesis were patients with in- and out-of-hospital cardiac arrest with initial PEA. Inclusion was based primarily on these criteria, but as has been accounted for, a proportion of eligible patients were excluded from the analyses due to several factors, of which missing defibrillator data was the most important. There was no reason to believe that this occurred systematically. Study I compared patients with cardiac arrest who did and did not have ROSC. There was a risk that patients that were not included in the study could differ substantially from those that were included. A comparison of demographic and clinical data between these groups can be found in Table 5-2, and the groups appeared to be comparable.

The data analyzed in study II was obtained from a study where patients were randomized to either have or not have access to intravenous drugs during ALS. But since the biological effect of adrenaline on the developments of ECG characteristics were of main interest in study II, randomization status was disregarded, and stratification was by whether adrenaline had actually been administered or not.

In all studies, the defibrillator files were gathered from defibrillators used by in-hospital emergency teams or defibrillators in the ambulance service. Both in-hospital and out-of-hospital, not all cardiac arrests are recognized or called in. This may be because of do not resuscitate orders, prior knowledge of the patient's comorbidities and wishes, or cardiac arrest occurring unwitnessed so that ALS efforts are obviously futile by the time the patient is found. In the coronary care unit (CCU) and ICU, some quickly resolved episodes of cardiac arrest might have been missed because the emergency team was never alerted. Very short episodes may also have been missed, if ROSC had been obtained before a defibrillator could be connected. It is impossible to control for differences between the patients included, and those not included because no emergency or ALS team attended the arrest. These selection mechanisms can be expected to be similar in most

cardiac arrest studies, however, and there is no reason to believe that this was particularly pronounced in the studies of this dissertation.

Information bias pertains to errors in measurements of covariates, exposure and disease that result in differences in the accuracy of information between comparison groups (125). The measurements of QRS width and heart rate were essential parts of the three studies included. The investigator that performed the actual measurements had full access to all data at the time of measurement. The heart rate measurements were relatively simple, in that only distances between QRS complexes needed to be measured. QRS width posed more of a challenge, with varying morphology of the complexes. As has been described in the methods section (Section 4.2.2), a systematic approach to the measurements was used, but the measurement of QRS complexes may represent a source of error in these studies. There is, however, no reason to believe that any such errors were not distributed evenly in the material, classified as "non-differential misclassification", which tends to obscure differences (123). In study III some of the included patients' ECGs had already been analyzed with respect to initial QRS widths in the study by Bergum and co-workers discussed in Section 2.6 (84). For these 26 patients the initial values from that study were compared to the mean values during the first 15 seconds of ALS obtained in study III. From these 26, 23 had available ECG tracings with measurements from the study by Bergum and co-workers, which were checked to ensure that the same complexes were compared. The results were plotted against each other, see Figure 7.1 with a line of equality (x=y), and the plot indicates that the measurements in study III tended to be judged slightly narrower than in Bergum and co-workers' study. This difference could potentially obscure differences, given that any measurement error was uniformly distributed between the groups compared in study III. Further, a Bland-Altman (126) plot of the differences of QRS width between the studies and the average QRS measurement for each occasion in the two studies can be seen in Figure 7.2, with the 95% limits of agreement (126). Again, the mean difference is negative, indicating if anything that the measures were mean 8 ms narrower in the measurements for study III, but it does not seem that there was any systematic difference or trend in the differences (e.g. no evidence of increasing differences with increasing average measurements).

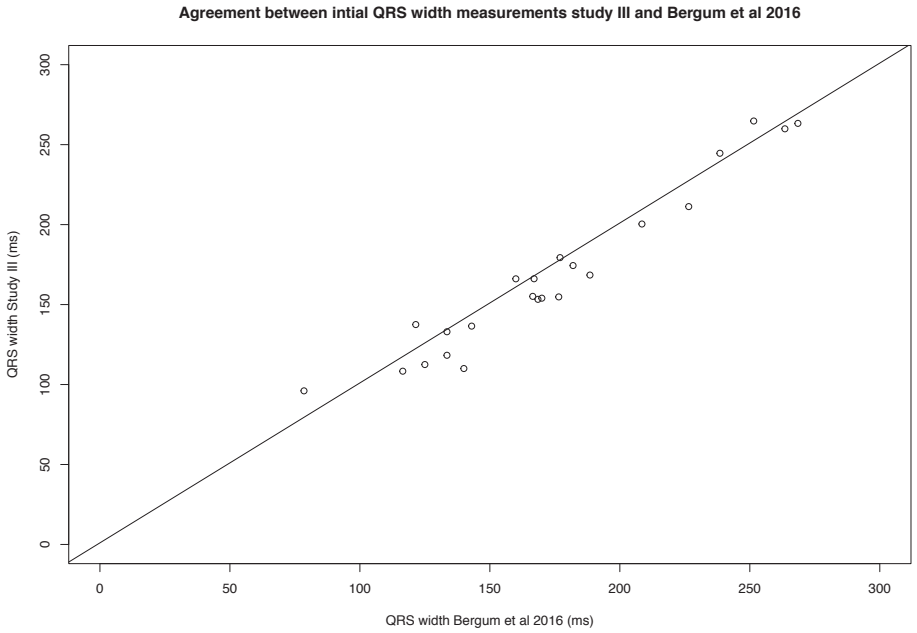

Figure 7.1 Comparison of QRS widths Study III and Bergum et al. 2016. Dots represent matched measurements (ms: milliseconds).

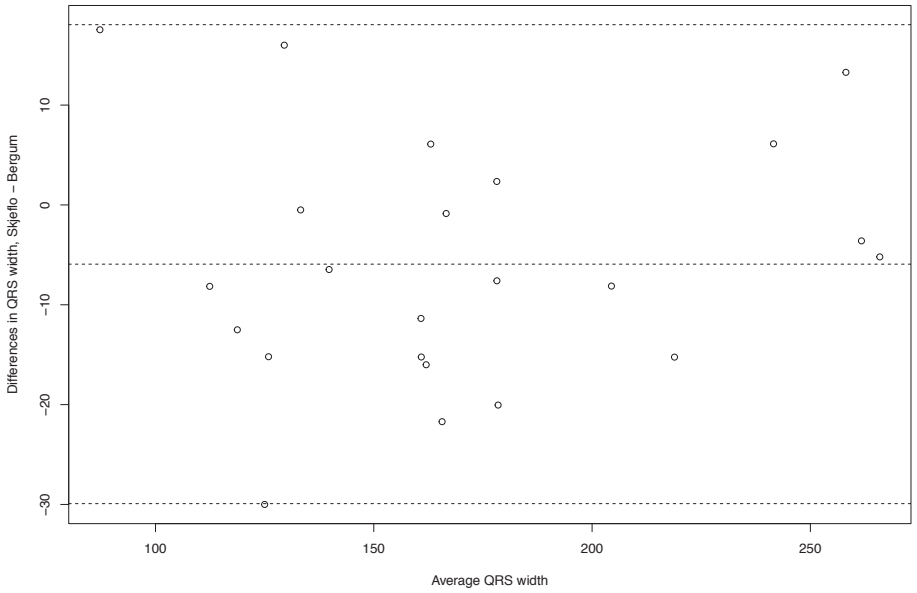

Figure 7.2 Bland-Altman Limits of Agreement. Middle dashed line, mean difference in QRS width measurements, plotted against the mean QRS width for each matched measure in the two studies. Upper and lower dashed line: upper and lower 95% limit of agreement.

Although only the initial QRS widths of these 23 patients could be compared, the result does not suggest systematic difference between the measurements, though the 95% limits of agreement are rather wide (about 30ms).

There was some controversy around the original study by Olasveengen and co-workers at the time that it was conducted. Some documented breaches of protocol, i.e. patients randomized to not have access to intravenous medication that did get intravenous medication occurred (79). We have no way of knowing whether any of the patients in the no adrenaline group in our study did in fact get adrenaline without this being recorded. If, in fact, this happened, it would be expected to have reduced the differences between the groups. The paramedics and doctors that participated in ALS for these patients were aware of the randomization status due to the nature of the intervention. Much of the

clinical data was extracted from Utstein style cardiac arrest forms, filled in by the participating ALS teams. Data from the defibrillators were recorded digitally.

In study III, the additional criterion of a known certain or probable cause of arrest may represent a danger of both information and selection bias, as it is possible that there are systematic differences between patients where the etiology of arrest could be ascertained, and those with causes of entirely unknown etiology. Also, it was demonstrated by Bergum et al. that the rate of recognition of causes by the ALS teams in cases with initial PEA was somewhat lower than in the study population as a whole (65% versus 75%) (43), and also that there were more patients with a recognized etiology that survived at least initially (60). It is also possible, and even likely, that certain causes of cardiac arrest are easier to ascertain, which could result in differences between the patients included and those excluded because of unknown etiology of arrest. These factors represent a danger of mainly information bias. Because of a limited number of patients included, different etiologies were grouped into either cardiac or non-cardiac etiology groups. This could have resulted in inhomogeneous groups, which could obscure any differences between the groups.

7.3 Confounding

A confounder is some other variable than the one under consideration which influences or is associated with both the exposure variable and the outcome independently (124).

In study I, we found an association between ROSC status and changes in QRS width and heart rate during ALS. There may exist numerous pathways that are patient or disease specific that may explain the association between ROSC and development of ECG characteristics; this is a topic for future studies.

In study II, ALS and other arrest related factors can be expected to have been similar in both the adrenaline and no adrenaline groups, though some differences have been demonstrated (127). There may exist unmeasured or unknown factors that may act as confounders in the association between adrenaline, ROSC and the development of the ECG characteristics. The same applies for study III, with regard to the relationship between etiology and the development of the ECG characteristics.

To control for confounding, either restriction(123), stratification or multivariate statistical modelling including a priori decided possible confounders is recommended (124,128). In studies II and III we attempted to control for the possible confounding effects of ROSC status on the relationship between adrenaline and etiology, respectively, and the development of ECG characteristics, by stratification.

7.4 External Validity

In the current Thesis, we analyzed data from two different patient populations. One from a single hospital and one from a single pre-hospital emergency system, both in Norway. In terms of generalizing to the entire in- and out-of-hospital cardiac arrest populations, data from a single hospital / pre-hospital emergency system may be seen as a weakness because the samples may not be representative for cardiac arrest patients in other parts of the world, though the population in Norway, and even in Scandinavia is relatively homogeneous on the global scale, so that the results may at least be applicable in this region. Concerning the in-hospital population, patients from CCUs and ICUs may be underrepresented, as these units do not always call the emergency team to episodes of cardiac arrest.

The limited sample size is a more general problem, and limits the precision of the results from the studies.

8 Implications for Future Studies and Clinical Practice

As stated earlier, a number of limitations apply to the studies in this Thesis. A replication of the studies in larger patient populations would be of great interest. Since the data for the present studies were collected, advances in the harvesting and storage of data from defibrillators make it possible to harvest data continuously and store this on servers. This should make replication without the large number of missing defibrillator files feasible. Automatic measurements of QRS width and heart rate would be another great advance; both to limit the impact of measurement errors and to make continuous measurements possible (given that noise from compressions can be filtered out).

From the results of the current studies, several questions arise. What are the cellular mechanisms behind the wide QRS complexes and slow heart rates that dominate in the early stages of ALS from PEA in our study? Although we have discussed several mechanisms in the original papers (Papers I-III), the science behind this does not address the question of electrical activity in PEA specifically. QRS width is the duration of ventricular depolarization, the inverse of which translate into a velocity of depolarization. Heart rate was, in the studies of this Thesis, calculated from the duration between the start of QRS complexes. The rate at which the heart depolarizes usually depends on automaticity in the sinus node, but all myocardial cells exhibit automaticity. The conduction velocity, as well as the coordinated depolarization of the myocardium depends on the function of specialized tissues within the heart. In disease, however, spread of electrical current can occur erratically (108–110,129). The ionic currents responsible for the automaticity of the normal pacemaker regions are different from the currents responsible for the depolarization and spread of current through the myocardium (130). This may explain why QRS width and heart rate were found to be partially negatively correlated: that both depend on the electrical function of the myocardium, but in part in different tissues, and in part by different processes. It is possible that both in-vitro studies, animal and human studies could shed further light on this question, including the nature of the association between the ECG characteristics and the outcome of cardiac arrest. From the studies in this Thesis it is not possible to establish a causal relationship between changes in ECG characteristics and ROSC, intravenous adrenaline or etiology. It seems likely that the ECG changes because the myocardial metabolic state

changes. An ability of therapeutic measures to impact on the development of ECG characteristics during ALS in a controlled setting, e.g. in an animal model, would strengthen this hypothesis.

Can ALS be adjusted dynamically during the provision of ALS based on the development of ECG characteristics in individual patients? This is a difficult question to answer, and depends in part on replication of the findings in this Thesis in larger samples, and in experimental studies. Some discussion follows.

Generally, lack of improvement in QRS width may prompt the ALS team to change their approach, and consider other measures to optimize the physiology of the patient while working on diagnosing and treating the underlying condition. Measures such as extracorporeal membrane oxygenation or cardiopulmonary bypass are relevant, novel strategies to be considered(131).

The effects of adrenaline on the heart during ALS for PEA are not clear. The association between adrenaline use and increased heart rate in PEA both without and with ROSC needs to be replicated, preferably in a way that enables temporal relation of any ECG changes to the administration of adrenaline. If our findings can be replicated, monitoring of heart rate concomitant with QRS width can prove a way of monitoring adrenaline effects during PEA, and possibly tailoring dosage and administration intervals. Here, animal models and prospective observational studies in humans may help establish any dose-effect relationship between adrenaline and ECG changes in PEA, and the temporal relationship between these factors.

Can etiology be predicted from changes in the ECG during ALS? The provision of ALS is, as previously mentioned, protocol driven, which ensures a uniform level of treatment to all cardiac arrest patients. The guidelines already stress search for and reversal of underlying conditions. From our limited data, it seems that development of ECG characteristics during ALS may depend on the different etiologies of PEA (paper III). Again, this finding needs to be corroborated, but given that it can be, there may be important clues as to the etiology of PEA in the development of ECG characteristics during ALS.

In the included studies, stratification of the patient population was on ROSC status, plus one additional factor (adrenaline and etiology) in studies II and III. Though ROSC is the immediate goal of all ALS, another relevant end point is of course long term

survival and especially neurologically intact survival. Because of the low number of long-term survivors in our material stratification on these end points did not make sense, but in a larger study this may be feasible.

9 Conclusions

This Thesis describes the temporal development of mean QRS width and heart rate for the duration of ALS in cardiac arrest with PEA. This is novel knowledge, previously not described.

We found that the average development of QRS width and heart rate during ALS was different in patients who attained ROSC compared to those that did not, and that the overall pattern of development was very similar in the in- and out-of-hospital cardiac arrest populations studied.

In patients with OHCA, those who received intravenous adrenaline had different developments of heart rate during ALS, while QRS width only differed between the ROSC and no ROSC strata. The difference between the adrenaline and no adrenaline groups was particularly pronounced in patients who did not attain ROSC.

The pattern of average QRS width development during ALS in IHCA was different in patients with cardiac etiology of arrest compared to patients with a non-cardiac etiology, while the development of heart rate depended only on whether the patients attained ROSC or not.

QRS width and heart rate were found to be partially negatively correlated, but exhibited different time-dependent patterns of development during ALS.

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Appendix - Papers

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Clinical paper

ECG changes during resuscitation of patients with initial pulseless electrical activity are associated with return of spontaneous circulation

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ABSTRACT

Background: Pulseless electrical activity (PEA) is a frequent initial rhythm in cardiac arrest, and ECG characteristics have been linked to prognosis. The aim of this study was to examine the development of ECG characteristics during advanced life support (ALS) and cardiopulmonary resuscitation (CPR) in cardiac arrest with initial PEA, and to assess any association with survival.

Methods: Patients with in-hospital cardiac arrest with initial PEA at St. Olav Hospital (Trondheim, Norway) over a three-year period were included. A total of 2187 combined observations of QRS complex rate (heart rate) and QRS complex width for the duration of ALS were determined from defibrillator recordings from 74 episodes of cardiac arrest.

Results: Increasing heart rate and decreasing QRS complex width during ALS was significantly more prevalent in patients who obtained return of spontaneous circulation compared to patients who were declared dead.

Conclusion: Changes in ECG characteristics during ALS in cardiac arrest presenting as PEA are related to prognosis. An increase in heart rate was observed in the last 3–6 min before ROSC was obtained.

Introduction

In-hospital cardiac arrest (IHCA) has been reported to occur in 1–5 per 1000 admissions [1]. The initial rhythm may be ventricular fibrillation (VF), pulseless ventricular tachycardia (VT), pulseless electrical activity (PEA) or asystole. PEA is the presenting rhythm in 25–42% of IHCA, and survival to hospital discharge for this subgroup has been reported to vary between 3 and 19% [2–6]. The proportion of cardiac arrest patients presenting with PEA has increased during the last decades, whereas the proportion of patients presenting with VF/VT has decreased [4,7,8].

In a previous study of IHCA with initial PEA, we found that most patients had wide initial QRS complexes and slow heart rates, but we found no association of initial ECG characteristics with aetiology or survival [9]. Previous studies on out of hospital cardiac arrest (OHCA) have reported conflicting results regarding the association between initial heart rate and QRS width and subsequent survival. While some studies report increased survival with higher heart rates and narrower QRS complexes, others report no such association [10–13]. An animal study on post-defibrillation PEA demonstrated increased likelihood of return of spontaneous circulation (ROSC) with higher initial heart rates and narrower QRS complexes [14]. While these studies investigated the impact of ECG characteristics at one time point, the dynamic nature of ECG development during advanced life support (ALS) with cardiopulmonary resuscitation has not yet been studied.

The aim of this study was to describe the development of ECG characteristics during ALS in patients with initial PEA, and to examine whether ECG characteristics were associated with ROSC.

Materials and methods

Adult patients (> 18 years) who experienced in-hospital cardiac arrest at St. Olav University Hospital (Trondheim, Norway) and received ALS by the hospital emergency team between January 2009 and January 2012 were prospectively included in the study. Details regarding the hospital and the collection of data have previously been described [3,15].

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Electrocardiographic characteristics

ECG and impedance signal data were collected from LifePack 20 and LifePack 1000 defibrillators (Physio-Control, Redmond, USA) as well as Zoll M-series defibrillators (Zoll Corporation, Chelmsford, MA, USA). Defibrillator files were analysed using the software MATLAB (R2014b, Math Works Inc., Natick, MA). Type of heart rhythms, QRS widths, and heart rates were evaluated during pauses in chest compressions for any reason (including end of efforts), or when ROSC was obtained.

The annotation of clinical state along the time axis (PEA, VF/VT, asystole, ROSC and declaration of death) has been described in a previous publication [3]. Briefly, PEA was defined as the presence of organized complexes exceeding 12 per minute, but not constituting VT or ROSC. To visualize, we further subdivided according to QRS width and rate as in the publication by Bergum et al. [9]; rates under 60/min were classified slow, rates between 60 and 100 were classified normal, and rates above 100/min were classified fast. QRS widths below 120 milliseconds (ms) were considered normal and QRS widths $>=$ 120 ms were considered wide. ROSC was defined as an organized rhythm without evidence of compressions along with clinical information suggesting ROSC either during the episode or at end of the episode.

The QRS width was defined as the interval between the initial deflection from the baseline towards the Q- or R-wave and the beginning of the ST-interval on the ECG. The QRS end-point was marked off where a clear break from the high frequency changes of the QRS complex (depolarization), towards the lower frequency change of the ST-interval (repolarization) was observed. In cases with no obvious transition from the QRS to the ST-interval, the point where the ECG tracing crossed the baseline towards the T-wave was marked off as the QRS end-point.

During analysis of ECG tracings, the exact points of measurement were labelled on each trace, both for reproducibility and to enable assessment by one of the co-authors (JPL) (Fig. 1). Two to three QRS complexes were measured at each pause in compressions, as determined from the impedance signal. Single complexes that differed substantially from neighbouring complexes with respect to morphology were disregarded. Heart rates were calculated from the intervals between the beginnings of measured QRS complexes.

Statistical analysis

We calculated Pearson's correlation coefficient between heart rate and QRS width. Development and consequences of ECG characteristics during the course of ALS were investigated in the following ways:

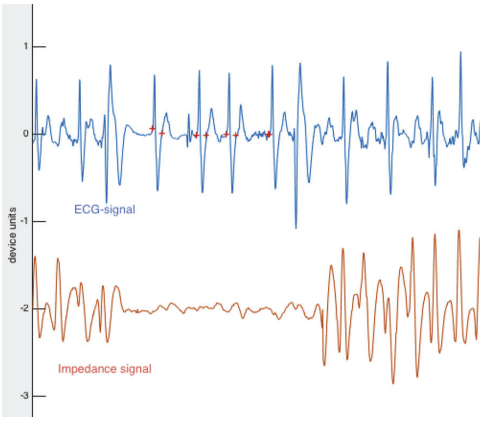

Fig. 1. Example ECG and impedance signal with QRS start/stop marked by red "+". (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

First, we fitted additive models [16] to smooth and visualize the development of the outcome variables heart rate and QRS width over the entire duration of ALS, and for the last 12 min of ALS before ROSC or termination of ALS efforts. We fitted separate models according to whether ROSC was achieved or not. As observations were nested within patients, a mixed effects model in which each patient is assigned an individual offset (known as "random intercept") was used. We expected that measures closer in time would be more similar than measures further apart and therefore allowed for autocorrelated residuals. This improved model fit.

Second, we plotted the values of QRS width and heart rate during ALS onto a two-dimensional (2D) plane. We constructed bivariate vectors of the change in mean heart rate and QRS width from the first 15 s to the last 15 s of each episode to illustrate the development from start to end of ALS. If asystole had occurred at the very end of the episodes, we used the values from the last preceding measurements during PEA. We tested the null hypothesis of no change using multivariate analysis of variance (MANOVA) [17].

Finally, we investigated the effects of heart rate and QRS width as continuous predictor variables on the cumulative intensity of transition from PEA to ROSC, using Aalen's additive regression model for time-to-event data [18].

The software R version 3.4.0 [19] and the R packages *nlme*, *gmodels, mgcv* and *timereg* were employed for the statistical analysis. We considered a p value < 0.05 to indicate statistical significance.

Ethics

The Regional Committees for Medical and Health Research Ethics approved the study. Informed consent was obtained from surviving patients, or from the next-of-kin if required. The study is registered at clinicaltrials.gov (NCT00920244).

Results

One hundred and fourteen adult patients with IHCA and an initial rhythm of PEA were included. Of these, 40 were excluded because of missing defibrillator files (n = 28), lack of consent (n = 5), illegible defibrillator file (n = 6), and ROSC before recording started (n = 1), leaving 74 episodes of IHCA for analysis. The data set included a total 2187 combined observations of QRS width and rate.

Table 1 shows demographic and clinical data, stratified on whether or not ROSC was achieved or not. In nine episodes, the defibrillator file was incomplete because the recording stopped before the end of ALS. Four of these were in the ROSC group, five in the no-ROSC group. Median duration of ALS was 6 min in the ROSC group (interquartile range: 3.7–12.8 min). Median duration of resuscitation was 13 min in the group without response to ALS (interquartile range: 8.3–24.4 min). Nine of the included patients (12%) survived to discharge.

Fig. 2 illustrates the changing prevalence of the different clinical states (ROSC, PEA, VF/VT, Asystole, and death) over time. The figure shows that wide-slow PEA rhythms dominated initially, and that almost all ROSC occurred before 21 min of ALS.

Fig. 3 shows the development of mean QRS width and rate during ALS, according to ROSC/no ROSC for the last 12 min before ROSC, or before the end of ALS efforts, by the additive mixed models. The development of heart rate and QRS width was different in patients obtaining ROSC compared to in patients with no response to ALS. In the ROSC group, a marked rise in heart rate started to occur at about 3–6 min prior to ROSC. The development of QRS width was more linear, with a gradual decrease in the ROSC group. In patients without response to ALS, both heart rate and QRS width were essentially unchanged or slightly decreased and increased, respectively, towards the end of ALS efforts. Plots of the predicted mean heart rates and QRS widths for the full duration of ALS from the beginning are provided in e-figure 1 in Supplementary material, the differences between the groups

Table 1
Demographics According to Etiology and ROSC group.

	ROSC	No ROSC
Age, median (IQ-range)	65 (60–80)	78 (68–84)
Males, n (%)	25 (76)	22 (54)
Department, n (%)		
Ward	12 (36)	28 (68)
CCU	13 (39)	9 (22)
ED	5 (15)	2 (5)
Other	1 (3)	2 (5)
ICU	2 (6)	0 (0)
Admission cause, n (%)		
Cardiac	12 (36)	15 (37)
Pulmonary	8 (24)	10 (24)
Surgical	7 (21)	5 (12)
Infectious diseases	2 (6)	5 (12)
Other Internal Medicine	0 (0)	3 (7)
Other	4 (12)	3 (7)
Arrest cause, n (%)		
Cardiac	11 (33)	15 (37)
Hypoxic	13 (39)	5 (12)
Pulmonary Embolism	4 (12)	4 (10)
Hypovolaemic	1 (3)	6 (15)
Sepsis	0 (0)	3 (7)
Other	3 (9)	4 (10)
Unkown	1 (3)	4 (10)

CCU: Coronary Care Unit. ED: Emergency Department. ICU: Intensive Care Unit.

are similar from this viewpoint, at least for the first 20 min of ALS. These estimates are increasingly uncertain with time as the number of patients still receiving ALS declines rapidly.

A bivariate scatterplot of heart rate and QRS width is given in Fig. 4. The scatterplot shows considerable variation in the individual responses at the beginning, during, and at the end of ALS.

The arrows illustrate that the patients' ECG courses were fundamentally different depending on whether the patients obtained ROSC at the end of IHCA or not. Both the ROSC and non-ROSC groups started out with an average heart rate slightly below 60/min and an average QRS width of about 160–180 ms. Those who obtained ROSC moved towards an increased heart rate and a narrow QRS, while those without any response had no change in heart rate and the QRS width increased (MANOVA: $p < 0.001$).

Increasing heart rate increased the intensity of transitions from PEA to ROSC significantly during the first 18 min of ALS (Aalens additive model, $p < 0.01$). A graphical representation of this finding is provided as an e-supplement (e-figure 2 in Supplementary material). Reduced QRS complex width (not shown) had the same effect ($p < 0.01$) but entering both variables into the model did not improve fit substantially since they by nature are highly correlated (Pearson's $r = -0.41$, $p < 0.01$).

Discussion

This study is, to our knowledge, the first to describe the development of ECG characteristics during ALS in in-hospital cardiac arrest with pulseless electrical activity as the initial rhythm.

Our main finding is that changes in ECG characteristics during ALS are strongly associated with the probability of ROSC. We observed increasing heart rate and narrowing of the QRS complexes during ALS among those with ROSC, with an accelerated change towards ROSC. In particular, an increase in heart rate was observed in the last 3–6 min before ROSC appeared. Different perspectives consistently indicate that the ROSC group developed increased heart rates and decreased QRS widths during ALS compared to the patients without response.

We have modelled the development of heart rate and QRS with for the last 12 min of ALS efforts. This ensures that data from all patients contribute to the model, and that the precision of the estimates improves close to the event of interest. The bivariate plot disregards the time dimension, but clearly shows the joint development of heart rate and QRS from start to end of ALS. Finally, the continuing "loss" of patients under observation over the course of ALS requires a proper way to handle time-varying covariates and censoring; here Aalen's additive

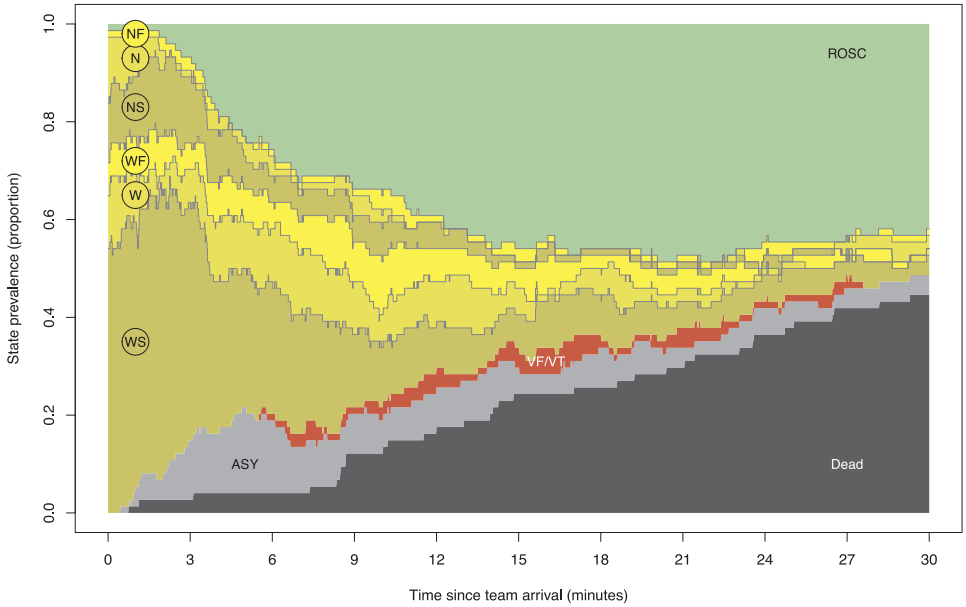

Fig. 2. Prevalence plot of the different states during ALS (From top to bottom: Green: ROSC. Yellow: PEA, NF: Narrow-Fast, N: Narrow, NS: Narrow-Slow, WF: Wide-Fast, W: Wide, WS: Wide-Slow. Red: VF/VT, Light Grey: Asystole, Dark-Grey: Dead).

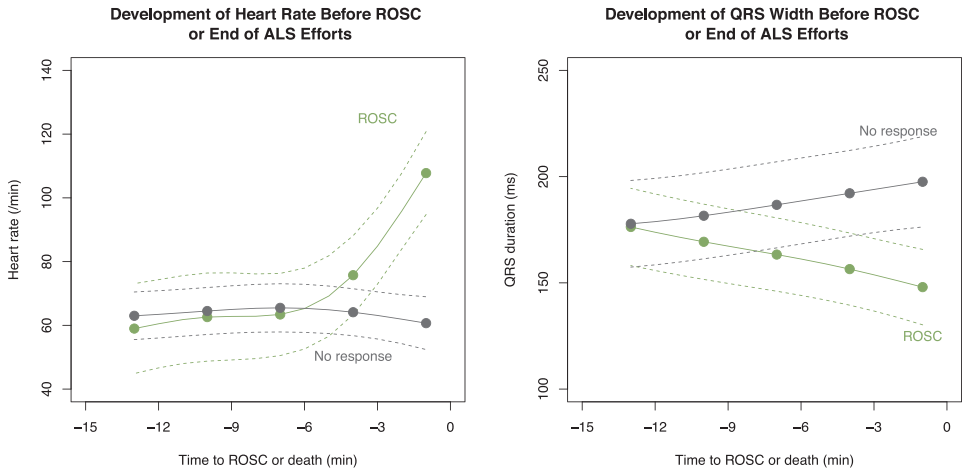

Fig. 3. Development of heart rate (left) and QRS width (right) for the last 12 min of ALS, i.e the last 12 min before sustained ROSC (green) or before ALS efforts were stopped (grey), according to the additive mixed effects model. Dots are placed every three minutes. Dashed lines: 95% confidence intervals. (ms: milliseconds. min: minutes. ROSC: return of spontaneous circulation"). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

regression model is suitable.

Changes in heart rate and QRS width are negatively correlated in general, but the development was different both regarding magnitude and time. This suggests that the development in one variable does not fully explain the change in the other, and may yield food for thought. Several studies have highlighted the fact that IHCA results from a combination of acute illness, underlying comorbidities, and gradual clinical deterioration over time [20–23]. Metabolic derangement of the myocardium may lead to changes in substrate availability and affect ionic concentrations and currents. This may cause slower pacemaker activity, reduced conduction velocity and delayed myocardial depolarization, leading to slower heart rates and wider QRS complexes

Fig. 4. Bivariate Plot of Heart rate vs QRS width. The arrows are vectors from beginning to end for the ROSC (green) and no-ROSC groups (grey). The green ellipses represent the 50, 75 and 90% coverage areas for the ROSC-group end estimate. For visualization, we assigned instances of VT/VF a heart rate of 320/minute and a QRS width of 50 milliseconds; and instances of asystole were assigned a heart rate of 10/minute and a QRS width of 400milliseconds. (ms: milliseconds, min: minutes.). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

[24,25]. The mechanism is not well known, but tissue acidosis and increased potassium concentrations may be part of the common pathophysiologic pathways in patients with PEA [26,27]. The baseline values in this study were slow heart rates and wide QRS complexes. The change in the ROSC group towards higher heart rates and narrower QRS complexes represent a move towards more normal values, perhaps because ALS efforts at least partially restored normal physiology in the heart. The different pattern of change in heart rate and QRS width suggest that the mechanisms underlying each variable may differ somewhat, and the potential clinical utility may also be different. It is possible that the QRS width narrows slightly before heart rate rises as the myocardial condition improves, and that this change is actually a prerequisite for heart rate increase and ROSC.

The goal of this study was first and foremost to describe the general development of heart rate and QRS width during ALS, thus clinical application of the results to any individual patient may be premature. With this caveat in mind, it does seem that patients with gradual narrowing of QRS complex width during ALS has a better chance of achieving ROSC, while sudden increases in heart rate may indicate that ROSC is about to occur. The predictive value of these variables with respect to ROSC development in the individual may possibly be analysed further via Bayesian methods.

In the setting of ongoing ALS, the heart rate is more easily monitored than the QRS width. In this study, almost all transitions to ROSC had occurred by about 20 min of ALS, but a few patients attained ROSC later than that. After 20 min an increase in heart rate may be seen as a positive prognostic factor, prompting continued efforts, rather than abandoning ALS efforts, especially if the QRS width has narrowed from the outset.

In three OHCA studies examining PEA characteristics, of which one was published more than 25 years ago and two more recently, similar initial heart rates but narrower initial QRS widths were found when compared to the results in our study [10–13]. None of these studies have examined the dynamics of the ECG-characteristics during ongoing ALS. The proportion of initial PEA in OHCA is usually lower than found in our and other in-hospital studies, while the proportion of asystole is usually higher. This is perhaps to be expected due to the natural increasing transition from PEA (and VF/VT) to asystole with time [8,28,29].

Limitations

This is a single-centre study with relatively few PEA episodes, potentially limiting the generalizability of our results. The demographics are nevertheless similar to a large IHCA study from the United Kingdom [30].

Some uncertainty applies to the measurement of QRS width, both due to the lack of an existing uniform definition of QRS interval endpoint, and due to a sometimes- aberrant appearance of ECG complexes found in this study. To address this uncertainty, a consistent approach to assess ECG complexes was applied to all electrocardiograms, and an experienced electro-cardiologist (JPL) was consulted in difficult cases.

Conclusion

Changes in ECG characteristics during ALS in cardiac arrest with pulseless electrical activity was related to prognosis. A move towards more normal ECG characteristics with increased heart rate and narrowing of the QRS during ALS efforts was found to be more prevalent in patients obtaining ROSC compared to patients who were declared dead at end of resuscitation efforts. A significant increase in heart rate was observed in the last 3–6 min before ROSC appeared.

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Conflict of interest statement

Gunnar Waage Skjeflo, Trond Nordseth, Jan Pål Loennechen, Daniel Bergum and Eirik Skogvoll all declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.resuscitation.2018.03.039.

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Clinical paper

The effect of intravenous adrenaline on electrocardiographic changes during resuscitation in patients with initial pulseless electrical activity in out of hospital cardiac arrest

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Abstract

Introduction: Presence of electrocardiographic rhythm in the absence of palpable pulses defines pulseless electrical activity (PEA) and the electrocardiogram (ECG) may provide a source of information during resuscitation. The aim of this study was to examine the development of ECG characteristics during advanced life support (ALS) from Out-of-hospital cardiac arrest (OHCA) with initial PEA, and to explore the potential effects of adrenaline on these characteristics.

Methods: Patients with OHCA and initial PEA, part of randomized controlled trial of ALS with or without intravenous access and medications, were included. A total of 4840 combined observations of QRS complex rate (heart rate) and width were made by examining defibrillator recordings from 170 episodes of cardiac arrest.

Results: We found Increased heart rate (47 beats per minute) and reduced QRS complex width (62 ms) during ALS in patients who obtained return of spontaneous circulation (ROSC); while patients who received adrenaline but died increased their heart rate (22 beats per minute) without any concomitant decrease in QRS complex width.

Conclusion: ECG changes during ALS in cardiac arrest were associated with prognosis, and the administration of adrenaline impacted on these changes.

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Introduction

Pulseless electrical activity (PEA), defined as an organized electrocardiographic rhythm in the absence of palpable pulses, is the presenting rhythm in about one quarter of patients with out of hospital cardiac arrest (OHCA).[1-4] The electrocardiogram (ECG) reflects the electric function of the myocardium.[5] Changes in the ECG may represent a source of information during the provision of advanced life support (ALS) to such patients.

In an observational study of in-hospital cardiac arrest (IHCA), we found an increase in PEA heart rate and a gradual narrowing of the QRS width the last 6-12 minutes (min) before return of spontaneous circulation (ROSC).[6] These findings may have prognostic importance, as well as raising questions about the electromechanical properties of the heart during PEA.

Administration of adrenaline (epinephrine) has been shown to increase the proportion of patients who achieve ROSC without increasing long term survival.[4,7,8] In one recent randomized controlled trial of adrenaline versus placebo in OHCA a larger proportion with ROSC was found in the adrenaline group, but long term survival was also higher in the adrenaline group.[9] Some authors have argued that adrenaline to patients with non-shockable rhythms (asystole and PEA) is as essential as defibrillation to shockable rhythms (ventricular fibrillation —VF and pulseless ventricular tachycardia —VT).[10,11] In cardiac arrest the presumed main effect of adrenaline is to improve coronary perfusion pressure by increasing aortic diastolic pressure.[12] A general effect of adrenaline is an increase in heart rate.[13] Despite being a routine drug in cardiac arrest, the immediate effect of adrenaline on ECG characteristics during ALS has not been studied. We hypothesized that possible beneficial effects of adrenaline could be associated with change in heart rate. The aim of this study was to investigate the development of ECG characteristics during ALS in patients with OHCA and initial PEA, and the effect of adrenaline on these characteristics.

Material and methods

Data collection and handling

A randomized controlled trial was conducted at the Oslo Emergency Medicine Services between 2003 and 2008 in adult OHCA patients. Patients were randomized to ALS with and without intravenous access and drug administration. Main outcomes were ROSC and survival to hospital discharge.[4,14] Patients from this study with initial PEA were included in the current sub-group analysis. Electronic signal data from Lifepak 12 defibrillators (LP 12, Physio Control, Medtronic, Redmond, WA, USA), clinical data from Utstein style cardiac arrest forms and data from hospital records acquired for the original study were analysed.[4]

Electrocardiographic characteristics

ECG and transthoracic impedance (TTI) data from LP 12 were analysed using Matlab (R2017b, Math Works Inc., Natick, MA), and annotated in terms of clinical states (Asystole, PEA, VF/VT, ROSC) as described in a previous publication.[15]

The ECG and TTI signals were plotted against time, QRS-rates (heart rate) and -widths were measured during pauses in chest compressions for any reason (including at end of efforts or when sustained ROSC was obtained), as long as measurable QRS complexes existed. The QRS width was defined as the interval between the initial deflection from the baseline towards the Q- or R-wave and the beginning of the ST-interval on the ECG. In cases when no obvious transition from the QRS to the ST-interval could be seen, the point where the ECG tracing crossed the baseline towards the T-wave was considered the QRS end-point, as described previously.[6] Each QRS width measurement was coupled to an instantaneous heart rate, calculated from the distance between the QRS complex in question and the succeeding QRS complex.

Statistical analysis

Patients were grouped by ROSC status, the ROSC group comprising all patients with ROSC at hospital admission; and by whether intravenous adrenaline was actually given. We disregarded the intention-to-treat status in the original study, as the biological effect of adrenaline was of main interest in this subgroup analysis.

We expected that heart rate and QRS width would be correlated; this was tested using Pearson's product moment correlation.

First, we investigated the combined change in heart rate and QRS width using bivariate analysis of variance (MANOVA)[16] according to ROSC and adrenaline. Here we employed the first and last 15 s averaged heart rate and QRS width in each patient. To satisfy the requirement of bivariate normality and homoscedasticity, we applied a square root transformation after adding a constant term to avoid negative values. Q–Q plots were satisfactory.

Second, we modelled the 15-s final averaged heart rate and QRS width separately using a linear model[17] using the initial 15-s heart rate or QRS width as continuous covariates, and ROSC and adrenaline as factors.

Third, to visualize the average development of the ECG characteristics for the last 12 min preceding ROSC or termination of ALS efforts, we fitted additive mixed effects models[18] of heart rate and QRS width in each group; with time as the fixed effect covariate, and patient identity as random effect. We specified autocorrelated residuals (which improved model fit) as we expected that measurements closer to each other in time would be more similar than measures further apart. The additive mixed models fit penalized regression splines to the data, by a process of cross validation.[18]

All measurements of heart rate and QRS that were made at or later than 12 min before ROSC or end of ALS were included in this model, irrespective of timing. No attempts were made to balance data with respect to number of or timing of measurements between patients.

The software R version 3.4.3,[19] running in RStudio version 1.1.419, with the packages mcgv, nlme and ellipse, and the software Stata,[20] were utilized for the statistical analyses. A p-value less than 0.05 was considered to indicate statistical significance.

Ethics

The Regional Committees for Medical and Health Research Ethics approved the study. The original study was registered at clinical-trials.gov with identifier NCT00121524.

Results

Two-hundred and thirty-three patients had initial PEA in the original study, of whom 170 patients (73%) were included in the current analysis. Patients

were excluded due to missing defibrillator file (n = 59) or that defibrillator files were illegible (n = 4). ROSC at admission to hospital was present in 41 patients (24%) and adrenaline was administered to 101 (59%) of the included patients. A total of 4840 combined observations of QRS rate and width were made from the defibrillator files from the included patients. Demographic and clinical data are presented in Table 1. The groups varied in size: the 'no ROSC' groups were larger. Otherwise, there was a notable difference in duration of ALS between the 'no adrenaline ROSC' group and all other groups, with shorter duration of ALS in this group. The 'no adrenaline ROSC' group also consisted of all but one male.

Changes in heart rate and QRS complex width from start to end of ALS

Heart rate and QRS width were found to be negatively correlated (Pearson's r: −0.35, $p < 0.0001$). Bivariate analysis of the combined change of heart rate and QRS width from the beginning to the end of ALS showed that these variables were significantly associated with both whether ROSC was obtained and whether adrenaline was administered ($p < 0.001$ for both). There was no evidence of interaction between ROSC and adrenaline status ($p = 0.86$). Univariate analysis of mean final heart rate or QRS width separately showed that the final mean heart rate was dependent on the mean initial heart rate (coefficient 0.28, $p = 0.01$), ROSC (46.6 bpm increase with ROSC, $p < 0.0001$), and adrenaline (21.7 bpm increase with adrenaline, $p < 0.0001$). Final mean QRS width depended on mean initial QRS width (coefficient 0.45, $p < 0.0001$) and ROSC (62 ms less with ROSC, $p < 0.0001$), but not adrenaline ($p = 0.4$). There was no evidence of interaction between ROSC and adrenaline status in the univariate analyses ($p = 0.8$ and 0.72 for heart rate and QRS width respectively).

The observed mean changes in heart rates and QRS widths are illustrated as arrows in Fig. 1. The individual measurements of QRS widths and heart rates at the beginning, during, and at the end of ALS are presented as bivariate scatterplots in Fig. 1; there was considerable variation in these measurements.

Time course of heart rate and QRS complex width during the last 12 min of ALS

The expected heart rate and QRS width during the last 12 min of ALS before ROSC or end of ALS efforts are presented in Fig. 2, based on predictions from the additive mixed models. In both the 'adrenaline' and the 'no adrenaline ROSC' groups, a marked rise in heart rate occurred between 3–6 min before ROSC. Heart rate increased slightly in a linear fashion in the 'adrenaline no ROSC' group, but was unchanged towards the end of ALS efforts in the 'no adrenaline no ROSC' group. We observed a sharp decrease in QRS width the last 6 min in the 'adrenaline ROSC' group. In the 'no adrenaline ROSC' group a more gradual narrowing of QRS widths occurred during the last 12 min of ALS. In both no-ROSC groups QRS width increased slightly.

Discussion

To our knowledge, this is the first study to examine changes in ECG characteristics during ALS in patients with OHCA and initial PEA for the duration of ALS. It is a secondary analysis of a randomized controlled trial of

Table 1 – Demographic and clinical data, stratified on ROSC and adrenaline status. (n = number, yrs: years, min: minute, IQ range: Interquartile range, mg: milligram).

	Return of spontaneous circulation (n = 41)		No return of spontaneous circulation (n = 129)	
	Adrenaline (n = 29)	No adrenaline (n = 12)	Adrenaline (n = 72)	No adrenaline (n = 57)
Age (yrs), median (IQ range)	61 (56-75)	65 (62-75)	78 (56-83)	77 (65-85)
Males, n (%)	15 (52)	11 (92)	47 (36)	34 (60)
Location				
Home, n (%)	20 (69)	5 (42)	41 (57)	41 (72)
Public, n (%)	5 (17)	5 (42)	20 (28)	11 (21)
Work, n (%)	0 (0)	1 (8)	1 (1)	0 (0)
Other, n (%)	4 (14)	1 (8)	10 (14)	5 (9)
Witnessed by layperson, n (%)	19 (66)	8 (67)	31 (43)	38 (67)
Witnessed by paramedic, n (%)	6 (21)	1 (8)	28 (38)	6 (11)
Bystander CPR, n (%)	12 (41)	3 (25)	26 (36)	27 (47)
Response time (min), median (IQ range)	7.9 (5.3-9.0)	10.6 (6.3-11.4)	6.1 (0-8.7)	9.6 (6.6-11.3)
Duration of ALS (min), median (IQ range)	20 (12.5-28.1)	6.7 (5.2-11.5)	26.5 (19.1-31.9)	21.4 (14.4-28.9)
Compression rate (/min), median (IQ range)	117 (112-120)	115 (112-126)	119 (112-126)	112 (107-120)
Hands off ratio, median (IQ range)	0.15 (0.1-0.26)	0.18 (0.12-0.28)	0.17 (0.12-0.25)	0.20 (0.13-0.29)
Defibrillation at least once, n (%)	4 (14)	0 (0)	24 (33)	7 (12)
Intubated, n (%)	27 (93)	9 (75)	62 (86)	45 (79)
Intravenous access, n (%)	29 (100)	8 (67)	71 (99)	7 (12)
Adrenaline dose (mg), median (IQ range)	2 (1-3)	0 (0)	3 (2-5)	0 (0)
Atropine, n (%)	8 (28)	0 (0)	35 (49)	2 (4)
Amiodarone, n (%)	0 (0)	1 (8)	9 (13)	0 (0)
Admitted to hospital, n (%)	29 (100)	12 (100)	22 (30)	11 (19)
Discharged from hospital alive, n (%)	1 (3)	3 (25)	0 (0)	1 (2)[a]

Missing data: witnessed (n = 1), age (n = 1), adrenaline dose (n = 19), duration of ALS (n = 1), IV access (n = 1).
[a] One patient without pre-hospital ROSC but admitted to hospital under ALS survived to hospital discharge.

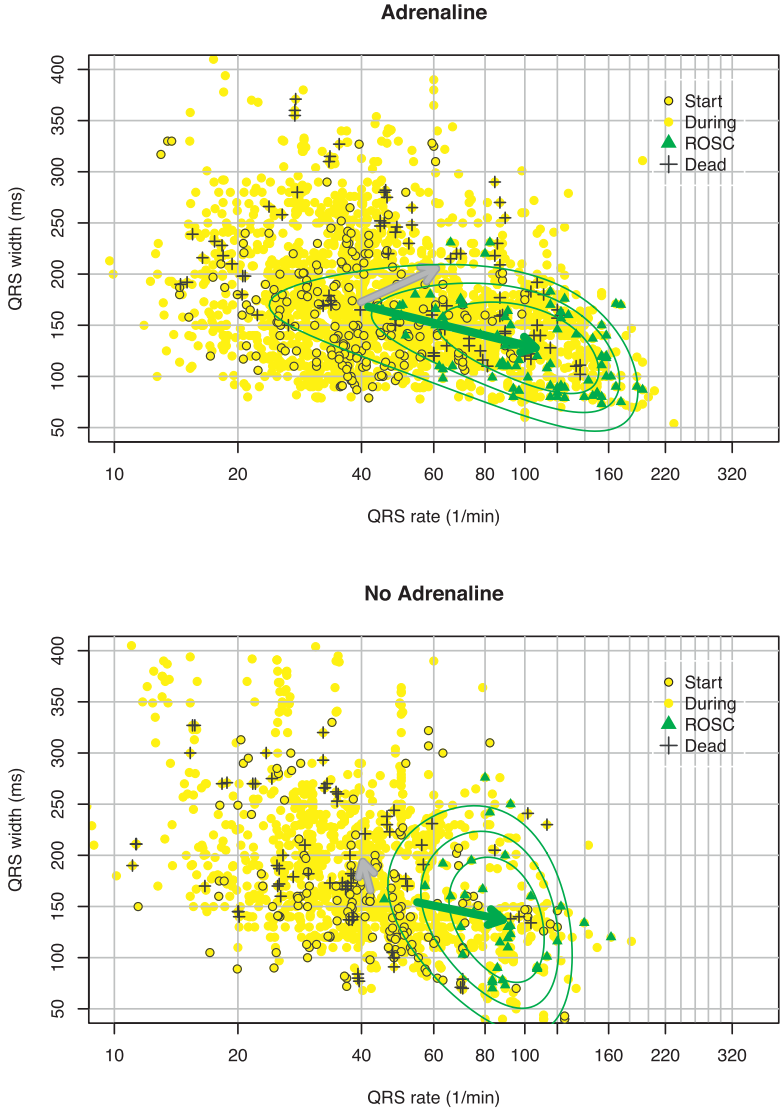

Fig. 1 – Bivariate Plot of Heart rate and QRS width, ms: milliseconds, min: minutes. The heart rate axis was log transformed for visualization purposes.
Top figure: adrenaline group, lower figure no-adrenaline group.
The circles, dots and plus signs represent individual measurements of heart rate and QRS width at the beginning, during and at the end of ALS. These are not grouped by either patient or ROSC status, but illustrate the variability in the individual measurements.
The arrows represent mean change from start of ALS (base of arrow) to end of ALS (tip of arrow). Green arrows represent the ROSC groups, grey arrows represent the no ROSC groups.
The green ellipses represent the 50, 75 and 90% coverage areas for the ROSC-groups' end points.

intravenous access versus no intravenous access in ALS, where adrenaline was only administered to the intravenous access group.

We discovered that patients who obtained ROSC had increased heart rates and decreased QRS widths before ROSC, in contrast to patients who were declared dead on scene. Patients given adrenaline had a larger mean change in heart rate, but a similar change in QRS width compared to patients who did not get adrenaline, both in the ROSC and no ROSC groups.

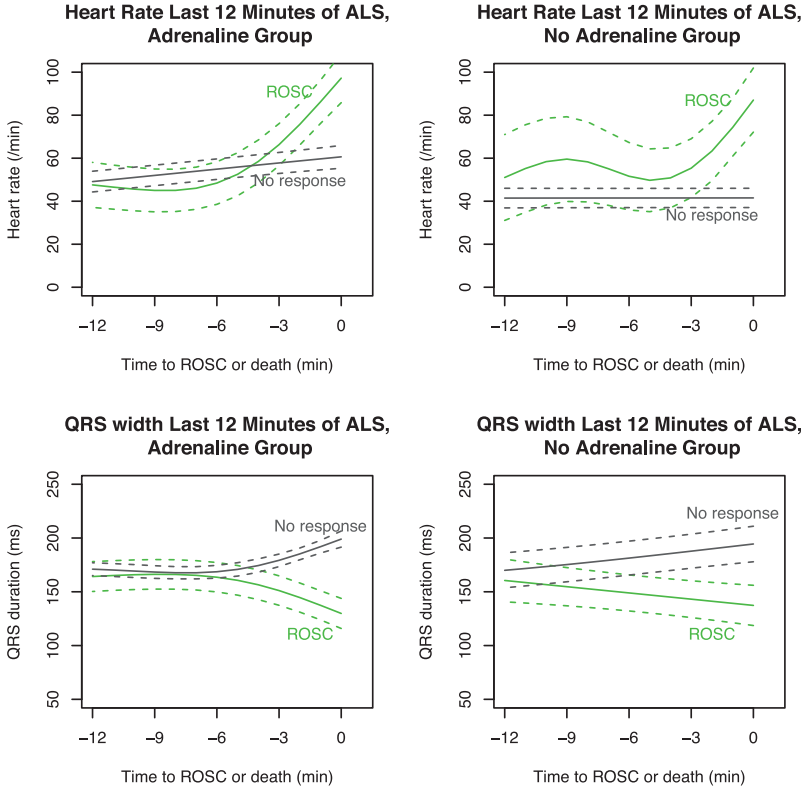

Fig. 2 – Development of heart rate (top) and QRS width (bottom) for the last 12 min of ALS, i.e. the last 12 min before sustained ROSC (green), or before ALS efforts were stopped (grey/ No response), according to the additive mixed effects model. The adrenaline group is at the left, the no-Adrenaline group is at the right. Dashed lines: 95% confidence intervals. (ms: milliseconds. min: minutes. ROSC: return of spontaneous circulation").

Overall, the pattern of increase in heart rate and narrowing of QRS width in the ROSC groups are consistent with the findings of our earlier study of in-hospital cardiac arrest with initial PEA.[6]

The increase in heart rate in the ROSC groups occurred mainly during the last 3–6 min before ROSC was obtained. In patients who received adrenaline, the QRS narrowed simultaneously with the increase in heart rate, while QRS width decreased more gradually in the 'no adrenaline ROSC' group. Interestingly, in patients who did not obtain ROSC; those who received adrenaline differed markedly from those who did not, in that heart rate increased in the adrenaline group while remaining unchanged in the no-adrenaline group.

The change of heart rate and QRS width in the ROSC groups in this study were changes towards more normal values. This is in line with other studies of OHCA that essentially have found a higher prevalence of normal initial ECG characteristics in survivors presenting with PEA.[21–23]

The mainly broad complexes without detectable atrial activity seen in this study were most likely of ventricular origin. Subendocardial Purkinje cells have been implicated in arrhythmogenesis after myocardial infarction, and has been observed to function as pacemakers in the damaged heart in dogs.[24] It has been shown that in ventricular Purkinje cells that survive acute ischemia, the resting membrane potential is less negative, with increased automaticity and prolonged action potentials.[25] Further, adrenaline has been shown to increase action potential generation in these cells, an effect that was abolished using a beta-blocking drug.[26]

Though heart rate and QRS width were inversely correlated in this study, the development over time differed. Both these variables depend on the electrical function of the heart, and are somewhat correlated in healthy humans as well, though the exact mechanisms are unclear.[27] Based on our results we speculate that the QRS width more closely reflects the underlying physiological state of the myocardium, but that the heart may be able to respond with increased heart rate to adrenaline even if the underlying metabolic state of the myocardium is not improved. This could theoretically explain the increase in heart rate and QRS width seen in the 'adrenaline no ROSC' group. The different pattern of QRS width narrowing in the ROSC groups may be due to a more sudden improvement in myocardial state in the 'adrenaline ROSC' group, perhaps, again theoretically, by a rapid adrenaline mediated increase in coronary perfusion pressure.

Based on the occurrence of ROSC in the adrenaline and no adrenaline groups, a larger number of survivors to hospital discharge in the adrenaline group would be expected. However, an increased proportion of patients with ROSC but a lesser or no increase in the proportion of survivors in the long term has repeatedly been shown in both observational studies and randomized clinical trials of adrenaline in ALS with undifferentiated initial rhythms.[7–9] This was also the main result of the study for which the

data analysed in the current study was gathered.[4] A number of factors may contribute to this, one of which is a possible detrimental effect of adrenaline on long term myocardial function. In animal models, beta-adrenergic stimulation of the heart during cardiopulmonary resuscitation (CPR) has been shown to increase oxygen consumption without improving oxygen supply.[28,29]

Adrenaline seems to increase the time window where it is possible to obtain ROSC.[15] The difference between the short duration of ALS in the 'no adrenaline ROSC' group and the longer duration of ALS in all other groups in the current study reflects this. It is possible that this increased time with low flow, or CPR dependent flow, results in irreparable damage to the brain and other organs in some patients.

The objective of this study was to explore the general development of heart rate and QRS-width during ALS in patients with PEA and the impact of adrenaline on these developments. But such overall trends cannot immediately be applied in decision making when providing care to individual patients. Caveat in mind, the clinical application of these findings may be to pay more attention to the development of heart rate and QRS width during ALS. Narrowing of QRS width and increase in heart rate is a possible marker of an overall positive clinical development that could motivate continuing ALS efforts. It is possible that absence of these changes could be utilized as feedback during ALS, prompting improvements in the ALS efforts or applying concurrent treatment modalities (e.g. fibrinolysis) to improve the myocardial state and thus increasing the probability of ROSC. An increase in QRS width seems to be a negative prognostic sign, even if heart rate increases after adrenaline administration. The time dependent effects of adrenaline could not be assessed in this study; thus, we do not know if QRS width or heart rate increased first in the adrenaline no ROSC group, or if the development of QRS width changed in any way after adrenaline administration. Any such pattern could have clinical impact and the temporal relation between adrenaline administration, heart rate increases and QRS width development is of great interest, and should be studied further.

Limitations

The number of patients included is relatively low and comprised only one pre-hospital emergency response system, potentially limiting generalizability. Whether or not a given patient present with PEA or asystole may depend on several circumstances and patients with initial asystole was not included in this analysis. Unfortunately, the exact time during ALS when adrenaline was administered is not known, as records could not be kept with enough detail in the EMS system. Thus, the immediate time dependent effects of adrenaline could not be examined. Demonstration of a time dependence between adrenaline administration and ECG changes would make the argument that the differences between the adrenaline and no adrenaline groups were due to adrenaline alone stronger.

Some uncertainty applies to the measurements of QRS widths, because of the sometimes aberrant morphology observed in the QRS complexes. A consistent approach to the measurement of QRS width as described in the methods section was utilized to reduce this uncertainty.

Conclusion

In patients with OHCA and initial PEA who obtained ROSC, heart rates increased and QRS widths decreased during ALS. In patients who did not have ROSC, heart rate decreased and QRS width increased, except in patients who did get adrenaline. In this group QRS width also increased, but heart rate increased.

Absence of decrease in QRS width during ALS may be a poor prognostic factor in OHCA with initial PEA.

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Conflict of interest

Gunnar Waage Skjeflo, Jan Pål Loennechen, Eirik Skogvoll, Theresea Mariero Olasveengen and Trond Nordseth declare no conflict of interest.

Lars Wik: NAKOS rep in MAB PhysioControl, Prinicpal investigator for CIRC, LUCAS2 AD study. Patent holder of patents licensed to ZOLL and PhysioControl.

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Title:

Changes in QRS Complex Width During Resuscitation Depend on Aetiology in Patients with Pulseless Electrical Activity

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Abstract

Introduction

Pulseless electrical activity is a frequent initial rhythm in in-hospital cardiac arrest. ECG changes during CPR have been linked to prognosis, specifically QRS complex narrowing and QRS-rate (heart rate) increase has been observed before return of spontaneous circulation. Our hypothesis was that ECG changes, and especially change in QRS complex width, could also be different depending on etiology of arrest.

Methods

Patients with cardiac arrest with initial PEA at St. Olav University Hospital (Trondheim, Norway) between January 2009 and January 2012 were prospectively included. QRS complex widths and heart rates were measured at all pauses in compressions. Etiologies were grouped in one 'Cardiac', and one 'Other' group. Change in QRS width and heart rate was analyzed together using bivariate analysis of variance. Trends in the material were inspected using additive mixed effects models for the last 18 minutes before ROSC or end of CPR and analyzed using linear mixed effects models based on these trends.

Results

A total of 63 patients were a reliable cause could be found were included in this study, 1844 combined observations of QRS width and heart rate were made. According to the additive mixed effects model the development in heart rate was similar in both etiology groups. The development of QRS width differed in patients who obtained ROSC, with the Cardiac group narrowing more than the other group, and both groups ending at essentially the same QRS widths at ROSC. In patients who did not obtain ROSC, the QRS width in the cardiac group was wider, but in both there was little change towards the end of resuscitation.

Conclusion

Development of QRS width during the last 18 minutes of ALS differed depending on etiology and whether ROSC was obtained, while development of heart rate depended only on whether ROSC was obtained.

Introduction

Pulseless electrical activity (PEA) is a frequent initial rhythm in in-hospital cardiac arrest (IHCA)(1–3). Reported survival is around 12% (1,3,4), and may improve by early recognition and treatment of the cause of arrest (5,6). Identification and treatment of the underlying causes of PEA during advanced life support (ALS) has been emphasised in the most recent version of the European Resuscitation Council (ERC) guidelines (7).

In two recent studies of in- and out-of-hospital cardiac arrest (IHCA/OHCA) with initial PEA, we discovered that the electrocardiographic characteristics (QRS complex width and rate), evolved differently during resuscitation in patients who were successfully resuscitated compared to those who were not. Specifically, the QRS width decreased and the QRS ("heart") rate increased before return of spontaneous circulation (ROSC) (8,9). In the out-of-hospital study, we found that the QRS complex narrowed in patients with ROSC, and widened in patients who did not obtain ROSC. Heart rate increased in the intravenous adrenaline (epinephrine) group, regardless of ROSC status (9). This led us to consider whether QRS width may be a more accurate marker of myocardial derangement than heart rate in the setting of cardiac arrest. We have previously not found any association between the initial ECG characteristics and the aetiology or mechanism behind PEA (10).

The aim of the current study was to examine the continuous development of ECG characteristics of PEA for the duration of resuscitation with regard to the underlying aetiology. We hypothesize that different PEA aetiology may give rise to different patterns of electrocardiographic development during resuscitation.

Materials and Methods

Adult patients (>18 years) with cardiac arrest treated by the emergency teams at St. Olav University Hospital (Trondheim, Norway) between January 2009 and January 2012 were prospectively included. Inclusion of patients and collection of data have been described in earlier publications (3,11). St. Olav University Hospital is a tertiary hospital in middle Norway with 755 somatic beds (2012), and an incidence of IHCA that has been estimated to 72 per 1000 beds per year, with an overall survival to hospital discharge of about 25% (3).

Electrocardiographic characteristics

ECG and impedance signal data were collected from Lifepak 20 / Lifepak 1000 defibrillators (Physio-Control, Redmond, USA) and Zoll M-series defibrillators (Zoll Corporation, Chelmsford, MA, USA). The data from the defibrillators were analysed using Matlab (R2014b, Math Works Inc, Natic, MA). Rhythms were annotated, and QRS widths and heart rates were measured during pauses in chest compressions. Measurements were also made when compressions were stopped due to ROSC or at termination of resuscitation, in the latter case if organized ECG activity was still present. The annotation of clinical state (PEA, VF/VT, Asystole, ROSC and death) over time has been described previously (11).

The method for measuring QRS complex widths has been described previously (8). Briefly the QRS width was defined as the interval between the start of the Q- or R-wave and the start of the ST-interval on the ECG. Heart rate was calculated from the distances between successive QRS complexes.

Aetiology of cardiac arrests

The aetiologies of cardiac arrests were determined by a team of anaesthesiologists, cardiologists and one pathologist, as described in an earlier publication (3). The condition that directly lead to the cardiac arrest was defined as the cause. Episodes with certain or probable aetiologies

were included. The different causes were then grouped into two main cause categories (cardiac or other, non-cardiac, aetiology) for the analyses in this study.

Statistical Analysis

We analysed the ECG development according to four strata (groups) defined by aetiology and short-term outcome: 'Cardiac aetiology ROSC', 'Cardiac aetiology no ROSC', 'Other aetiology ROSC' and 'Other aetiology no ROSC'.

Correlation between QRS width and heart rate was assessed using Pearson's product moment correlation.

The combined change in heart rate and QRS width was analysed using bivariate analysis of variance (MANOVA) (12), according to ROSC and aetiology. In this analysis, we averaged the first and last 15 seconds of heart rate and QRS width in each patient. To satisfy the requirement of bivariate normality and homoscedasticity, we applied a square root transformation of the QRS difference after adding a constant term to avoid negative values. We found the Q-Q plots to be satisfactory in order to meet these assumptions.

To visualize the development we fitted additive mixed effects models for each of the dependent variables QRS width and heart rate for the last 18 minutes of resuscitation before ROSC, or the end of efforts (13). From inspection of these plots and to get more interpretable parameter estimates, we fitted linear mixed effects models of QRS complex width and heart rate during the same period (14). For heart rate, we fitted linear splines with a knot placed at 6 minutes before ROSC or end of ALS based on the additive mixed model plots. To account for the repeated measures nature of the data, both the additive and linear mixed effects models were specified with patient specific random intercepts, and a continuous autoregressive correlation structure for the residuals.

The software R version 3.4.3 (15), running in RStudio version 1.1.419, with the packages *mcgv, nlme, lspline* and *gmodels*, was utilized for the statistical analyses. A p value < 0.05 was considered to indicate statistical significance.

Results

There were 114 eligible patients in the main study, of whom 63 patients were included in the current analysis. Reasons for exclusion were missing defibrillator files (n=28), lack of consent (n=5), illegible defibrillator signals (n=6), ROSC before recording started (n=1) and uncertain or unknown aetiology of arrest (n=11). Measurement of QRS width and heart rate resulted in a total of 1844 combined observations of these variables. Demographic and clinical data, stratified by aetiology group and whether ROSC was obtained or not, are presented in Table 1. The main aetiologies grouped in the 'other aetiology' group are also presented here.

Changes in heart rate and QRS complex width from start to end of ALS

Heart rate and QRS width were found to be negatively correlated (Pearson's r: -0,37, $p < 0.001$). Bivariate analysis of the combined change of heart rate and QRS width from the beginning to the end of ALS showed that change was significantly associated with whether ROSC was obtained ($p<0.001$), but not with aetiology ($p=0.8$). There was no evidence of interaction between ROSC and aetiology in this analysis ($p= 0.1$).

Time course of heart rate and QRS complex width during the last 18 minutes of ALS

Figure 1 shows the development of QRS width and heart rate with 95% confidence intervals during the last 18 minutes of resuscitation, as predicted from both the additive mixed effects models and with the predictions from the linear mixed effects models superimposed. In both groups with cardiac aetiology the average QRS width was wider compared to the other aetiology groups, when measured at 18 minutes before ROSC or end of ALS. The 'cardiac aetiology ROSC' group narrowed towards ROSC: Both ROSC groups had about the same mean QRS width of approximately 150 ms when ROSC was obtained. The 'cardiac aetiology no ROSC' group had wider QRS intervals compared to the 'other aetiology no ROSC' group

during the last 18 minutes of ALS, otherwise the development was similar. According to the additive mixed effects models there were trends in the development of QRS width in both the `cardiac aetiology ROSC´ group ($p<0.001$) and the `cardiac aetiology no ROSC´ group ($p<0.001$), but not in the `other aetiology ROSC´ group ($p=0.6$). In the `other aetiology No ROSC´ group some evidence for a trend ($p=0.04$) was found. As can be seen from Figure 1, the development in QRS width was very close to linear in all groups. The linear mixed effects model of QRS width during the last 18 minutes of ALS underscore the findings in the additive mixed effects model: QRS width development depended significantly on ROSC status ($p= 0.02$) and aetiology group ($p < 0.01$).

The development of heart rate was essentially similar with respect to aetiology: In both ROSC groups heart rate increased rapidly during the last 6 to 3 minutes before ROSC, while heart rate was unchanged for the last 18 minutes of ALS in the no ROSC groups. The additive mixed models show a trend in both ROSC groups (both p's <0.001), but not in either of the no ROSC groups (smallest p value= 0.2). By the linear mixed effects models with linear splines, development of heart rate depended on ROSC status ($p <0.001$), but not on aetiology group ($p=0.3$).

Discussion

The main finding in this study was that the average QRS complex width developed differently according to aetiology during the last 18 minutes of CPR.

With cardiac aetiology, a wide QRS complex narrowed towards ROSC and ended at the same values as patients with other aetiology, whose QRS complex widths essentially remained unchanged during the course of CPR. Average heart rate development, however, was similar according to aetiology but different with respect to short-term outcome.

We have earlier shown both in- (8) and out-of-hospital (9), that QRS complexes narrowed towards ROSC, and that heart rate increased rapidly between 10 and 5 minutes prior to ROSC. The current study, which show separate courses of QRS complex width and heart rate during CPR, suggests different pathophysiological backgrounds for these changes according to aetiology. We have previously hypothesized that QRS width is a more sensitive marker of the myocardial physiological state than heart rate (9). Even though there was no difference between the initial QRS widths and heart rates depending on the aetiology of arrest, we found the development over time during ALS to be different. Myocardial ischemia decreases conduction velocity which may produce prolonged QRS complexes in the ECG, as has been observed clinically and experimentally (16,17). Increased QRS width has been linked to risk of sudden cardiac death in adults with cardiovascular disease (18), and in other studies of sudden cardiac death (19–21). Attin and co-worker`s found increased QRS width within the last hour before IHCA in patients with cardiac disease. The authors also found deceleration of heart rate the last 15 minutes before arrest, and changes in QRS morphology occurring a median two hours before arrest (22). To be noticed, the pattern of change in mean heart rates during the last 15 minutes before arrest in Attin and co-worker`s study is opposite of the change seen in the ROSC groups in the current study (Figure 1). This suggest a reversal of the pathological mechanisms before ROSC. A possible mechanism behind the results of the present study may consequently be that

in PEA with cardiac aetiology the myocardium may be in a more deranged state at the time of arrest than in non-cardiac aetiologies, and may respond differently to ALS interventions. Although the current CPR guidelines to a lesser degree recommend different overall treatment strategies for cardiac and no-cardiac arrests, this may be a field for further research.

The lack of change in QRS width in the 'other aetiology ROSC' group may have several reasons. This is a heterogeneous group of aetiologies, but some patients may present with what has been dubbed 'pseudo electromechanical dissociation'. This has been defined as a condition in which the heart contracts, but produces an inadequate cardiac output (23). Recognized causes of include severe shock states and central pulmonary embolisms. Paradis and co-workers speculate that in PEA with cardiac contractions the myocardial function is less deranged than in PEA with cardiac stand-still (23).

From a clinical point of view, the changes in QRS width seen in the 'cardiac aetiology ROSC' group are changes towards more normal values and may represent effect of ALS. Observation of increase in heart rate and narrowing, or at least not increase in QRS width, may prove a positive prognostic sign during ALS.

Limitations and strengths

The single centre study design limits the generalizability of our results. Also, relatively few patients with initial PEA were included. The limited number of episodes necessitated merging of different aetiologies into two main groups, creating a heterogeneous mix of aetiologies in the 'other aetiology' group, which may obscure differences.

The duration of resuscitation varied between the groups and within the groups, and the timing of pauses in compressions makes sampling uneven and unbalanced. Utilizing the described statistical methods and modelling the change in ECG parameters towards ROSC/end of resuscitation efforts rather than from the beginning ensured that each patient contributed as much information as possible, and that estimates increased in precision towards the end point. It also left the time scale unaltered, which eased interpretation. The bivariate analysis of change in QRS/heart rate from the beginning to the end of ALS using only the average QRS widths and heart rates from the first and last 15 seconds of ALS did not show any significant association between aetiology and the change in these ECG characteristics. The association between ROSC status and change in QRS width and heart rate has been shown in an earlier publication (8). The discrepancy between the results of the bivariate analysis and the additive mixed models and linear mixed effects models (for QRS width) may be entirely due to the different materials analysed. The additive mixed models and linear mixed effects models incorporate more information than what is possible in a bivariate analysis. Finally, some uncertainty applies to the measurement of QRS width, both due to the lack of an existing uniform definition of QRS interval end-point, and due to a sometimes-aberrant appearance of ECG complexes found in some patients. To address this uncertainty, a consistent approach to assess ECG complexes was applied to all electrocardiograms, and an experienced electro-cardiologist (author JPL) was consulted in difficult cases.

Conclusion

The development of QRS width during the last 18 minutes of resuscitation in patients with initial PEA differed depending on the aetiology of cardiac arrest and whether ROSC was obtained, while the development of heart rate depended only on whether ROSC was obtained. PEA with a cardiac aetiology had wider QRS complexes during ALS in this study, but this narrowed during the last 18 minutes of ALS in the group of patients who obtained ROSC.

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Legend to Figure and Table:

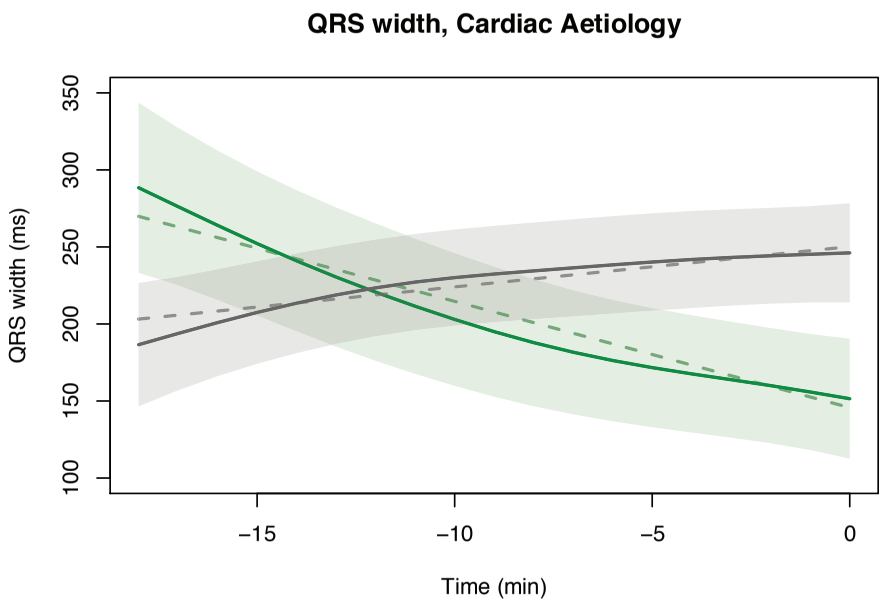
Table 1:

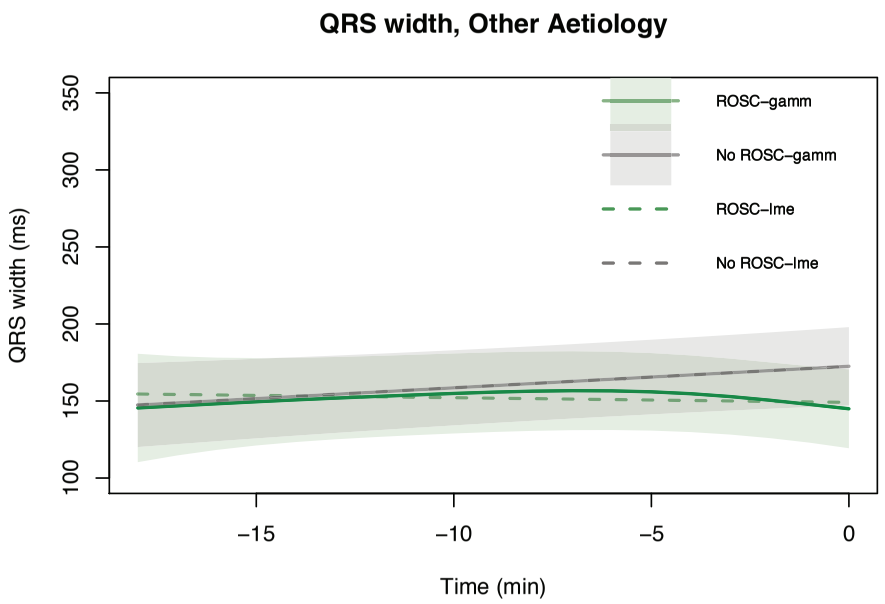
Demographic and Clinical Data by aetiology group. (IQ-range: interquartile range, min: minutes).

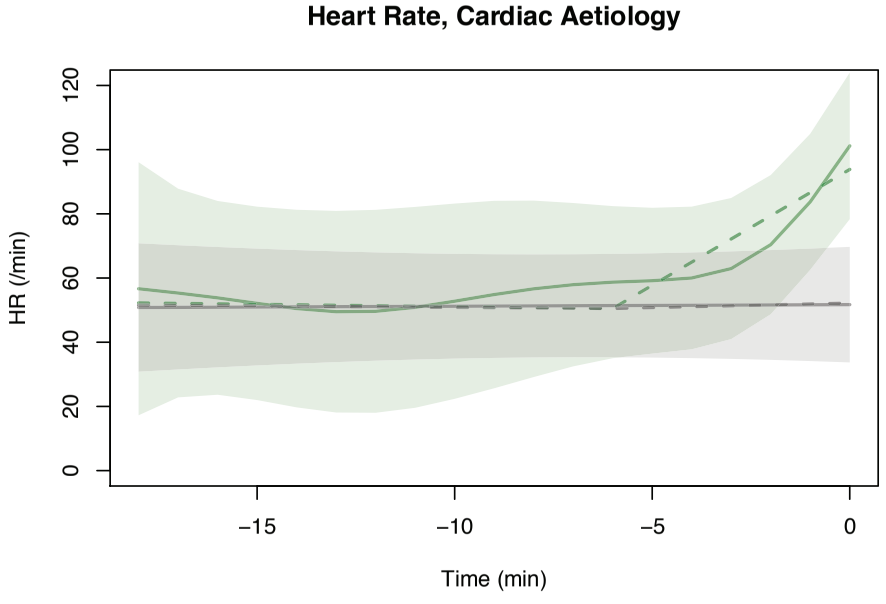
Figure 1:

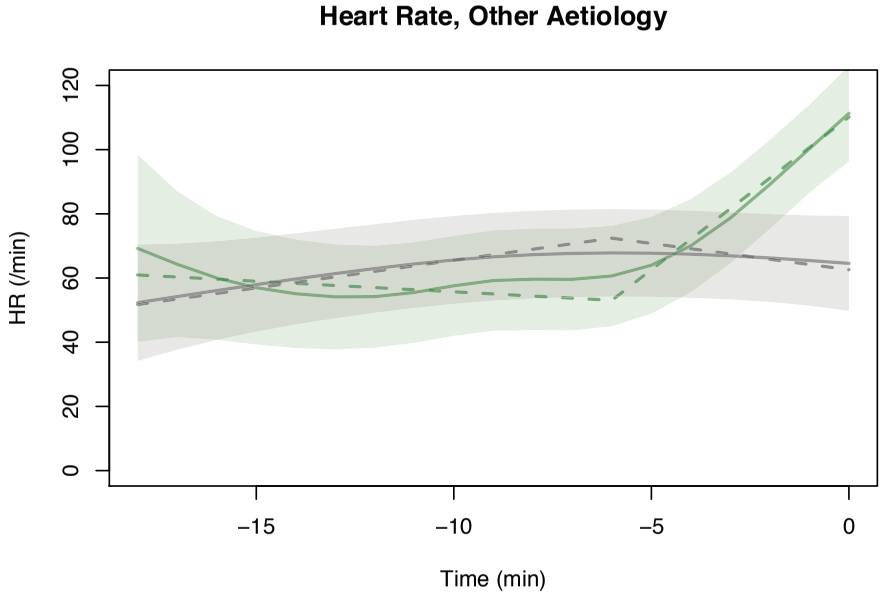
Development of QRS width and Heart rate during the last 18 minutes of ALS according to the additive mixed effects models (solid lines) with 95% confidence interval (shaded) and the predictions by the linear mixed effects models superimposed (dashed lines). (ms: milliseconds, min: minutes, /min: per minute, gamm: (generalized) additive mixed effects model, lme: linear mixed effects model, ROSC- Return of Spontaneous Circulation.)

	Cardiac Aetiology (n=24)		**Other Aetiology** (n=39)	
	ROSC (n=9)	No-ROSC (n=15)	ROSC (n=20)	No-ROSC (n=19)
Male sex, n (%)	7 (77)	8 (53)	15 (75)	9 (47)
Age, median (IQ-range)	64 (63-80)	78 (65-86)	65 (57-74)	75 (67-81)
Duration of ALS (min), median (IQ-range)	5 (3-26)	9 (2-16)	6 (2-12)	7 (2-14)
Location of arrest, n (%)				
Ward	2 (22)	10 (67)	8 (40)	12 (63)
Coronary Care Unit	3 (33)	4 (27)	8 (40)	5 (26)
Emergency department	2 (22)	1 (7)	3 (15)	
Intensive care unit	1 (11)		1 (5)	
Other	1 (11)			2 (11)
Admission Cause, n (%)				
Cardiac	8 (89)	10 (67)	2 (10)	4 (21)
Pulmonary		1 (7)	7 (35)	6 (32)
Surgical	1 (11)	2 (13)	6 (30)	3 (16)
Infectious disease		1 (7)	2 (10)	2 (11)
Other internal medicine		1 (7)	1 (5)	1 (5)
Other			2 (10)	3 (16)
Arrest Cause, n(%)				
Cardiac	9 (100)	15 (100)		
Hypoxic			12 (60)	4 (21)
Pulmonary Embolism			4 (20)	4 (21)
Hypovolaemic			1 (5)	5 (26)
Sepsis			1 (5)	3 (16)
Other			2 (10)	3 (16)


QRS width, Cardiac Aetiology
QRS width (ms)
100
150
200
250
300
350
−15
−10
−5
0
Time (min)


QRS width, Other Aetiology
QRS width (ms)
100
150
200
250
300
350
−15
−10
−5
0
Time (min)
ROSC−gamm
No ROSC−gamm
ROSC−lme
No ROSC−lme


Heart Rate, Cardiac Aetiology
HR (/min)
0
20
40
60
80
100
120
−15
−10
−5
0
Time (min)


Heart Rate, Other Aetiology
HR (/min)
0
20
40
60
80
100
120
−15
−10
−5
0
Time (min)