Graduate thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Circulation and Medical Imaging

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The Effect of Adrenaline in In-Hospital Cardio-Pulmonary-Resuscitation

Graduate thesis in Medicine
Supervisor: Eirik Skogvoll
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Table of Contents

Abstract

Introduction

During cardiac arrest it is paramount to apply chest compressions and ventilations as quickly as possible to maintain a minimum of circulation and oxygenation. The patient may be in either ventricular fibrillation or tachycardia (VF/VT), pulseless electric activity (PEA) or asystole before either obtaining return of spontaneous circulation (ROSC) or being declared dead. Adrenaline has been a part of the advanced treatment of cardiac arrest for the past 70 years. However, there is still some uncertainty regarding what physiological effect adrenaline has during cardiac arrest and how this drug might contribute to ROSC. Previous prehospital research has shown an increase in QRS-rate after administration of adrenaline. In addition, one study found an increase in QRS frequency as well as a narrowing of QRS complexes in patients who later obtained ROSC. Based on these previous findings from our research group we hypothesised that administration of i.v. adrenaline during in-hospital cardiac arrest with PEA would result in an increase in heart rate (HR) and a shortening of the duration of the QRS-complex.

Materials and methods

We collected defibrillator files, information about timing of adrenaline, and supplementary clinical data from episodes of cardiac arrest at St. Olav University Hospital. Each defibrillator file provided a one lead ECG which was thoroughly assessed and annotated regarding the clinical state (PEA, asystole, and VF/VT). Every QRS-complex in patients with PEA was measured and the HR determined. The HR and QRS-duration were then plotted against time before and after administration of adrenalin.

Results

88 episodes where adrenaline was administrated were collected between 2018 and 2022. The presumed cause of arrest was cardiac in 39 of the episodes (44%), 61 (69%) of the patients were male and the average age was 72 years. In 40 episodes the patient was continuously monitored when the episode occurred. In 13 of the episodes (15 %) the patient survived to discharge.

We observed a significant increase in HR between 0 and 2 minutes (p=0.003) after administration of the first dose of adrenaline. There was a slight increase in HR before administration of the second dose. We observed an increase in the prevalence of ROSC from

about 5% at the time of administration of the first dose to about 20% 6 minutes after and a similar rise in ROSC prevalence after administration of the second and third dose as well. We observed a small increase in QRS-duration in the minutes before administration of the first dose

Conclusion

Adrenalin administrated during cardiac arrest with PEA in-hospital seems to result in an immediate increase in HR after the first dose as well as a noticeable rise in the prevalence of ROSC immediately after adrenaline was administrated after the first, second and third dose.

1 Introduction

The clinical definition of cardiac arrest utilised by both the European and Norwegian Resuscitation council is described as the cessation or abrupt reduction of cardiac output to levels insufficient for the perfusion of vital organs, and this is recognised as a patient who is unresponsive and not breathing properly (1, 2). When cardiac arrest occurs, it is paramount to immediately perform cardio-pulmonary-resuscitation (CPR) to maintain a minimum of oxygenation and circulation (1). Resuscitation attempts have been performed for a long time, stretching back to the first written description of mouth-to-mouth ventilations in the Bible. CPR in today's term with chest compressions and ventilations has been practised since the 1960s with the first official guidelines published in 1966 (3). Advanced life support (ALS) is performed by healthcare professionals and consists of CPR, defibrillation, advanced airway management and i.v. drugs including adrenaline. Adrenaline has been a part of the treatment of cardiac arrest for 70 years, with the first experimental use of adrenaline in cardiac arrest described in the 1960s with doses of 1mg by either intravenous or intracardiac administration (4, 5).

Patients in cardiac arrest receive different treatment based on the ECG obtained by the defibrillator. We differentiate between patients with shockable and patients with non-shockable rhythms. The shockable rhythms are ventricular fibrillation (VF) and ventricular tachycardia (VT), which can be terminated by a DC-shock from a defibrillator. External defibrillation was first described in 1956 and is a well-established and lifesaving treatment for these lethal arrhythmias (6). The non-shockable rhythms are pulseless electric activity (PEA) and asystole. PEA is defined by the European Resuscitation Council as cardiac arrest in the presence of electric activity (other than VT) that would normally be associated with a palpable pulse (1, 7). PEA is thus a clinical state and cannot be determined by the ECG alone. Asystole represents the absence of electric activity in the heart and corresponds to a flat line on the ECG. The treatment for asystole and PEA is CPR, airway management and administration of i.v. adrenaline (1, 2).

The goal of any resuscitation attempt is survival with good neurological outcome. Return of Spontaneous Circulation (ROSC) is prerequisite for this. In addition to sustained ROSC, ROSC can also occur for shorter periods of time during a resuscitation attempt between relapses back into cardiac arrest and is referred to as temporary ROSC. If ROSC is not obtained the patient

is eventually declared dead. This is often a team decision based on multiple factors and does not always correlate to specific biological events.

As mentioned, the treatment of the shockable rhythms is effective and well documented. However, we have far less knowledge on the treatment of non-shockable rhythms with adrenaline. Animal models have shown that adrenaline increases the perfusion pressure in the coronary arteries which again increase the probability for ROSC (8). On the contrary, we also know that adrenaline increases the risk of lethal arrhythmias (8).

Several clinical trials have been performed to investigate what role adrenaline plays and should play in ALS. A randomised trial from Oslo studying adrenaline in out of hospital cardiac arrest (OHCA) showed that patients receiving adrenaline had a better chance to survive until hospital admission but showed no significant difference in long term survival. The patients in this study were randomised to either receive a peripheral venous catheter or not, and in that way randomising who could receive i.v. adrenaline and not (9). Nordseth et.al investigated the same data from the study in Oslo and found that adrenaline increased the window for obtaining ROSC (10). An Australian study showed similar results as the study in Oslo with improved likelihood of achieving ROSC but no improvement in survival to discharge (11). In 2018 we got the first doble blinded RCT looking at the effect of adrenaline vs placebo administrated in OHCA. The conclusion was that patients who received adrenaline had a higher 30-day survival, but when looking at neurological outcome after an equally long time there was no significant difference (12).

The studies referred to above provide interesting insights but are all based on prehospital data. A review of in-hospital cardiac arrest published in 2019 showed that prehospital timing of advanced life support drugs was approximately 20 minutes after the onset of cardiac arrest, and in-hospital 5-10 minutes (13). In addition, the average time to initial rhythm analysis in Denmark is two minutes in-hospital compared to ten minutes out of hospital (14). Donnino et.al found that adrenaline administrated in-hospital has the biggest impact on survival and neurological outcome when administrated early (15). These findings was strengthened when Khera et.al found that hospitals with long delay in adrenaline administration had a lower survival among cardiac arrest patients with non-shockable rhythms compared to hospitals with a short time to administration (16). In summary adrenaline seems to have the largest effect when administrated early, and time to adrenaline is much shorter in-hospital than out of

hospital. Thus, the knowledge on what effect adrenaline shows out of hospital is not directly applicable in an in-hospital settings which demand more research.

The randomized studies referred to above mainly consider hard endpoints like long term survival and neurological outcome. Skjeflo et.al studied the physiological effect of adrenaline on PEA by observing the relation between adrenaline and ECG-changes in OHCA-patients with PEA using heart rate (HR) and QRS-duration as bio markers. They found an increase in QRS frequency as well as a narrowing of the QRS complex in patients who obtained ROSC. They also showed that patients who received adrenaline had an increase in HR independent of whether they obtained ROSC or not (17, 18). Medical students Bakke and Borgen elaborated on these findings with a pilot study investigating the effect adrenalin had on 19 ECG-segments with PEA from 10 in-hospital patients. They observed an association between adrenaline and narrowing of the QRS complex and a less apparent gradual increase in HR (19).

To summarize there is much we still do not know about how effective adrenaline is in treatment of cardiac arrest. We know that it contributes to ROSC in an out-of-hospital setting, still it has not been investigated much physiologically in an in-hospital setting. Furthermore, it seems likely that the effect would be bigger in-hospital due to shorter time to administration. The mentioned findings of Skjeflo et.al and Bakke & Borgen et.al points at an association between increased HR and narrowing of the QRS-complex and ROSC both out of and in-hospital, where adrenaline may play a role. In other words, HR and QRS-duration may be used as biomarkers during CPR to give prognostic information regarding probabilities for ROSC.

The aim of this thesis is to investigate how adrenaline effects the ECG characteristics of frequency (“heart rate” - HR) and QRS duration in patients with pulseless electric activity.

2 Materials and methods

2.1 Data collection

The data was gathered prospectively at St. Olav university hospital in Trondheim between 2018 and 2022. The hospital has approximately 100 episodes of cardiac arrest each year. When cardiac arrest occur the hospital personnel will start CPR immediately and at the same time alert the emergency team which consist of personnel specially trained in ALS. All episodes where CPR is performed were screened for eligibility.

All patients in cardiac arrest at the hospital will be connected to a defibrillator which provides a one lead ECG, often corresponding to lead II in a standard ECG. There are LifePak1000 defibrillators (Medtronic, Dublin) located on numerous places and at each ward of the hospitals. These defibrillators are often attached to the patient immediately on the location of the cardiac arrest. The ALS-team will often switch to their own LifePak20 (Medtronic, Dublin) defibrillator up on arrival due to added functionality. After the event every defibrillator file from each episode is uploaded to a secure server and assessed by personnel at the hospitals research department. Our research group is notified about each episode so that we can start the process of gathering all relevant information. This includes reviewing the defibrillator files, record notes and talking with the personnel involved in the resuscitation attempt. The goal was to specify the times of adrenaline administration as exactly as possible, as well as other relevant info. In many cases a nurse from the hospital's emergency department is present to register the time of adrenaline administration directly on the defibrillator. In other cases, we had to rely on the memory of the present personnel to determine the timing of each dosage after the event.

2.2 Data handling

Defibrillator files from included episodes were processed in a custom-made graphical application in Matlab (R2022a, Math Works Inc., Natick, MA) developed by engineers at the University of the Basque Country in Bilbao. This allowed us to annotate each clinical state, as well as measure the duration of the QRS and mark periods of chest compressions as shown in fig 1. Periods of compressions was identified based on the impedance signal which is measured by the defibrillator and traces the trans-thoracic impedance to electrical current (20). The clinical states (VF/VT/asystole/PEA) were only annotated in compression pauses due to noise during compressions.

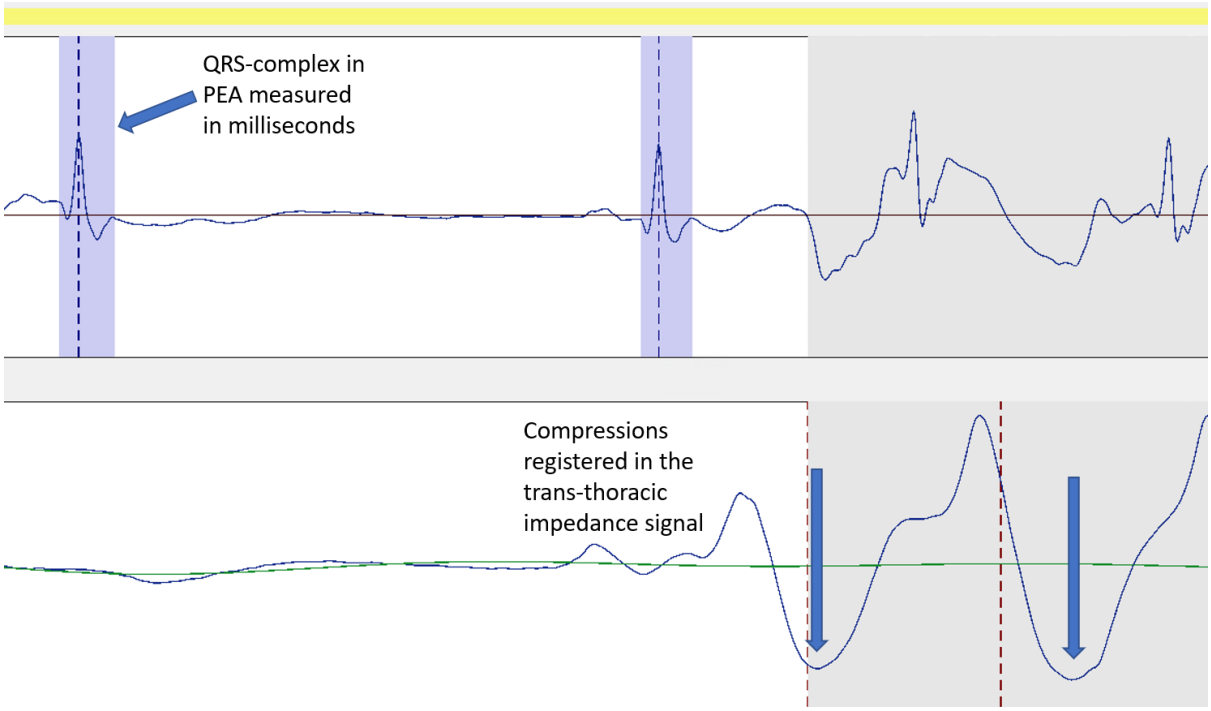

Figure 1 The ECG obtained by the defibrillator was assessed and annotated in a custom-made graphical application in Matlab. Each QRS in PEA was measured in milliseconds and chest compressions was detected by the trans-thoracic signal also obtained by the defibrillator. The distance between QRS-complexes gives the QRS-frequency (HR).

PEA was annotated when the ECG showed an organized electric activity with frequency >12 QRS/min in compression pauses lasting less than a minute. If the pause in compressions last longer than a minute and the patient had an organized rhythm, it was annotated as a period of temporary ROSC, reflecting bedside clinical management by the emergency personnel. Asystole was annotated if the ECG showed a flat line or QRS frequency <12/min. VF and VT was determined by its distinct morphology (21). At the end of each episode the patient was either declared dead or obtained sustained ROSC. Whether an episode ended in ROSC or death was based on information from the ALS-team and is not possible to determine based on the ECG alone.

We determined the duration of each QRS-complex in PEA by a combination of automatic and manual measurement of the distance in milliseconds from the first deflection from a quiet baseline to the beginning of the ST-interval on the ECG. The beginning of the ST-interval was set to the point where the rapid depolarization of the QRS ended, and the low frequency changes of the ST-interval (repolarization) began. In cases with no obvious transition the end of the QRS-complex was set to the point where the ECG crossed the baseline before the T-wave (18).

2.3 Statistical methods and modelling

After all episodes had been checked and approved, we proceeded to plot HR and QRS-duration for the whole material against time. There are several reasons for why the number of measurable QRS-complexes between episodes might vary. The most important is variations in HR, where patients with high HR in PEA will have more measurable QRS-complexes than episodes with a slow HR. In addition, the time spent during chest compressions affect how many QRS-complex that's available for analysis. We therefore calculated the mean HR and QRS-duration every 20 seconds to avoid overrepresentation of data rich episodes in comparison to episodes with fewer QRS-readings. Both HR and time spent during chest compressions could potentially be linked to outcome, which is important to bear in mind when we balance the episodes against each other by measuring average HR and QRS-duration instead of plotting each individual complex.

The mean values of HR and QRS-duration respectively was plotted as one measurement on a scatterplot to which we fitted a locally weighted regression (lowess: locally weighted scatterplot smoothing) to get an impression of the trend in relation to adrenalin. Lowess is a smoothening technique for calculating the moving average over time. The lowess-estimate at a point can be described by imagining a "box" centred at time t. The estimate is calculated by fitting a straight line to the data within the box using a robust regression technique which gives more weight to the observations closest to the centre of the box and down-weight potential outliers. The lowess-estimate at time t is thus the predicted value from the fitted regression line. The lowess-curve is then made by moving the imagined box from the first measurement to the last and repeating the same process every time with the box having a fixed width. The wider the box the smoother the resulting curve will be. The box width is set at a size to give the best trade-off between bias and prediction (22-25).

To identify any significant changes both before and after administration of adrenalin we applied a piecewise linear spline regression. A linear regression model is a parametric model in its simplest form and used to describe a trend in longitudinal data with the use of a single slope parameter representing a rate over time that is either increasing or decreasing. This curve can be extended by having a sequence of joined lines that together produce what is called a piecewise linear spline. The idea behind this is simply to divide the time axis into smaller segments and fitting a linear regression to each segment. Each segment is joined at fixed times to provide a continuous line. The points where the lines meet and are tied together are referred

to as knots. This allows for detection of decreasing or increasing means as time proceeds depending on the slope of the lines in the different segments (25).

The R-package ggplot2 was used to create Sankey plots to visualise how patients move between different states during CPR before either obtaining ROSC or being declared dead. Sankey plots are a type of flow diagram originally developed to visualise changes in networks over time. The plots consist of classes that are stacked without gaps for different categories in a process. The stacked sets at each category can be interpreted as a stacked bar plot. Weighted flows between categories form one class to another in the process are represented by ribbons. The width of the ribbon denotes the volume of flow (26). In our case the categories are different timepoints and the classes are different states during cardiac arrest at a specific timepoint (PEA, asystole, VF/VT). The ribbons show how patients flow between states from one timepoint to another.

3 Ethical considerations

The project is approved by the regional ethics committee (REK) with REK number 2019/785. The study is performed without consent from the included patients. However, surviving patients were informed of the inclusion and had the option to withdraw from the study. This is according to the Norwegian law on personal information §9, which states that personal information including health information can be handled without consent from the patient if the treatment is necessary for purposes related to scientific research. Furthermore, it is underlined that the public interest in that the treatment takes place clearly must outweigh the disadvantage for the individual patient.

It is important to emphasize that there were no experimental interventions in this project. The data is gathered from established and highly necessary treatment without interruption. Sensitive information on the study participants was strictly protected through procedures for data handling according to the privacy law and rules for management of sensitive data. Identifiable information is only stored on a secure server at St. Olav University hospital, and all data extracted are de-identified and transferred to a server with two factor authentication. On this stage it is not possible to connect episodes to individual patients.

Cardiac arrest is a significant burden for the person inflicted, next of kin and the community in general. It is a serious condition which result in costly rehabilitation and long treatment in intensive care units. It is therefore in the public and patients interest that thorough and representative research is performed on the field. All surviving patients included in the study receives an information letter three months after the event.

4 Results

272 episodes of cardiac arrest was collected at St. Olav University Hospital between 2018 and 2022, of which 25 was collected by the author (EU) of this thesis. Adrenalin was administrated in 122 of them. 34 episodes were excluded, and a total of 88 episodes was eventually included in the analysis. Figure 2 gives an overview of included and excluded episodes.

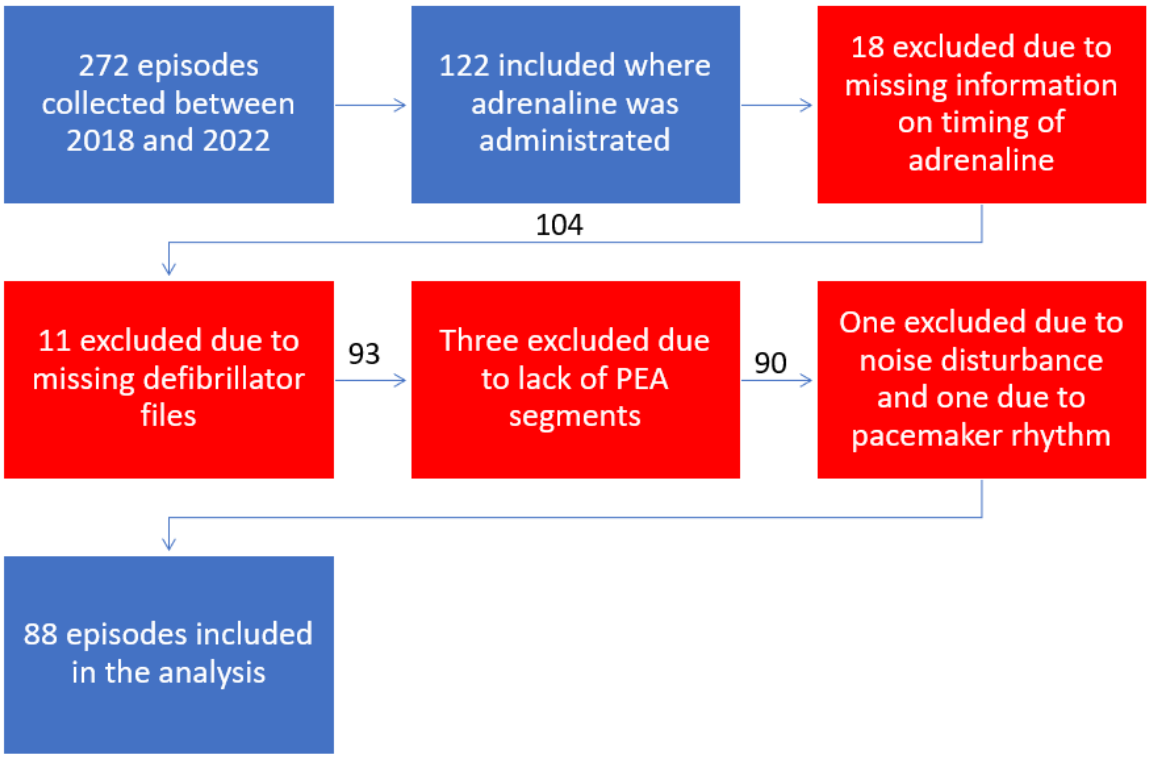

Figure 2 Overview of excluded and included episodes. 272 episodes was prospectively collected at St. Olav hospital in Trondheim between 2018 and 2022. Adrenaline was administrated in 122 of them. Among these 18 was excluded due to missing information on the timing of adrenaline. 11 was excluded due to missing defibrillator files, either from the ward or from the ALS-team. Three episodes was excluded due to a lack of PEA segments. One episode was excluded due to noise disturbances in the ECG-signal because of internal chest compressions during a thoracotomy and one was excluded due to pacemaker rhythm in PEA.

In 13 of the 88 episodes the patient survived until discharge, 61 of the patients were male and the average age was 72 years. The presumed cause of arrest was cardiac in 39 of the episodes (44%). The patient was continuously monitored in 40 of the episodes.

4.1 How the First Dose of Adrenaline Impacts HR and ROSC

Figure 3 plots heart rate (HR) in PEA before and after administration of the first dose of adrenaline at time zero. The left curve displays averaged HR every 20 sec of patients who receive adrenaline at time zero and display PEA with analysable QRS complexes at some point

during the 15min time interval (in total 72 patients). The right plot displays averaged HR for every 20 sec for patients who receive adrenaline at time zero and display PEA with analysable QRS complexes at some point during the 8min time interval (in total 67 patients). The plot is fitted with a piecewise linear spline from three minutes before administration to five minutes after. Time zero is the timing of adrenaline.

There is large variation in average HR between episodes ranging from 12 to 175. However, we see a clear rise in HR in the first five minutes after administration of the first dose of adrenaline up to a peak at 6.5 minutes before it decreases. There is a significant increase in HR between 0 and 2 minutes (p=0.003) after administration of adrenaline when fitting piecewise linear spline. Table 1 shows the coefficients, confidence intervals (CI) and p-values for the linear regression models for HR against time for the first, second and third dose of adrenaline. Since the second and third dose had no impact on HR nor QRS-duration, we have not depicted their scatterplots.

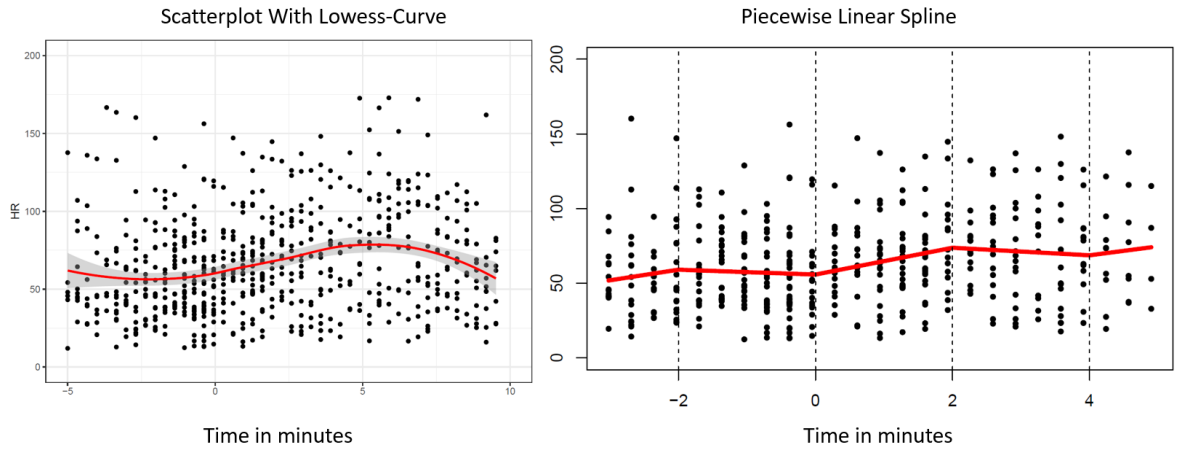

Figure 3 Development of HR from five minutes before administration of the first dose of adrenalin to ten minutes after fitted with a lowess curve to the left and HR in PEA fitted with a piecewise linear spline from three minutes before to five minutes after administration to the right. Each dot represents the average HR in one episode the past 20 seconds in both plots. There is an overall increase in the average HR after administration of adrenaline at time zero from an average at about 55 to a peak at about 75 at 6.5 minutes after administration. There is a significant increase in HR between 0 and 2 minutes after administration of adrenaline with a p-value of 0.003.

We also observed an increase in the prevalence of ROSC immediately after adrenalin was administrated. Figure 4 shows a prevalence plot for the five possible states during resuscitation: Death (dark grey), asystole (grey), VF/VT (red), PEA (yellow) and ROSC (green). PEA is further subdivided into three groups based on its HR: PEA <60, PEA 60-100, PEA >100. The white area represents episodes that are not yet classified because a defibrillator was not attached but these episodes were later included. This group is rather big initially as guidelines encourage

early adrenaline administration for patients with non-shockable rhythms. The small group of patients in ROSC that we see before adrenaline administration are in temporary ROSC (they have already arrested once and gained ROSC) and were about to re-arrest. The dotted line at time zero represents the timing of the first dose of adrenaline. There is a clear 3-fold increase in the prevalence of ROSC after adrenaline is administrated, from about 5% before administration to about 20% 6 minutes after administration.

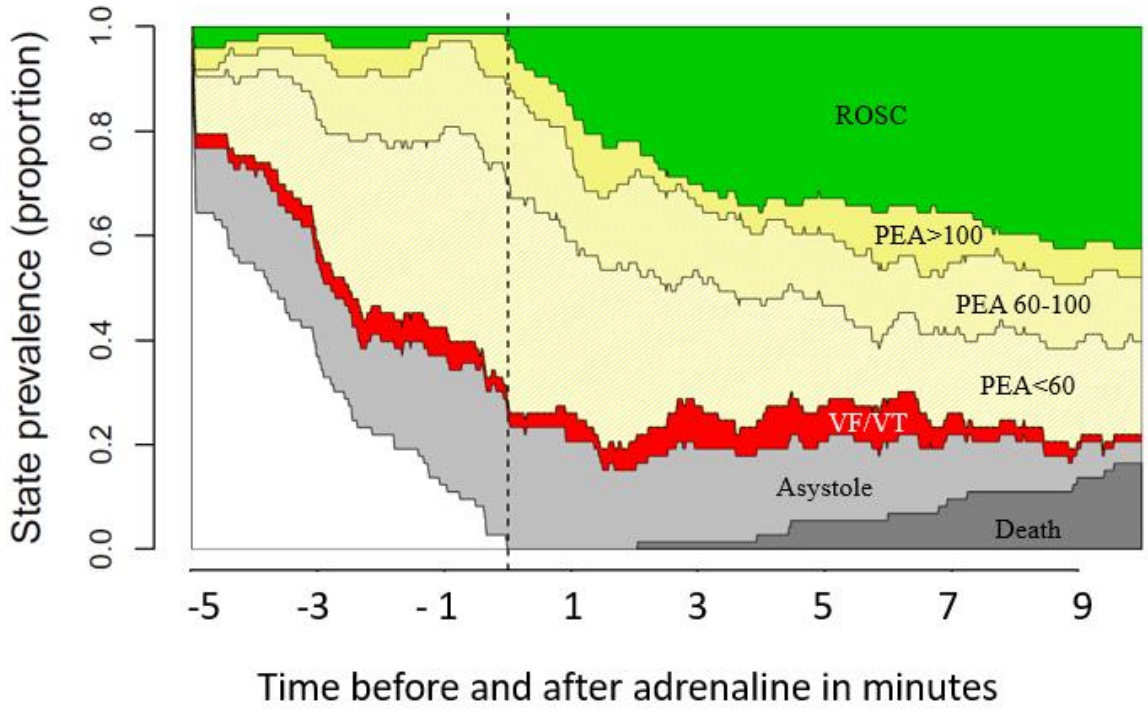

Figure 4 Prevalence plot of the different states. From the bottom: Death, asystole, VF/VT, PEA <60, PEA 60-100, PEA >100 and ROSC. The white area represents episodes that are yet to be included. There is a clear rise in the prevalence of ROSC corresponding to the time immediately after administration of adrenaline. (All patients experience PEA during this period number of patients: 72)

To provide more context to the phenomenon observed in Figure 4 we have visualized how these patients move between states from one minute to the next with a Sankey plot in Figure 5. The pillars show the number of patients occupying each state over time (death, asystole, VF/VT, PEA, and ROSC) with PEA being subdivided into the same three categories based on their HR as in fig 4. During the first minute after administration of adrenaline, most of the patients in PEA who obtain ROSC are recruited from the group with a HR below 60. From one minute after administration and onwards the patients in PEA who obtain ROSC mainly arise from the group with HR from 60 and above. At the time of administration of the first dose, two patients had obtained ROSC. One minute later the count is 11, further increasing to 16 and 22

two and three minutes after administration respectively. Note that some patients have not experienced their first arrest (i.e., they were not included yet) up until administration.

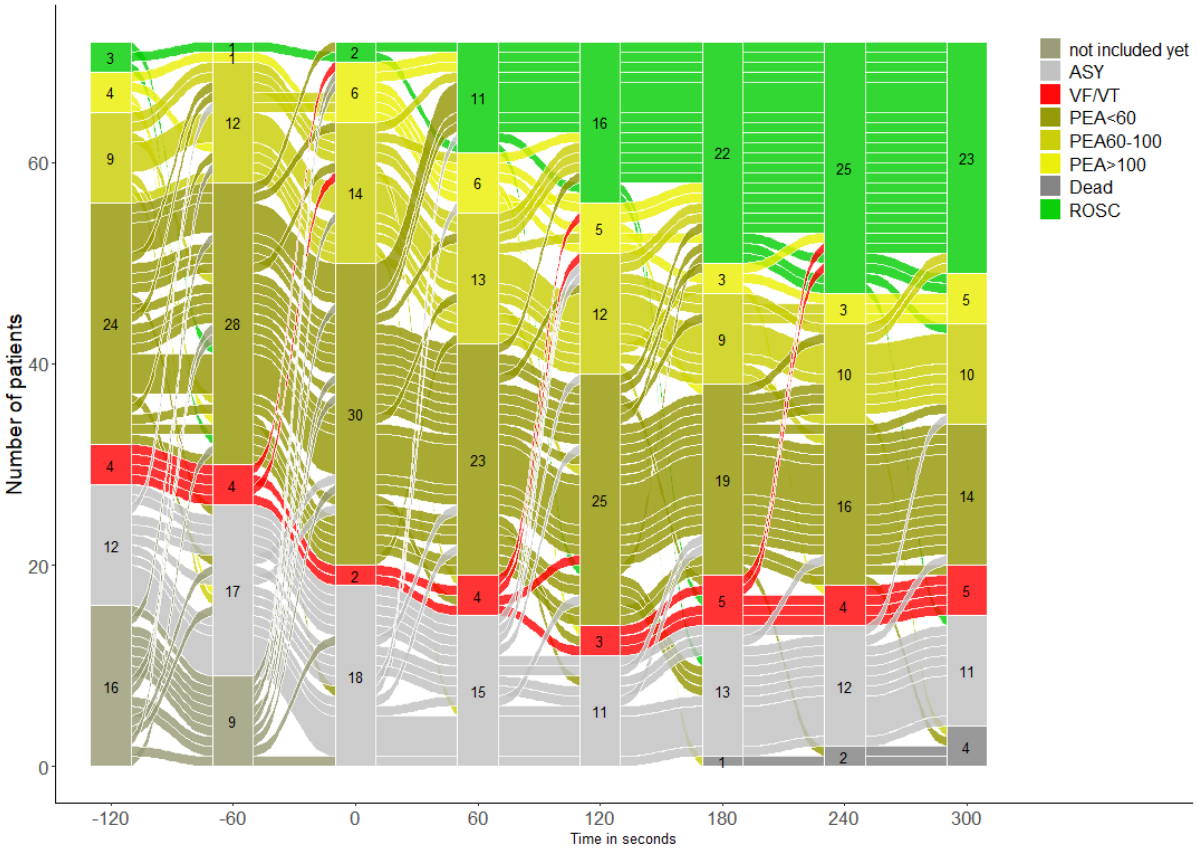

Figure 5 A plot visualizing which states the patients move between from one minute to the next. There is a clear increase in the prevalence of ROSC corresponding to the time immediately after administration of adrenaline. At time zero when adrenaline is administrated there is two patients occupying ROSC. One minute after administration 11 of the episodes has obtained ROSC, further increasing to 16 and 22 at two and three minutes after administration. During the first minute after administration of adrenaline most of the patients who obtain ROSC comes from the group with PEA with HR below 60. From one minute after administration and onwards the patients in PEA who obtain ROSC mainly arise from the PEA group with HR from 60 and above. Note that 16 patients are yet to be included from the start, and 9 are yet to be included one minute before administration.

4.2 How the Second and Third Dose of Adrenaline Impact HR and ROSC

Regarding HR there is no significant changes before or after administration of the second or third dose when applying piecewise linear splines as shown in table 1. In figure 6 we have plotted the average HR every 20 seconds for each episode from five minutes before to 10 minutes after administration of adrenaline and fitted a lowess-curve. We can see a slight increase in HR from three to two minutes before administration of the second dose of adrenaline. For the third dose there is no noteworthy development before or after administration.

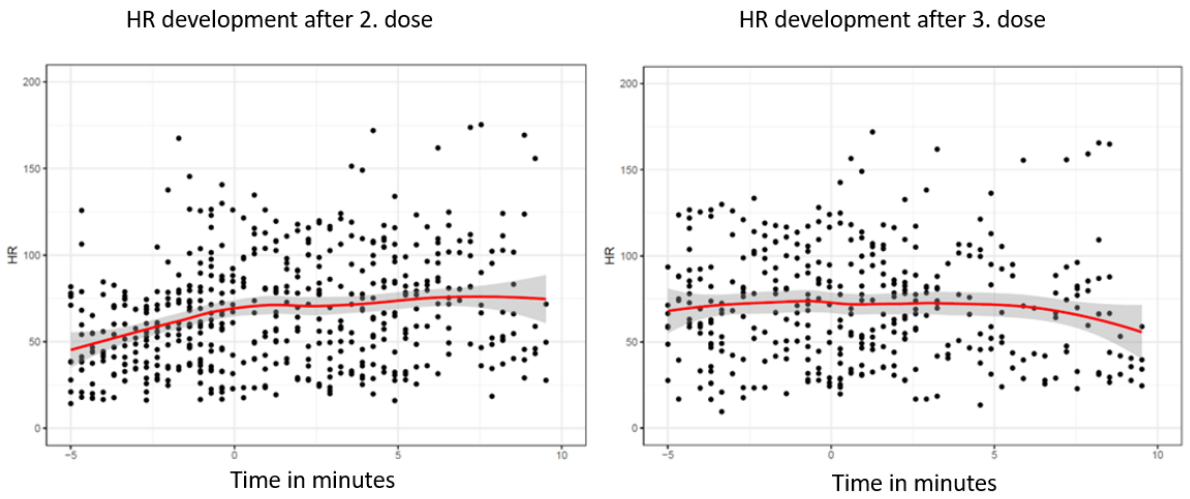

Figure 6 The development of HR before and after administration of the second and third dose of adrenaline. There is a slight increase in HR before administration of the second dose of adrenaline with a p-value of 0.057 when applying a piecewise linear regression as seen in table 1. There are no mentionable changes before or after administration of the third dose. There were 58 and 40 episodes with PEA between five minutes before and 10 minutes after administration of the second and third dose of adrenaline.

Regarding how ROSC develops in relation to the second and third dose of adrenaline, there is a slight increase both after the second and third dose compared to the prevalence at the time of administration. However, the effect is not as pronounced as after the first dose. The prevalence of ROSC seems to be reduced slightly in the minutes before administration. Figure 7 shows how patients move between states in relation to the second and third dose of adrenalin.

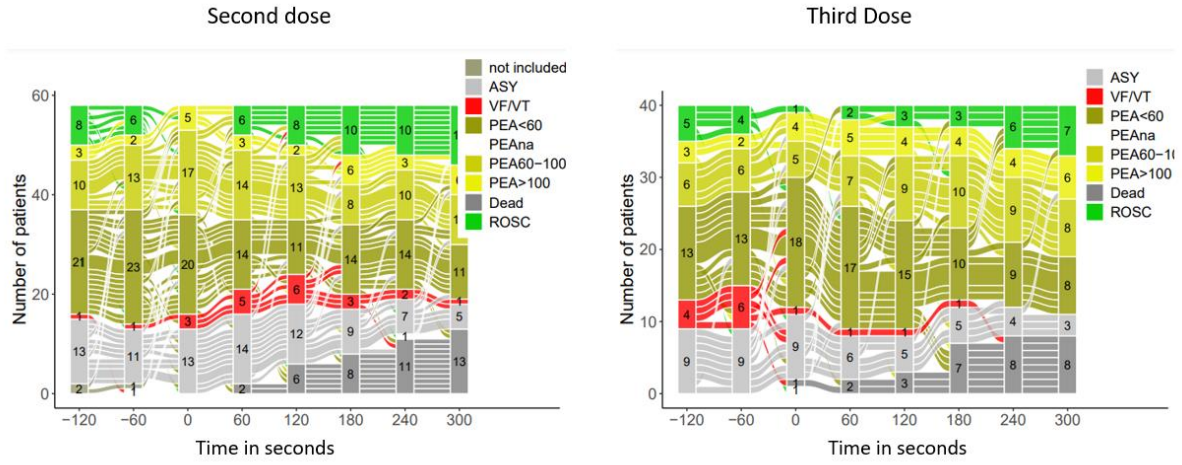

Figure 7 A visualization of how the patients move between states before and after the administration of the second and third dose of adrenalin. Time zero represents the timing of the first dose of adrenalin in the figure on the left and timing of the third dose in the figure on the right. There is an increase in the prevalence of ROSC corresponding to the time immediately after administration of adrenaline both after the second and third dose.

4.3 How Adrenalin Affects the QRS-complex width

Figure 8 shows the development of QRS duration from five minutes before administration of adrenaline to 10 minutes after the first dose. The dots in the scatterplot represents the average values in milliseconds for the past 20 seconds in one episode and is fitted with a lowess-curve. We observe an initial increase in QRS width which levels out and decreases slightly shortly after adrenaline. There was an increase in QRS-duration from two minutes before administration of the first dose to time zero with a p-value of 0.043 when applying a piecewise linear spline. Otherwise, there was no noteworthy changes after the first, second or third dose. Table 2 shows coefficients, p-values, and CI for a piecewise linear spline model for changes in QRS-duration from three minutes before administration to five minutes after.

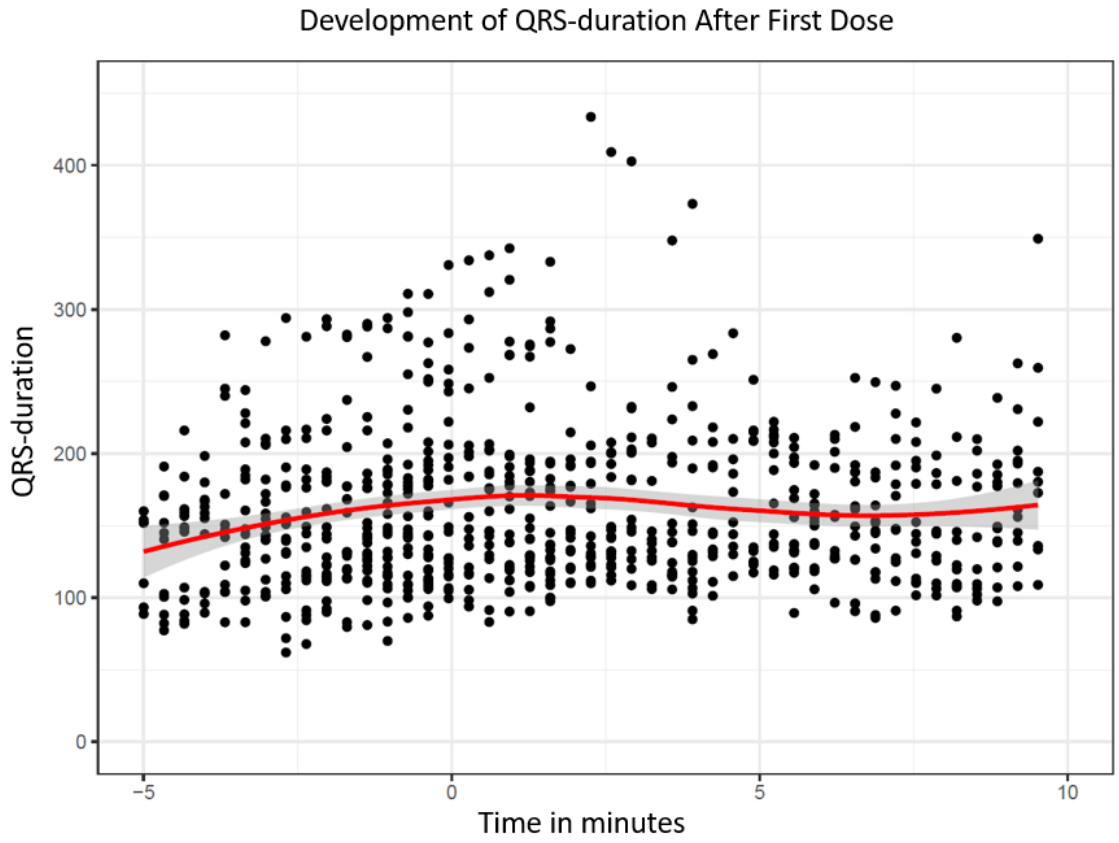

Figure 8 Development of QRS-duration from five minutes before administration of adrenaline to 10 minutes after. Each dot represents the average QRS-duration the past 20seconds for one episode. The scatterplot is fitted with a lowess-curve. There was an increase in QRS-duration before administration of adrenaline and otherwise no noteworthy changes.

Heart rate		-3 to -2 min	-2 to 0 min	0 to 2 min	2 to 4 min	4 to 5 min
First dose	p-value	0.4	0.6	0.003	0.5	0.7
	95% CI	-8.7, 23	-7.8, 4.5	3.2, 15	-9.7, 4.7	-22, 34
	Beta	7.1	-1.6	9.0	-2.5	6.0
Second dose	p-value	0.057	0.6	0.5	0.3	0.062
	95% CI	-0.58, 38	-5.6, 9.7	-4.5, 9.7	-12. 4.1	-1.2, 49
	Beta	19	2.1	2.6	-4.1	24
Third dose	p-value	0.5	0.2	0.6	>0.9	>0.9
	95% CI	-17, 34	-15, 3.4	15.9, 10	-12, 12	-45, 42
	Beta	8.5	-6.0	2.2	0.23	-1.2

Table 1 The p-values, confidence intervals and beta-values for the piecewise linear spline model applied from three minutes before adrenalin is administrated to five minutes after. Beta represents the slope of the line. If beta < 1 it means average HR is decreasing and if beta > 1 average HR is increasing. The only significant change in HR was observed from zero to two minutes after administration of the first dose of adrenalin with a p-value of 0.003 and beta of 9.0.

QRS-duration		-3 to -2 min	-2 to 0 min	0 to 2 min	2 to 4 min	4 to 5 min
First dose	p-value	0.9	0.043	0.5	0.6	0.5
	95% CI	-31, 26	0.39, 24	-14, 7.6	-17, 10	-38, 72
	Beta	-2.2	12	-3.3	-3.2	17
Second dose	p-value	>0.9	0.8	0.7	0.5	0.9
	95% CI	-31, 32	-14, 11	-14, 9.2	-19, 8.8	-46, 40
	Beta	0.43	-1.3	-2.6	-5.0	-3.0
Third dose	p-value	>0.9	0.4	0.15	0.5	0.2
	95% CI	-36, 32	-6.5, 17	-18, 2.7	-10, 21	-93, 23
	Beta	-2.0	5.3	-7.6	5.3	-35

Table 2 The p-values, confidence intervals and beta-values for the piecewise linear spline model for changes in the QRS-duration from three minutes before administration of adrenalin to five minutes after. Beta represents the slope of the line. If beta < 1 it means average QRS-duration is decreasing and if beta > 1 average QRS-duration is increasing. The average QRS-duration increases slightly from two minutes before administration of adrenalin with p-value 0.043.

5 Discussion

In this thesis we have shown that administration of the first dose of i.v. adrenaline during in-hospital cardiac arrest seem to have an immediate effect by increasing the HR in patients with PEA. Furthermore, we observe a marked rise in the prevalence of ROSC immediately after adrenaline is administrated. The rise in ROSC-prevalence is most prominent after administration of the first dose but is also present to a lesser degree after the second and third dose.

5.1 The Effect of Adrenalin on HR

It is well known that adrenaline will increase the HR of any healthy individual by binding to the beata-adrenergic receptors in the heart. Therefore, it may not come as a surprise that we have observed an increase in HR after administration of adrenaline. However, the setting of cardiac arrest is unique in that the organs in the body are no longer adequately circulated and dependent on chest compressions to maintain a minimum of circulation. PEA is a state with absence of a palpable pulse but where the electrical signalling in the heart is preserved. Thus, adrenalin still performs an effect on the heart even in these special circumstances. The effect seems to be almost immediate.

As mentioned, there was a significant increase in HR the first two minutes after administration of the first dose of adrenaline. As for the second dose we observed a HR increase in the minutes *before* adrenalin was registered. This might be due to some delay from when adrenaline is administrated to when it gets registered, and delay caused by CPR because we are only able to determine HR in pauses between compressions every 2-3 minutes.

The rise in HR after adrenaline might in part be due to patients transitioning out of the group of patients in PEA with HR < 60. If these patients transit to ROSC, asystole, VF/VT or are declared dead they are removed from the risk set which again lead to a relative increase in the average HR of the group of patients still left in PEA. The observed increase in HR is likely a combination of an absolute increase and an effect of patients transitioning to other states.

Of equal importance is that we have only investigated changes in HR during PEA, so patients who transit to ROSC are excluded at the point of transition. A consequence of this is that we don’t know how the HR develops after administration of adrenaline in patients who immediately obtain ROSC. These patients probably also have increased their HR after the transition and might be the same patients who respond with an increase in HR during PEA. Whether or not this is the case mandates further investigation.

5.2 Adrenaline and its Relation to ROSC

As we have seen, there is a noteworthy relationship between the timing of the first dose of adrenalin and a following increase in the prevalence of ROSC. The timely development suggests a causal relation, but other factors like the effect of CPR also need to be considered. The finding is prominent enough and match the observations by Nordseth et.al from 2012 showing that adrenaline had a significant clinical effect by facilitating the transition to ROSC from PEA, and should encourage further corroboration (10). The rise in prevalence of ROSC after administration of adrenalin was present after both the first, second and third dose. That said, a significant proportion of the episodes was not included before up until administration of the first dose of adrenaline. This phenomenon is in part caused by the guidelines stating that adrenaline should be administrated immediately in non-shockable rhythms (1).

As mentioned earlier, most episodes that obtain ROSC are recruited from the PEA groups with HR from 60 and above just after adrenaline is administrated. This may indicate a relation between HR and probability of ROSC, as Skjeflo et.al demonstrated in pre-hospital data, stating that an increase in HR is associated with higher probability of ROSC (18). Whether the observed increase in HR after administration of the first dose of adrenaline directly contributes to ROSC or not must still be considered unknown, but perhaps not unlikely. This strengthens the relevance of HR as a biomarker during ongoing CPR form PEA.

5.3 The effect on QRS-duration

The QRS-complex on an ECG represents activation of the ventricles. The conduction of the electrical impulse leading to ventricular depolarisation may be influenced by impairment of conduction which again can be caused by a disturbance in the metabolic state of the myocardium (27, 28). In cardiac arrest the heart will usually not get the amount of oxygen it demands, leading to ischemia in the myocardium which again alters it metabolic state increasing the risk of impaired conduction. Skjeflo et.al observed that QRS-width differed between patients who later obtained ROSC and patients who did not (18). We observed an increase in duration in the minutes before the first dose of adrenaline was administrated and no change after administration. This might indicate that adrenaline has some effect, possibly preventing further increase in QRS-width. We did not observe any other changes in QRS-width and timing of adrenaline in our data, but did not investigate any relation between QRS-duration and ROSC. It is still likely that the conduction in the heart alters during cardiac arrest and that

this possibly could be linked to prognosis. However, more research is needed to investigate this further.

5.4 Limitations

The timing of adrenalin administration can be hard to determine, and the quality of this information varies between episodes. In episodes where adrenaline is registered directly on to the defibrillator the point of registration often comes shortly after it was administrated, simply because it takes time to pass on the information and manually register it. In other cases, timing of adrenalin was based on an interview with the personnel present at the event. The personnel often remembered the rhythm assessments well and could relate timing of adrenaline to this, or other longer pauses in chest compressions due to intubation or other interventions that may be found in the defibrillator file. However, a margin of uncertainty of some minutes remains.

Furthermore, we were only able to measure HR and QRS-duration in compression pauses. Therefore, any possible changes after administration of adrenaline would first be detected in these same pauses leading to some delay in when a potential effect could be registered.

There are also some uncertainties regarding the measurement of the QRS-complexes. This is primarily due to difficulties with identifying the endpoint of the QRS-complex. Noise interfered with the ECG signal in many of the episodes, sometimes making exact and consistent measurements challenging.

Finally, this is a single centre observational study. That limits the generalizability of our findings. In addition, we cannot state that there is a causal relation between the intervention (adrenaline) and the observed effect (increased HR and prevalence of ROSC). Other interventions like quality of chest compressions and ventilations also affect the probability of ROSC, making the isolated effect of adrenaline hard to determine with this study design.

6 Conclusion

In this thesis we have shown that there is a clear association, possibly causal, between administration of the first dose of adrenaline and a rise in HR immediately after in patients with PEA during cardiac arrest. In addition, there is a similar association, possibly also causal, between timing of adrenaline and a subsequent increase in the prevalence of ROSC in our material. We observed a tendency of increasing QRS-width before administration of the first dose of adrenaline. It is likely that HR can provide information as a biomarker for ROSC, but more research is mandated to know to what extent.

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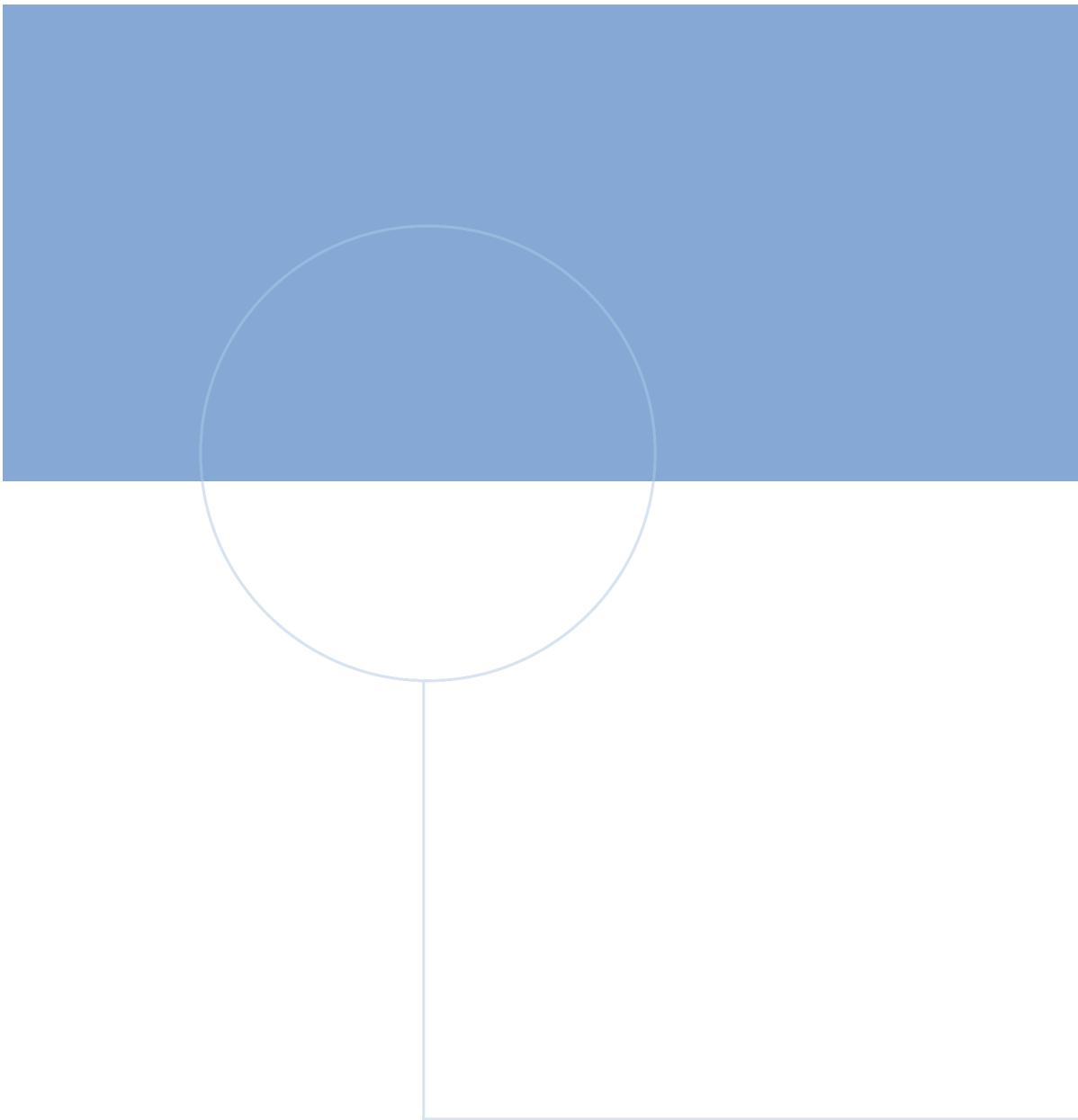

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