# PULSELESS ELECTRICAL ACTIVITY IN PATIENTS WITH IN-HOSPITAL CARDIAC ARREST

Thesis for the degree of Philosophiae Doctor

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# Contents

# 1 Preface

## 1.1 Norsk sammendrag

I Norge opplever 4000 personer hjertestans hvert år. Basert på behandling, deles hjertestans ofte inn i en sjokkbar type og en ikke sjokkbar type. Den sjokkbare typen kan behandles med støt fra en hjertestarter og har vesentlig bedre overlevelse enn den ikke-sjokkbare som kun kan behandles med hjerte- lungeredning (HLR), og eventuelt medisiner. I tillegg skiller vi også mellom hjertestans som oppstår utenfor sykehus og hjertestans som oppstår hos pasienter innlagt på sykehus. Det har tradisjonelt vært mindre forskning på hjertestans som oppstår inne på sykehus og hjertestans med ikke sjokkbare rytmer.

I denne avhandlingen har vi satt søkelys på pulsløs elektrisk aktivitet (PEA), en ikke sjokkbar rytmene som ofte oppstår inne på sykehus. Vi har undersøkt muligheten for å forutsi det umiddelbare utfallet til pasienten ved å se på endringer i type hjertestans og endringer i hjertets elektriske aktivitet underveis gjennom undersøkelse av pasientens elektrokardiogram (EKG). I tillegg har vi undersøkt hva som skjer med pasientens EKG etter behandling med adrenalin og om dette er forbundet med tiden det tar før pasienten får tilbake egen sirkulasjon.

Vi har gjennomført tre studier for finne ny kunnskap om disse fenomenene.

### Studie I:

I denne studien undersøkte vi EKG fra til sammen 700 episoder med hjertestans fra forskjellige tidsperioder og forskjellige sykehus. Vi delte PEA inn i fire forskjellige grupper basert på type hjertestans forut for PEA og observerte at gruppene hadde forskjellig sannsynlighet for å gjenoppnå pulsgivende rytme. I tillegg var PEA ofte en forløper til pulsgivende rytme hos pasienter med andre typer hjertestans. En overgang til PEA kan derfor være et godt tegn.

### Studie II

I denne studien fokuserte vi på endringer i EKG under HLR hos pasienter med PEA. Vi så på endringer i hjertefrekvens (tilsvarer pulsfrekvens hos friske) og endringer i de elektriske signalene i EKG. Vi inkluderte 327 episoder fra tre sykehus. Vi fant at bestemte endringer i frekvens og utseende kunne forutsi sannsynligheten for å få tilbake egen sirkulasjon. En kan tenke seg at modellen på sikt kan brukes som veiledende under HLR,  et steg på veien til å individualisere hjertestansbehandlingen.

### Studie III

Det er kjent fra andre studier at adrenalin øker sjansen for å få tilbake egen sirkulasjon. I denne studien undersøkte vi effekten av adrenalin minutt for minutt etter behandling. Vi fant at adrenalin øker sjansen for gjenvinning av egen sirkulasjon mer enn 3 ganger hos pasienter

med PEA. I tillegg så vi at det tar bare noen minutter fra adrenalin er gitt til pulsen kommer tilbake hos de som responderer. Litt overraskende fant vi kun økning i hjertefrekvens uten at vi så endringer i EKG'ets elektriske signaler etter behandling med adrenalin.

## Konklusjon

Denne avhandlingen viser at PEA utvikler seg vesentlig forskjellig avhengig av utgangspunktet til tilstanden. Videre kan lett tilgjengelige markører brukes til å identifisere pasienter som responderer på behandling. Dette kan på sikt gi mulighet til å tilpasse seg pasientens utvikling. Til slutt så vi at adrenalin er viktig for pasienter med PEA, og egen sirkulasjon kan forventes i løpet av få minutter hos et stort antall.


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## 1.2 English summary:

Cardiac arrest is often divided into a shockable and a non-shockable type according to effective treatment. Patients with shockable rhythms may regain pulse after an electric shock and have significantly better survival than patients with non-shockable rhythms. In addition, we also divide cardiac arrest according to location, in-hospital and out-of-hospital cardiac arrest. In the last decades, shockable rhythms outside the hospital have received far more attention than cardiac arrest inside the hospital.

This thesis focuses on pulseless electrical activity (PEA, one of the two non-shockable rhythms) occurring at the hospital. Based on readily available ECG markers, we have investigated the possibility of predicting the immediate outcome of the patient. In addition, we have also investigated the impact of adrenaline on these markers and looked at the delay between the administration of adrenaline and the return of pulse.

### Study I

We investigated 700 episodes of cardiac arrest collected at different hospitals and different periods. PEA was divided into four different groups, and we found different tendencies to regain pulse among these. We also found PEA to be a precursor to the return of pulse in patients with other types of cardiac arrest. A transitioning to PEA may therefore be a sign of improvement.

### Study II

In this study we focused on changes in ECG appearance and heart rate (equal to pulse in the healthy) during the resuscitation of patients with PEA. We included 327 episodes and found that changes in ECG could predict pulse return. This is innovative as it could be possible to use the model bedside, a step towards a more individualized treatment of PEA.

### Study III

Adrenalin increases the probability of regaining pulse. In this study, we found that adrenaline increased this probability more than three times in patients with PEA. In addition, we observed that patients started to regain pulse immediately after administration and continued to do so for approx.. 4 min. Surprisingly we only found an increase in HR and no changes in ECG appearance.

### Conclusion

This thesis shows that readily available markers may identify patients responding to treatment. This may provide an opportunity to adapt treatment to the situation. Adrenaline is important for patients with PEA, and the expected response is within minutes.

## 1.3 Acknowledgements

It is more than ten years ago that one of the intensive care nurses at Orkdal hospital requested my assistance. The heart rate of her patient had suddenly dropped, and she worried that cardiac arrest would follow. To my surprise, she was right. How could she predict such an event? Little did I know how much this event would inspire me and be so closely related to my future thesis.

The process of learning new things is deeply satisfying to me. Whether its learning to ride a motorcycle, play a new piece on the piano or understanding a new statistic approach, the feeling of mastering something new has been conditioned into my brain from young age. Making me search the unknown looking for new things to learn. I must thank all my teachers through time for making learning something fun, inspiring, and motivating to me. From my mother and father who thought me to smile some 38 years ago, Inger-Johanne Huke who created a safe learning environment throughout primary school, Sverre Vesterfjell who thought us to dress properly for the great outdoors by showing up in class wearing long underwear and then dressing up for a night out in the cold snow, prof. Jelinek who wore a tie when teaching the embryonal development of the heart and many, many more.

As a young clinician scientific work was something scary that I did not understand. Ten years after graduating from medical school I decided to do something about this fear and started to think about becoming a Ph.D student. I'm very grateful that my supervisor prof. Eirik Skogvoll invited me into his world of science. His dedication and great interest in our project have been indispensable for my progress and my growing interest in this topic. Without him, this would not have been possible!

Daniel Bergum, thank you for always being there helping me overcome difficult hurdles that suddenly popped up on my way.

Prof. Jan Pål Loennechen, thank you for putting ends to difficult, and at times very confusing QRS complexes.

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I would also like to thank our collaborators that have helped us along the way. Trygve Eftestøl, Benjamin Abella, Abhishek Bhardwaj, David Buckler, Elisabete Aramendi and Jon Urtega. I would also like to send my warm thoughts to the family of late Unai Irusta Zarandona who passed away too early. His help was invaluable to me and my project.

I'm very grateful to my former and present leaders Sigurd Fasting and Åsa Susanne Askim for letting me take a break from my clinical duties. I'm also very grateful towards all my colleagues in the Clinic of anesthesia and intensive care medicine for encouraging my work and filling my absence when attending duties related to my project.

Finally, I would like to show my gratitude towards my family who have always been there in my life. To my parents, Harald and Elisa, thank you for providing a safe environment when exploring new and unknown horizons. You have always been my safety net. To my sisters, Guro, Nina and Mari, thank you for caring and looking out for me during different phases of life. To my wife to be, Linn Mari, thank you for loving me! To my children, Einar, Sigurd and the boy we are waiting for, you are the ultimate meaning of my life.

## 1.4 List of publications

Study I

**Pulseless Electrical Activity in In-Hospital Cardiac Arrest – A crossroad for decisions**

Norvik A, Unneland E, Bergum D, Buckler DG, Bhardwaj A, Eftestøl T, Aramendi E, Nordseth T, Loennechen JP, Abella BS, Kvaløy JT, Skogvoll E

Resuscitation 2022 Vol. 176 p117–124

Study II

**Heart rate and QRS duration as biomarkers predict the immediate outcome from Pulseless Electrical Activity.**

Norvik A, Kvaløy JT, Skjeflo GW, Bergum D, Nordseth T, Loennechen JP, Unneland E, Buckler DG, Bhardwaj A, Eftestøl T, Aramendi E, Abella BS, Skogvoll E

Resuscitation 2023 Vol. 185

Study III

**Adrenalin, changes in heart rate and return of spontaneous circulation in in-hospital cardiac arrest**

Norvik A, Unneland E, Bergum D, Loennechen JP, Kvaløy JT, Aramendi E, Urtega J, Skogvoll E

Resuscitation (submitted)

# 1 Introduction:

## 1.1 Time is everything

Cardiac arrest (CA) is an abrupt and sustained cessation of blood flow throughout the body, leaving the person unconscious with abnormal or absent breathing. This is a medical emergency demanding immediate intervention for the person to possible survive. It is essential that someone willing to perform cardiopulmonary resuscitation (CPR) observe the collapse or immediately find the collapsed person. Every minute without CPR worsens the patient's outcome.[1] The next important step to survival is the attachment of a defibrillator. The defibrillator will identify shockable rhythms (Ventricular fibrillation (VF) and ventricular tachycardia (VT)), that may revert to spontaneous circulation by an electric shock and discern those from the non-shockable rhythms (Pulseless electrical activity (PEA) and Asystole (ASY)). This is a time-critical event for patients with a shockable rhythm, as delayed defibrillation reduces survival.[2, 3] The patients with non-shockable rhythms rely on reversal of the cause of arrest, high-quality CPR and possibly quick administration of adrenaline to survive. [4]

## 1.2 Etiology

Cardiac arrest may also be categorized by etiology. This is useful as different causes of CA may need different treatment, in addition to CPR to regain ROSC. Patients with cardiac etiology may need a percutaneous coronary intervention, patients with hypothermic arrest need rewarming, those with hypoxic arrest need securing of their airway and oxygen while those with traumatic arrest might need a series of interventions like massive transfusion, surgical bleeding control, draining of a pericardial tamponade or relieving a tension pneumothorax.[5]

### 1.2.1 In-hospital cardiac arrest vs. Out-of-hospital cardiac arrest

Cardiac arrest may not only be categorized based on treatment or etiology, but also according to the location of the arrest. It is often divided into out-of-hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA), as they are considered different entities. This may not be the case. Høyby et al. compared patient characteristics and arrest characteristics in 3501 patients with IHCA and 8846 patients with OHCA based on Danish registry data. [6] They found the two groups to be similar in demographics and comorbidities. Still, the IHCA group had more hospital contacts, underwent more cardiac procedures, and received more cardiovascular drugs indicating higher morbidity. Despite being sicker, long-term survival was higher among patients with IHCA (30-day survival 24% and 1-year survival 18%) than those with OHCA (30-day survival 17% and 1-year survival 13%), mainly due to differences in arrest characteristics and not patient characteristics or location. For example, the difference in time to initial cardiac rhythm analysis was 9.3min between IHCA and OHCA, and 98% of patients with IHCA received early CPR (not specified) compared to 69% of patients with OHCA.

Adjusting for these two factors made the difference in survival almost disappear. In other words, it comes down to time.

## 1.3 The big knowledge gap

The incidence of IHCA is reported between 1.5-2.8 per 1000 hospital admissions in Europe and 6-7 per 1000 hospital admissions in the USA. [7] Shao et al. collected data from 10198 cardiac arrests during 2014 in 12 hospitals in Beijing and reported an overall incidence of 17.5 per 1000 admissions. The hospital with the highest incidence exceeded 50 arrests per 1000 admissions. However, this incidence also included over 7000 patients where resuscitation was not attempted, breaching the current Utstein definition of cardiac arrest, which only includes attempted resuscitation by chest compression or defibrillation. [8] Based on unpublished data, the Norwegian incidence is 1.8 per 1000 admissions.[7] Figure 1.3.1 suggests an substantial increase in the annual incidence of IHCA in Norway, however this is probably a result of more complete reporting of IHCA.

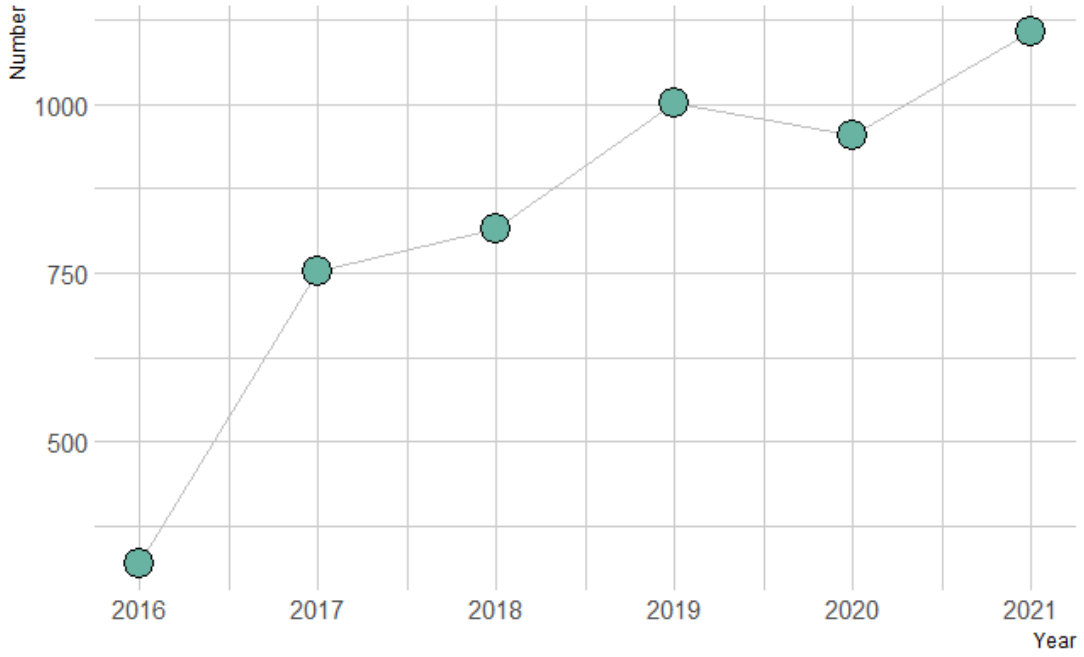


Figure 1.3.1: The reported number of IHCA in Norway from 2016 to 2021. [9]

In 2021, 3723 episodes of OHCA were registered in Norway (69 per 100 000 inhabitants). Of these, 2801 episodes were treated by ambulance personnel. Asystole was reported as initial rhythm in 53% of these, ventricular fibrillation (VF) in 21%, pulseless electrical activity (PEA) in 20%, ventricular tachycardia (VT) in 1.8%, and the rest (2.8%) were unknown. In total, 1016 patients were registered with IHCA in 2021. Approximately (not reported as exact numbers) 37% had PEA, 27% had asystole, 16% had VF, and 10% had VT as primary rhythm. The remaining 10% had unknown initial rhythm. Survival after 30 days was 27%. The Norwegian

cardiac arrest registry describes both treatment and long-term outcome of patients with OHCA in detail. This is not the case for IHCA. Important measures like state of consciousness after the event, coronary angiography after the event, temperature management, and Cerebral performance category score are not registered for this group. [10] This illustrates some of the knowledge gap between OHCA and IHCA in Norway.

Searching PUBMED underscores this problem. Using the term; "out-of-hospital cardiac arrest" renders approx. 9600 hits, while "in-hospital cardiac arrest" only gets 1400. A systematic review of randomized controlled trials (RCT) on cardiac arrest treatment found 92 RCTs published between 1995 and 2014, including 64309 patients.[11] Only 4 of these studies, including 724 patients, were exclusively devoted to IHCA. Big questions like the effect of adrenaline, temperature management, and coronary angiography have not been raised in randomized controlled trials including adult patients suffering from IHCA.[12, 13] From my point of view, this is a big problem, also for those suffering from OHCA. The determining factor when comparing patients with OHCA with IHCA, is time/delay to intervention/treatment. This difference is reflected in several studies. Time to the arrival of ambulance range between 6 to 10 minutes for OHCA [6, 14-17] while an observed CA at the hospital renders immediate resuscitation by trained health professionals. Logically, time to adrenaline is also significant longer outside the hospital. Perkins et al. published an RCT on adrenaline vs. no adrenaline in 2018. The median time to administration of the study agent was 21 minutes.[18] A hospitalized patient with a peripheral venous cannula may receive adrenaline within very few minutes after the collapse. Target temperature management is also a debated intervention showing no effect on long-term survival after OHCA in randomized controlled trials.[19, 20] In the TTM2 study, the median time from arrest to randomization was approx. 130 min. It is possible that a substantially shorter time to CPR and randomization, which is achievable in patients with IHCA, would change the outcome of such an RCT. It should be mentioned that Moler et al. found no significant difference in 1-year survival between children treated with hypothermia and normothermia after IHCA. [21] Even thou several studies have concluded with few differences in both pre- and intra-arrest factors[6, 22] between the two groups, the time factor will always differ between the two groups. The overly focus on OHCA the last decades might therefore be viewed as wasted opportunities. Results from IHCA could possibly be applied to OHCA but results from OHCA can't be applied to the patients suffering IHCA due to the time difference. Therefore, we need more research performed on hospitalized patients.

Despite being the most common initial rhythm in IHCA and commonly encountered with increasing prevalence in OHCA, there has also been relatively little focus on PEA when compared to eg. VF.[23] This may also be demonstrated through a quick search in Pubmed. The the following search strategy "(VF) OR ("ventricular fibrillation")) AND ("cardiac arrest")"

renders over 5300 hits while “(PEA) OR ("pulseless electrical activity")) AND ("cardiac arrest")” only renders approx. 800 hits.

## 1.4 Predicting outcome of cardiac arrest

A marker that can reliably predict long-term survival and neurological function after CA has been sought for decades. A review and metanalysis from 2019 by Fernando et al. aimed at determining the impact of important characteristics on survival after IHCA.[24] They found that male sex, increasing age, active malignancy, and chronic kidney disease, tracheal intubation, and prolonged resuscitation reduced survival. Witnessed arrest, monitored setting, arrest during daytime hours, and initial shockable rhythm were associated with increased survival. This is valuable knowledge actively used in decision-making during cardiac arrest. Still, it is difficult to rely only on such characteristics when assessing single individuals suffering from CA. Even though a patient has a poor prognosis based on the above factors, he/she may still respond to CPR and survive the event with a good outcome.

To study the patient response to treatment, one must investigate changes in intra-arrest factors during CPR and relate them to any ROSC (both temporary and sustained) rather than long-term outcome. There is a much closer relation between an intra-arrest factor and any ROSC than with the long-term outcome; the latter is also affected by factors unrelated to the CA. ECG characteristics like QRS rate, duration, amplitude, QT time, and presence of p-waves are examples of such markers. The ECG is always present, for all patients, during the whole course of advanced cardiopulmonary resuscitation and presence of p-waves and QRS rate might be assessed in an instant. These characteristics have been investigated, but the results are diverging. [25-31] Most of these studies have focused on the initial ECG presentation without exploring the potential of change.

End-tidal carbon dioxide ($ETCO_2$) is another variable that may change in response to treatment of CA. It is only available in intubated patients attached to a capnograph. In 2018 Pavia et al. published a systematic review where the aim was to investigate levels of $ETCO_2$ associated with return of spontaneous circulation (ROSC) or survival.[32] They found that levels above 10mmHg (1.3kPa) were associated with ROSC. Non standardized minute ventilation was regarded as a major limitation as this will greatly impact $ETCO_2$. Based on current literature, they concluded that $ETCO_2$ could not reliably predict ROSC but that a higher $ETCO_2$ level is probably better. This is reflected in the current guidelines as values above 10mmHg at intubation or after 20min of resuscitation could be used to predict ROSC (weak recommendation), and values above 10mmHg at intubation or 20mmHg after 20min of resuscitation could be used to predict survival to discharge (weak recommendation). In addition, the guidelines strongly recommend against using $ETCO_2$ as a mortality predictor.[33]

Regional cerebral oxygen saturation ($rSO_2$) is a non-invasive and easily obtainable measurement of brain oxygenation. This has also been investigated as a prognostic marker during CA. Schnaubelt et al. reviewed 26 studies with data from 2620 patients exploring the relationship between $rSO_2$ values and outcome.[34] They found that the mean of those achieving ROSC was 41% (+/- 12%) while the mean value among those not achieving ROSC was 30% (+/- 12%), a difference that was statistically significant (p=0.009). They calculated the average change in $rSO_2$ to be 22% and 7% before ROSC and death respectively and reported that ROSC became highly unlikely when the mean $rSO_2$ was below 23%. They concluded that $rSO_2$ might be helpful when terminating futile resuscitation and that further studies with a more uniform design was needed to clarify the potential link between $rSO_2$ values and outcome.

A major drawback to many of the referred studies on ECG, $ETCO_2$, and $rSO_2$ is comparing average values within the ROSC group with average values within the noROSC group. In a clinical setting, and on the individual level, it is difficult to interpret these results since the outcome is unknown. It is particularly challenging to terminate resuscitation based on this knowledge. An average value may only be calculated after the episode[35], the treating team does not know when they are faced with the final[36] or maximal value[37], and values measured at specific time points[38] of treatment may not reflect response to treatment.

Cardiac ultrasound has also been investigated as a prognostic tool. Reynolds et al. published a review to inform the 2020 update to international resuscitation guidelines about the predictive capabilities of point-of-care echocardiography. [39] They found that individual studies were difficult to interpret and that heterogeneity and risk of bias among the investigated studies precluded them from performing a meta-analysis. They concluded that the evidence for using cardiac ultrasound as a prognostic marker during cardiac arrest is poor with a high risk of bias. Guidelines recommend against using the absence of cardiac motion on ultrasound to terminate resuscitation and state that the evidence of using ultrasound to predict the outcome is low.

## 1.5 Pulseless electrical activity

Patients with PEA has spontaneous organized cardiac electrical activity and absence of consciousness and pulses.[23] The ventricles are depolarized, but the heart cannot provide sufficient circulation to keep the patient alive. PEA makes up almost 50% of initial rhythms in IHCA and 20-30% in OHCA.[23, 40] Survival after IHCA with PEA as initial rhythm is about 10%. PEA may be classified into cardiac and non-cardiac and further sub-classified according to cause within each category. [23] Hypovolemia due to massive bleeding or obstructive causes like tension pneumothorax, cardiac tamponade or massive pulmonary embolism are examples of non-cardiac causes. Heart failure or myocardial ischemia are examples of cardiac causes. PEA

has also been described as primary when it is the presenting rhythm or as secondary when following termination of VF/VT.

Figure 1.5.1 shows an example of the ECG of a patient with PEA included in this thesis.

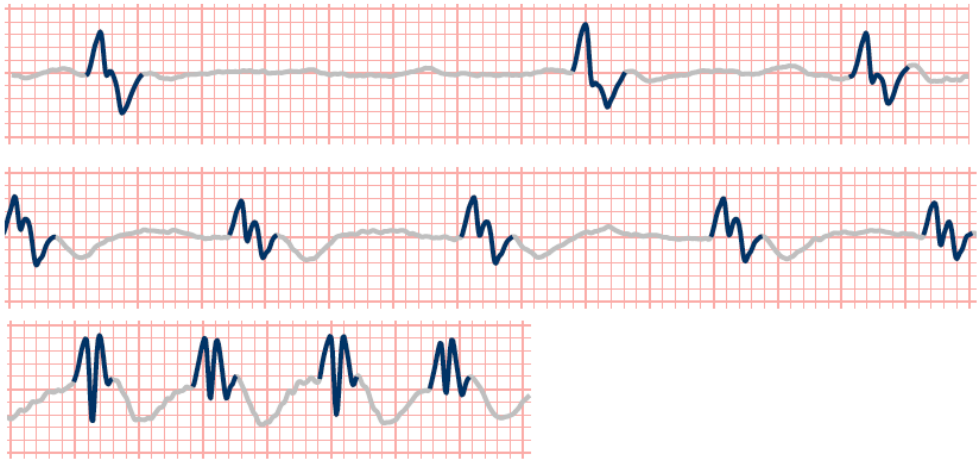

Figure 1.5.1 (published as Figure S7 in supplementary material in Study II): ECG recorded at different timepoints in a patient with PEA. In this patient we observe increasing heart rate and a narrowing of the QRS complex.

## 1.6 Adrenaline during cardiac arrest

According to current CPR guidelines, intravenous administration of adrenaline is recommended to all patients with cardiac arrest of a certain duration regardless of initial rhythm. Its effect has been under investigation and debate for decades. Much has changed since Pearson and Redding resuscitated asphyxiated dogs by administering 1mg of Adrenaline into the heart in 1963.[41] Despite negative findings and criticism through time, 1mg of adrenaline still remains in the current recommendations on advanced cardiopulmonary resuscitation.

Early observational studies on the effect of adrenaline during CPR in the 90s and early 2000s concluded, contrary to animal findings and the presumed effect of adrenaline, that adrenaline decreased survival.[42-45] These studies were prone to "resuscitation time bias. [46, 47] A patient receiving a time-dependent intervention during cardiac arrest (i.e., adrenaline, intubation, extracorporeal cardiopulmonary resuscitation) can only achieve ROSC after the intervention. In contrast, those not receiving the intervention may achieve ROSC at any time. In contrast to the intervention group, the non-intervention group contains all patients that achieve ROSC during early phases of treatment. To overcome this, one must compare those receiving the intervention at a given time with those at risk of receiving the intervention at the same time.

In 2009, Olasveengen et al. published a randomized controlled trial comparing patients with OHCA randomized to an intravenous line or not.[16] They randomized 851 patients and found

that adrenaline increased ROSC and admission to hospital with ROSC, but not survival to hospital discharge. In 2011, Jacobs et.al published the first double-blinded RCT comparing the effect of adrenaline to placebo in patients with OHCA. [15] They randomized 262 to the placebo group and 272 to the adrenaline group. Like Olasveengen, they found increased ROSC and admission to hospital in the adrenaline group but equal rates of survival to discharge. A major limitation to their study was the small study group without power to show differences in long term survival so the discussion about the use of adrenaline could not be put to rest. Perkins et.al[17] published in 2018 PARAMEDIC2 a double blinded RCT comparing patients with OHCA receiving adrenaline or placebo. They randomized 8014 patients in the United Kingdom finding a significant higher proportion of achieved ROSC, hospital admissions with ROSC and 30-day survival in the adrenaline group. In 2019, Holmberg et.al published a review and metanalysis to update a Consensus on science and treatment recommendations issued by the International Liaison committee on Resuscitation. They concluded that adrenaline increased ROSC, survival to hospital admission and discharge as well as a slight increase in 3-months survival.[48] These results were mostly based on findings by Perkins et al. Remarkably, very little has been done to investigate the effect of adrenaline during IHCA. Only one RCT investigated the effect of vasopressors during IHCA. This trial compared adrenaline to vasopressin as first drug dose and found no difference in survival to 1-hour and hospital discharge.[49]

Hence, current guidelines on adrenaline administration to patients with IHCA, relies on findings in the OHCA population. It is of course reasonable to think that adrenaline also causes ROSC in the IHCA population, but it is difficult to estimate to what extent and even more difficult to determine its long-term effects. The main reason for this is the difference in time to adrenaline in patients with IHCA and OHCA. In PARAMEDIC2 the median time to adrenaline was approximately 21 minutes while in an in-hospital setting adrenaline may be administered shortly after the collapse. Several studies have shown that early administration of adrenaline increases survival in patients with non-shockable rhythm in both patients with IHCA and OHCA.[47, 50]

# 2 The aims of this study

It is estimated that approximately 4 patients suffer from IHCA every day (approx. 1500/year) and only one of these survive to hospital discharge. The most observed initial rhythm is PEA, having significantly lower survival than VF/VT.
Considering the paucity of IHCA knowledge and the poor survival after PEA, it was important for us to focus the research of this thesis on this field.

We wanted to investigate:

- Whether transitions to PEA are associated with the probability of gaining ROSC
- Whether changes in QRS duration and QRS rate during PEA are associated with the probability of gaining ROSC
- How long it takes for ROSC to develop after the administration of adrenaline
- Whether adrenaline is associated with changes in QRS duration and QRS rate in patients with PEA

# 3 Method

## 3.1 Overall method

### 3.1.1 Study setting and population

We included episodes from the University of Chicago Hospital, USA, (collected between 2005 and 2008, n=159), from the Hospital of the University of Pennsylvania, USA (collected between 2008 and 2010 n=187), from the Penn Presbyterian Medical Center, USA (collected between 2008 and 2010, n=54). The episodes from St Olavs University Hospital, Norway, (collected in two periods, between 2008-2013 and 2018-2022).

The first episodes from St. Olav University Hospital (2008-2013) and the episodes from University of Chicago Hospitals had been annotated and included in a previous study and were not re-annotated for this purpose.[30, 51]

Episodes from four US hospitals were collected as part of a quality assurance initiative while episodes at St. Olavs hospital were collected for research purposes only.

### 3.1.2 Data collection and processing

Data recorded by defibrillators are central to this thesis. Defibrillators record ECG, chest compressions, ventilations, and electrical shocks in relation to a well-defined timeline during CPR. In addition, some units allow the treating team to record other CPR related events, like drug administration or intubation. This has provided us with highly detailed information about all included episodes of cardiac arrest and given us the possibility to recreate the episode and relate central events to a clearly defined timeline. All events were manually assessed and annotated using a custom-made graphical application developed in MATLAB by a collaborating group at the University of the Basque Country. The start of an episode was defined when the first resuscitative effort was identified (chest compressions or shock). This usually correalted with attachment of the defibrillator to the patient. The initial CA rhythm was determined based on clinical records (monitored CA) or arrest rhythm during the first pause in chest compressions. We excluded episodes with large noise disturbances, no compression data, or no ECG signal.

Chest compressions were detected as fluctuations either in the transthoracic impedance (TI) signal acquired by the defibrillation pads, or in the compression depth signal recorded by the CPR assistance pad.[52, 53] Defibrillators record transthoracic impedance to ensure correct placement of the defibrillatorpads and to calibrate the shock energy delivered to the patient. The impedance changes abruptly when the chest configuration changes during chest comperssion-decompression. [54, 55] Figure 2 illustrates how the impedance signal changes when chestcompressions are performed.

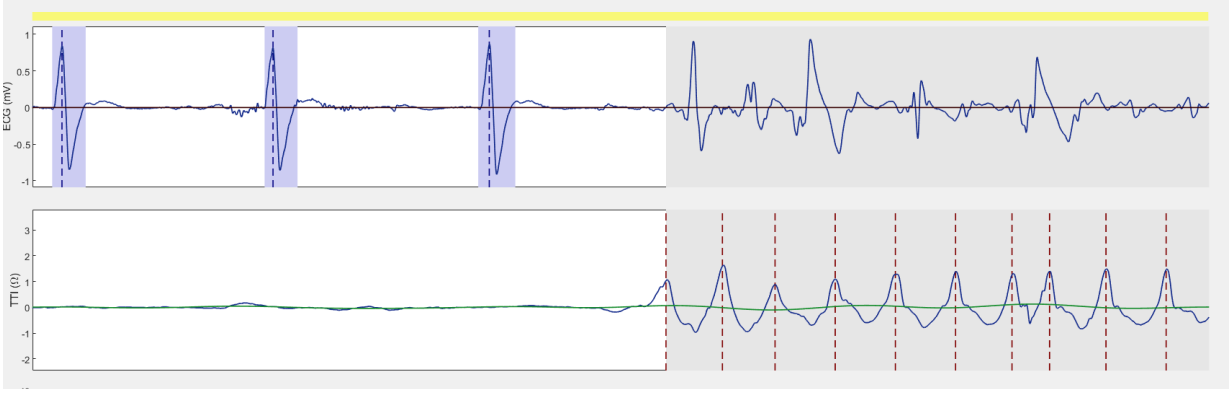


Figure 3.1.2.1: This is a screenshot from our Matlab application that we used to analyze the defibrillator files. This illustrates a short pause in chest compressions, as indicated by the flat transthoracic impedance signal (bottom signal). There is a distinct change in the impedance signal as chest compressions are resumed (right gray part of the picture). During the pause, we see a organized rhythm compatible with spontaneous circulation (ECG signal at the top). Since the treating team find it nessesary to resume chestcompressions within a minute, this is chategorized as PEA. We also see that the ECG signal is disturbed by the chest compressions

Due to the noise generated by chest compressions, the ECG was only evaluated during chest compression pauses (Fig. 3.1.2.1).

ASY was defined as no measurable cardiac electrical activity, or an organized rythm slower than 12 QRS/min. VF and VT were categorised by their unique morphologies.[56] PEA was defined as an organized rhythm compatible with spontaneous circulation in addition to pauses in chest compression shorter than one minute. This reflected the need of continuing CPR in a assumed pulseless patient. In addition PEA was sub-chategorized based on the preceeding rhythm; primary PEA ($PEA_{PRI}$) when PEA was the initial rhythm, PEA forllowing temporary ROSC ($PEA_{ROSC}$), PEA following VF/VT ($PEA_{VF/VT}$) and PEA following ASY ($PEA_{ASY}$) (Fig 3.2.1.2).

ROSC was defined as an organized rhythm comptible with spontaneous circulation and differed from PEA and pulseless VT by a pause in chest compressions lasting longer than one minute. Temporary ROSC was declared when ROSC lasted less than 20min and sustained ROSC was declared if spontaneous circulation lasted longer than 20min. We defined a new episode if a new cardiac arrest ensued in the same patient beyond 20 min after last ROSC. For patients declared dead, time of death was defined at the last chest compression or defibrillation attempt.

A segment of PEA, ASY or VF/VT was defined as a subset of an episode and is illustrated in Figure 3.2.1.2.

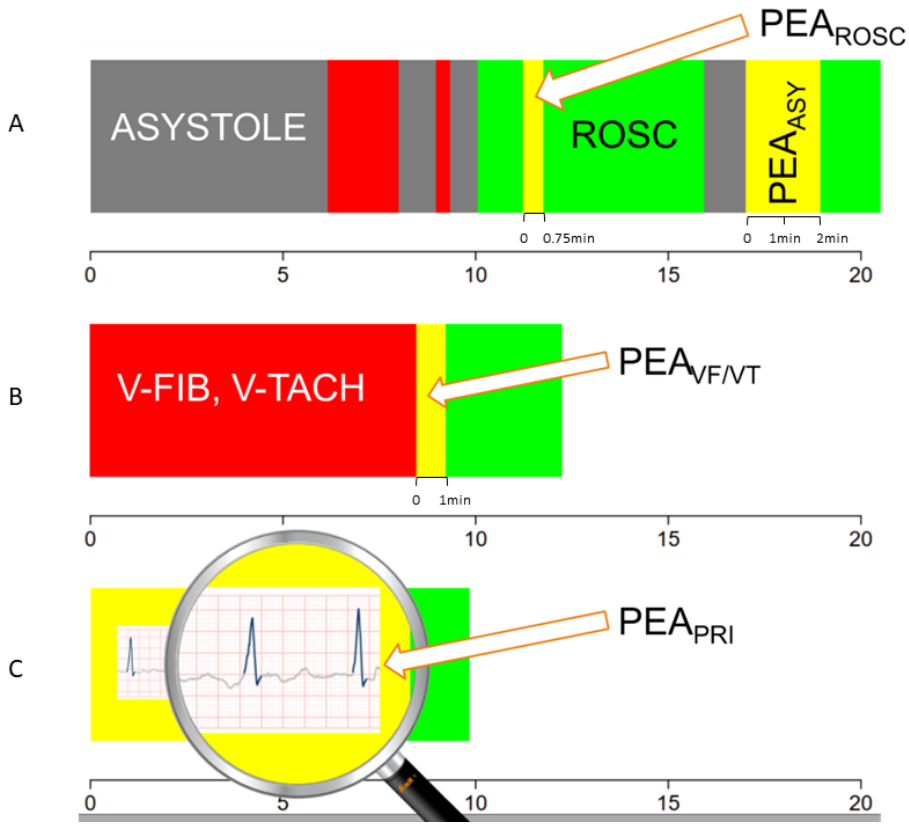


Figure 3.1.2.2 (published as Figure 1 in Study II): Illustration of three episodes (A-C) of cardiac arrest, showing all four types of PEA segments (yellow with arrows). Incidentally, all ended in ROSC. Also illustrated are the two different timelines at work; episode time from start of resuscitation, and PEA segment time in which the clock is "reset" to 0. Color coding: Asystole (gray), VF/VT (red), PEA (yellow), ROSC (green).

HR and QRSd were determined in every PEA segment by me for all available QRS complexes in pauses of chest compression. The start of QRS was defined as a sudden upwards or downwards deflection from a stable baseline. The end of QRS was defined at the J-point, i.e. first part of deflection on the terminal upstroke or downstroke of the QRS. [57] In cases where the J-point could not be defined, the end was defined where the downstroke of the R-wave or the upstroke of the S-wave crossed the baseline. Cases with an unclear J-point were reviewed with an electrophysiologist for adjudication (JPL). HR in beats per minute (bpm) was determined by dividing 60000 by the RR-time in milliseconds (i.e., time from one R-wave to the next).

Time of adrenaline administration was registered in episodes collected at St. Olavs University Hospital from 2018 to 2022. The cardiac arrest team was instructed to document administration of adrenaline in real time using the defibrillator. We considered this the best way to synchronize timing of adrenaline and changes in ECG. In cases where adrenaline administration was not documented using the defibrillator, we interviewed those present at the arrest relying on their memory.

### 3.1.3 Statistical analysis

The focus of this thesis has been factors associated with immediate outcomes (both sustained and temporary ROSC) during the course of IHCA. Time-to-event analysis (often known as "survival" analysis when the outcome is life or death) has been a cornerstone in this work and has been applied in all three studies. This powerful tool can absorb the complexities encountered in cardiac arrest dynamics and provide measures of effect that are directly interpretable in a clinical context.

In multistate time to event model, patients may reach other clinical states than just being alive or dead. Figure 3.1.3.3, demonstrate the different states that one may encounter during cardiac arrest. We also see all possible transitions between the different states. We define our model as consisting of five possible clinical states, between which transitions may occur.

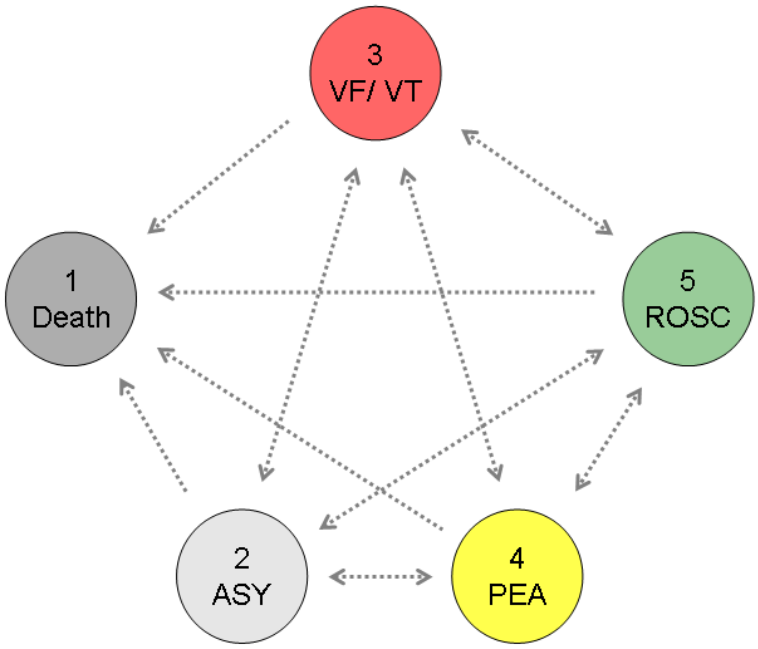


Figure 3.1.3.3: Illustration of transitions between different states during cardiac arrest.

The transition intensity rate (in simple survival models this is known as the hazard rate, because it measures the hazard of dying) is the fundamental entity in survival analysis that describes patient progression through different clinical states.[58] The rate may vary from 0 to unlimited and reflects the probability of a transition from in a given state (e.g., PEA) to another state (e.g., ROSC) in a short period of time. So, if 100 patients are in PEA at time 0 and 10 have developed ROSC after one minute, the transition intensity equals 0.1 per minute. In cardiac arrest, transitions between different states (asystole, PEA, VF/VT and ROSC) occurs

frequently and the estimated rates may express what to expect from the patient the next minute.

In the Figure 4.1.1 there were about 400 patients in PEA at time 0, while in the final state about 200 had developed ROSC directly from ROSC. Assuming a median time of 7 minutes this amounts to a transition intensity of 200/ (7 min*400) = 0.07/min, which agrees quite well with the estimated intensity functions in Figure 4 (Study I).

The Cox model estimates a transition intensity ratio between two groups without the need to specify the underlying transition intensity rate of each individual group.[59] This is very useful when comparing the effect of covariates on survival time between groups but the actual rate for the individual groups cannot be expressed.

Time-to-event models that can estimate the baseline transition intensity *rate* are very useful when studying state transitions during cardiac arrest. These may directly estimate the association between a covariate and a transition of interest (often ROSC) and how this may change over time. For example, one may directly estimate the impact of PEA type on the transition intensity to ROSC and how it changes during resuscitation. Examples of such models are the parametric Weibull and Greenwich model. These models are generalizable but may struggle with reflecting the true variation in the population. At the other end of the spectrum, we have the Royston Parmar model that follows data with splines allowing for complex shapes of the cumulative intensity function. Royston-Parmar models more faithfully reflect the data at the cost of generalizability.

### 3.1.4 Ethical considerations

The Regional Committees for Medical and Health Research Ethics in central Norway approved the study (reference number 2019/785). The need for consent was waived by the committee for patients from the two North American hospitals and analyzed anonymously. The need for consent was similarly waived for patients included from July 2019 and onwards at St. Olav University Hospital. The remaining patients provided written consent personally or through a next-of-kin.

## 3.2 Method specific to Study I

### 3.2.1 Study setting and population

We included episodes from St. Olav University Hospital, the University of Chicago Hospital, the Hospital of the University of Pennsylvania, and the Penn Presbyterian Medical Center.

### 3.2.2 Data collection and processing

All episodes were annotated according to the principles described under 3.1.2.

### 3.2.3 Statistical Methods and Modelling

Plotting the transition intensity functions (i.e., how the transition intensity changes over time) yields information about how the probability of gaining ROSC changes during resuscitation. In Study I we used both non-parametric and parametric time-to-event analysis for visualizing the evolution of transitions to PEA, and transitions from different types of PEA ($PEA_{PRI}$, $PEA_{ROSC}$, $PEA_{VF/VT}$ and $PEA_{ASY}$), to ROSC. By using several different models we could view the same process from different angels. Finally, we also plotted the overall time average transition intensity (as if constant over time) by fitting an exponential model.

## 3.3 Method specific to Study II

### 3.3.1 Study setting and population

For Study II, we reviewed episodes of CA from three hospitals: St. Olav University hospital in Norway (2018-2021), the Hospital of the University of Pennsylvania, USA (2008-2010), and the Penn Presbyterian Medical Center, USA (2008-2010). We also included 74 episodes with primary PEA from St. Olav University Hospital registered between 2009 and 2012, annotated and included in a previous study[30].

### 3.3.2 Data collection and processing

Episodes were annotated according to the description in section 3.1.2.

### 3.3.3 Statistical analysis

To investigate a possible association between the dynamic covariates HR and QRSd and the fixed covariates PEA type and segment start time on outcome we applied a Joint model. [60]

#### *3.3.3.1 The joint model*

Joint models estimate the effect/association between one or several biomarkers and outcomes of interest.[61-63] This is estimated by calculating a longitudinal profile of the biomarker course (i.e., development over time) and linking this to an event of interest (here transition from PEA to ROSC). The basic parameters estimated are the *transition intensity ratios* that are equivalent to *hazard ratio* in a conventional Cox survival model. A ratio is calculated by dividing two rates of two distinct groups. This is a ratio between the transition intensity *rates* (equivalent to hazard rate) of two distinct groups. The transition intensity rate expresses the

immediate probability of moving to a different state given the current state he or she is in. The ratio between two rates therefore communicates the relative probability of transitioning to ROSC.

We fitted linear mixed effect models to express the longitudinal profile of the two dynamic biomarkers, HR and QRSd. Their actual value and their slope, as an expression of change, were included as covariates in their profile. We used two Cox-models to express the intensities of each of the two competing transitions: from PEA to ROSC and from PEA to no-ROSC. When combining the linear mixed effect model and the Cox-model within the joint model, we were able to investigate a possible association between the biomarkers and the immediate outcome.

Notice that a "clock reset" model governed the segment timeline, meaning that each included PEA segment started at time zero regardless of whether PEA was a primary or secondary rhythm (Fig3.1.2.2). We however recognized that segments starting later in the episode may have a lower chance of ROSC, so to account for this, the difference between segment start and episode start was added as a fixed covariate to all the secondary PEA segments. It was also thought that PEA type would affect immediate outcome, and this was also added as a fixed covariate ; PEA as the primary rhythm ($PEA_{PRI}$), PEA following a period of ROSC ($PEA_{ROSC}$), PEA following VF/VT ($PEA_{VF/VT}$) or PEA following asystole ($PEA_{ASY}$). [64] (Fig. 3.1.2.2)

To illustrate the clinical application of the model we created prediction plots to visualize the dynamic changes in the estimated outcome 4 minutes ahead. These estimations are deducted from past observations of HR and QRSd (left part) and shown in the right part of the plot.

## 3.4 Method specific to Study III

### 3.4.1 Study setting and population

This was a prospective observational study. Consecutive cardiac arrests were registered between 2018 and 2022 at the St. Olav University Hospital in Trondheim, Norway.

### 3.4.2 Data collection and processing

The defibrillator file and the patient's clinical records were reviewed to determine when the adrenaline was administered. Each defibrillator file was further analyzed as described in 3.1.2

### 3.4.3 Statistical analysis

Prevalence and Sankey plots ("flow plots") were generated to give an overview of state transitions 3min before and 5 min after the 1st, 2nd, and 3rd dose of adrenaline was administered in all episodes receiving adrenaline.

A Cox time-to-event analysis for the transition from PEA to ROSC quantified the adrenaline effect.

To investigate changes in HR and QRSd, we included all patients who received adrenaline and were in PEA at some point from 2 min before to 4 min after adrenaline administration and fitted a piecewise linear spline to all available HR and QRSd data. This allowed us to investigate changes between and within three time intervals (from -2 min to 0 min, from 0 min to 2 min, and from 2 min to 4 min) in conjunction with the first, second, and third dose.

The results of the linear spline model might well be affected by data missing not at random (MNAR) caused by informative drop-outs and drop-ins (i.e. patients with high HR gain ROSC and patients with low HR remain in PEA).[65] By categorizing the PEA group based on HR we could visualize flow of patients in and out of HR categories and between HR categories in a Sankey plot. This could visualize whether PEA patients in certain HR categories were more prone to transitions out of PEA changing the HR distribution within the PEA group causing over- or underestimation of changes in HR after administration of adrenaline.

# 4 Results

In the following section, the most important results from the three studies are pinpointed.

## 4.1 Specific results from Study I

We included 700 episodes of IHCA from 642 individual patients. For detailed descriptive data, see Study I.

Figure 4.1.1 shows the flow of patients from their initial rhythm, through the penultimate state, until the final endpoints of sustained ROSC or death. There may be several transitions between the primary and the penultimate state or none. For example, many of the patients gaining ROSC, with VF/VT as both primary and penultimate state, transition directly from VF/VT to ROSC after a shock within the first minute of resuscitation. Approximately half of those who gain ROSC with VF/VT as primary state transit through PEA and almost all who gain ROSC with asystole as primary rhythm transit through PEA. Also, most patients with initial PEA and subsequent degradation to VF/VT or asystole are later declared dead.

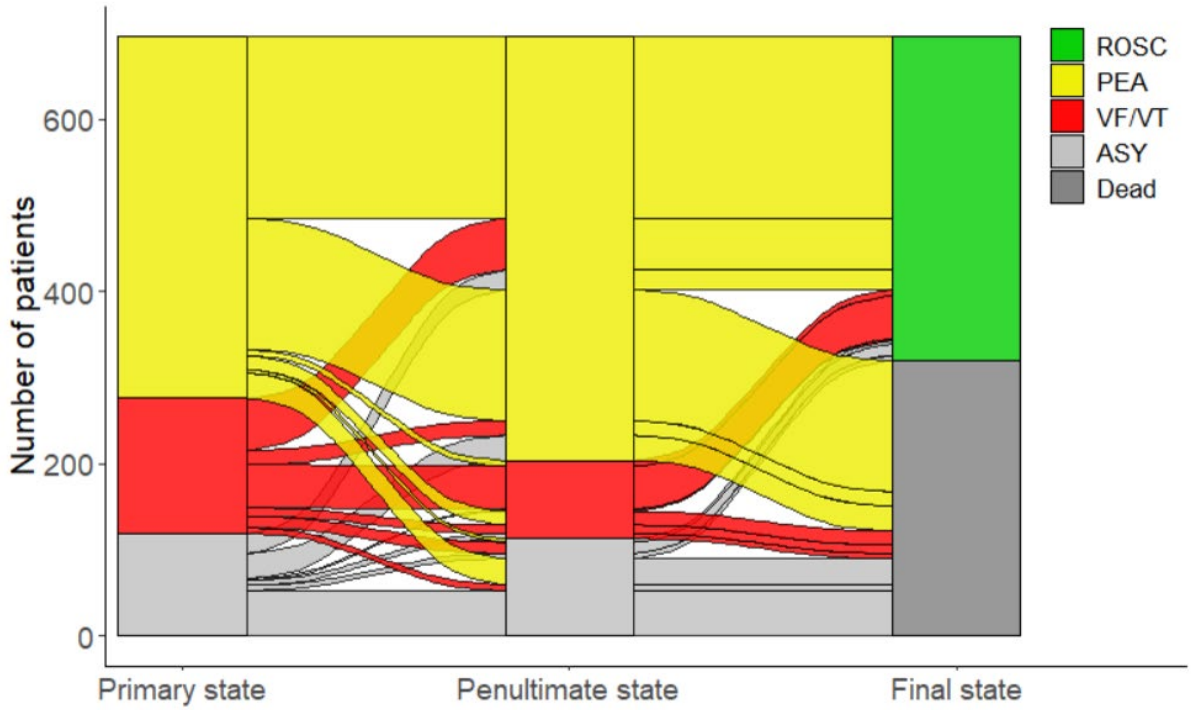


Figure 4.1.1 (published as Figure 2 in Study I): Sankey (flow) plot. Here we see the flow of patients between different states, from the primary state (initial rhythm) through the penultimate state to the final state. Many patients with VF/VT and asystole as primary rhythm transit through PEA before reaching ROSC. A degradation from PEA to VF/VT or asystole is an ominous sign.

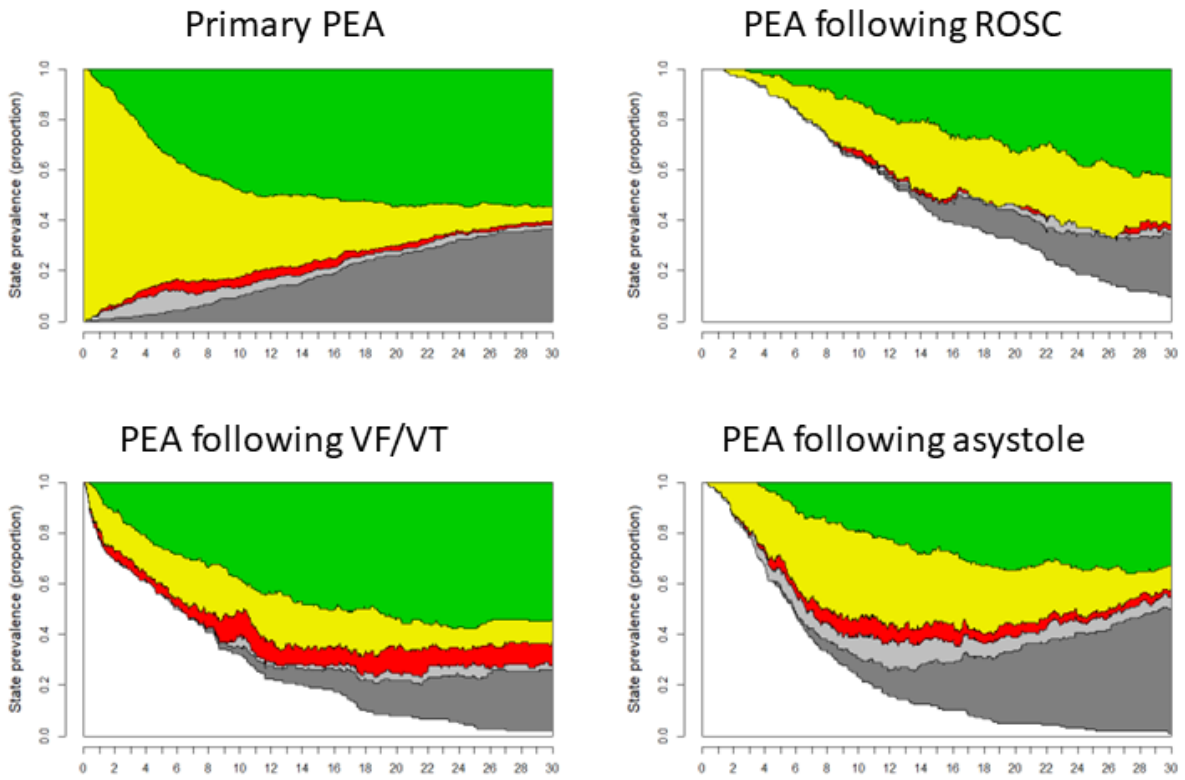


Figure 4.1.2: Prevalence plots of the four different PEA types. Here we see the development of the four types of PEA related to time since the start of the episode. The primary event in all the plots is the transition to PEA. Primary PEA I acquired at the start of the episode while secondary PEA is acquired later. The white area seen in the three plots describing secondary PEA represents episodes about to gain secondary PEA. The slope of the white border therefore represents the rate of transitions to secondary PEA within a given time period.

Figure 4.1.2 shows an overview of the four PEA types. For $PEA_{PRI}$, most ROSC is gained within 10 minutes and there are only a few transitions to VF/VT and asystole. Transitions to $PEA_{ROSC}$ occur at a steady pace from four minutes and on. $PEA_{VF/VT}$ and $PEA_{ASY}$ on the other hand mainly occurs during the first 10 min. Transitions to ROSC occur almost immediately after entering the respective PEA state except for $PEA_{ASY}$. Here we see a delay from the first transition into $PEA_{ASY}$ to the first transition from $PEA_{ASY}$ to ROSC.

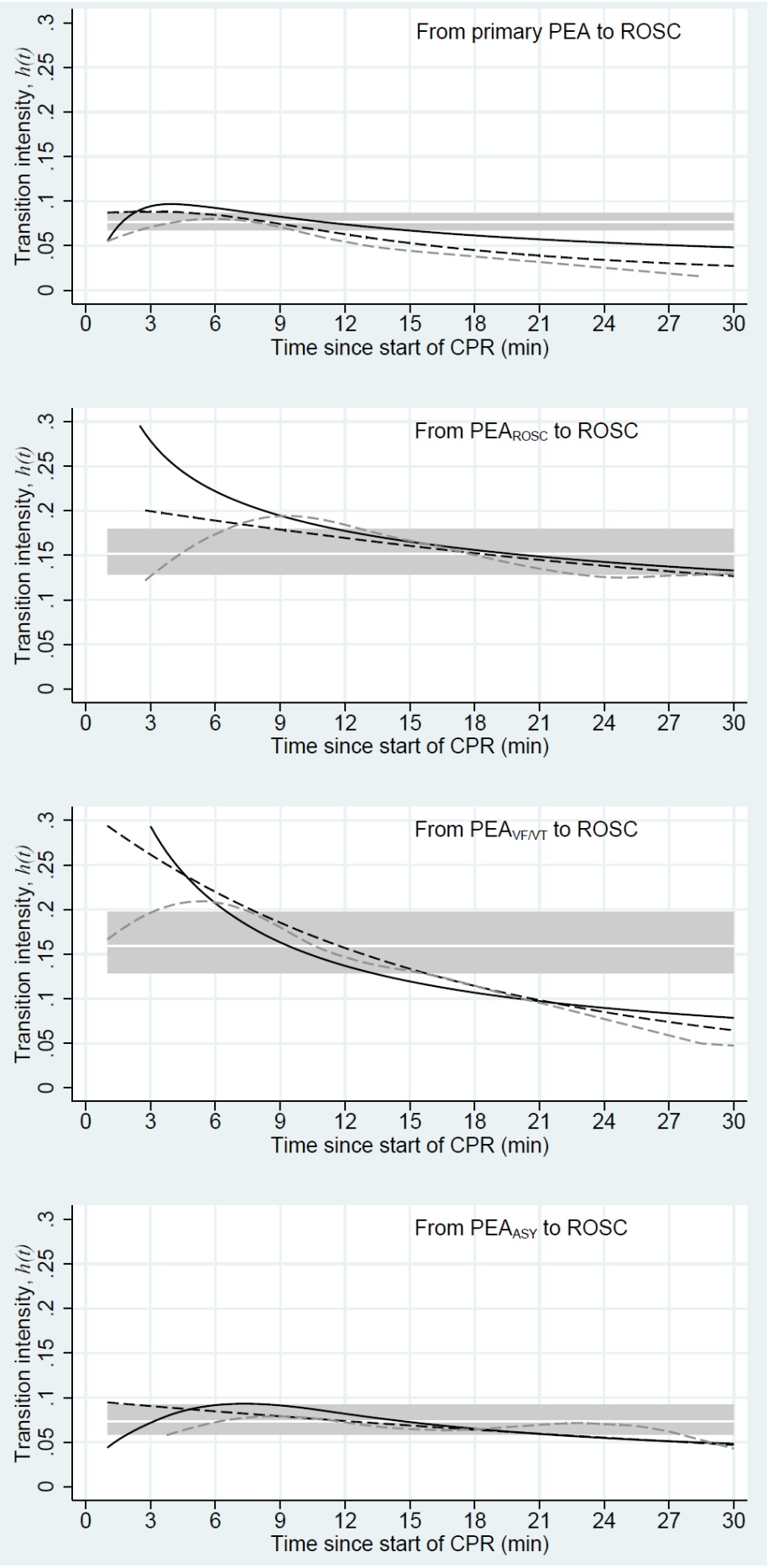


Figure 4.1.3: (published as Figure 4 in study I) The transition intensity functions to ROSC during the first 30 min of resuscitation, from primary PEA, from PEA after temporary ROSC, PEA after VF/VT, and PEA after ASY. Interrupted lines [- - -] show non-parametric estimates (grey: differentiated cumulative intensity; black: b-splines). Continuous lines [ ____ ] show the parametric estimates (white: exponential model; black: Royston-Parmar model). Grey shading indicates a 95% confidence region for the exponential model.

Figure 4.1.3 shows four different ways to visualize and describe the intensity functions for transitions from the four PEA types into ROSC. For the transition from $PEA_{PRI}$ to ROSC, a unimodal transition intensity showed the best fit with an increasing intensity to approx. 0.1 at 4 minutes.

The transition intensity function for $PEA_{ROSC}$ to ROSC starts out high at 0.20 and decreases to 0.12 in 30 min (Figure 4.1.3).

The best fitting transition intensity function of $PEA_{VF/VT}$ to ROSC is decreasing and (Figure 4.1.3) starts high at 0.30, declining towards 0.05 in 30 min. This indicates a high likelihood of gaining ROSC initially and a shorter time spent in $PEA_{VF/VT}$ before the transition in the early phases of resuscitation. This is also reflected in Fig. 4.1.2. Some of the earliest transitions happen almost spontaneously, i.e., almost without chest compressions, but intensity falls with time, and time to ROSC increases.

The best fitting intensity function for transitions from $PEA_{ASY}$ to ROSC has a unimodal shape (Fig. 4.1.3) and low intensity of 0.09 peaking at 7 min. Such a unimodal development with a lower peak value for patients in $PEA_{PRI}$ and $PEA_{ASY}$ indicates lower ROSC probabilities and a longer time to ROSC. These patients do not spontaneously gain ROSC like patients with $PEA_{VF/VT}$ and seem to need a minimum of 3-4 min of CPR.

Figure 4.1.4 illustrates the overall length of stay in each PEA category showing that patients remain longer in $PEA_{PRI}$ and $PEA_{ASY}$ (6.9 and 9.7 min respectively for the 50% percentiles) compared to $PEA_{VF/VT}$ and $PEA_{ROSC}$ (4.0 min).

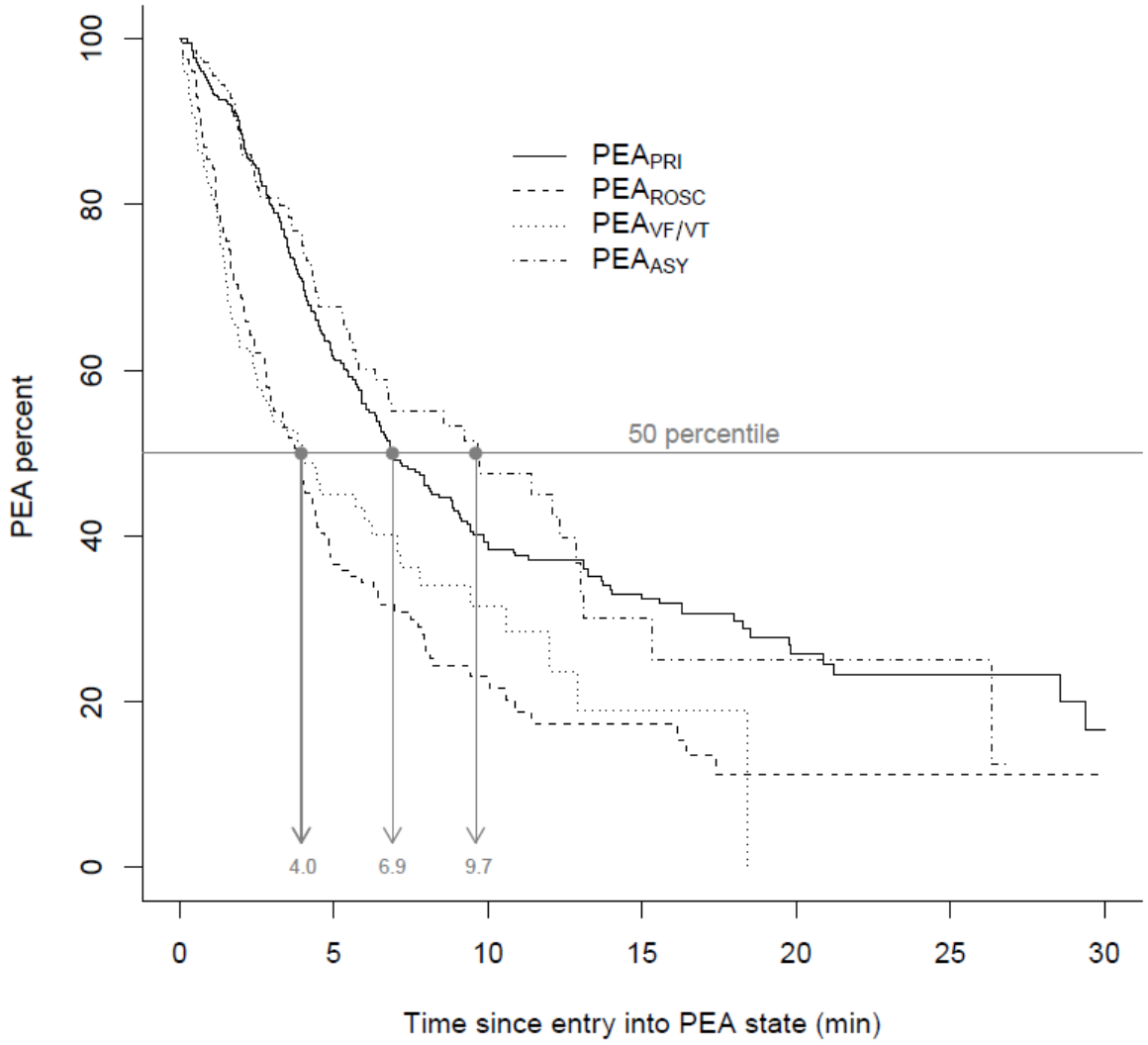


Figure 4.1.4 (published as Figure 4 in Study I): Half-lives of the different PEA types are shown as arrows, showing that $PEA_{ROSC}$ and $PEA_{VF/VT}$ are the most unstable.

## 4.2 Specific results from Study II

Figure 4.2.1 summarizes the inclusion and exclusion process. Detailed descriptive data can be found in Study II Table I.

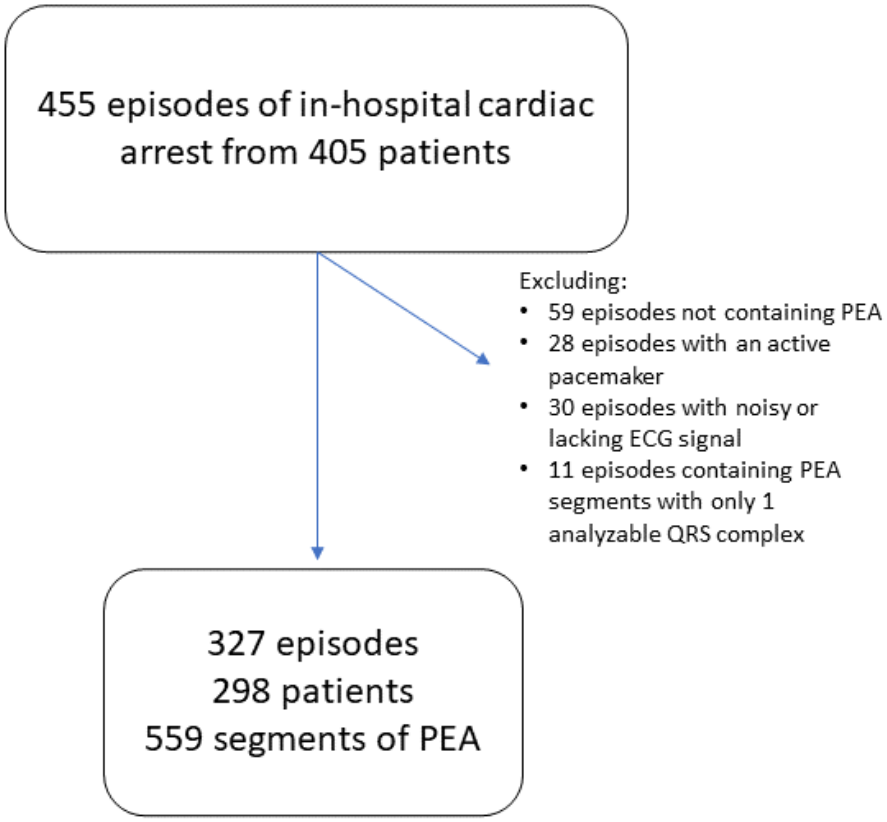


Figure 4.2.1: Exclusion of episodes from Study II

Sustained ROSC was achieved in 175 episodes (54%), and 35 patients (12%) eventually survived to discharge.

Figure 4.2.2 visualizes average HR and QRSd as well as the HR slope and QRSd slope among segments ending in ROSC and segments that did not reach ROSC (transitions to VF/VT, ASY, or death). This gives a quick overview of the differences in HR and QRSd among the two groups. Almost all segments with average HR > 130 bpm end in ROSC, and the same is true for segments with average QRSd below 100ms. Most segments with an increase in HR of more than 10 bpm/min end in ROSC, and most segments where QRSd increases by more than 10 ms/min end in noROSC

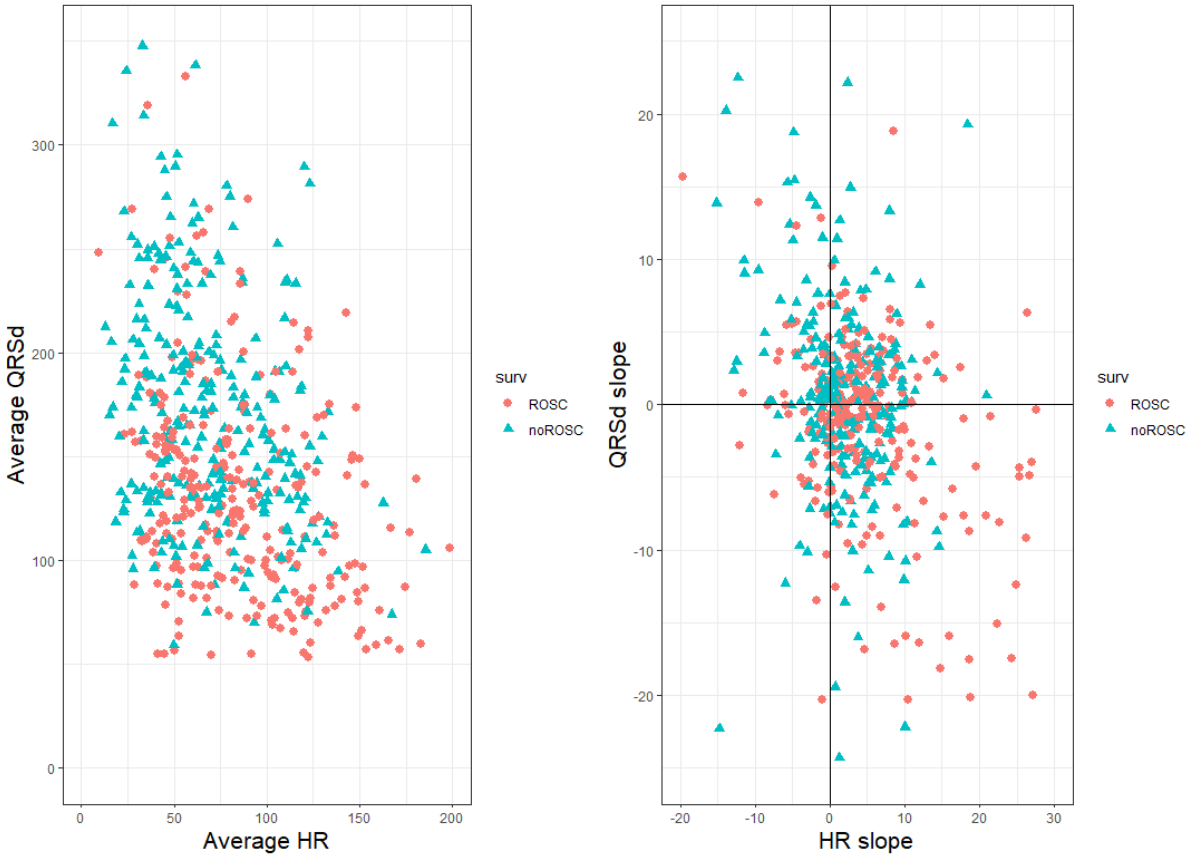


Figure 4.2.2 (published as figure S4 in the supplementary material of Study II): Bivariate plots showing the correlation between average HR and QRSd in each included PEA segment (dot). Also shown is the covariation between the HR slope and QRSd slope for each segment in the right plot. Average values and slope estimates overlap between segments moving to ROSC and not, but there is still a notable difference between the two groups. PR and no-PR correspond to ROSC and noROSC. This is a retrospective and static picture of the development of HR and QRSd

The overall results are expressed as intensity ratios (found in Table 2 in study 2) and through estimated immediate outcome probabilities visualized in the dynamic prediction plots. Higher HR ($p<0.001$), increasing HR ($p<0.001$), lower QRSd ($p<0.001$), and decreasing QRSd ($p=0.023$) increase the probability of gaining ROSC. I have chosen to focus on the prediction plots as they are easy to understand and communicate the results in a clinical applicable fashion.

To introduce the reader to the dynamic prediction plot, we defined a "typical patient" as having primary PEA with HR of 80 bpm and QRSd of 130ms that remain constant during the first four minutes of resuscitation (Fig. 4.2.3). These HR and QRSd values were chosen because they were close to the global average HR and QRSd (Fig 4.2.x). Based on the HR and QRSd values obtained at 0 min (initial rhythm analysis), 2 min, and 4 min and their change during this period (expressed as the slope of the linear estimate), the model estimates the probability

of gaining ROSC or transitioning to other states in the coming 4 minutes. New updated estimates may be calculated as new HR and QRSd values are added.

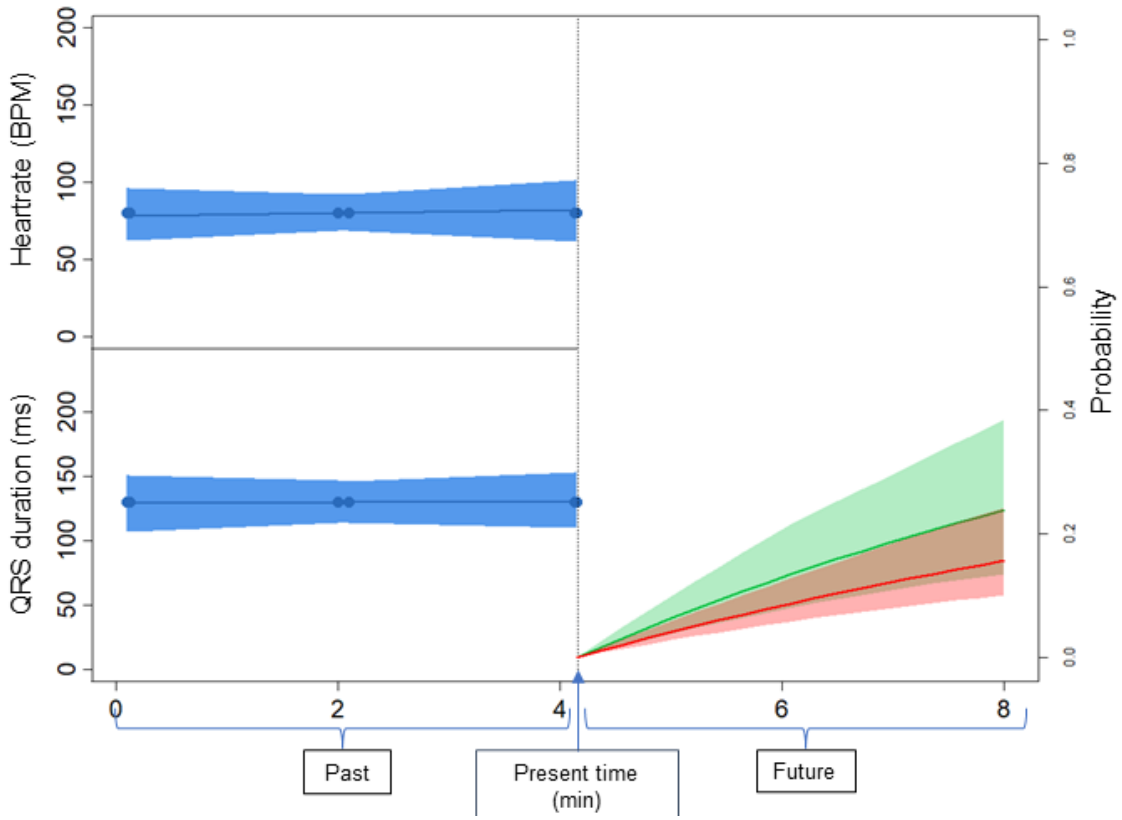


Figure 4.2.3 (published as Fig 2 in Study 2): Prediction plot of the "typical patient" who has been in PEA$_{PRI}$ for approx. 4 min. During this period, HR has been constant at 80 bpm, and QRSd has been constant at 130 ms (blue dots), as illustrated by the left part of the figure. The right part of the figure shows the probabilities of the different immediate outcomes (state following the PEA segment). The probability of ROSC in the next 4 minutes is illustrated by the green line with 95% credible interval (green area), and the estimated probability of noROSC is illustrated by the red line with 95% credible interval (red area). The estimated probability of remaining in PEA is not shown but equals one minus the sum of ROSC and noROSC. The calculation of these probabilities is based on the slope/changes in HR and QRSd up the to present time (slope equals zero in this case), the absolute value of HR and QRSd at present time (80 bpm and 130 ms), the estimated trajectory of HR and QRSd the next 4 minutes (extending the blue line, also at 80 bpm and 130 ms) together with PEA type and time from episode start.

Figure 4.2.4 illustrates how changes in the different dynamic covariates affect the estimated immediate outcome. Patients experiencing high and increasing HR, together with a low and decreasing QRSd have the highest estimated probability of ROSC.

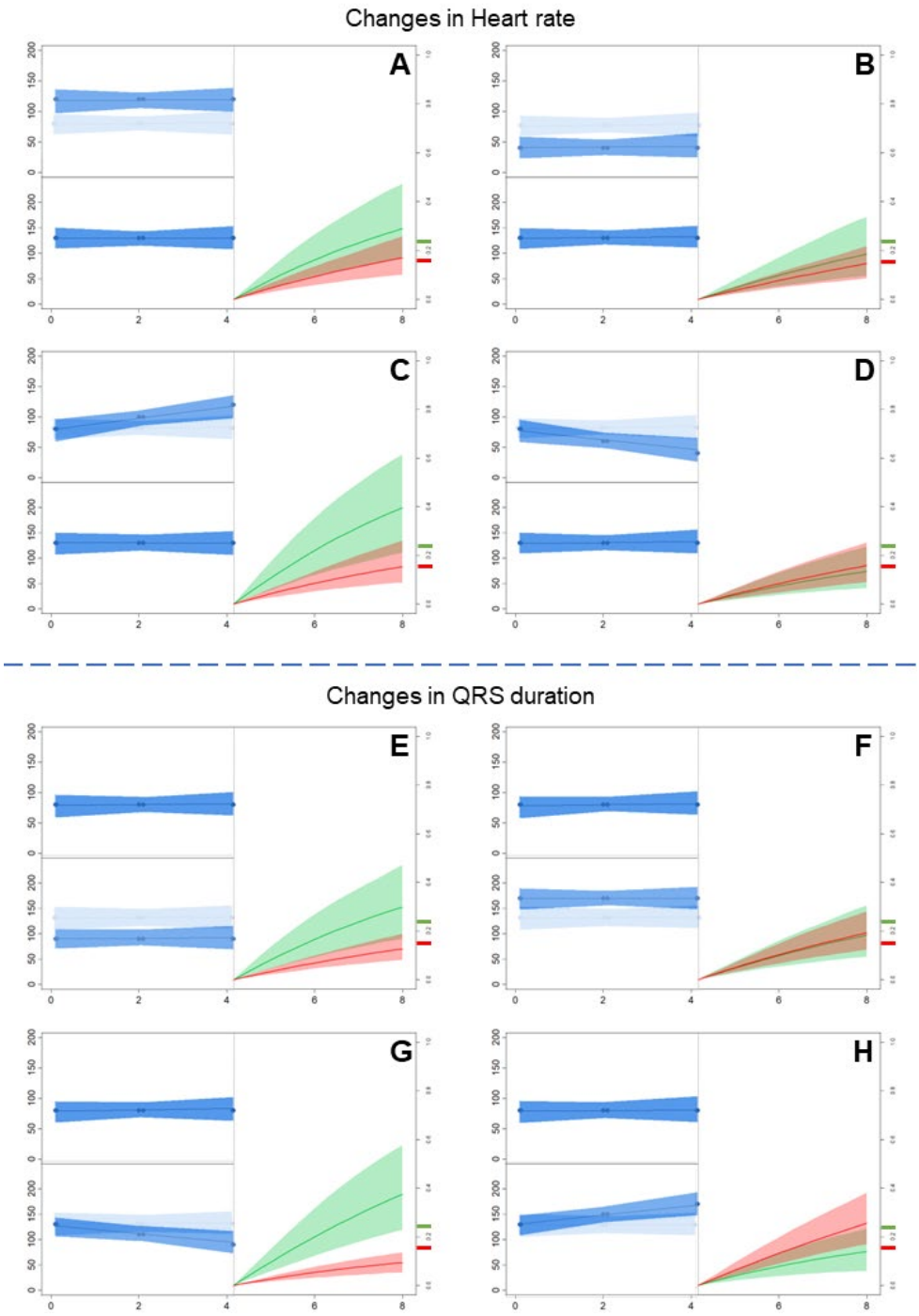


Figure 4.2.4: This figure illustrates how changes in HR and QRSd affect the probability of an immediate outcome estimated by the model. For reference, HR and QRSd values from the "typical patient" can be seen as light shadows. The estimated probability of ROSC and no-ROSC of the "typical patient" can be seen as a thick green and red lines respectively on the probability axes. A: The impact of 40 bpm higher HR. B: The impact of 40 bpm lower HR. C: The impact of HR increasing by 10bpm/min, combining the effect of a higher absolute value and change in HR over time. D: The impact of an HR decreasing by 10 bpm/min. E: The impact of a 40 ms lower QRSd. F: The impact of a 40 ms higher QRSd. G: The impact of a QRSd decreasing by 10 ms/min H: The impact of a QRSd increasing by 10 ms/min.

According to the model, a patient with primary PEA and an HR of 120 bpm has a 1.39 (1.21-1.58) times higher transition intensity to ROSC compared to the typical patient and a (non-significant) 1.07 (0.91-1.26) times higher transition intensity to no-ROSC (Table 2 in Study II). In sum, this yields an increased probability of ROSC, an essentially unchanged probability of no-ROSC (Fig. 4.2.4 A), and (implicitly) a decreased probability of remaining in PEA. Also, a shrinking QRSd reflects an increased transition intensity to ROSC and a decreased intensity to no-ROSC (Fig. 4.2.4E).

As in Study I, the probability of ROSC is related to the type of PEA. With $PEA_{PRI}$ as a reference, $PEA_{ROSC}$ and $PEA_{VF/VT}$ reflect an increased transition intensity to ROSC. $PEA_{ASY}$ is not associated with changes in the transition intensity to ROSC compared to $PEA_{PRI}$. Still, due to the accumulated time since the start of the episode, $PEA_{ASY}$ has a lower probability of ROSC as every additional minute is associated with decreased transition intensity to ROSC and increased transition intensity to no-ROSC according to this model.

A high QRSd and a positive QRSd slope reflect an increased probability of no-ROSC (Fig. 4.2.4F and H). Still, 87 segments with a QRSd increase of more than 1 ms/min and 23 segments with a QRSd increase of more than 5 ms/min gained ROSC (Figure 4.2.2).

In Figure 4.2.5, we have used HR and QRSd data from two of the included PEA segments and plotted their immediate outcome probabilities in dynamic prediction plots. Despite both gaining ROSC, there is a big difference in estimated ROSC probability by the end of the segments. This illustrates the clinical application of our model and underscores the importance of not using the model to predict death, ASY or VF/VT.

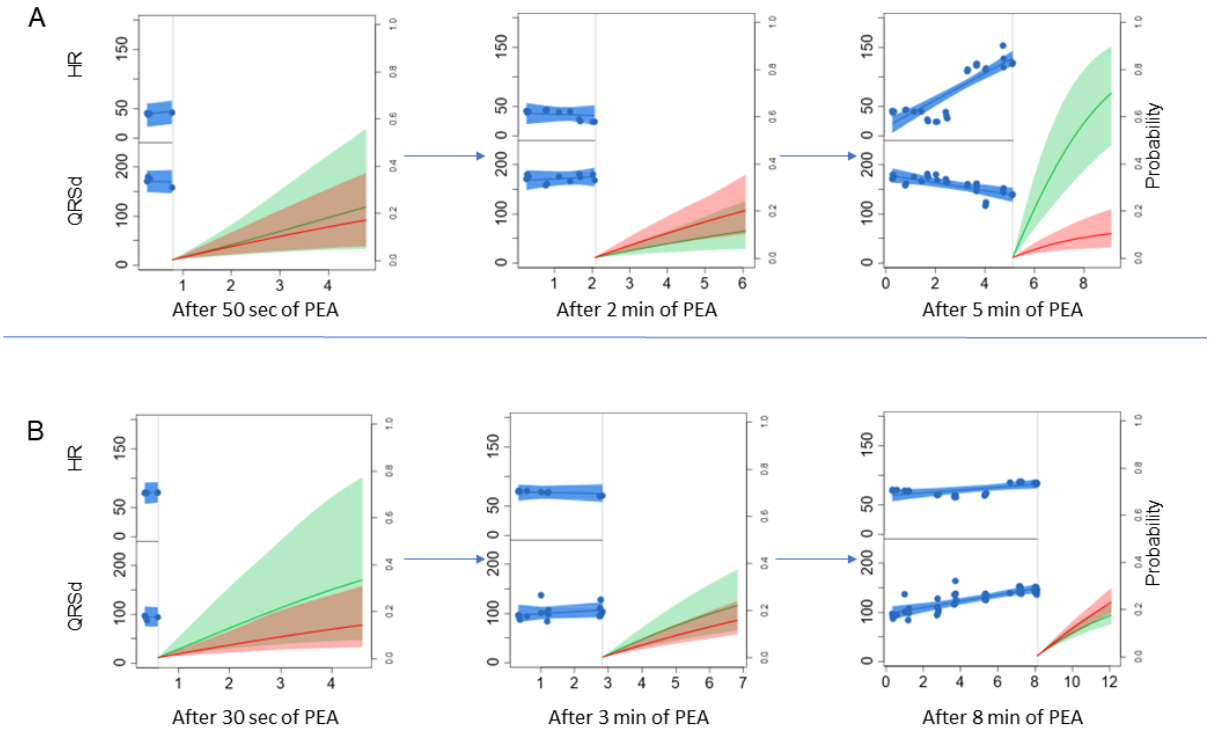


Fig 4.2.5 (published as Fig 4. In study 2): PEA segments from two patients illustrate actual but different HR and QRSd developments in $PEA_{PRI}$ during CPR. Patient A, in the upper row, gained temporary ROSC at approximately 7 minutes, but rearrested and was later declared dead. Patient B, in the lower row, transitioned to sustained ROSC at 8 minutes and 25 seconds; illustrating that resuscitation should not be terminated based on this observation alone.

## 4.3 Specific results from Study III

We registered 280 episodes of cardiac arrest in 265 patients between August 2018 and October 2022.

Adrenaline was administered in 120 episodes, and 93 were eligible for analysis. The reasons for excluding episodes are illustrated in Figure 4.3.1.

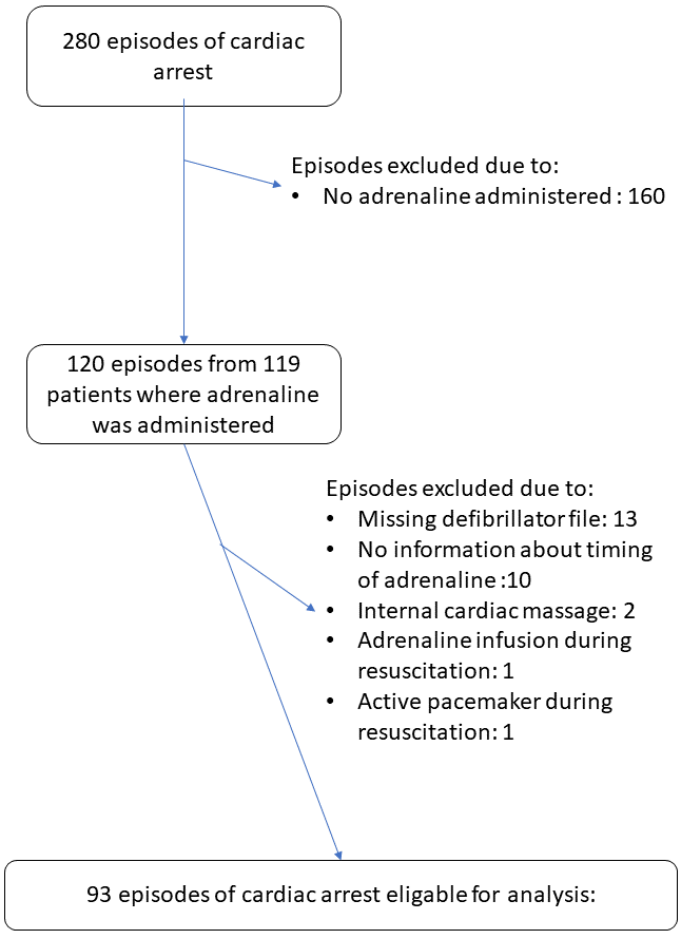


Figure 4.3.1: Exclusion of episodes from Study III

The exclusion process was seemingly random, with similar characteristics for episodes included or not (Table 4.3.1).

The prevalence plots and the Sankey plots provide an overview of changes in clinical states during 8 min (-3 min to 5 min after adrenaline) in all episodes receiving adrenaline (Fig. 4.3.2). Visually, ROSC occurred quickly after adrenaline. The first dose was associated with the highest ROSC rate (29%) at 3 minutes. Hence, most patients who respond to adrenaline did

so within minutes of administration, and the probability of ROSC was largest after the first dose.

| | **All patients experiencing cardiac arrest (n=265)** | **All patients receiving adrenaline (n = 119)** | **Patients eligible for adrenalin analysis (n = 93)** |
|---|---|---|---|
| Male gender | 175 (66%) | 79 (66%) | 63 (68%) |
| Mean age | 70.0 years (min 22, max 97) | 71.5 | 71.7 (min 37, max 91) |
| Survived to discharge | 113 (43%) | 20 (17%) | 15 (16%) |
| | | | |
| | **All cardiac arrest episodes (n = 280)** | **Cardiac arrest episodes receiving Adrenaline (n = 120)** | **Episodes eligible for adrenaline analysis (n= 93)** |
| Initial rhythm<br>• PEA<br>• VF/VT<br>• Asystole<br>• Unknown | <br>92 (33%)<br>128 (46%)<br>43 (15%)<br>17 (6%) | <br>66 (55%)<br>21 (18%)<br>31 (25.5%)<br>2 (1.5%) | <br>51 (55.5%)<br>14 (15.2%)<br>26 (28.2%)<br>1 (1.1%) |
| Witnessed collapse | 237 (85%) (20 with unknown status) | 95 (79%) (12 with unknown status) | 69 (75%) (11 unknown) |
| Occurred in units with continuous monitoring | 152 (54%) | 58 (48%) | 45 (50%) |
| Cardiac etiology | 164 (59%) (45 with uncertain etiology) | 53 (44%) (23 with uncertain etiology) | 42 (46%) (20 with uncertain etiology) |
| Number of episodes with ROSC | 177 (67%) (5 put on mechanical circulation) | 45 (37.5%) (5 put on mechanical circulation) | 35 (38%) (1 to ECMO) |

Table 4.3.1 (published as Table 1 in study III): Detailed overview of patient characteristics.

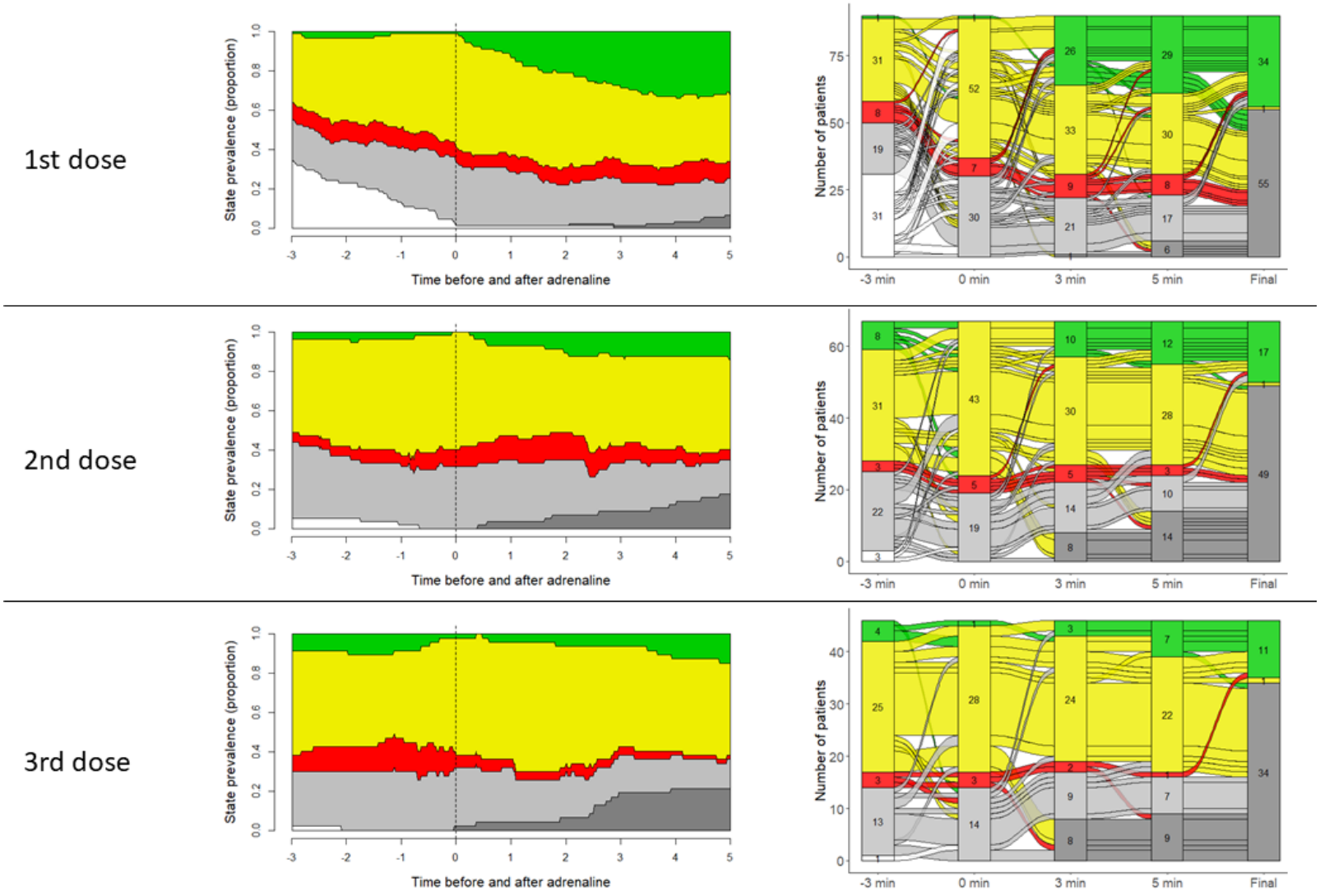




Figure 4.3.2 : The prevalence plots (at the left) show changes occurring before and after the administration of adrenaline (time 0, dashed line). We see a substantial recruitment of patients to ROSC after the first dose. The Sankey plots (to the right) show details about the flow between different states. Patients gaining ROSC are mainly recruited from PEA.

The Cox model estimated an intensity ratio ("hazard" ratio) from primary PEA to ROSC of 3.5 (p=0.01) associated with the first adrenaline dose.

In the linear spline models, we included 69 episodes in conjunction with the first dose, 55 with the second dose, and 40 with the third dose. Figure 4.3.3 depicts changes in HR in conjunction with the first dose. We observed a significant increase in HR the first two minutes after administering the first dose (9.5 bpm per min, p = 0.025). There was also a significant change in HR slope (p=0.05) when comparing the interval from administration to 2min after the preceding interval (2min before until administration). Neither the second nor third dose affects HR or QRSd according to this model.

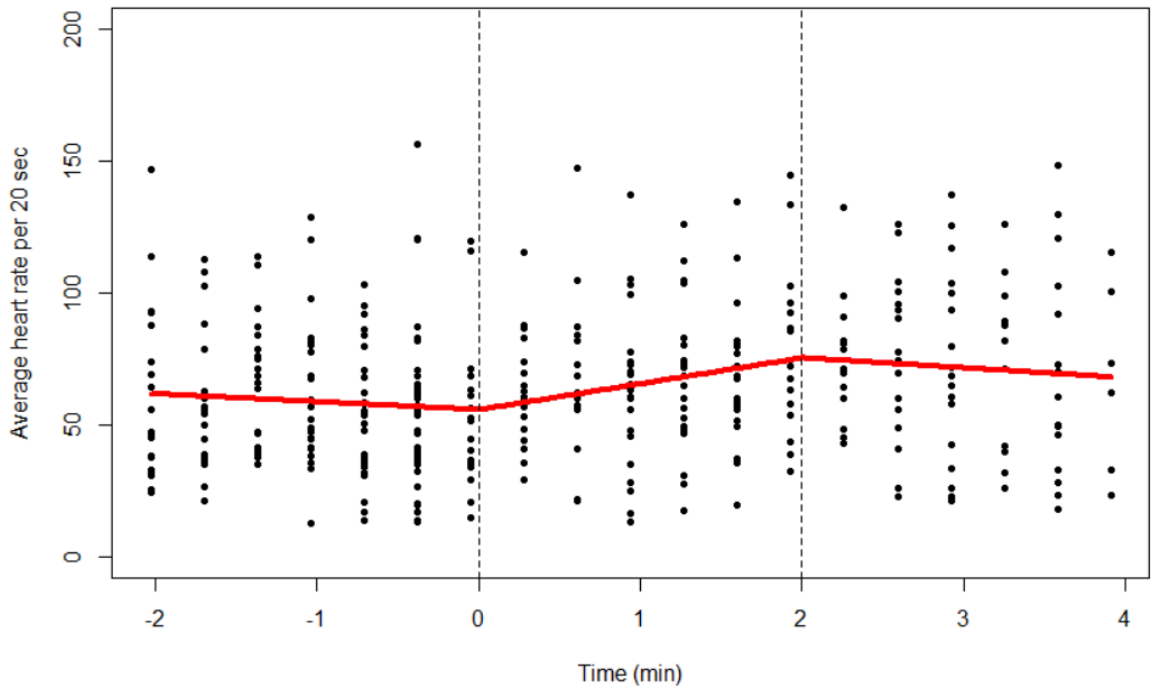


Figure 4.3.3: The linear spline model depicting changes in heart rate before and after administration of adrenaline (time 0). There are significant changes in heart rate the two first minutes after administration, and the slope of this segment is significantly different from the preceding segment.

Figure 4.3.3 illustrates changes in HR within episodes and HR changes within the whole PEA two minutes after administration of the first dose of adrenaline. Here we see that patients in PEA experienced both increasing and decreasing HR during this period. There seems to be a net increase in HR during this period.

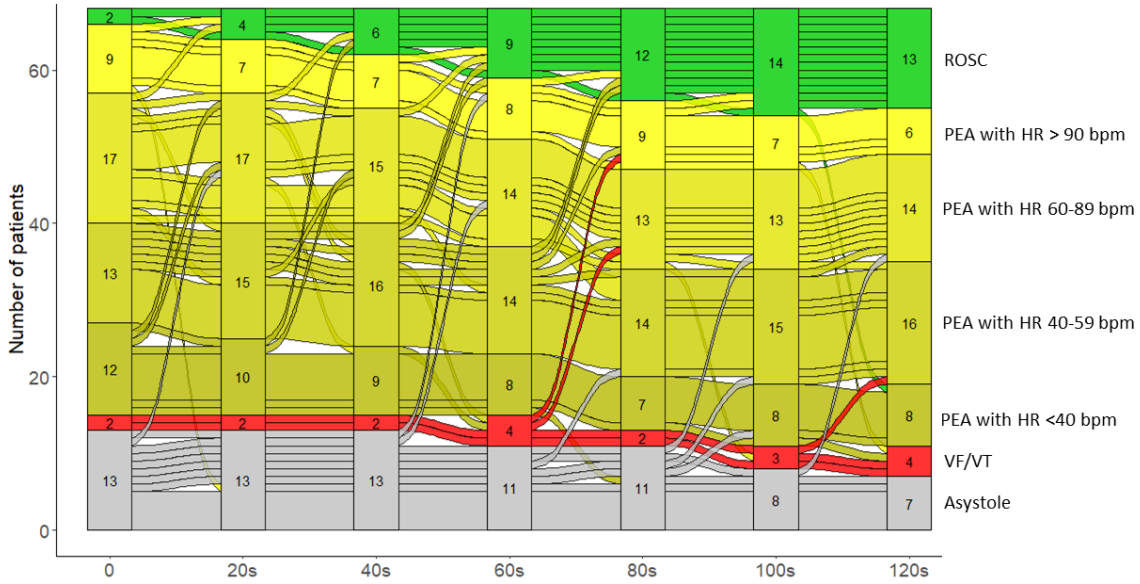


Figure 4.3.3 (Figure 3 in Study III): Detailed overview of transitions between different states and different HR groups during the first 120s after administering the first adrenaline dose. There seems to be a net increase in HR among individual PEA segments, and there is a relatively more extensive efflux of patients from the PEA group with HR over 90 bpm.

We should also take note of transitions in and out of PEA as these may change HR distribution, blunting or exaggerating HR's response to adrenaline. We observe 12 transitions from other states to PEA and 19 from PEA to other states during this period. There is a net efflux of patients from the PEA groups with HR >90 bpm and HR<40 bpm and a balanced transition to and from the PEA groups with HR 40-89. Since the efflux is largest from PEA >90 bpm, the magnitude of the HR increase observed after administering the 1st adrenaline dose may be underestimated by the spline model.

Figure 4.3.4 show the cumulative administration of adrenaline for patients in primary PEA. Approximately 80% have received their first dose within 6 minutes.

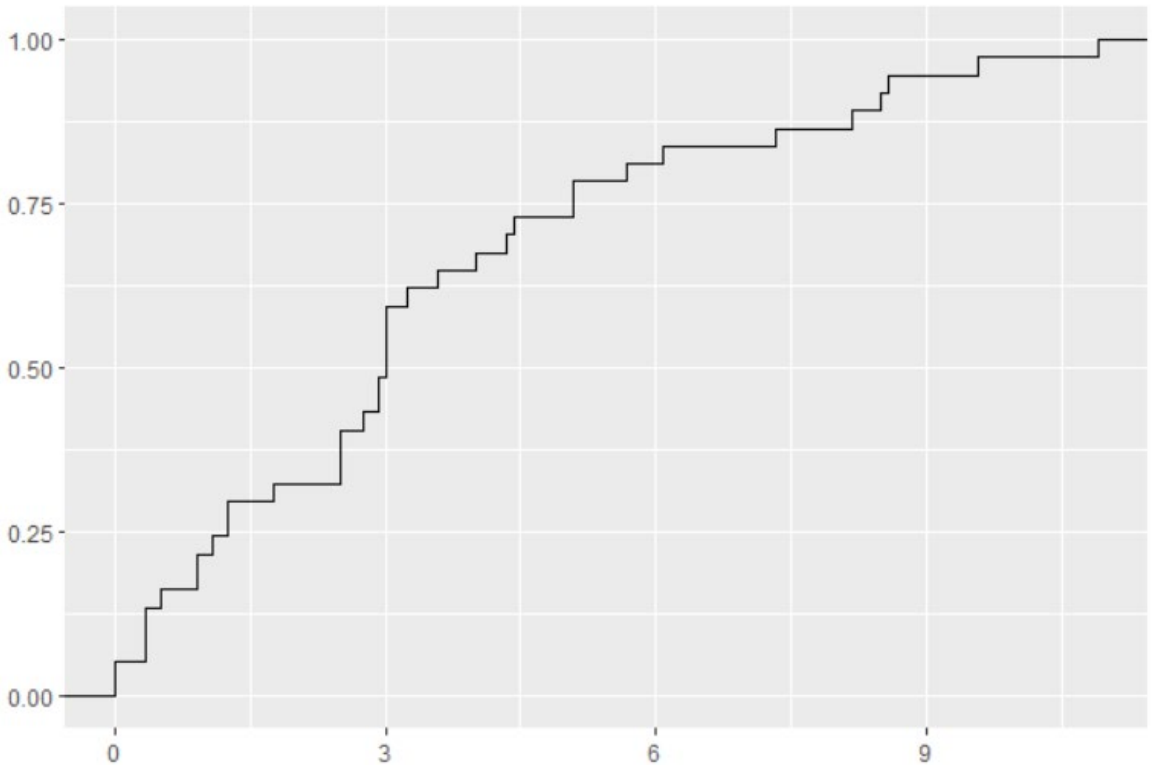


Figure 4.3.4: Cumulative timing of adrenaline administration *during PEA$_{PRI}$*. Administration of adrenaline is spread out in time (min, x-axis), approximately 80% (y-axis) receive their first dose within 6 minutes, and the highest administration rate is observed during the first three minutes.

# 5. Discussion

In this thesis, we have focused on PEA during in-hospital cardiac arrest. We have found that PEA is a central and very important clinical state when resuscitating patients with IHCA. PEA was the most common initial arrest rhythm (60%) in Study I and was observed at some time in almost 85% of all 700 episodes included in this study. We also observed that PEA preceded 75% of all transitions to ROSC. This underscores the importance of understanding this arrest rhythm. By stratifying PEA based on origin, we could identify critical key transitions on the road to ROSC and show that PEA of different origins behaves differently. Expanding on this, we explored changes in QRS frequency and QRS width, characteristics unique to PEA. We evaluated their ability to predict ROSC during PEA and found that high and increasing HR or low and decreasing QRSd reflected an increasing probability of ROSC. To better understand the driving forces behind ROSC, we investigated changes in clinical states after adrenaline administration and found that patients started to gain ROSC immediately. We expected that changes in both HR and QRSd could possibly reflect adrenaline effect, but we only saw a significant increase in HR after the administration of the first adrenaline dose.

## 5.1 Do arrest rhythms occur at random?

Respiratory, cardiac, and metabolic conditions seem to be the dominating causes of PEA.[66, 67] The recent experimental findings of Ambinder et al. are interesting in this context.[68]. They hypothesized that the left ventricular function would determine whether a pig heart developed PEA or VF/VT when subjected to ischemia. They included one group of healthy pigs and one group with severe left ventricular failure. The left ventricular failure was induced by a 2-hour occlusion of the right coronary artery and the left circumflex artery performed one week apart. After occluding the left descending coronary artery of the healthy pigs, 18 of 34 individuals developed VF (mean time to VF was 23.5min after the occlusion). All 18 pigs with severe left ventricular dysfunction (mean ejection fraction of 15%) developed PEA within minutes (mean time to PEA was 1.7min after the occlusion), and 16 of these pigs experienced a subsequent degradation into VF. Those who underwent ischemic preconditioning experienced significantly longer times to VF (33.8, +/-7.7 min vs. 12.3 +/-5.0 min). Stankovic et al. found an association between cardiac disease, witnessed or monitored IHCA, and initial shockable rhythm.[69] They also found that non-cardiovascular disease, higher age, and female gender were associated with a non-shockable presenting rhythm. When comparing the characteristics of ASY and PEA in IHCA, Høybye et al. found that female sex, age >90 years, and non-witnessed arrest predicted ASY.[70] Meany et al. found that patients with shockable rhythms were more likely to have pre-existing cardiac disease, ongoing myocardial infarction, and congestive heart failure. On the other hand, they were less likely to have hypotension, respiratory insufficiency, and renal failure.[71]

## 5.2 In and out of PEA

The preceding discussion indicates that PEA patients are sicker than patients presenting with a shockable rhythm, and the patient's physiological state may determine the initial rhythm of cardiac arrest. Subsequent changes in arrest state likely occur as a response to treatment or the underlying condition. This may explain why patients with secondary PEA tended to relapse to the original arrest rhythm, as demonstrated in Study I (Fig. 4.1.3). A similar tendency was seen in out-of-hospital CA, where the initial clinical state affected later changes.[58] Changes in CA rhythms may help the treating team better understand the evolution of the patient's situation. Based on Figure 4.1.1, the transition from PEA to VF may reflect worsening of the patient's condition. The work of Ambinder et al. supports this, and it was also shown by Meany et al.[71]

The relapse from ROSC to PEA should be seen as a sign that the pathological process causing the arrest has not yet been halted. This should encourage a reevaluation of the underlying cause. Albeit the disappointment a relapse might bring, the treating team must remember that the probability of re-achieving ROSC is relatively high, and resuscitation should continue.

## 5.3 "Are we there yet?"

A common question from children in cars is "Are we there yet?" The interest in progress is universal to humans. Objective markers of a process are essential in modern medicine. Identifying a subtle worsening or improvement allow clinicians to change strategy before it's too late. The C-reactive protein is measured daily to surveil the effect of antibiotic treatment. Troponin T is measured repeatedly to detect even the smallest myocardial infarctions. An arterial blood gas may be analyzed several times per hour to optimize the treatment of patients with respiratory failure.

When treating cardiac arrest, we do not have an equivalent to the C-reactive protein. Therefore, we cannot objectively monitor the effect of treatment and change strategy if needed. A systematic review of pre- and intra-arrest factors and their relation to the outcome of IHCA found that increasing age, active malignancy, and male gender were associated with reduced survival. In contrast, shockable rhythm, witnessed arrest, and arrest during daytime were associated with increased survival. [24] These are primarily static parameters that apply to a population but may be challenging to use when assessing individual patients. Elderly patients may also survive IHCA with good neurological outcomes. [72] Change in the clinical state, HR or QRSd, on the other hand, are dynamic biomarkers that may reflect an underlying process within the individual, either positive or negative.

Patients with $PEA_{VF/VT}$ during the first minutes of resuscitation had a very high likelihood of achieving ROSC, but the probability decreased with time. In some cases, $PEA_{VF/VT}$ may

therefore actually represent (undetected) ROSC. The classification of $PEA_{VF/VT}$ may partially be a consequence of the current resuscitation algorithm, which instructs personnel to resume CPR for one minute immediately after a shock before checking for pulse or evaluating the rhythm.[73] Nonetheless, patients categorized with $PEA_{VF/VT}$ probably "accepted" the continuation of chest compressions, a sign that they did not wake immediately after the shock.

Patients with $PEA_{ASY}$ showed the lowest probability of gaining ROSC compared to the other PEA types. Albeit 2/3 of the patients with primary ASY and sustained ROSC as their final rhythm were in PEA during their final stages of resuscitation. A transition from ASY to $PEA_{ASY}$ may indicate improvement in the patient's condition and justifies the continuation of resuscitation efforts.

Common to the four different PEAs is the high probability of gaining ROSC during the early resuscitation phases. The initial high transition intensity also reflects a shorter time to ROSC in this phase. Later, when intensities are lower, we should expect longer times to ROSC. This time dependent variation in ROSC probability is not reflected in Study II due to different methodology, but the overall probability of gaining ROSC from the different PEA types is similar in both Study I and Study II.

## 5.4"ARE WE THERE YET???"

The question is usually repeated countless times during a trip. The tone in which it is asked reflects the child's emotional state. The answer "we have passed Steinkjer" is useful but not very precise. Based on GPS data, the estimated time of arrival (ETA) could maybe soothe the child, but one should also inform about the assumptions behind this estimation.

In addition to taking note of changes in clinical state, PEA also presents several ECG characteristics that may change during resuscitation. We chose to look closer at HR and QRSd as changes may be visually appreciated bedside. HR is always easy to gauge, but small QRSd changes may be more challenging to estimate, but large changes are observed easily.

The duration of the QRS complex responds quickly to changes in the cardiac homeostasis and may be affected by diseases that could cause cardiac arrest. Whether there is a correlation between HR and QRSd in healthy individuals has been debated, and the question remains unsolved. [74-76] Hyperkalemia is known to widen the QRS complex and in its most severe form, cause fusion with the T wave creating a sinusoidal pattern in the ECG and cardiac arrest. [77] Several studies have shown that changes in coronary perfusion change the QRS duration. This has been demonstrated both in animals and humans. Hamelin et al. found QRS widening after inducing myocardial infarction by injecting ceramic microspheres into the left circumflex artery of anesthetized dogs. [78] They found a significant increase in QRSd from 48 ms to 90 ms 2-5 min after the procedure.

Holland et al. reported that the intrinsicoid deflection (time from the beginning of the QRS complex to the top of the R wave) would increase 2-3 times relative to baseline values after ligating the left descending coronary artery in porcine hearts. The values returned to normal 2-4 heartbeats after releasing the occlusion. [79]

Ahnve et al. published results showing exercise-induced QRSd prolongation in humans with angina.[80] Pranata et al. published a meta-analysis in 2019 where they summed up the knowledge on changes in QRS complex as a predictor of successful reperfusion in patients with ST-elevation myocardial infarction.[81] They found a significant narrowing of QRSd of 6-17 ms immediately after the intervention when the myocardial blushing grade (an angiographic measure of myocardial microcirculation) indicated successful microvascular reperfusion. These findings show that ischemia of the myocardium may increase the depolarization time and that resolving the local circulatory problem immediately restores depolarization towards normal and shortens the QRSd.
Duc H et al. studied ECG changes in telemetry recordings of 81 patients at least three hours before IHCA and found an increase in QRSd of at least 20 ms prior to arrest in 15 out of 81 IHCA.[82] This change was most common among patients with multi-organ failure and mostly led to bradyasystole or PEA. In 2020 they described continuous ECG changes leading up to asystole or PEA due to right ventricular strain[83]. They also reported that the continuous widening of the QRS complex was a central change leading up to the right bundle branch block before arrest. On average, the first sign of right ventricular strain was seen 7.2 min before the arrest.

Skjeflo et al. found narrowing of the QRS complex 3-6 minutes prior to ROSC and widening prior to death, which resulted from conditioning on the outcome.[30]

HR is affected during cardiac arrest. Bhalala et al. found that among 98 patients with IHCA outside the ICU, 53 had had antecedent bradycardia, defined as cardiac arrest with at least two minutes of continuous HR <60 bpm preceding the event. [84]
Do et al. found that bradyarrhythmia preceded cardiac arrest in 23 out of 81 patients, and in approximately 50% of these patients, changes started less than 10 min before the cardiac arrest[82]. Shan et al. described increasing HR after onset of hypoxia and a sudden decrease in HR during decompensation prior to PEA.[85]

The results of these studies support the findings in Study II showing that patients with higher/increasing HR and narrower/decreasing QRSd have a higher probability of gaining ROSC. It is likely that the QRS complex, in some instances, widens prior to/during the cardiac arrest because of hyperkalemia, myocardial ischemia, or right ventricular strain. The narrowing of the QRS complex observed in our study may be a response to the correction of

these processes during advanced life support. This knowledge may instantly provide the treating team with an probability of ROSC. We have focused four minutes ahead, reflecting on two international cycles of CPR. When the estimate is updated as new values are entered, the treating team may reveal improvements in the patient's condition as the probability of ROSC increases. A positive development, as observed in Fig. 4.2.5 A, could encourage one to carry on and avoid hands-off time.

A neutral development, as observed in Fig. 4.2.5B, may prompt one to reconsider some aspects of resuscitation, like evaluating the quality of chest compressions and searching more closely for reversible factors.

A negative development (decreasing probability of ROSC over time) caused by high/increasing QRSd is associated with increased transition intensity to VF/VT, ASY, or death. This is also a statistically significant result (Table 2 in Study II). Still, such development should not be interpreted too strongly, as it was commonly seen in segments ending in ROSC (Figure 4.2.2). For this reason, QRS widening cannot be used alone to terminate the resuscitation effort, nor be used as the only indication of worsening of the patient's condition.

Adrenaline increases ROSC. Could changes in HR and QRSd be a reflection of the adrenaline effect? Based on the results in Study III, it seems likely that adrenaline increases HR in some patients. QRSd, on the other hand, does not seem to be affected by adrenaline. Considering the results of Study II, one could be tempted to think that the increasing HR observed after adrenaline administration is later followed by ROSC. This may not be the case as patients with increasing HR after adrenaline administration must remain in PEA during the observation period to exhibit this change (two first minutes after administration). Still, they may develop ROSC at a later stage.

Skjeflo et al. investigated the plausible association between adrenaline and changes in HR and QRSd in patients with OHCA and primary PEA included in Olasveengens RCT on intravenous access during OHCA. [16, 86] He stratified patients based on ROSC and adrenaline status and found that patients receiving adrenaline and gaining ROSC experienced both HR increase and QRSd decrease. Patients achieving ROSC and not receiving adrenaline experienced similar changes, but HR increased to a lesser degree. On the other hand, patients who were declared dead after receiving adrenaline experienced an increase in HR and QRSd, while patients being declared dead and not receiving adrenaline experienced only an increased QRSd. These findings indicate that adrenaline increases HR in patients with primary PEA but does not affect QRSd. Our results are not directly comparable to these. We investigated IHCA while Skjeflo looked at OHCA. We report the overall association between adrenaline and changes in HR and QRSd regardless of initial rhythm and outcome, while Skjeflo et al. stratified his

population. Our timeline is related to the administration of adrenaline, while Skjeflo et. at. did not know when the adrenaline was administered. Despite these differences, our results point in the same direction. The most important limitation of our study was not to include a control group for comparison; hence we can't know whether the observed changes are due to adrenaline. Despite this, when interpreting our results in the context of Skjeflo's results, which are based on randomly assigned groups, we find it likely that the changes seen in HR are due to adrenaline. Also of interest, we observed increasing HR both in the ROSC group and in the noROSC group as seen in Figure S5 in the supplementary material of Study II.

## 5.5 "Finally, now we are here!"

After countless peeing brakes and other brakes, the initial ETA has been passed by hours. The frustration in the backseat rises to new levels as the kids realize that we are still not there. You pull over at the nearest gas station, fill up with JET petrol, fire up the engine, now roaring like a fighter jet and in an instant, you reach the destination regretting that you did not do this earlier.

It is known that adrenaline causes ROSC[15-17, 48], but in what manner has not yet been described to the best of our knowledge. In Study III, patients started to gain ROSC immediately after adrenaline was administered; the first dose was associated with the highest ROSC rate. From the prevalence plot, we see a steady increase in ROSC the first 4 minutes after the first dose of adrenaline was administered. Most of these patients are recruited from PEA. This is expected as most patients with VF/VT as initial rhythm already has gained ROSC after defibrillation. Now, reconsider Figure 4.1.3 in light of Figure 4.3.4. The rate of adrenaline administration for patients in $PEA_{PRI}$ is highest during the first 3 minutes of resuscitation (Fig. 22). Interestingly, this coincides with the quick rise and top of the transition intensity to ROSC, seen in Study I (Fig 4.1.3).

As we do not have an independent control group, we cannot necessarily claim a causal relationship between adrenaline administration and ROSC. However, each patient will in principle act as his/her own control: adrenaline is administered at different times (fig 4.3.4) after initiation of resuscitation. The main limitation is therefore not the lack of control group but rather that the timing of adrenaline was not randomized. The "aggressiveness" of treatment may possibly have been related to some aspect the patient's condition (e.g., a very slow HR), or that the patient was already monitored. However, it is natural to expect that patients with the perceived worse prognosis gets the more aggressive treatment, so the observed effect may in fact be underestimated. Furthermore, the relationship between adrenaline and ROSC has already been firmly established, so it is therefore likely that the observed transitions to ROSC are mainly due to adrenaline.[48]

Adrenaline speeds things up. Patients who have not achieved ROSC yet did so quickly after administering the first dose, as illustrated by the prevalence plots in Fig. 4.3.2. Interestingly, 38% of those receiving adrenaline achieved sustained ROSC. This ROSC rate is comparable to the rate seen in the adrenaline arm of the three OHCA RCTs (24% Jacobs et al., 32% Olasveengen et al., 36% Perkins et al.). We expected the in-hospital rate of ROSC to be higher due to earlier administration of adrenaline and better long-term survival observed in this group. Also, several studies show that early adrenaline administration during IHCA may improve survival. [3, 4, 87] A secondary analysis of the study population in PARAMEDIC2 found higher but not significantly different survival to hospital discharge, 30-day survival and survival with favorable neurological outcome between patients receiving early adrenaline or early placebo.[88] These results should be interpreted with caution as PARMEDIC2 was not designed to answer these questions and the number of patients receiving adrenaline early was small. One should also remember that the initial rhythm of the studied population was dominated by ASY (43%).

The response to the third dose is interesting. Only 7% gain ROSC within 3 minutes and 15% within 5min, indicating possibly little or no effect from adrenaline. Despite this low initial ROSC rate, 24% of these patients have gained ROSC by the end of the resuscitation efforts. These patients may circulate adrenaline slower due to patient or CPR factors. Alternatively, they do not respond to adrenaline at all; if that is the case, adrenaline may harm these patients.

Nordseth et al. claimed that adrenaline extended the time window for ROSC development in patients with OHCA and PEA. [89] This was also found by Perkins et al as the ROSC ratio between the adrenaline arm and placebo arm increased during the later phases of resuscitation. Ischemic myocardium may be viable for several hours and the most common cause of death after a successful resuscitation is anoxic brain injury indicating that the heart often tolerates the arrest. [90 91]

To summarize, it seems like adrenaline could be viewed as a tool to gain ROSC and help to bring the patient out of the acute circulatory collapse. This is a necessary step for long term survival. Long term survival on the other hand is determined by several factors, like pre-arrest comorbidity, the global ischemic insult caused by the arrest, and post arrest complications. These factors may not be reflected in the process of gaining ROSC. Therefore, long-term survival is not a suitable outcome when studying treatment response during CA. It's not so hard to gain ROSC but it may be difficult to stay alive afterwards.
I believe that ROSC should be the primary goal for the arrest team. They dispatch to a chaotic situation around an unknown patient in an unfamiliar location. This is not a good setting to determine a good and reliable long-term prognosis. This is better dealt with in the intensive

care unit when the patient is stable and all information about the patient has been made available.

## 5.6 ECG characteristics and outcome

Study II is not the first to investigate the predictive ability of the ECG during PEA. A structured literature search in PubMed, Embase, and Web of Science was performed between 26.04 and 27.04.2021. The findings of the 8 studies retrieved from this search are summarized in the following discussion. A detailed overview of the search strategy applied can be found in the Appendix.

### Aufderheide et al (1989):

This was the first study to investigate the predictive value of ECG during resuscitation from PEA in humans (formerly known as electromechanical dissociation or EMD)[25]. They analyzed the ECG from 503 patients experiencing out of hospital cardiac arrest (OHCA) with PEA as their presenting rhythm. Of these, 405 patients were declared dead, 98 patients were admitted to the emergency department, and 22 survived to hospital discharge. Three investigators evaluated the initial and final ECG recordings before terminating CPR or at the end of transport before admitting the patient to the emergency department. They measured the QRS rate, width, QT intervals, and presence of P waves indicating sinus rhythm. The statistical approach was simple comparisons of means. The mean initial QRS rate in survivors and non-survivors was 75/min and 55/min, respectively. This was a statistically significant difference. The mean QRS interval was 90 milliseconds (ms) in survivors and 120ms in non-survivors a statistically significant difference. The QT interval was 460ms in survivors and 560ms in non-survivors a statistically significant difference. P waves were present in 42.9% of the survivors and 21.0% of the non-survivors, also a statistically significant difference. In addition, he observed that survivors could increase their QRS rate, shortening their QT interval and producing P waves during treatment. Those who died during their hospital stay experienced an increased QRS rate over baseline and had tachycardia at admission to the ED. In those who were discharged from the hospital, the QRS rate normalized at admission to the ED.

The study is mainly limited by lacking a detailed description of the data collection process and study population. It should also be pointed out that the results are over 30 years old.

### Hauck et al (2015):

This was a retrospective chart review of 262 patients over 18 years of age with OHCA[27]. They excluded patients with an initial shockable rhythm, unavailable outcome data, and patients whose initial ECG was not interpretable, including QRS complexes broader than 200ms. The primary outcome was defined as survival to hospital discharge, and the secondary outcome was defined as neurological intact survival. Twenty-three patients survived to hospital

discharge, and 17 with a good neurologic outcome (cerebral performance category 1 or 2). They measured the average QRS width and rate during the first 20 seconds of ECG recording. Means were compared by two-sample t-tests and the Wilcoxon rank sum test. They found no statistical difference in ECG characteristics between survivors and non-survivors. The mean QRS width was 98.8ms in survivors and 101.4ms in non-survivors. The mean QRS rate was 51/min in survivors and 59.2/min in non-survivors.

As opposed to the other authors, they excluded patients with QRS width >200ms. They used only one ECG investigator.

### Bergum et al 2012:

These investigators looked at ECG characteristics and their relation to survival and the cause of cardiac arrest in patients with IHCA. [92] They prospectively gathered ECG data from cardiac arrests at St. Olavs hospital in Trondheim, Norway identifying 302 episodes from 2009-2013. One hundred forty-four patients had PEA as primary rhythm, but only 51 patients were included since they were the only ones with both a readable ECG file and a reliable cause of arrest. Of these, 21 survived beyond 1 hour, and 6 were discharged from the hospital. They measured the QRS rate, QRS width, and presence of P waves from two to three QRS complexes in the first pause of chest compression. They found no association between these characteristics and survival or the cause of cardiac arrest. The median QRS rate among non-survivors was 51/min, 45/min among 1h survivors, and 42/min among discharged patients. The median QRS width was 167ms among non-survivors, 182ms among 1h survivors, and 145ms among those who were discharged. As for median QTc time it was 439ms for non-survivors, 475ms for 1h survivors, and 513ms for those discharged from the hospital.

This study has a small study population and only included patients with IHCA making it challenging to compare results with the other studies.

### Skjeflo et al (2018):

This study used a different concept of studying ECG characteristics and survival[30]. They included patients over 18 years of age suffering from cardiac arrest at St. Olavs hospital between 2009 and 2012. PEA was the primary rhythm in 114 episodes of cardiac arrest, and 74 episodes were included. The primary outcome was ROSC. They measured the QRS width and rate of 3 QRS complexes in each chest compression pause throughout cardiopulmonary resuscitation. They investigated the relationship between changes in QRS characteristics and ROSC by fitting three different statistical models to their data. Based on these models' results, they describe a strong relationship between changes in these characteristics and ROSC. They concluded that the QRS width got narrower, and the QRS rate increased towards physiological values the last 3-6 minutes before ROSC. Patients that died did not exhibit these changes.

Skjeflo et al. gathered data prospectively using several ECG investigators. They used a completely different methodological approach compared to 6 of the other studies.

### Ho et al (2018):

This was a secondary analysis of patients prospectively enrolled in the OPALS and PRIMED study. They included 332 patients suffering from non-traumatic OHCA from several emergency medical service districts in Ontario, Canada [28]. All had PEA as presenting rhythm. They measured the QRS width and rate of the first 15 seconds or the first six QRS complexes. The patients were stratified based on QRS width (over and under 120ms) and rate (over and under 60/min). Based on a multivariate regression analysis with a stepwise inclusion of variables, they found no significant difference between survivors and non-survivors. However, in their univariate analysis of each variable, they found a significant association between QRS rate <60 and death. The mean QRS rate was 56.8/min in the survivor group and 52,0/min in the non-survivor group. The mean QRS width was 128.7ms in the survivor group and 129.6ms in the non-survivor group.

This is the only multi-center study among the studies.

### Weiser et al (2018):

This group hypothesized that higher initial QRS rates were associated with survival [31]. They included 504 patients from the Vienna cardiac arrest registry from 2013 to 2015. All patients were over 18 years of age and had non-traumatic OHCA and PEA as initial rhythm. Patients with an agonal ECG pattern described as slow(<10/min) and very wide QRS complexes, patients without interruption of chest compression during the first 60 seconds, patients with too much noise in the ECG recording, and patients with pacemakers were excluded. The included patients were stratified into four groups based on their QRS rate, 10-24/min, 25-39/min, 40-59/min, and 60-150/min. The primary outcome was survival to day 30 post cardiac arrest and good neurologic outcome (cerebral performance category 1 or 2). Based on a logistic regression model, they calculated the odds ratio for the different variables included. They also fitted a Kaplan-Meyer survival analysis. They found that having an initial QRS rate above 60/minute significantly increased the chance of 30-day survival with good neurologic outcome.

Weisser et al. collected a large sample size, but it was done retrospectively. The analysis of ECG was done manually, but it is not reported whether someone overlooked the process. The QRS rate was only treated as a categorical variable.

### Skjeflo et al (2019):

In his second study, Skjeflo looked at the dynamics of QRS rate and width and the effect of adrenaline on these characteristics in an OHCA material from Oslo[86]. He included 170 patients

excluding those with missing ECG data. Their statistical approach was similar to the one used in 2018[30]. They found that the QRS rate increased 3-6 minutes before ROSC, and the QRS width decreased before ROSC. They also saw that adrenaline altered the pattern of change. They did not see the same changes in the patients that died.

Skjeflo et al. gathered data from a previous study using only one ECG investigator. They used a completely different methodological approach compared to 6 of the other studies.

### Kim et al (2021):

The most recent study on this topic was published in 2021.[29] They included 576 patients enrolled in a South Korean OHCA registry between 2016 and 2018. All patients over 18 years of age, with a readable ECG and PEA as their primary rhythm, were included. They excluded patients with a non-medical cause of cardiac arrest, patients declared dead immediately after arriving in the emergency department and patients with a 'do not resuscitate' order. They measured the width, amplitude, and rate of the first three analyzable QRS complexes. The primary outcome was survival to hospital discharge, and the secondary outcome was good neurological status at discharge, defined as a CPC score of 1 or 2. They conducted a multivariable logistic regression analysis, including all the QRS characteristics in one model. They found that QRS amplitude was significantly related to survival when adjusting for age, sex, heart disease, place of arrest, presence of a witness, bystander CPR, implementation of advanced airway management, administration of adrenaline, response time, transport time, and QRS characteristics. Increasing the QRS amplitude by 1mm increases survival by 1.084 (Odds ratio) and survival with favorable neurological outcome by 1.123 (odds ratio). Patients with a QRS complex narrower than 120ms had 3.21(95% CI; 1.568-6.584) times higher chance to survive and 5.103 times(95% CI, 1.682-15,482) higher chance to survive with favorable than those with QRS complexes broader than 120ms. QRS rate did not affect survival in this material.

Kim et al. collected a large sample size using two investigators to analyze the ECG. The variables that were analyzed as categorical were also analyzed as continuous variables with consistent results.

From my point of view, the full potential of the ECG as a prognostic marker has not been investigated in the studies summarized above. Most of them include only ECG characteristics from the initial rhythm analysis and do not investigate the information that may lay in changes occurring during treatment. Also, the main focus was on OHCA and long-term survival.

The two studies by Skjeflo et al. include ECG information from the whole episode and may therefore describe change over time.[30] However, the methodology used had a few limitations making it difficult to use the results for prognostic purposes. During cardiac arrest, patients

with certain characteristics enter and exit PEA throughout resuscitation, as demonstrated in study I. This may cause data missing not at random. Skjeflo did not account fully for this process (i.e., data missing not at random, informative drop in and drop out). To a certain degree this was accounted for by not allowing transitions to ROSC or Death during the observation period (from 12 min before ROSC or death) but transitions to and from VF/VT and ASY could still occur. Also, patients could enter the risk set at any point, and episodes of short duration, with the highest probability of ROSC would enter closest to the end of the observation period. Hence, it is difficult to know whether the observed changes were due to changes within the individual episodes or changes occurring on the group level due to altered group composition towards the end. Also, conditioning on the outcome is not useful when creating predictive tools. The joint model accounts for both these limitations.

Compared to previous studies investigating ECG characteristics and outcome, study II stands out by including ECG data throughout the entire episode, by using a proper statistical method that is not conditional on the outcome, and finally by linking both values and changes in the biomarkers as dynamic predictors – as opposed to simple averages – to the outcome. To our knowledge, this is the first time a joint model has been used to model changes in a dynamic biomarker and its ability to reflect an outcome of interest during cardiac arrest.

# 6. Methodological considerations

## 6.1 Study design:

This thesis is based on observational data and their analysis are limited in several ways. [93] Confounding bias may occur when exposure 1 is related to exposure 2 that is also related to the outcome of interest. This may be accounted for when the exposure 2 is known and measured. When exposure 2 is unknown, the apparent relation between exposure 1 and the outcome is biased. Study I and II describe a process and an observational design is the only option. For example, one cannot randomly assign patients with PEA to high or low HR or $PEA_{PRI}$ and $PEA_{ROSC}$. Due to the possibility of confounding we may only claim an association between adrenaline, ROSC, and HR increase in Study III. In this setting, blinding and randomization of adrenaline administration were possible, and this would have provided us with a causal relation. Since the relationship between adrenaline and ROSC has already been established, this was unnecessary in this context.

Information bias refers to inaccurate assessment of outcome or exposure. This could be a problem in study III where we often relied on the memory of the treating team to determine timing of the adrenaline administration. Also, the uncertainties around our definition of ROSC could lead to information bias.

Selection bias occurs when the study population fails to mirror the target population. We included all available episodes (with some exceptions) to create a generalizable result. Still, we do not know if all episodes of CA at the different hospitals were captured.

From my point of view, the three studies could be viewed as a mix of cohort and case control study.[94] The retrospective aspect of a case control study is reflected in the historical cases not collected for the purpose of our study. Also, when analyzing the cases, we were not blinded to their outcome which could affect our judgement. At the same time, the prospective aspect of a cohort study is also present as the defibrillator files provided us with the opportunity to dissect each episode and mark events of interest as time passes. In all three studies the population consists of patients with cardiac arrest and the outcome is ROSC. In Study I the exposure is the transition to one of the four types of PEA and the different probabilities of ROSC is compared across the different PEA groups. In Study II the main exposure could be defined as different values of HR and QRSd. In Study III, adrenaline is the exposure.

We described Study II and Study III as prospective. The use of this term could be confusing to the reader and should therefore be debated. According to Vandenbroucke, there are two ways to think of the terms retrospective and prospective. [95] The strictest school states that the baseline characteristics of the study population is collected for the sole purpose of the study and that the follow up is done as the researcher ages with the subjects. The other school states that any follow-up is prospective, also when the cohort is historical. In Study II, most of the

cohort was collected for other purposes and included in retrospect. Still, the defibrillator file provided us with the opportunity to follow the patient prospectively from the time of defibrillator attachment to the end of resuscitation allowing us to take note of changes occurring along the way. In Study III, the cohort was collected for the sole purpose of investigating adrenalin's effect on state transitions, HR and QRSd falling in line with the strictest definition. Still, as in Study II, the transitions, timing of adrenaline and changes in HR and QRSd were all determined in retrospect. Hence, the descriptive term prospective or retrospective may be inaccurate and a detailed description of what was actually done would be better. [96]

## 6.2 Inclusion of participants:

The data from the three hospitals in the USA was collected as part of a quality assurance initiative, while the material from St. Olavs hospital was collected for research purposes. No selection criteria other than age over 18 years dictated the collection process. All available episodes were included to enhance the generalizability of our results. This was important and regarded as a major strength.

We only included covariates of interest in our analyses. It is possible that gender, age, and initial rhythm would affect the results, but this would also decrease the power of our analysis as the stratified groups would become smaller and smaller with the addition of covariates (i.e., women between 60 and 70 years with VF/VT as initial rhythm now being in $PEA_{ASY}$ with an HR of 65 bpm and a QRSd of 115 ms).

The study population in Study III differs from other studies as 43% have an initial shockable rhythm. This is approx. twice of what is usually seen. [6, 9, 66] There could be several reasons for this. Missing a large proportion of the episodes could cause this, but we don't think this is the case. We closely surveilled the activity of the arrest team gathering information from several sources (alarm log, defibrillator database and Utstein recordings). We therefore believe that we captured most of the cardiac arrests at St. Olavs university hospital between August 2018 and October 2022. Another reason for the high proportion of shockable rhythms could be including procedure-related arrests from the coronary angiography laboratory. These are mostly shockable rhythms, but not in great enough numbers.

We have collected data during the COVID-19 pandemic and this has probably affected the composition of the population. Trøndelag was relatively spared during the pandemic, with a COVID-related death rate of only approx. 60 while Troms and Finnmark had 97 per 100 000.[97] Still we probably benefitted fully from the decrease in death due to lung-related diseases like Influenza and pneumonia during this period. Preliminary data also suggest a decrease in cardiovascular-related deaths. It is expected that this might affect the incidence of IHCA and could have contributed to a skewed distribution of initial rhythms.

## 6.3 Choice of statistic method

In Study I we wanted to express the direct association to between the different types of PEA and ROSC and how this may change during resuscitation. Hence, only models expressing the transition intensity were suitable.

In Study II, we chose a joint model because it was able to express the probability of ROSC based on changes in HR and QRSd during resuscitation. It was also important that the model accounted for informative drop-out as patients in PEA with high HR and low QRSd were expected have higher probability of gaining ROSC. Finally, its ability to dynamically predict an outcome during resuscitation was also very positive feature.

In Study III we used a linear spline model to investigate changes in HR and QRSd before and after administration of adrenaline. We were aware of its inability to account for informative drop out but chose to use this model as we could substantiate the impact of drop-outs through a Sankey plot. The use of a joint model was considered, but abandoned since this would interpolate missing HR and QRSd values possibly creating artificial changepoints in HR and QRSd. The effect of adrenaline on transitions to ROSC were described through Sankey and prevalence plots and quantified by using a Cox model.

## 6.4 Relevance of the study:

We think our results are relevant for future resuscitation strategies. The three studies are innovative because they describe events *during* cardiac arrest with a high degree of detail which is not common in cardiac arrest research. The focus on IHCA is a considerable advantage when investigating pathways to ROSC, because survival is greater after IHCA and as most IHCA are witnessed, data collection may start immediately after collapse capturing the entire process. PEA is the most common arrest state encountered during IHCA and with its relatively lower survival it is particularly important to increase the knowledge of this field to improve outcomes.

The primary outcome of our analysis has been any ROSC, both sustained and temporary. This contrasts with most studies where long-term outcome is of primary interest. We wanted to identify factors that may communicate treatment response during CPR. In this context, sustained and temporary ROSC is the only interesting outcome. These are the outcomes that are closest related to the underlying processes leading to ROSC *during* CA. Again, ROSC is a prerequisite for long-term survival.

# 7. Limitations:

## 7.1 The definitions controlling our universe:

Before diving into this unknown material, we had to set some rules and boundaries to recreate the episodes with as high precision as possible. To do this, certain assumptions had to be made, and these limited our results. The main ones will be summarized here.

Defining the start of an episode as the first sign of resuscitative efforts in the defibrillator file could set the start later than the actual start. Attachment of the defibrillator could be delayed, i.e., a monitored patient with a non-shockable rhythm may receive CPR without a defibrillator. We do not think this is common as most clinicians will follow guidelines and attach a defibrillator as soon as possible after the collapse in case a shockable rhythm emerges.

The absence of an objective measure of ROSC limits the results. Patients regaining spontaneous circulation may relapse before one minute and pauses in chest compression lasting longer than one minute may be due to other resuscitative efforts like securing a difficult airway or attempts at draining pericardial fluid in a patient without circulation. Hence, it's reasonable to believe that some of the patients classified with PEA have ROSC, and some patients classified with ROSC still have PEA. Figure 7.1.1 show the distribution of the duration of all 329 segments of temporary ROSC included in this thesis. We see that 31 segments lasted less than 1 minute, not meeting our definition of ROSC. In total, 14 of these segments are preceded and proceeded by a shockable rhythm. Here the patients were shocked to an organized rhythm not followed by resuscitative efforts from the team, then quickly deranging to VF/VT again. In total, 14 segments of temporary ROSC were proceeded by PEA and 8 of these lasted longer than 50 seconds. Furthermore, we see that the majority of transient ROSC segments last longer than 2 min. Dewolf et al. investigated interruptions during CPR and found that only 4.3% were longer than 1 minute adding to the validity of our definition.[98] It is difficult to know whether ROSC is over or underestimated, despite my claim of overestimation in study I and II. An objective measure of ROSC could be obtained by using ultrasound measuring flow in great arteries. Our group is currently working on expanding the knowledge within this field.[99]

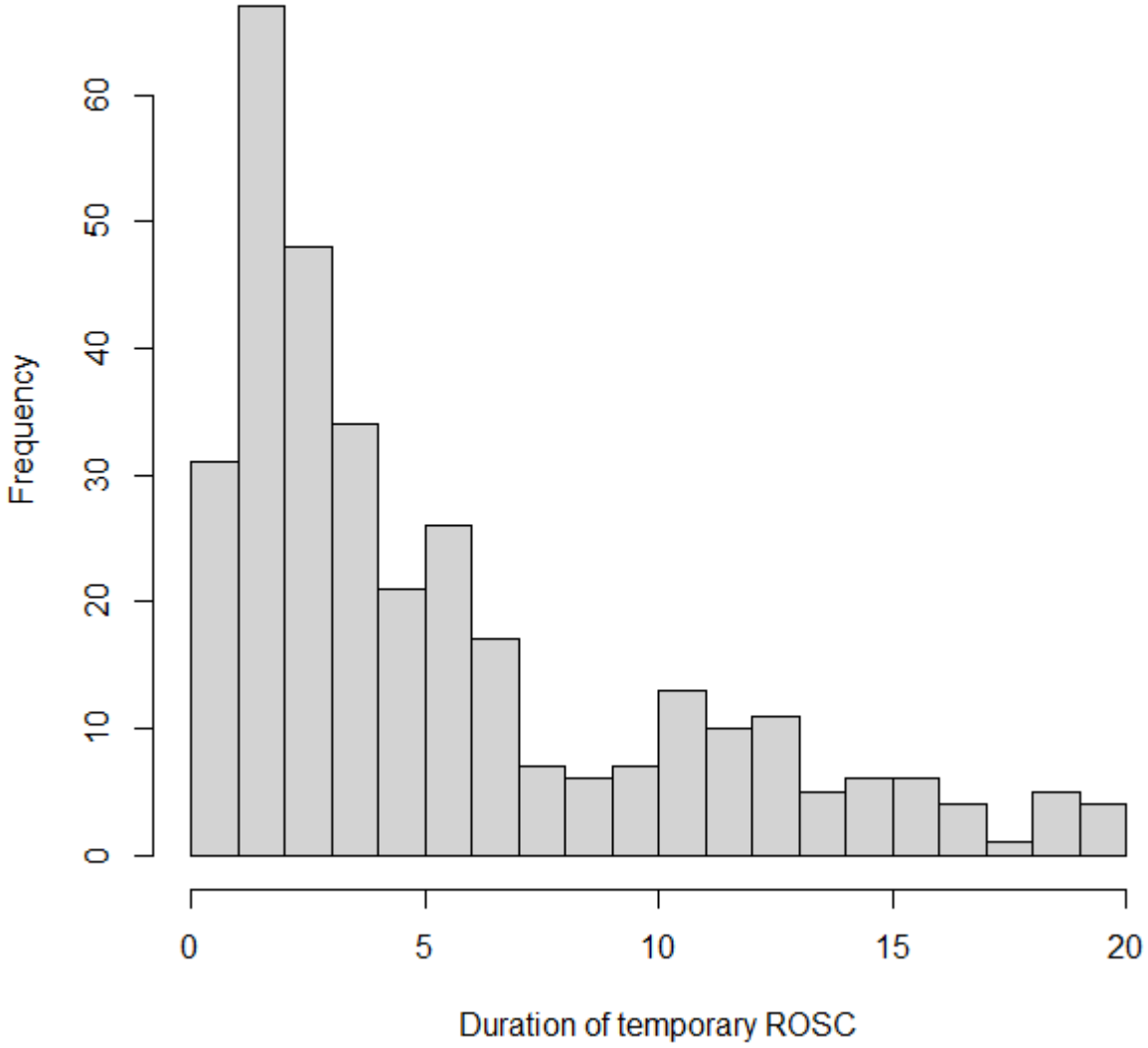


Figure 7.1.1: Duration of temporary ROSC in all the 770 episodes included in this thesis.

The definition of asystole (flat ECG or rhythm with less than 12 QRS complexes/min) reflects an underlying uncertainty when differing asystole from PEA. Dewolf et al. found that the most common cause of pauses lasting longer than 10 seconds were pulse/circulation checks (51%). This was followed by the attachment of LUCAS which caused 11% of all interruptions longer than 10s.[98] A flat ECG line is never compatible with circulation and the arrest team will usually quickly resume chest compression as extended circulation checks are not warranted. A interruption of up to 5 sec could mask a slow PEA with a frequenzy of less than 12 bpm.

Also, differing asystole with a noisy baseline from ventricular fibrillation could be impossible. These cases have been resolved by relying on the indirect cues provided by the treating

personnel. Defibrillation attempts would point towards fibrillation while the opposite would point towards asystole.

Declaration of death is not the opposite of achieving ROSC. ROSC only occurs when it is physiological achievable, death on the other hand may be declared despite a ROSC potential. The declaration of death is a decision based the total situation of the patient, and the ability of the heart to regain spontaneous circulation is often only part of this evaluation. Also, perceived futility may lead to premature termination. This has been referred to as prognostication bias and may cause an underestimation of the ROSC potential in our analyses.[100]

# 8. Conclusion

This thesis has explored PEA in the setting of IHCA. Through this work we have been able to draw a road-map of this central clinical state of cardiac arrest identifying crossroads that we must be aware of when trying to resuscitate these patients. Transitions in and out of PEA do not seem to occur at random and are a response to an underlying process that either improves or worsens the patient's condition.

Study I showed that PEA of different origins has different probabilities of gaining ROSC at different timepoints during resuscitation. Hence, changes in arrest states during resuscitation may communicate the probability of a transition to ROSC. Paying close attention to changes in the ECG may reveal the direction the patient is heading in. Study II found that changes in QRS complex duration and QRS rate are associated with the probability of remaining in PEA, gaining ROSC or transitioning to a noROSC state. Observing an increasing probability of ROSC in a patient may change how the treating team perceive the situation, encouraging continuation of resuscitation efforts and allowing the treating team to be ahead of time. Unfortunately, we could not identify factors that robustly reflected worsening in the patient's condition.

In Study III we found that patients started to gain ROSC immediately after adrenaline was administered and most patients gaining ROSC, did so within 3 to 5 minutes. Further, we also found that the first dose of adrenaline was associated with an increasing HR in patients remaining in PEA the two first minutes after administration. There were no significant changes in QRSd after adrenaline administration and no significant changes in HR after the second and third dose of adrenaline.

# 9. Future perspectives

During my work with this thesis, I have dreamt of conducting a large double blinded randomized controlled trial that could reveal the effect of adrenaline on short and long-term survival in patients with IHCA. Today, I find it likely that adrenaline increases long term survival after IHCA and that it would be unethical to conduct such a study. I think we are past discussing whether adrenaline should be administered and should focus our efforts on how adrenaline should best be administered. This could be done by randomizing the dose size, time of initial administration, and also interval of administration. This would need a large study population to ensure sufficient power within each subgroup and a multicenter in-hospital approach to ensure generalizability of the results.

The results of Study II are highly significant, but the predictive ability of the model may not be precise enough for clinical practice. Further work is needed to elucidate the potential of biological markers during cardiac arrest. Finding a robust marker that objectively communicates both improvements and worsening of the patient's condition would provide us with a powerful tool to improve treatment through further research and ease clinical decision making. To achieve this goal, we first need a tool that objectively detects ROSC. It is well known that manual palpation of pulse is inaccurate,[101, 102] and this may propagate to analyses conducted downstream to this. It is unlikely that we find one marker so maybe a set of markers in combination would prove useful. The Joint model would be a powerful tool to elucidate these relations.

A simpler approach to follow improvement, would be to stratify asystole and VF/VT based on their origin and estimate their transition intensities to ROSC, like we did to PEA. This could prove very useful as we would obtain the probability of ROSC for every arrest rhythm the patient may encounter during a cardiac arrest (i.e., the patient has been in primary ASY for 9min and has approximately 1% chance of gaining ROSC the next minute). This would also provide an opportunity to determine whether a transition brings the patient closer to, or further away from ROSC, i.e. at 12 min the same patient has transitioned to $PEA_{ASY}$ with a transition intensity to ROSC of 7 %. By knowing these two intensities and keeping track of time since episode start, the treating team would know that the condition of this patient is improving.

# 10. Appendix:

# The prognostic value of ECG during resuscitation from pulseless electrical activity.

a structured literature search by Anders Norvik

**Scientific question:** What is the prognostic value of the ECG recorded during resuscitation from pulseless electrical activity?

**Table 1:** Concept table

| Cardiac arrest | Pulseless electrical activity | Electrocardiography |
|---|---|---|
| Heart arrest(Med/Em/To)<br>Cardiac arrest(Ft)<br>Heart arrest(Ft) | Pulseless electrical activity(Ft)<br>Electromechanical dissociation(Ft)<br>PEA(Ft)<br>EMD(Ft) | Electrocardiography(Med/Em/To)<br>ECG(Ft)<br>EKG(Ft) |

Med = MeSH from MEDLINE, Em = Emthree term from Embase, To= Topic from Web of Science, Ft = Free text

**Method:**

The search was conducted between the 26.04.21 and 27.04.21 in PubMed, Embase and Web of science. In all databases the search was constructed based on the following concepts (see table 1): cardiac arrest, pulseless electrical activity and electrocardiography. No filters were used in the search. In PubMed and Embase the Mesh and Emthree term in each concept was added to the freetext terms (see Table 1) by the Boolean operator OR to ensure the broadest search strategy within each concept. Each concept was added together with the Boolean operator AND to ensure that all three concepts were represented. Each term was enclosed within quotation marks to reduce noise in the result and inactivate helping algorithms in PubMed. The same search strategy was applied in the Web of science database, but each term was included both as a topic and a free text term.
All results were manually evaluated based on their title. Articles thought to be relevant were added to Endnote. Each article was then reevaluated based on its abstract. Conference abstracts were excluded.

**Results:**

Table 2: Search results

| **Database** | **Search type** | **References** | **Precision** |
|---|---|---|---|
| PubMed | Structured | 223 | 7/223 |
| Embase | Structured | 451 | 6/451 |
| Web of science | Structured | 93 | 4/93 |
| Total after duplicate removal | | 611 | |

The results from PubMed yielded 14 articles of interest. After reviewing their abstract, five were excluded and seven were included for the review.

The results from Embase gave 8 articles of interest. After reviewing their abstract, 2 were excluded and 6 were included.

The results from Web of science included 4 articles of interest also after reviewing their abstract.

The included results from Embase and Web of science were the same as in PubMed.

**Discussion:**

Based on this search strategy I was able to find 7 studies looking at the prognostic value of ECG during resuscitation from pulseless electrical activity.

In total the search strategy included 767 results from three different databases. This was a feasible amount to review manually. The search result in Embase included 245 conference abstracts. These were excluded since they often are based on preliminary data and the same data is often presented in peer-reviewed articles after the conference.

The QRS complex is often the ECG characteristic of interest in these studies. Introducing the QRS complex as a concept would substantially reduce the number of results. In PubMed I was left with only 24 results when doing this. All the seven articles of interest were found in this search, but this strategy would not include studies looking at other ECG characteristics and was therefore abandoned.
Including "QRS" as a free text within the electrocardiography concept increased the number of results. In PubMed it increased by 50 yielding no other relevant articles. To reduce noise in the result-list this strategy was also abandoned.

*Search strategy in Embase:*

Embase <1974 to 2021 April 23>

| | | |
|---|---|---|
| 1 | "Heart arrest".mp. or exp heart arrest/ | 101927 |
| 2 | "Cardiac arrest".mp. | 60615 |
| 3 | "Pulseless electrical activity".mp. | 1975 |
| 4 | "PEA".mp. | 17828 |
| 5 | "Electromechanical dissociation".mp. | 576 |
| 6 | "EMD".mp. | 7404 |
| 7 | electrocardiography.mp. or exp electrocardiography/ | 167132 |
| 8 | ECG.mp. | 119740 |
| 9 | EKG.mp. | 11408 |
| 10 | 1 or 2 | 111083 |
| 11 | 3 or 4 or 5 or 6 | 26966 |
| 12 | 7 or 8 or 9 | 251077 |
| 13 | 10 and 11 and 12 | 451 |

*Search strategy in PubMed:*

| Number | Search term | Results | Time |
|---|---|---|---|
| 1 | ((("pulseless electrical activity") OR ("PEA")) OR ("EMD")) OR ("Electromechanical dissociation") | 22,493 | 09:53:23 |
| 2 | ((heart arrest[MeSH Terms]) OR ("heart arrest")) OR ("cardiac arrest") | 72,294 | 09:54:52 |
| 3 | ((electrocardiography[MeSH Terms]) OR ("ECG")) OR ("EKG") | 235,054 | 09:54:35 |
| 4 | ((((heart arrest[MeSH Terms]) OR ("heart arrest")) OR ("cardiac arrest")) AND (((electrocardiography[MeSH Terms]) OR ("ECG")) OR ("EKG"))) AND ((((("pulseless electrical activity") OR ("PEA")) OR ("EMD")) OR ("Electromechanical dissociation")) | 223 | 09:55:16 |

*Search strategy in Web of science:*

| Nr | Search term | Results |
|---|---|---|
| 4 | #3 AND #2 AND #1<br>*Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI*<br>*Timespan=All years* | 93 |
| 3 | ALL=("cardiac arrest") OR TS=("cardiac arrest") OR TS=("heart arrest") OR ALL=("heart arrest")<br>*Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI*<br>*Timespan=All years* | 45,306 |
| 2 | **ALL FIELDS:** ("pulseless electrical activity") *OR* **TOPIC:** ("pulseless electrical activity") *OR* **TOPIC:** ("PEA") *OR* **ALL FIELDS:** ("PEA") *OR* **TOPIC:** ("Electromechanical dissociation") *OR* **ALL FIELDS:** ("Electromechanical dissociation") *OR* **TOPIC:** (EMD) *OR* **ALL FIELDS:** (EMD)<br>*Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI*<br>*Timespan=All years* | 60,963 |
| 1 | **ALL FIELDS:** (Electrocardiography) *OR* **TOPIC:** (Electrocardiography) *OR* **TOPIC:** ("ECG") *OR* **ALL FIELDS:** ("ECG") *OR* **TOPIC:** ("EKG") *OR* **ALL FIELDS:** ("EKG")<br>*Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI*<br>*Timespan=All years* | 86,904 |

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# 12. Study I-III

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Clinical paper

# Pulseless electrical activity in in-hospital cardiac arrest – A crossroad for decisions

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## Abstract

**Background**: PEA is often seen during resuscitation, either as the presenting clinical state in cardiac arrest or as a secondary rhythm following transient return of spontaneous circulation (ROSC), ventricular fibrillation/tachycardia (VF/VT), or asystole (ASY). The aim of this study was to explore and quantify the evolution from primary/secondary PEA to ROSC in adults during in-hospital cardiac arrest (IHCA).

**Methods**: We analyzed 700 IHCA episodes at one Norwegian hospital and three U.S. hospitals at different time periods between 2002 and 2021. During resuscitation ECG, chest compressions, and ventilations were recorded by defibrillators. Each event was manually annotated using a graphical application. We quantified the transition intensities, i.e., the propensity to change from PEA to another clinical state using time-to-event statistical methods.

**Results**: Most patients experienced PEA at least once before achieving ROSC or being declared dead. Time average transition intensities to ROSC from primary PEA ($n$ = 230) and secondary PEA after ASY ($n$ = 72) were 0.1 per min, peaking at 4 and 7 minutes, respectively; thus, a patient in these types of PEA showed a 10% chance of achieving ROSC in one minute. Much higher transition intensities to ROSC, average of 0.15 per min, were observed for secondary PEA after VF/VT ($n$ = 83) or after ROSC ($n$ = 134).

**Discussion**: PEA is a crossroad in which the subsequent course is determined. The four distinct presentations of PEA behave differently on important characteristics. A transition to PEA during resuscitation should encourage the resuscitation team to continue resuscitative efforts.

**Keywords**: Pulseless electrical activity (PEA), Electrocardiography (ECG), Cardiopulmonary resuscitation (CPR), Return of spontaneous circulation (ROSC), Dynamics

## Introduction

The clinical course during resuscitation from cardiac arrest (CA) is variable. While the importance of the initial rhythm is well documented, changes in rhythm during adult CA has not been thoroughly investigated.[1] PEA is the typical presenting clinical rhythm, with reported incidences of 20–30% in out-of-hospital and up to 40–60% in in-hospital cardiac arrest (IHCA).[2–5] It may also be encountered at later stages of resuscitation,[6] as a secondary rhythm after a period of temporary return of spontaneous circulation (ROSC), after ventricular fibrillation/tachycardia (VF/VT), or after asystole (ASY). PEA may behave differently in these settings. In the following we call them $PEA_{PRI}$, $PEA_{ROSC}$, $PEA_{VT/VF}$, and $PEA_{ASY}$, respectively.

Over the last decades the prevalence of PEA in IHCA has grown. In a study from 2012 Girotra found an increase in prevalence of PEA from 36% in 2000 to 46% in 2009 when investigating the Get with the Guidelines-Resuscitation registry.[7] Other studies have also found the same tendency out of hospital.[8,9] It is increasingly important to understand the dynamics of PEA during resuscitation to adjust treatment and increase the probability of survival.[5]

Shorter time to ROSC is associated with better long-term survival.[1,10] The actual transition *intensities* (how quickly the patient responds) are thus of direct clinical interest. A transition intensity quantifies the immediate probability of a patient to transient to a different clinical state in a short time (e.g., transition from ROSC to PEA). Both, the shape of the transition intensity function and its values, are important. If time is measured in minutes, values below 0.1

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roughly correspond to the probability of a transition during the next minute and may be directly interpreted clinically. The shape confers details of the transition, as in a function that is possibly constant, decreasing, increasing, or unimodal (increasing and then decreasing over time). A similar, if not identical, simulation experiment indicates that a decreasing function for the transition intensity from PEA to ROSC may suggest that patients are moving away from ROSC as time passes and an increasing transition intensity function may suggest the opposite; a unimodal function may suggest an intermediate initial starting point.[11]

The aim of this study was to quantify, describe and explore the time course of transitions from different types of PEA to ROSC during IHCA.

## Materials and methods

### Study setting and population

All episodes were recorded by emergency response personnel in a quality assurance initiative, with no inclusion criteria other than age > 18 years. A total of 406 novel episodes of IHCA with available defibrillator files from three different hospitals were reviewed. Episodes with disturbed or missing ECG signal during resuscitation (12 and 7 respectively), episodes lacking both transthoracic impedance signal and compression depth (5 episodes) and duplicated episodes (1 episode) were excluded. A total of 381 episodes were further analyzed: St. Olavs hospital, Norway, ($n$ = 140 between 2018 and 2021), the Hospital of the University of Pennsylvania, USA, ($n$ = 187 between 2008 and 2010), and the Penn Presbyterian Medical Center, USA, ($n$ = 54 between 2008 and 2010). Episodes from the University of Chicago Hospital, USA, ($n$ = 159 between 2002 and 2005) and episodes from St. Olav University Hospital, Norway, ($n$ = 160 between 2009 and 2012) had been annotated and included in a previous study.[6]

### Data collection and handling

Defibrillators recorded ECG, chest compressions and ventilations during CPR. Data were recorded using HeartStart MRx-defibrillators (Philips Medical Systems, Andover, Massachusetts, USA), Zoll M series (Zoll Medical Corporation, Chelmsford, Massachusetts, USA), LIFEPAK 20 (Physio-Control, Redmond, USA) and LIFEPAK 1000 (Physio-Control, Redmond, USA). All events were manually assessed and annotated using a custom-made graphical application in MATLAB (version R2020a).

The start of an episode was defined when regularly performed chest compressions were identified. The initial arrest rhythm was determined based on clinical records (monitored CA) or arrest rhythm during the first pause in chest compressions.

Chest compressions were detected as fluctuations either in the transthoracic impedance (TI) signal acquired by the defibrillation pads, or in the compression depth signal recorded by the CPR assistance pad.[12,13] Due to the noise generated by chest compressions, the ECG was only evaluated during chest compression pauses. ASY was defined as no measurable cardiac electrical activity, or a rhythm with QRS-like complexes slower than 12 complexes/min; corresponding to a "flat" line on a monitoring scope (see also "limitations"). PEA was defined as an organized rhythm with frequency > 12 QRS/min lasting less than 1 min before being interrupted by compressions. VF and VT were categorised by their unique morphologies.[14] ROSC was defined as an organized rhythm lasting > 1 min without signs of chest compressions. Sustained ROSC was declared if spontaneous circulation lasted longer than 20 min; in the statistical model the patient was still considered at risk for relapse during that period. We defined a new episode if a new cardiac arrest ensued in the same patient beyond 20 min. For patients declared dead, death was defined at the last chest compression or defibrillation attempt. PEA was classified into four categories as described in the introduction.

### Statistical methods and modelling

The software R version 4.0.0[15] and Stata version 17[16] were used for the visualization and the statistical analysis. The transition intensity is a fundamental entity in time-to-event analysis as it governs patient progression through different clinical states. It is known as the "hazard" in classical survival analysis. We used both non-parametric and parametric methods to analyze the rhythm evolution process and provide information of the overall shape and the constraints on the shape, respectively. First, we employed a b-spline method for non-parametric smoothing of the intensity function employing the R-package "bshazard".[17] Second, we differentiated and smoothed the cumulative intensity functions estimated by Aalen's non-parametric additive model.[18] To investigate the shape of the intensity function we fitted and plotted the parametric exponential model yielding a time-constant transition intensity (with 95 % CIs) as well as the parametric Royston-Parmar spline model of the cumulative intensity function of log time with 3 degrees of freedom. To accommodate for dependence between events, patient identity was included as a normally distributed random effect if the transition under study contained more than 10 clusters (i.e. patients) who experienced at least two events and this improved model fit. We compared the fit of the constant exponential model, the monotone (increasing or decreasing) Weibull model, and the unimodal (increasing to peak, then decreasing) Greenwich model by Akaike´s and Bayesian information criteria (AIC and BIC). We generally favored simplicity to avoid artefacts and overfitting. All parametric models were estimated using the Stata package merlin.[19]

### Ethical aspects

The observations from the University of Chicago Hospitals were approved by their respective institutional review boards and transferred in anonymized form to our research group.[6] The data from the University of Pennsylvania was de-identified and made available in anonymized form. Collection and analysis of the most recent episodes from St. Olav's hospital were approved by Regional Ethics Committee data analysis (2019/785) as pseudo-anonymized.

## Results

The 700 episodes of IHCA concerned 642 individual patients; the median age was 68 years (IQR 57–77), 57% of patients were male, and in 48% of the episodes the presumed cause was cardiac. Two thirds (67%) of the episodes occurred in units with continuous patient monitoring, adrenaline was administered in 83% of the episodes. PEA was the initial rhythm in 60% of the episodes, ASY in 18%, and VF/VT in 22%. A total of 593 episodes (85%) contained PEA. Sustained ROSC was observed in 376 episodes (53%). Overall survival to discharge was observed in 103 patients (17%); among these 36 (9%) presented with PEA, 60 (43%) presented with VF/VT, and 7 (6%) presented with ASY as the first recorded rhythm of the first episode.

The running prevalence of clinical states over the first 30 minutes of resuscitation is shown in Fig. 1, and it can be observed that PEA is the most common arrest state in that period. Most of the transitions occur during the first 15 min. After 20 min only minor alterations are visible in the distribution of the clinical states. Fig. 2 shows the flow of patients from the start, through the penultimate state, until the final endpoints of sustained ROSC or death.

Table 1 describes the number, characteristics, and timing of the transitions from the four types of PEA. A total of 1101 PEA sequences were considered, 519 of which did evolve to ROSC.

Fig. 3 depicts the intensity functions for transitions into the different types of secondary PEA, and Fig. 4 the intensity functions for transitions from the four PEA types into ROSC. The functions with the best fit will be described in the following section. For the transition from $PEA_{PRI}$ to ROSC, a unimodal transition intensity function with patient id as a random effect peaking at 4 min can be observed (Fig. 4), with a time averaged value of about 0.10 decreasing to 0.05 at 30 min. The transition intensity function (Fig. 3) from temporary ROSC to $PEA_{ROSC}$ has a constant much lower value of 0.02, while the transition intensity function for $PEA_{ROSC}$ to ROSC starts out high at 0.20 and decreases rapidly to 0.12 in 30 min (Fig. 4).

The transition intensity function for VF/VT to $PEA_{VF/VT}$ (Fig. 3) starts out high at 0.25 and decreases to 0.13 in 30 min, reflecting that the first transitions occur immediately after the start of resuscitation by defibrillation. The transition intensity function of $PEA_{VF/VT}$ to ROSC (Fig. 4) starts high at 0.30 but rapidly declines towards 0.05 in 30 min. This indicates a higher likelihood of gaining ROSC, and shorter time spent in $PEA_{VF/VT}$ before the transition occurs during early phases of resuscitation. Some of the earliest transitions happen almost spontaneously, but intensity falls with time and time to ROSC increases.

The transition intensity function from ASY to $PEA_{ASY}$ (Fig. 3) has a unimodal shape with a peak value of 0.16 after about 8 min, indicating that these patients need a period of CPR before transitions to PEA occur. Similarly, further transitions from $PEA_{ASY}$ to ROSC (Fig. 4) occur at a low intensity of 0.09 peaking at 7 min. Such a unimodal development with a lower peak value for patients in $PEA_{PRI}$ and $PEA_{ASY}$, indicates lower ROSC probabilities and longer time to ROSC. These patients do not spontaneously evolve to ROSC like patients with $PEA_{VF/VT}$. They seem to need a minimum of 1–2 min of CPR.

A further visualization, also considering transitions to other states than ROSC, is to consider the overall length of stay in each PEA category. Fig. 5 shows that patients remain longer in $PEA_{PRI}$ and $PEA_{ASY}$ (6.9 and 9.7 min respectively for the 50% percentiles) compared to $PEA_{VF/VT}$ and $PEA_{ROSC}$ (4.0 min).

## Discussion

In this study we show that PEA is present in four fifths of the IHCA episodes analyzed and they evolve differently depending on origin. PEA is a critical intermediate state on the pathway to ROSC or death. We viewed the same processes from different angles, using non-parametric approaches to yield a general idea of the shape of the transition intensity function, and parametric models to put informative and different constraints to its shape. Our findings underscore the importance of understanding this arrest rhythm.

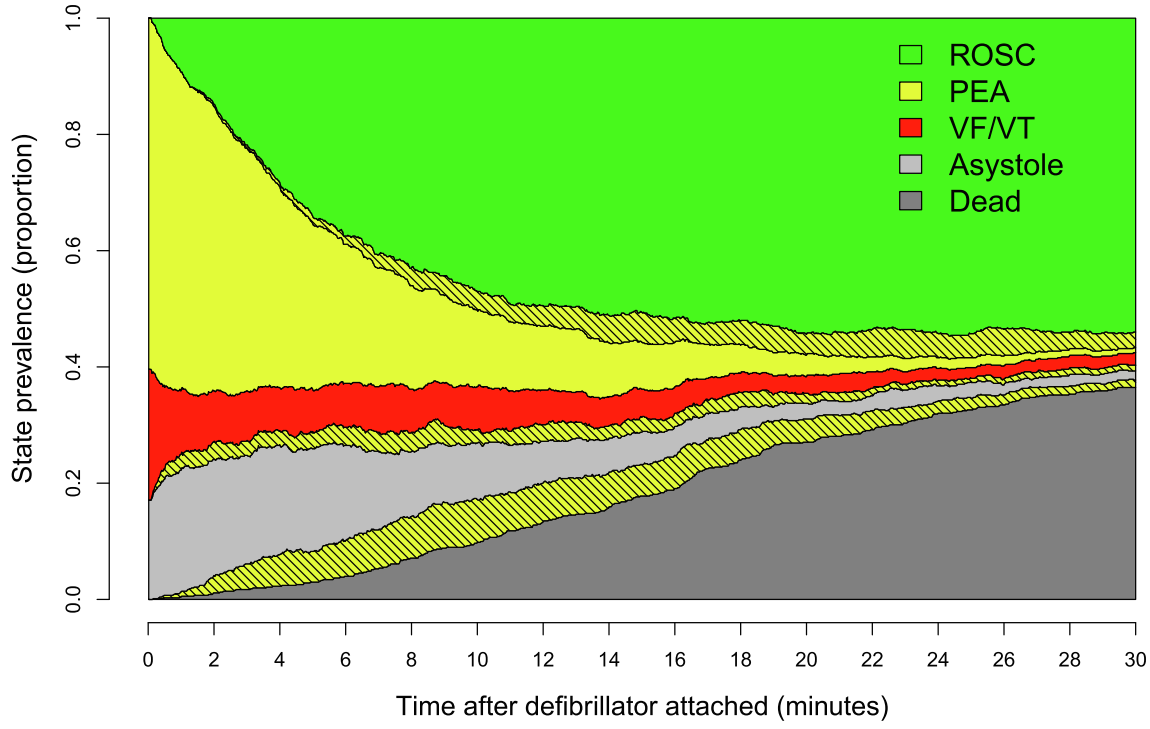


**Fig. 1 – The running prevalence of clinical states during the first 30 minutes of resuscitation. The secondary PEA states are line-shaded and placed under their respective states of origin. For example, $PEA_{ASY}$ is plotted between ASY (light grey) and Dead (dark grey). All clinical states except "Dead" are communicating, i.e., they may be entered and left at any time.**

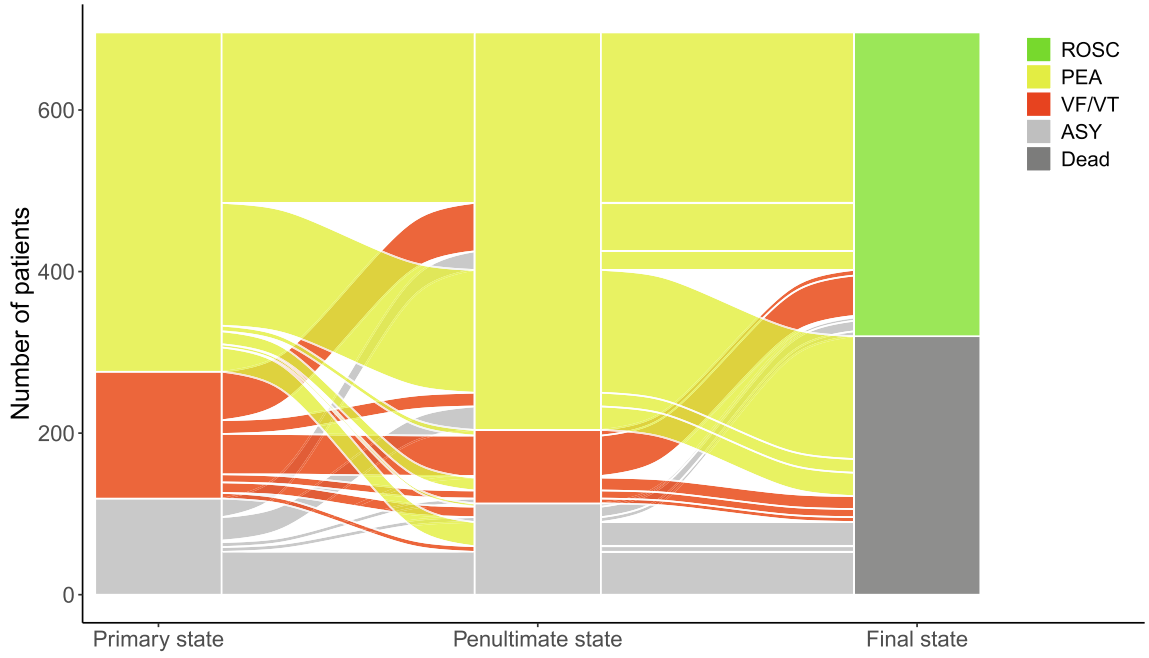


**Fig. 2 – The "flow" of patients from their primary clinical state via the penultimate state to their final state. Approximatley half of the patients with primary VF/VT who achieved ROSC went through PEA. Approximatley of patients with initial ASY who achieved ROSC went through PEA.**

**Table 1 – Overview of median entry times to PEA and the median exit times to ROSC for the different PEA types.**

| PEA type | No. of sequences | Entry time (min) with median (IQR) | No. of transitions to ROSC | Exit time to ROSC (min) with median (IQR), and (min, max) |
|---|---|---|---|---|
| $PEA_{PRI}$ | 423 | 0 | 230 | 4.1 (2.3–6.8), (0.3, 61.6) |
| $PEA_{ROSC}$ | 202 | 17.2 (10.3–27.2) | 134 | 19.6 (12.3–29.5), (2.8, 76.9) |
| $PEA_{VF/VT}$ | 232 | 8.9 (3.2–17.1) | 83 | 7.9 (3.0–14.3), (0.3, 59.8) |
| $PEA_{ASY}$ | 245 | 8.2 (4.2–15.1) | 72 | 10.9 (6.4–17.9), (3.52, 43.3) |

### *The origin of PEA*

Respiratory, cardiac and metabolic conditions seem to be the dominating causes of PEA.[1,20] Stankovic et al. found an association between cardiac disease, witnessed, or monitored IHCA and initial shockable rhythm.[21] They also found that non-cardiovascular disease, higher age, and female gender were associated with a non-shockable presenting rhythm. When comparing the characteristics of ASY and PEA in IHCA, Høybye et al. found that female sex, age > 90 years and non-witnessed arrest predicted ASY.[22] Of interest is also the recent findings of Ambinder et al.,[23] as they reported that all pigs with severe left ventricular dysfunction quickly responded to ischemia by developing PEA, while only half of the healthy pigs suffered VF after some time when subjected to the same stimuli. In our study, patients in secondary PEA tended to relapse to the original arrest rhythm. A similar tendency was seen in out-of-hospital CA, where changes in clinical state were determined by the initial clinical state.[24]

Based on our findings we firmly believe that the initial state and later changes are not random, but the result of underlying pathophysiological processes responding to ALS. Understanding these behaviors of CA rhythms may help in adapting the resuscitation efforts to the patient, increasing the transition probabilities towards ROSC.

### *Achieving ROSC*

A systematic review of studies investigating pre- and intra-arrest factors relation to outcome of IHCA found that increasing age, active malignancy and male gender were associated with reduced survival while shockable rhythm, witnessed arrest and arrest during daytime were associated with increased survival.[10] These are mostly static parameters without the ability of reflecting response to resuscitation. In this study we focused on the patient's response during resuscitation looking for crossroads of IHCA. The transition from VF/VT, ASY and ROSC to PEA can be considered as such. Although PEA amounts to 60% of the initial rhythms in the analyzed episodes, PEA precedes 75% of the transitions to ROSC. As illustrated by Fig. 2, half of the patients with initial VF/VT who achieve ROSC pass through PEA before reaching ROSC. The same phenomenon is observed with initial ASY. A transition to PEA could therefore be a sign of response to ALS. The patient's heart exits a malignant rhythm and starts generating organized electrical impulses, a prerequisite for ROSC.

The relapse from ROSC to PEA frequently occurs in the later phases of resuscitation. Sometimes this is regarded as a poor prognostic sign and resuscitation may be terminated. This study suggests

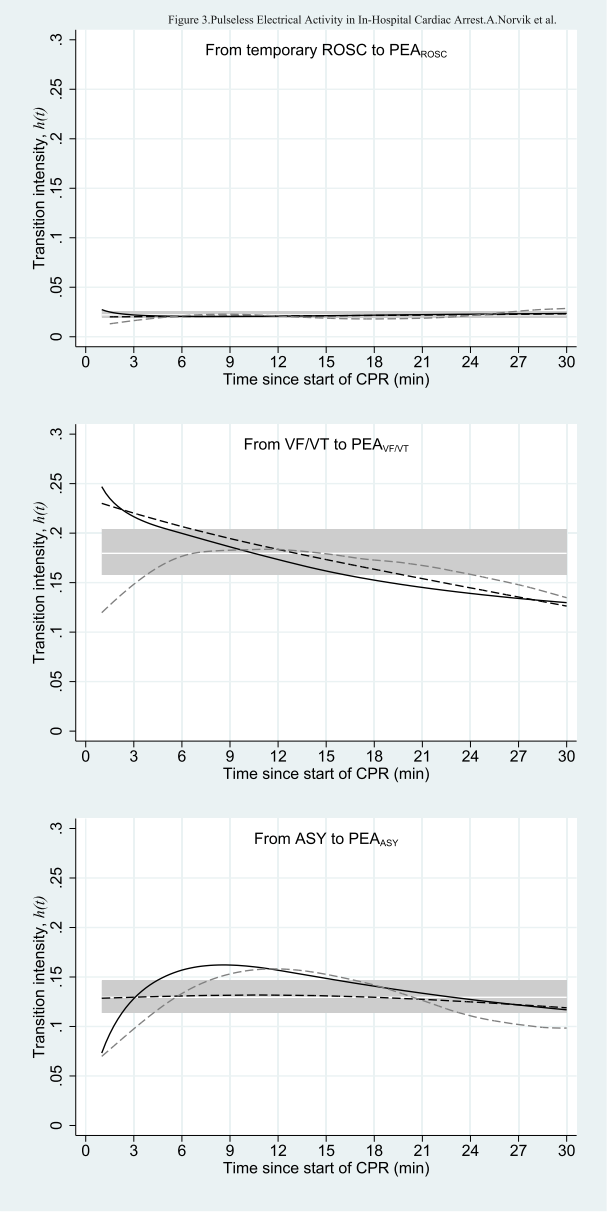


**Fig. 3 – The transition intensity functions to PEA during the first 30 min of resuscitation, from temporary ROSC, VF/VT and ASY. Interrupted lines [- - -] show non-parametric estimates (grey: differentiated cumulative intensity; black: b-splines). Continuous lines. [ ___ ] show the parametric estimates (white: exponential model; black: Royston-Parmar model). Grey shading indicates 95% confidence region for the exponential model.**

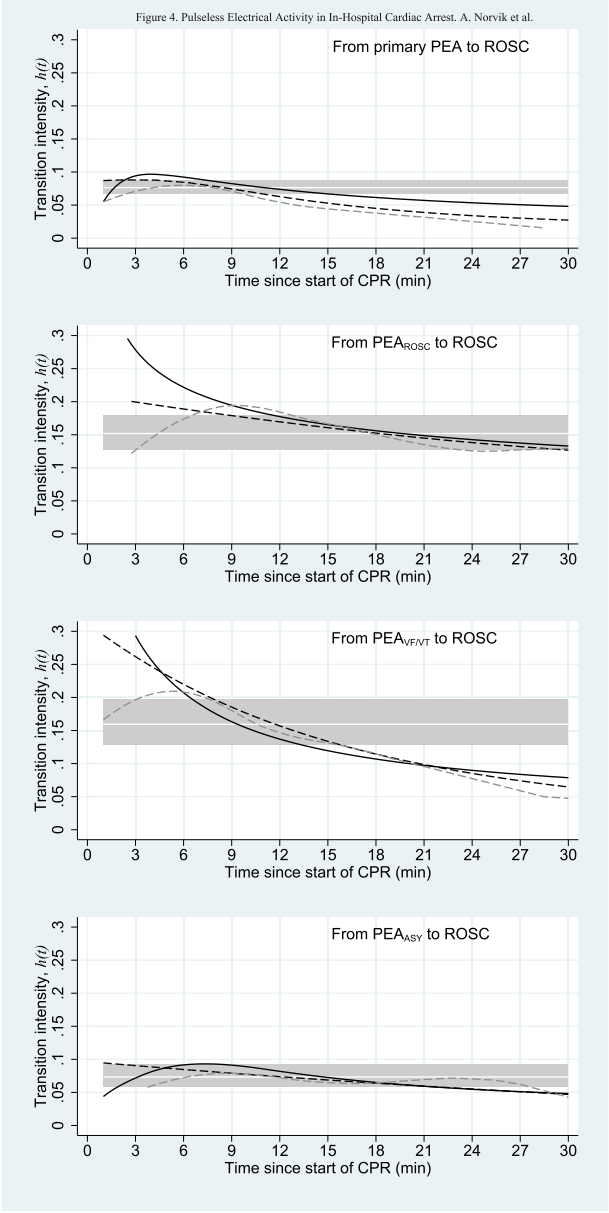


**Fig. 4 – The transition intensity functions to ROSC during the first 30 min of resuscitation, from primary PEA, from PEA after temporary ROSC, PEA after VF/VT, and PEA after ASY. Interrupted lines [- - -] show non-parametric estimates (grey: differentiated cumulative intensity; black: b-splines). Continuous lines [ ___ ] show the parametric estimates (white: exponential model; black: Royston-Parmar model). Grey shading indicates 95% confidence region for the exponential model.**

the contrary. Once ROSC is achieved, the probability of re-achieving ROSC is high, especially during early phases of resuscitation.

Patients with PEA$_{VF/VT}$ during the first minutes of resuscitation showed a very high likelihood of achieving ROSC, but the probability decreased with time. In many cases, we believe that PEA$_{VF/VT}$ may represent (undetected) ROSC. The very classification of PEA$_{VF/VT}$ may partially be a consequence of the current resuscitation algorithm, which instructs personnel to resume CPR for one minute immediately after a shock, before checking for pulse or evaluating the rhythm.[25]

Patients with PEA$_{ASY}$ showed the lowest probability of gaining ROSC when compared to the other PEA types. Considering that 2/3 of the patients with primary ASY and sustained ROSC as their final rhythm achieve PEA during their final stages of resuscitation, it is evident that a transition from ASY to PEA$_{ASY}$ justifies continuation of resuscitation efforts.

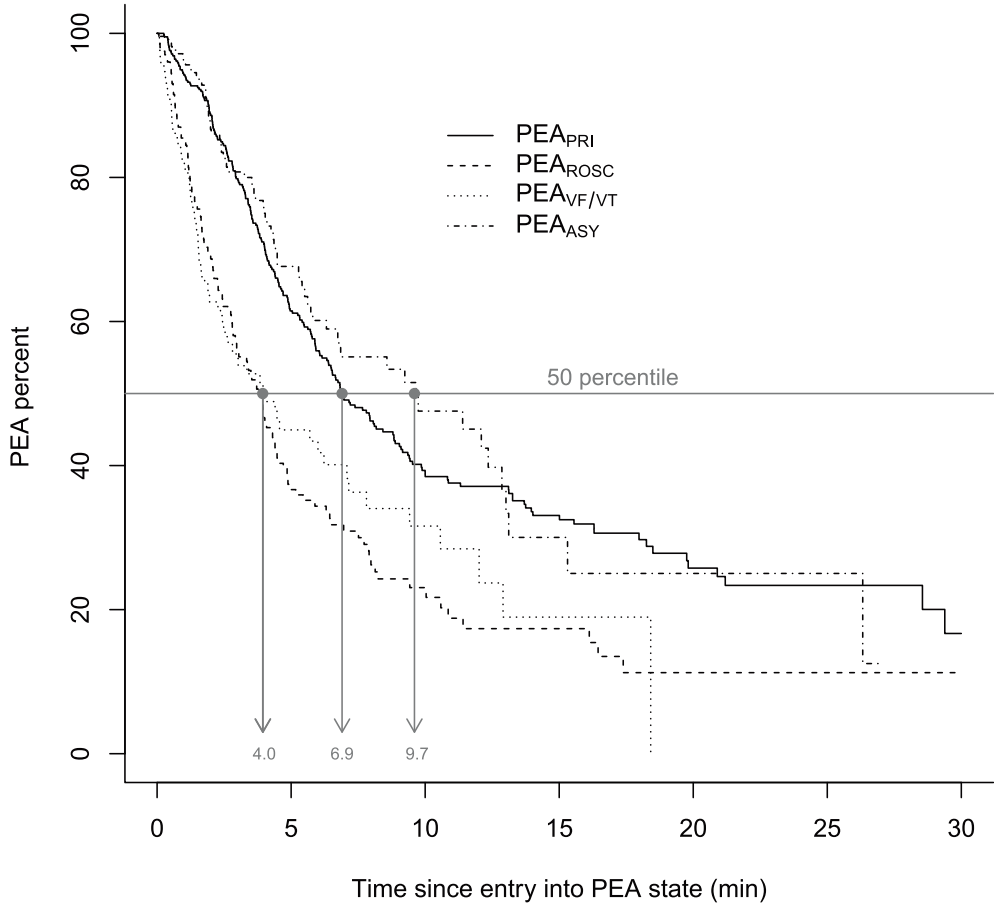


**Fig. 5 – Observed sojourn times in the four PEA states.**

Common to the four different PEAs is the high probability of gaining ROSC during early phases of resuscitation. The initial high transition intensity also reflects shorter time to ROSC in this phase. Later, when intensities are lower, we should expect longer times to ROSC.

Identifying these crossroads and exploring the roadmap of IHCA is important in resuscitation science as it prepares the resuscitation team for what might be expected during CA. Meaningful conclusions may be drawn from the rhythm trends shown in this study. (1) Transition to PEA may indicate improvement in the patient condition and should encourage the resuscitation team to continue the resuscitation efforts. (2) Patients with $PEA_{PRI}$ and $PEA_{ASY}$ need longer resuscitation to achieve ROSC than $PEA_{ROSC}$ and $PEA_{VF/VT}$.

## Conclusion

Changes in rhythm during resuscitation may be a sign of treatment response and the emergency team should take record of these changes. PEA appears as a critical intermediate state in which the subsequent course is determined. This study showed that the four distinct types of PEA behave differently on important characteristics, which should be kept in mind during resuscitation. A transition to PEA during resuscitation should be regarded as an improvement of the patient's condition and encourage further resuscitative efforts.

## Limitations and strengths

This study has several limitations as well as strengths. The start of the episode (initiation of CPR) was not accurate in the cases with a long delay between collapse and defibrillator attachment. We believe that this was not common as a delayed defibrillator attachment would be a deviation from current recommendations.[25]

ROSC was defined as an organized rhythm compatible with circulation within a pause of compressions longer that 1 min. It is fair to assume that the resuscitation team would not have taken their hands off a patient without adequate circulation. However, we cannot know for sure if this represented a period of ROSC. Information on mechanical activity of the heart or flow in great arteries was not available, thus the occurrence of temporary ROSC may have been overestimated. It can sometimes be difficult to differentiate between a slow PEA rhythm and ASY since our analysis is restricted to pauses in compressions, i.e., a 5 second pause will not capture a PEA rhythm with a QRS frequency of less than 12/min. This uncertainty is reflected in our ASY definition. Most transitions are interval censored, i.e., the transition has already occurred when first observed. One may also ask whether the observed dynamic course of PEA has changed significantly over the 20 years of observation. We briefly investigated this graphically without noting signs of this (data not shown).

This analysis is subject to prognostication bias as described by Grunau et al.[26] The declaration of death is a decision based on a

subjective evaluation of the arrest situation and perceived futility may lead to premature termination. Some of the patients included might have achieved ROSC with longer resuscitation efforts. This may cause an underestimation of the transition intensity to ROSC.

This study has some notable strengths as well. It is based on numerous real and well-recorded IHCA episodes, with well-organized and quick emergency responses to medical emergencies.

## Conflict of interest

All authors declare no conflicts of interest.

### *CRediT authorship contribution statement*

**A. Norvik:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **E. Unneland:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **D. Bergum:** Conceptualization, Investigation, Data curation, Writing – review & editing, Supervision. **D.G. Buckler:** Data curation, Writing – review & editing. **A. Bhardwaj:** Writing – review & editing. **T. Eftestøl:** Writing – review & editing. **E. Aramendi:** Conceptualization, Software, Writing – review & editing. **T. Nordseth:** Conceptualization, Investigation, Data curation, Writing – review & editing. **B.S. Abella:** Writing – review & editing. **J.T. Kvaløy:** Writing – review & editing. **E. Skogvoll:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – review & editing, Supervision, Project administration, Funding acquisition.

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Clinical paper

# Heart rate and QRS duration as biomarkers predict the immediate outcome from pulseless electrical activity

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## Abstract

**Introduction**: Pulseless electrical activity (PEA) is commonly observed in in-hospital cardiac arrest (IHCA). Universally available ECG characteristics such as QRS duration (QRSd) and heart rate (HR) may develop differently in patients who obtain ROSC or not. The aim of this study was to assess prospectively how QRSd and HR as biomarkers predict the immediate outcome of patients with PEA.

**Method**: We investigated 327 episodes of IHCA in 298 patients at two US and one Norwegian hospital. We assessed the ECG in 559 segments of PEA nested within episodes, measuring QRSd and HR during pauses of compressions, and noted the clinical state that immediately followed PEA. We investigated the development of HR, QRSd, and transitions to ROSC or no-ROSC (VF/VT, asystole or death) in a joint longitudinal and competing risks statistical model.

**Results**: Higher HR, and a rising HR, reflect a higher transition intensity ("hazard") to ROSC ($p < 0.001$), but HR was not associated with the transition intensity to no-ROSC. A lower QRSd and a shrinking QRSd reflect an increased transition intensity to ROSC ($p = 0.023$) and a reduced transition intensity to no-ROSC ($p = 0.002$).

**Conclusion**: HR and QRSd convey information of the immediate outcome during resuscitation from PEA. These universally available and promising biomarkers may guide the emergency team in tailoring individual treatment.

**Keywords**: In-hospital cardiac arrest, Prognostics, ECG, Pulseless electrical activity

## Introduction

During resuscitation from cardiac arrest, the potential for obtaining return of spontaneous circulation (ROSC) is important and may influence treatment decisions. Such considerations are often based on static factors (i.e., arrest etiology and context, patient comorbidity and presenting rhythm), which by themselves do not reflect treatment response. Dynamic intra-arrest factors such as end-tidal carbon dioxide ($EtCO_2$),[1] cardiac ultrasound[2] and cerebral oxygen saturation[3] have been proposed as prognostic markers, but international guidelines[4] only suggest the use of $EtCO_2$ in this respect.

Heart rate (HR) and QRS duration (QRSd) are biomarkers that are in principle universally available both during the initial and subsequent rhythm checks. The impact of HR and QRSd during the initial rhythm check on survival from pulseless electrical activity (PEA) is unclear. Ho et al, Hauck et al and Bergum et al found no correlation between initial QRSd, HR and survival.[5–7] Weisser found a correlation between initial HR and survival, but not with QRSd.[8] Kim found a correlation between initial QRSd and survival but not with HR,[9] while Aufderheide found a correlation between both HR, QRSd and survival among several studied ECG characteristics.[10]

Skjeflo et al stratified patients with PEA according to whether they achieved ROSC or were declared dead, and investigated the changes in HR and QRSd over the last 12 min preceding these events.[11] Patients who achieved ROSC experienced increasing HR and decreasing QRSd, while those who were declared dead experienced the opposite. It is difficult to apply these results for predictions, however, since they were retrospective and conditional on the outcome.

Joint models have been used to examine the relationship between changes in one or several biomarkers over time and disease outcome.[12] The relationship between the longitudinal

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development of HR and QRSd and the immediate development of ROSC can be studied within this framework.

The aim of this study was to investigate how HR and QRSd as biomarkers are related to the immediate probability of any ROSC during resuscitation from PEA.

## Materials and methods

### *Study setting and population*

This was a prospective observational study of in-hospital cardiac arrest (IHCA) among adults, partly due to a quality assurance initiative, that included ECG signals. We reviewed 381 episodes of CA from three hospitals: St. Olav University hospital in Norway (2018–2021), the Hospital of the University of Pennsylvania, USA (2008–2010), and the Penn Presbyterian Medical Center, USA (2008–2010). We also included 74 episodes with primary PEA from St. Olav's hospital registered between 2009 and 2012, annotated and included in a previous study.[11]

### *Data collection and processing*

Defibrillators from different manufacturers (see supplementary material) recorded ECG and impedance during cardiopulmonary resuscitation (CPR) from which chest compressions (including pauses) and ventilations could be determined. All episodes were manually assessed and annotated using a custom-made graphical application in MATLAB.[13]

We evaluated cardiac arrest rhythms and ECG only during chest compression pauses, as compressions introduce noise. PEA was defined as an organized rhythm and different from ROSC if interrupted by chest compressions within one minute, suggesting lack of clinical signs of spontaneous circulation.[14] Temporary ROSC (tROSC) lasted less than 20 min whereas sustained ROSC (sROSC) lasted more than 20 min; the latter defined the end of an episode even if a new arrest ensued. Time of death was defined as the time of the last chest compression or defibrillation attempt if the patient did not obtain ROSC. A detailed description of the data collection process and annotation of arrest rhythms can be found in supplementary material.

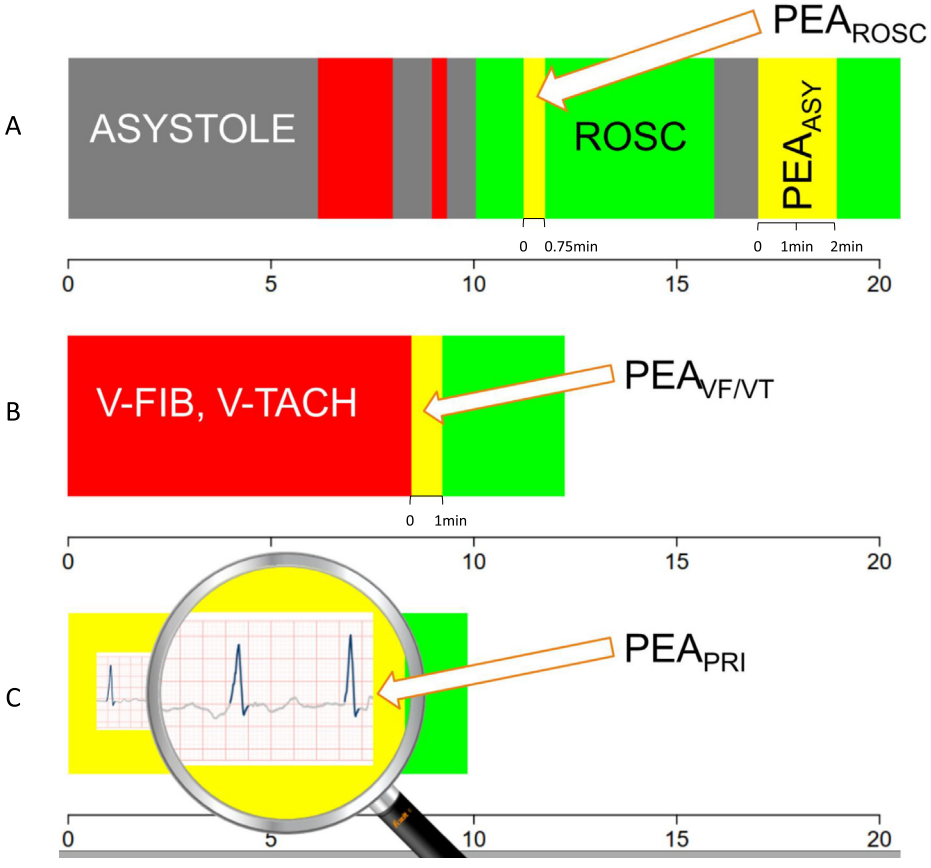



**Fig. 1 – Illustration of three episodes (A-C) of cardiac arrest, showing all four types of PEA segments (yellow with arrows). Incidentally, all ended in ROSC. Also illustrated are the two different timelines at work; episode time from start of resuscitation, and PEA segment time in which the clock is "reset" to 0. Color coding: Asystole (gray), VF/VT (red), PEA (yellow), ROSC (green). Episode A contains two PEA segments from different origins. Initially we see transitions between asystole and VF/VT, before ROSC at 10 min. The patient rearrests with $PEA_{ROSC}$ at approximately 12 min. At approx. 16 min the patient enters asystole and gains $PEA_{ASY}$ at approx. 17 min, then regaining ROSC at 19 min. Episode time is cut at 20 min. Episode B shows a transition from VF/VT to $PEA_{VF/VT}$ at approx. 9 min and a transition from $PEA_{VF/VT}$ to ROSC at about 9 min. Episode C illustrates a direct transition from $PEA_{PRI}$ to ROSC at 8 min. As this is primary PEA, segment time coincides with episode time.**

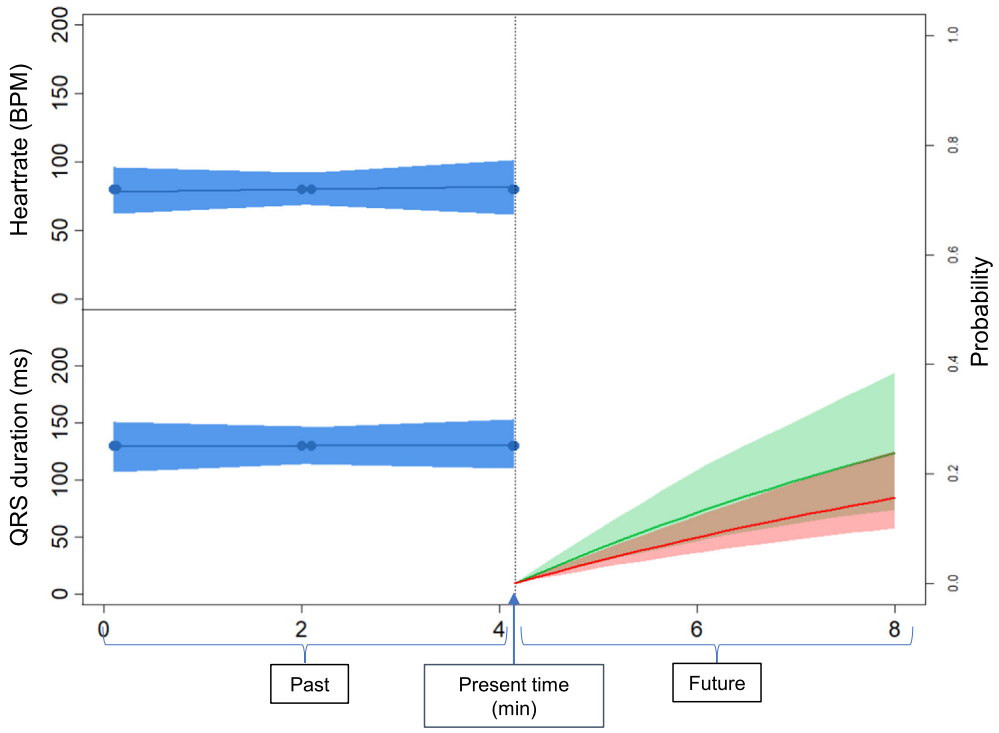



**Fig. 2 – Illustration of the "typical patient" who has been in PEAPRI for approx. 4 min. During this period, HR has been constant at 80 bpm and QRSd has been constant at 130 ms (blue dots) as illustrated by the left part of the figure. The right part of the figure illustrates the probabilies of the different immediate outcomes (state following the PEA segment). The probability of ROSC the next 4 minutes is illustrated by the green line with 95% credible interval (green area), the estimated probability of noROSC is illustraded by the red line with 95% credible interal (red area). The estimated probability of remaining in PEA is not shown but equals 1 minus the sum of ROSC and noROSC. The calculation of these probabilities is based on the slope/changes in HR and QRSd up to present time (slope eqals zero in this case), the absolute value of HR and QRSd at present time (80 bpm and 130 ms), the estimated trajectory of HR and QRSd the next 4 minutes (extending the blue line, also at 80 bpm and 130 ms) together with PEA type and time from episode start.**

A PEA segment was defined from where PEA was first observed until a transition to another clinical state (ROSC, VF/VT, ASY, or death) was noted. One episode of cardiac arrest may thus contain several PEA segments, and one patient may experience more than one episode. Fig. 1 illustrates transitions in three episodes of cardiac arrest from two patients: showing a total of four PEA segments.

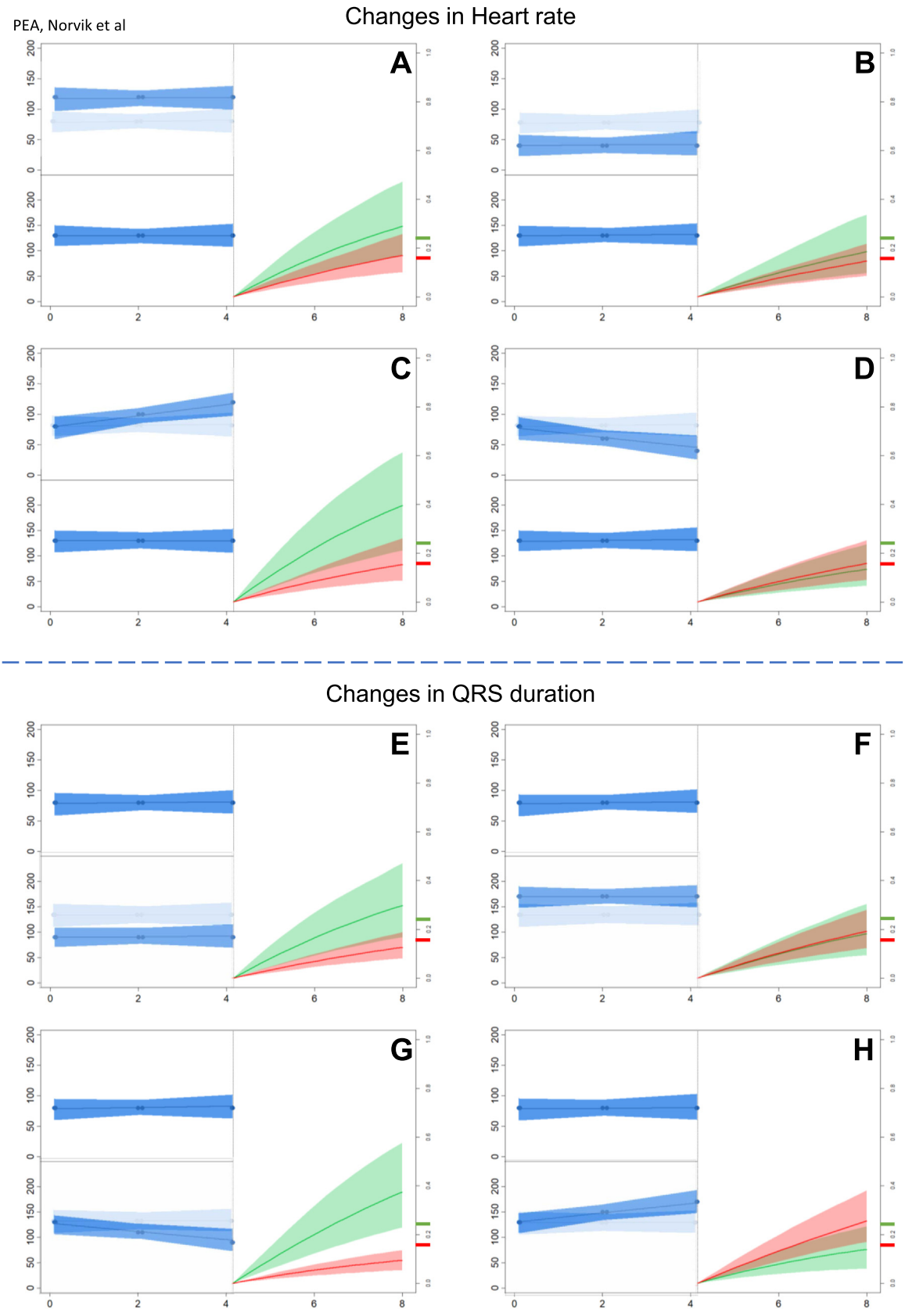
HR and QRSd were determined for all available QRS complexes of every PEA segment by the first author (AN). Start of QRS was defined as a sudden upwards or downwards deflection from a stable baseline. The end of QRS was defined at the J-point, i.e. first part of deflection on the terminal upstroke or downstroke of the QRS.[15] In cases where the J-point could not be defined, the end was defined where the downstroke of the R-wave or the upstroke of the S-wave crossed the baseline. Cases with an unclear J-point were reviewed with an electrophysiologist for adjudication (JPL). HR in beats per minute (bpm) was determined by dividing 60,000 by the RR-time in milliseconds (i.e., time from one R-wave to the next).

### *Statistical analysis*

A joint model relates the longitudinal development of one or more covariates over time to a time-to-event outcome of interest. In the current study, we simultaneously considered the *longitudinal development* of HR and QRSd using linear mixed effect models, and the *time to events* ROSC or no-ROSC (VF/VT, ASY or death) as competing risks; using Cox models in a Bayesian framework. We included both the actual value of HR and QRSd and their estimated slopes. In S1 (supplementary material) we illustrate calculation of the average HR change over time (ΔHR/Δtime, i.e., slope) in one PEA segment. For a thorough introduction to joint models, we refer to supplementary material, Baart et al., Cekic et al. and Elashoff et al.[16–18] We employed the package JMBayes2 version 0.3-0[19] in R version 4.2.1.[20]

A "clock reset" model governed the timeline of the segments, meaning that each PEA segment started at time zero regardless of whether PEA was a primary or secondary rhythm (Fig. 1). Time since start of the episode was added as a fixed covariate along with type of PEA[21]; PEA as the primary rhythm ($PEA_{PRI}$), PEA following a period of ROSC ($PEA_{ROSC}$), PEA following VT/VF ($PEA_{VF/VT}$) or PEA following asystole ($PEA_{ASY}$) (Fig. 1).

The basic outcome measures were the *transition intensities* from PEA to ROSC, and to no-ROSC (equivalent to *hazard rates* in conventional survival models). A transition intensity is the immediate probability that the patient moves to another clinical state in a short time (e.g., the next minute) given the state he or she is currently in.


PEA, Norvik et al
Changes in Heart rate
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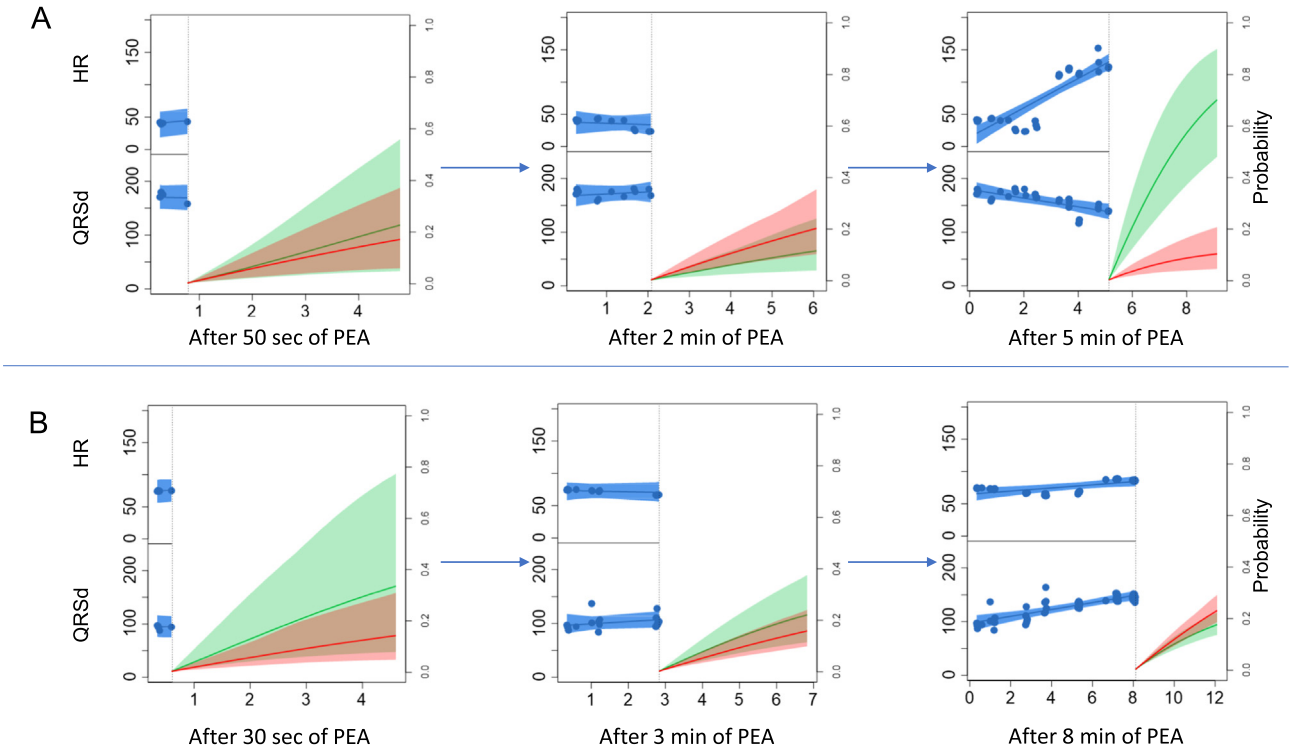


**Fig. 4 – PEA segments from two patients that illustrate actual but different HR and QRSd developments in $PEA_{PRI}$ during CPR. Patient A in the upper row gained temporary ROSC at approximately 7 minutes, but rearrested and was later declared dead. Patient B, in the lower row, transitioned to sustained ROSC at 8 minutes and 25 seconds; illustrating that resuscitation should not be terminated based on this observation alone.**

Dynamic prediction plots (Figs. 2–4) were used to illustrate the clinical application of the model by showing the estimated probability of ROSC and noROSC the next 4 min (right part). These estimations are deducted from past observations of HR and QRSd (left part) and the estimations are updated as new values are added. To roughly assess the models' ability to predict ROSC within the next 4 min, we calculated the area under the receiver operating characteristic (ROC) curve and positive predictive values using the 559 PEA segments.

### *Ethics*

The Regional Committees for Medical and Health Research Ethics in central Norway approved the study (reference number 2019/785). The need for consent was waived by the committee for patients from the two North American hospitals and for 72 of the patients included from the Norwegian hospital. The remaining patients provided written consent personally or through a next-of-kin. Data were further analyzed anonymously.

## Results

A total of 455 episodes from 405 patients comprised the initial dataset. We excluded episodes with noisy or lacking ECG signal, episodes without PEA segments, episodes with an active pacemaker during resuscitation, and episodes containing PEA segments with only one analyzable QRS complex (S3 in supplementary material). From the remaining 327 episodes we extracted 559 segments of PEA in 298 patients (Fig. 1). The median age was 68 years (quartiles 57, 78) and 167 patients were male (56%). Cardiac etiology was presumed in 139 (49%) episodes, 235 (73%) episodes occurred in units with continuous monitoring, and adrenaline was administered in 266 (88%) episodes. Sustained ROSC was achieved in 175 episodes (54%), and 35 patients (12%) eventually survived to discharge (Table 1).

Any ROSC developed in 282 PEA segments, one segment remained in PEA, 70 transitioned to VF/VT, 108 to ASY, and death was declared at the end of 98 segments. The median duration of

**Fig. 3 – A. The impact of 40 bpm higher HR. HR and QRSd values from the reference segment can be seen as light shadows. The estimated probability of ROSC and no-ROSC of the reference segment can be seen as thick green and red lines on the probability axes. Fig. 3B. The impact of 40 bpm lower HR. Fig. 3C. The impact of a HR increasing by 10 bpm/min combining the effect of a higher absolute value and change in HR over time. Fig. 3D. The impact of a HR decreasing by 10 bpm/min. Fig. 3E. The impact of a 40 ms lower QRSd. Fig. 3F. The impact of a 40 ms higher QRSd. Fig. 3G. The impact of a QRSd decreasing by 10 ms/min. Fig. 3H. The impact of a QRSd increasing 10 ms/min.**

**Table 1 – Descriptive data.**

| | |
|---|---|
| ***Patient characteristics (total 298)*** | |
| Male (proportion) | 167 (56%) |
| Median age (quartiles) | 68.0 years (quartiles 57–78) |
| Patients surviving to discharge | 35 (12%) |
| - PEA as primary rhythm | 23 |
| - VF/VT as primary rhythm | 12 |
| - ASY as primary rhythm | 0 |
| ***Episode characteristics (total 327)*** | |
| Cardiac etiology | 139 (49%, 41 missing) |
| Adrenaline administration | 266 (88%, 24 missing) |
| Arrests in units with continuous monitoring | 235 (73%, 6 missing) |
| Median chest compression rate | 110 (quartiles 104–115) |
| Median chest compression fraction | 0.88 (quartiles 0.81–0.92) |
| Presenting rhythm | |
| - PEA | 257 (79%) |
| - VF/VT | 44 (12%) |
| - ASY | 26 (8%) |
| Episodes ending in sustained ROSC | 175 (54%) |
| ***PEA segment characteristics (total 559)*** | |
| Median duration of PEA segment | 225 sec (quartiles 105–415 s) |
| Median number of QRS complexes per segment | 18 (quartiles 7 – 48.5) |
| Median HR | 86.9 (quartiles 54.5 – 120.0) |
| Median QRSd | 135.1 (quartiles 103 – 172) |
| Median slope (HR (quartiles), QRSd (quartiles)) | |
| - Segments ending in sROSC (n = 145) | 3.9 (0.4–8.9), − 0.1 (-3.7–2.5) |
| - Segments ending in tROSC (n = 137) | 2.4 (-0.6 – 6.8), −0.2 (-3.7–2.4) |
| - Segments ending in VF/VT (n = 70) | 3.4 (-0.2 – 7.7), 0.3 (-3.7 – 3.7) |
| - Segments ending in ASY (n = 108) | 1.4 (-2.0 – 5.3), 0.5 (-3.8 – 4.6) |
| - Segments ending in death (n = 98) | 0.8 (-1.5 – 4.2), 0.7 (-1.3 – 3.7) |

**Table 2 – The association between changes in HR, QRSd and the transition intensity ratios (PEA to ROSC and PEA to noROSC). Note that the effect is linear across the range of HR and QRSd values and slopes. PEA class also affects outcome. In addition, we see that the secondary PEA types get a time penalty as they start later in the episode compared to $PEA_{PRI}$. E.g, $PEA_{ASY}$ has the same fixed intensity of ROSC as $PEA_{PRI}$, but since $PEA_{ASY}$ always occurs later in the episode and the transition intensity to ROSC decreases with time – so will also the $PEA_{ASY}$ to ROSC transition intensity. bpm = beats per minute, HR = heart rate.**

| | PEA to ROSC transition intensity ratio, (95% credibility interval and P-value) | PEA to noROSC transition intensity ratio, (95% credibility interval and P-value) |
|---|---|---|
| HR, per 40 bpm (value) | 1.39 (1.21–1.58) (<0.001) | 1.07 (0.91–1.26) (0.387) |
| QRS duration, per −40 ms (value) | 1.26 (1.13–1.40) (<0.001) | 0.84 (0.78–0.91) (<0.001) |
| HR slope, per 10 bpm $min^{-1}$ (increase) | 1.37 (1.15–1.64) (<0.001) | 0.84 (0.69–1.14) (0.349) |
| QRSd slope, per 10 ms $min^{-1}$ (decrease) | 1.18 (1.02–1.35) (0.023) | 0.76 (0.65–0.89) (0.002) |
| $PEA_{ROSC}$ | 2.48 (1.47–4.13) (0.001) | 0.88 (0.49–1.54) (0.688) |
| $PEA_{VF/VT}$ | 1.92 (1.25–2.92) (0.003) | 2.17 (1.43–3.24) (<0.001) |
| $PEA_{ASY}$ | 1.10 (0.71–1.66) (0.660) | 2.04 (1.45–2.87) (<0.001) |
| Time from episode start (minute, only applicable to $PEA_{VF/VT}$, $PEA_{ROSC}$ and $PEA_{asy}$) | 0.98 (0.966–0.998) (0.028) | 1.01 (1.004–1.024) (0.008) |

the PEA segments was 225 s (quartiles 105, 415 s) (S2). In total 20,344 QRS complexes were included in the analysis. S4 and S5 in the supplementary material visualizes the individual linear developments of HR and QRSd for all PEA segments.

The overall results are displayed in Table 2 and in the dynamic prediction plots in Figs. 2 and 3A-H, as well as in Animations 1 and 2 in supplementary material. To illustrate, we define a "typical patient" as having primary PEA with HR of 80 bpm and QRSd of 130 ms (close to the global average HR and QRSd) that remained constant over time, i.e., with slopes of zero (Fig. 2). A PEA segment with a HR of *40 bpm higher* than 80 bpm (i.e., 120 bpm) has a 1.39 (1.21–1.58) times higher transition intensity to ROSC, and a (non-significant) 1.07 (0.91–1.26) times higher transition intensity to no-ROSC (Table 2). This yields an increased probability of ROSC, an

essentially unchanged probability of no-ROSC (Fig. 3A), and (implicitly) a decreased probability of remaining in PEA. Also, a shrinking QRSd reflects an increased transition intensity to ROSC and a decreased intensity to no-ROSC (Table 2 and Fig. 3E).

The rate of change in HR and QRSd (the slope) also reflect the transition intensity to ROSC. A *10 bpm/*min higher HR slope is related to an increased transition intensity to ROSC by 1.37 (1.15–1.64) times, and a non-significant decrease in the intensity to noROSC (Fig. 3C). A lower QRSd slope is related to an increased transition intensity to ROSC and a decreased intensity to no-ROSC (Fig. 3G).

Type of PEA is also related to the transition intensities. With $PEA_{PRI}$ as reference, $PEA_{ROSC}$ and $PEA_{VF/VT}$ reflect an increased transition intensity to ROSC. $PEA_{ASY}$ is not by itself associated with changes in the transition intensity to ROSC compared to $PEA_{PRI}$. But due to the accumulated time since start of the episode, $PEA_{ASY}$ has a worse outcome as every additional minute is associated with decreased transition intensity to ROSC and increased transition intensity to no-ROSC.

A high QRSd and a positive QRSd slope reflect an increased probability of no-ROSC (Fig. 3F and H). Still, 87 segments with a QRSd increase of more than 1 ms/min and 23 segments with a QRSd increase of more than 5 ms/min, gained ROSC (S4 in supplementary material).

Fig. 4 illustrates the clinical application of our model using observation at three timepoints from two actual PEA segments. This is also illustrated by the two videos in the online supplementary material. Animation 1 corresponds to the segment illustrated in Fig. 4A and Animation 2 corresponds to the segment illustrated in Fig. 4B.

The AUC of the ROC curve was 0.74 (CI 0.70–0.78) (S6) when comparing the outcome of each segment with predicted ROSC four minutes ahead. A threshold probability of ROSC higher than 50% yielded a PPV of 80% (Table 1 in supplementary material).

## Discussion

To our knowledge, this is the first study to quantify how heart rate and QRS duration may predict the immediate outcome *during ongoing resuscitation* from pulseless electrical activity. Our study stands out by including ECG data throughout the entire episode, by using a proper statistical method that is not conditional on the outcome, and finally by linking both values and changes in the biomarkers as dynamic predictors – as opposed to simple averages – to the outcome.

### *Clinical implications*

An immediately available biomarker allows one to monitor progress of the patient and may allow for personalization of treatment. *How* is a matter for debate. However, while HR is easily observed on the monitor, judging QRS duration may require more sophistication. Our study shows that patients with higher/increasing HR and narrower/decreasing QRSd have higher probability of gaining ROSC. A positive development, as observed in Fig. 4A, could encourage one to carry on resuscitation and not change much, in particular avoiding hands off time. Further research may clarify whether, for example, titrating the dose of adrenaline may also be guided by this biomarker response.

A neutral development as observed in Fig. 4B, may prompt one to reconsider some of the aspects of resuscitation, like evaluating the quality of chest compressions and searching more closely for reversible factors. Further research may clarify if alternative sources of information like focused echocardiography, rSO2 or EtCO2 proves useful here.

A high/increasing QRSd is associated with increased transition intensity to VF/VT, ASY or death. This is a statistically significant result (Table 2), but such development should not be interpreted too strongly and was commonly seen in segments ending in ROSC (S4 in supplementary material). For this reason, QRS widening cannot be used alone to terminate the resuscitation effort, nor be used as the only indication of worsening of the patient's condition (Fig. 4B). However, it is nevertheless a signal that may prompt for re-evaluating the situation. Thus, while significant changes in HR and QRSd following an intervention or altered strategy may provide immediate feedback, the response characteristics (time and degree) by these biomarkers remain to be investigated.

PEA type is also related to the probability of gaining ROSC, as described in our previous paper.[21] It is interesting to note that $PEA_{VF/VT}$ develops quickly into either ROSC or no-ROSC states (VF/VT, ASY and death). This is not a contradiction but expresses the inherent instability of $PEA_{VF/VT}$ compared to primary PEA.

Our results are highly significant. Still, we stress that understanding and quantifying the information obtained by the biomarkers are more important than making precise predictions. While we do not believe that survival can be increased by forcing the HR to increase or the QRS complex to shrink, we find it reasonable that these biomarkers reflect the underlying process (see below). To further improve the utility of HR and QRS measurements beyond inspecting the ECG, one may consider automatic and possibly filtered capture and display of these characteristics on the monitor. Other promising biomarkers like ETCO2, and rSO2 could also be investigated with focus on changes during the episode, rather than merely their average values. The joint model is a powerful tool for this purpose.

### *The QRS complex reflects changes in the physiological state of the heart*

Heart rate and the QRS complex duration respond quickly to changes in the cardiac homeostasis. Several studies have shown that acute myocardial ischemia increases QRS duration and relieving the ischemia normalizes QRS duration immediately. Injecting ceramic microspheres into the left circumflex artery of anesthetized dogs has shown to increase QRSd[22] and Holland et al. reported that the intrinsicoid deflection (time from beginning of QRS complex to the top of the R wave) would increase 2–3 times relative to baseline values after ligating the left descending coronary artery in porcine hearts and return to normal within 2–4 heartbeats after releasing the occlusion.[23]

Investigators have also found exercise-induced QRSd prolongation in humans with angina[24] and significant narrowing of the QRS complex immediately after successful reperfusion in patients with ST-elevation myocardial infarction.[25] Telemetry recordings have shown an increasing QRSd of at least 20 ms prior to arrest in 15 out of 81 IHCA.[26] Continuous QRS widening prior to asystole or PEA due to right ventricular strain has also been described.[27] In addition, hyperkalemia is also known to widen the QRS complex.[28] Changes in QRSd during cardiac arrest has also been described.[11]

The narrowing of the QRS complex observed in our study may be a response to improved myocardial perfusion or relieved right ventricular strain during resuscitation.

HR also changes in conjunction with cardiac arrest. Several investigators have demonstrated bradycardia in patients prior to arrest[26,29] and HR changes during resuscitation possibly due to chest compressions and/or epinephrine.[11,30]

## Limitations

Defining ROSC as an organized rhythm without chest compressions for more than one minute is one of the major limitations in this study. Differing between ROSC and PEA in retrospect is difficult without objective measures of circulation. While impedance signals might assist in differentiating ROSC form PEA, this information is not available to the treating team.[31] This definition may have caused an overestimation of temporary ROSC.

Using 1-lead ECG to analyze QRSd is a limitation.[32] A multi-lead ECG would make it easier to capture the true QRS duration. Many of the included QRS complexes have a very pathological appearance with no clear J-point making it difficult to define the end. By consistently measuring the same parts of the QRS complex within each episode one may minimize this measurement bias. Annotations were performed by the first author only, except in cases with morphologically challenging QRS complexes. Confidence in the data would have improved with duplicate revision of the data. We also note that the first author was not blinded to patient outcome during the annotation process.

Only episodes containing PEA segments with at least two measurable electrical heart cycles were included in our study. Also, a linear slope is admittedly a simple model for biomarker development. However, actual values are included, and more complex models were both hard to make converge and to interpret and did not improve diagnostic performance.

The calculation of AUC and PPV was done using the dataset included in the model. This produces optimistic estimates of performance.[33]

Finally, the decision to declare a patient dead is based on several factors and not only the isolated ability of the heart to regain ROSC. Our study may thus be subject to some degree of prognostication bias, since some of the patients declared dead could have achieved ROSC (but not necessarily long-term survival) with longer resuscitation time.[34] This may lead to an underestimation of the impact of HR and QRSd on ROSC achievement. Even though the condition of the patient's heart is improving with increasing HR and decreasing QRSd, the resuscitation effort may still be terminated due to conditions unrelated to the heart.

## Conclusion

Heart rate and QRS complex duration conveys information of the immediate outcome of PEA. These are universally available and promising biomarkers that may guide the emergency team in tailoring individual treatment. A high and/or increasing HR and a low and/or decreasing QRS duration suggests imminent ROSC and encourages further efforts. Absence of such changes are nonspecific, however, and should encourage re-evaluation rather than termination of resuscitation.

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## Conflicts of interest

All authors state no conflicts of interest.

## CRediT authorship contribution statement

**A. Norvik:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **J.T. Kvaløy:** Conceptualization, Formal analysis, Methodology, Writing – review & editing, Visualization. **GW. Skjeflo:** Conceptualization, Data curation, Writing – review & editing. **D. Bergum:** Conceptualization, Investigation, Data curation, Writing – review & editing, Supervision. **T. Nordseth:** Conceptualization, Writing – review & editing. **J.P. Loennechen:** Conceptualization, Data curation, Writing – review & editing, Supervision. **E. Unneland:** Data curation, Writing – review & editing. **D.G. Buckler:** Data curation, Writing – review & editing. **A. Bhardwaj:** Writing – review & editing. **T. Eftestøl:** Writing – review & editing. **E. Aramendi:** Software, Writing – review & editing. **BS. Abella:** Writing – review & editing. **E. Skogvoll:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – review & editing, Supervision, Project administration, Funding acquisition.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2023.109739.

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# Adrenalin, changes in heart rate and return of spontaneous circulation in in-hospital cardiac arrest

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# Abstract

Introduction:

Adrenaline provides inotropic, chronotropic and vasopressor effects. It is a cornerstone drug for resuscitation in Pulseless Electrical Activity (PEA); in which a high or increasing QRS rate ("heart rate, HR) and a short or decreasing QRS complex duration (QRSd) signals Return of Spontaneous Circulation (ROSC). This study of in-hospital cardiac arrest aims to describe the development of ROSC and characterize changes in HR and QRSd in PEA after administration of adrenaline.

Method:

Recordings from in-hospital cardiac arrests at St. Olav University Hospital (Norway) were prospectively collected between 2018 and 2022. Timing of adrenaline, with minutes precision, was obtained by interviewing personnel and reviewing clinical records. We investigated transitions to ROSC and changes in HR and QRSd after adrenaline administration by means of graphical plots, a time-to-event (Cox) model, and piecewise linear splines.

Results:

Adrenaline was strongly associated with the transition from primary PEA to ROSC, with an intensity ("hazard") ratio of 3.85 (p=0.005). Most transitions to ROSC occurred within 4 minutes of administration. The first dose was associated with a HR increase of 9.5 bpm/min (p=0.002) two minutes after administration, and a significant change in HR slope (p=0.025) when compared to the preceding interval. Subsequent doses of adrenaline had no substantial impact. No change in QRS duration was observed.

Conclusion:

We found a rapid and strong increase in the transition intensity from PEA to ROSC after adrenaline administration. Patients who remained in PEA exhibited an increasing HR two minutes after the first adrenaline dose, other effects were minimal.

# Introduction

Adrenaline is administered to all patients with cardiac arrest (CA) who do not obtain ROSC early during resuscitation. Its effect and role have been discussed for decades and observational studies during the 90s and early 2000s showed worse outcome for patients receiving adrenaline.[1-4] These did not account for "resuscitation time bias", however, and underestimated the effect of adrenaline on survival.[5, 6] Later, randomized trials on out-of-hospital cardiac arrest (OHCA) have established that adrenaline increases the probability of ROSC[7-9]. Although the effect was small, Perkins et al. also found increased 30-day survival among the 4015 patients receiving adrenaline during OHCA. [9]

It is reasonable to expect similar effects for in-hospital cardiac arrest (IHCA), but no randomized controlled trial (RCTs) has been conducted to explore this.[10] Furthermore, the effect size cannot be inferred from prehospital data as there is a high proportion of initial asystole and substantial differences in causes and time to adrenaline between the two groups. Time to treatment is very important for survival after cardiac arrest. Delayed CPR and delayed defibrillation reduce survival. [11, 12] Observational studies on IHCA have concluded that delayed adrenaline administration also reduces survival, but in a sub analysis of PARAMEDIC2 one could not find a significant difference in long-term survival and neurological outcome between patients receiving early adrenaline or placebo.[11, 13, 14]

Adrenaline has chronotropic, inotropic and vasopressor effects.[15] It has been suggested that increasing coronary perfusion pressure promotes ROSC [16, 17], and a recent study from our group showed that high/increasing heart rate (HR) and low/decreasing QRS duration (QRSd) during PEA reflect a process towards ROSC.[18] While these biomarkers qualify as dynamic predictors of the immediate outcome during IHCA, the HR and QRSd response may also reflect an effect of adrenaline.

The aim of this study was to characterize and describe development of ROSC and changes in HR and QRSd after adrenaline administration, during in-hospital resuscitation.

# Method

## Study setting and population

This prospective observational study was conducted between August 2018 and October 2022 at St. Olav University Hospital in Trondheim, Norway. This tertiary care facility covers all medical specialties, with approximately 900 beds, 60 000 admissions per year, and a cardiac arrest incidence of about 1.3-1.7 per 1000 admissions (80-100 episodes per year). All hospital employees are trained in basic life support. A cardiac arrest team consisting of a physician on call in the cardiology unit, a physician on call in the anesthesiology/intensive care unit, a nurse anesthetist, a nurse from the emergency department, and an orderly is alarmed in case of CA. A defibrillator records the ECG, the transthoracic impedance, and events that are registered manually by the rescuers or automatically by the defibrillator (LifePak 20 or LifePak 1000, Physio-Control, Redmond, USA).

## Data collection and processing

The defibrillator file and the patient's clinical records were reviewed to determine whether and when adrenaline was administered. If timing of adrenaline had not been documented, we interviewed those present at the event, attempting to link and reconcile this information with other registered events (e.g., a DC shock, change of defibrillators etc.).

Each defibrillator file was analyzed in a graphical tool developed in Matlab® as described in earlier publications and in the supplementary material.[18, 19] Briefly, from the ECG and transthoracic impedance signals we determined the development of clinical states (asystole, PEA, VF/VT, ROSC) throughout the episode. ROSC was defined as a cardiac rhythm compatible with spontaneous circulation and distinguished from PEA if chest compressions were interrupted longer than one minute as reflected by the impedance signal. QRSd and RR interval during PEA were measured by the first author (AN). The ECG was only analyzed during compression pauses to avoid artifacts.

## Statistical analysis

Plots showing the prevalence of each state in continuous time and Sankey plots (flow of patients between each state, including the final state of each episode) were generated to visualize the

development of clinical state transitions from 3 min before until 5 min after the first, second, and third dose of adrenaline. All available episodes in which adrenaline was administered were included in these plots.

We performed a Cox regression analysis of the transition from primary PEA ($PEA_{PRI}$) to ROSC with adrenaline as a time-dependent covariate; entered as a triangular function starting at 0 at administration, rising to 1.0 at 1 min, and decreasing to 0 at 3 min after administration.

To investigate changes in HR and QRSd, we included all patients who received adrenaline and were in PEA at some point from 2 min before to 4 min after adrenaline administration. We then fitted a piecewise linear spline to all available observations of HR and QRSd. Knots were placed at 0 and 2 minutes allowing for analysis of changes between and within the following intervals: -2 to 0 min, 0 to 2 min, and 2 to 4 min. The piecewise linear spline is prone to informative drop-out because patients with high or low HR/QRSd have a higher chance of transitioning to ROSC or no-ROSC respectively, causing data missing not at random (MNAR).[18] Informative "drop-in" is also a possible source of bias as patients with specific characteristics may transition to PEA from other states. To overcome these limitations and visualize transitions and changes in HR within individual episodes, we created a Sankey plot showing the flow of patients between different states the first two minutes after adrenaline was administered. We interpolated HR values for each episode, defining PEA HR categories as <40, 40-59, 60-89, ≥ 90 bpm. The flow between different PEA groups would indicate a change in HR within episodes, while flow between states (ROSC, ASY, VF/VT) represents changes of the PEA group composition.

## Ethical considerations

The Regional Committees for Medical and Health Research Ethics in central Norway approved the study (reference number 2019/785). The need for consent was waived by the committee for patients included after June 2019. The remaining patients provided written consent personally or through a next-of-kin.

# Results

We registered 280 episodes of cardiac arrest in 265 patients. Mean age of the patients was 70.0 years (min 22, max 97), and 113 (42.6%) survived to discharge (Table 1).

Adrenaline was administered in 120 episodes from 119 patients, and 93 episodes in 93 patients were eligible for analysis. Reasons for exclusion were missing defibrillator files (n=13), unreliable information on the timing of adrenaline (n=10), internal cardiac massage (n=2), ongoing infusion of adrenaline during resuscitation (n=1) and pacemaker rhythm during resuscitation (n=1). Characteristics of included and not-included episodes were similar (Table 1).

Among all patients receiving adrenaline, 45 patients achieved sustained ROSC, 69 were declared dead, and five were on mechanical circulatory support. In total, 20 patients (17%) survived to discharge (Table 1).

The prevalence plots and the Sankey plots provide an overview of changes in clinical states from three minutes before to five min after adrenaline in the 93 included episodes (Fig. 1). Visually, ROSC occurred rapidly after adrenaline administration, and the first dose was associated with the highest ROSC rate (29%) at 3 minutes. Among episodes that received the first dose of adrenaline, 38% ended in ROSC. The effect of the second dose was less prominent, and only 15% gained ROSC by 3 min. In total, 25% had gained ROSC by the end of the efforts. Only 7% gained ROSC 3 minutes after the third dose.

Still, at the end of the resuscitation, 24% of those who received three or more doses also gained ROSC. Hence, most patients who respond to adrenaline did so within minutes of administration, and the effect was largest after the first dose. We estimated the intensity ratio (“hazard” ratio) of transitioning from primary PEA to ROSC after the first dose of adrenaline as 3.85 ($p<=.005$).

In the analysis of HR and QRSd evolution we included 69 episodes in conjunction with the first dose, 55 in conjunction with the second dose, and 40 in conjunction with the third dose (Fig. 2). We observed

a significant increase in HR the first two minutes after the administration of the first dose (9.5 bpm per min, p = 0.025) (Tab.2). There was also a significant change in HR slope (p=0.05) when comparing observations 2 min before and 2 min after administration. Visually, QRSd increased prior to the first dose of adrenaline, but this increase apparently levelled off afterwards (ns). Neither the second nor the third dose of adrenaline affected HR or QRSd.

Figure 3 shows changes in HR and arrest states the first two minutes after the administration of the first adrenaline dose, the only time interval where we observed a significant change in HR.
Patients in PEA experienced both increasing and decreasing HR during this period. The transitions between the different PEA groups indicated an overall increase in HR. Transitions in and out of PEA may change the HR distribution within the PEA group as patients with high HR tend to gain ROSC. This may under or overestimate changes in HR observed in the linear spline model. We observed 12 transitions from other states to PEA, and 19 transitions from PEA to other states during this period. There was a net efflux of patients from the PEA groups with HR >90 bpm and HR<40 bpm and a balanced transition to and from the PEA groups with HR 40-89. Since the efflux is largest from PEA >90 bpm the magnitude of the HR increase observed after administering the first adrenaline dose is probably underestimated.

Figure 4 show the cumulative administration of adrenaline for patients in primary PEA. Approximately 80% did receive their first dose within 6 minutes.

## Discussion

The main finding in this study of adrenaline in in-hospital cardiac arrest was an almost immediate return of spontaneous circulation from PEA after administration of adrenaline. Those who remained in PEA exhibited an increased HR two minutes after the first adrenaline dose. There were no significant HR changes after the second and third dose and no significant changes in QRS duration. As we do not have a randomized design with a control group, we cannot infer a causal relationship between adrenaline and ROSC. However, our results certainly support a causal relation as adrenaline was administered at different times after initiation of CPR (Fig.4), leading to a differential distribution of adrenaline timing between and within patients.

Although it is known that adrenaline increases the probability of ROSC[7-10] the details surrounding the actual transition to ROSC has, to our knowledge, not yet been described in humans. Patients started to gain ROSC immediately after adrenaline was administered and the first dose was associated with the highest ROSC rate within 3 and 5 min. From the prevalence plot, we saw a steady accrual of ROSC the first 4 minutes after the first dose of adrenaline was administered. Most of these patients were recruited from PEA. This was expected, as most patients with VF/VT as initial rhythm already had gained ROSC after defibrillation.

In total, 38% of those receiving adrenaline achieved sustained ROSC. Somewhat surprisingly, this is comparable to ROSC rates in the adrenaline arms of the three RCTs (25, 36 and 40%). We expected that the immediate availability of adrenaline would cause even higher rates of ROSC since early administration of adrenaline is associated with higher survival.[13, 20, 21] This finding could indicate that the higher survival amongst patients receiving adrenaline early may be due to early ROSC and underscores the importance of administering adrenaline early in patients with non-shockable rhythms.

Nordseth et al. showed that adrenaline extended the time window for ROSC development in patients with OHCA and PEA. [22] This is supported by findings of Perkins et al. that found an increasing ROSC ratio between the adrenaline and placebo group during later phases of resuscitation.[14] Within the

context of coronary disease and percutaneous reperfusion therapy the ischemic myocardium may be viable for several hours. [23] Therefore the heart is usually not the limiting factor in post-arrest treatment as anoxic brain injury is the most common cause of death.[24] Adrenaline is a tool to achieve ROSC, also during later phases of resuscitation. For this reason, its effect on long-term survival may therefore be underestimated. ROSC is necessary for long-term survival and long- term survival is influenced by an array of factors both related and unrelated to the arrest itself. From our point of view, long-term survival should not be the focus when treating patients in cardiac arrest because the treating team usually don't know the patient and will not be able to achieve a proper understanding of the patients medical history or current situation.

The episodes included in conjunction with the second and third doses were mainly those who did not respond to the first dose. The second and third doses are therefore expected to be less effective. Also, some of those gaining ROSC after the second and third dose have re-arrested after gaining ROSC after the first dose.

The response to the third dose is interesting. Only 7% gain ROSC within 3 minutes and 15% within 5min, indicating possibly little or no effect from adrenaline. Despite this low initial ROSC rate, 24% of these patients gained sustained ROSC by the end of the resuscitation efforts. These patients may circulate adrenaline slower due to patient or CPR factors, or possibly they do not respond to adrenaline at all.

In a previous study by our group, we found that high and increasing HR and short or decreasing QRSd are associated with ROSC.[18] Based on our results, it seems likely that adrenaline increases HR in some patients. QRSd, on the other hand, does not seem to be affected by adrenaline, but then any effect may be masked by informative drop-outs to ROSC. Skjeflo et al. investigated the plausible association between adrenaline and changes in HR and QRSd in patients with OHCA and primary PEA that were first included in Olasveengen's RCT on intravenous access during OHCA. [8, 25] He stratified patients based on ROSC and adrenaline status and found that patients receiving adrenaline and gaining ROSC

experienced both HR increase and QRSd decrease. Patients gaining ROSC who did not receive adrenaline experienced similar changes, but HR increased to a lesser degree. On the other hand, patients who received adrenaline and were eventually declared dead experienced an increase in HR and QRSd, while patients who did not receive adrenaline and were eventually declared dead only experienced increased QRSd. These findings indicate that adrenaline increases HR in patients with primary PEA but does not affect QRSd. Our results are however not directly comparable to this OHCA cohort. We report the overall association between adrenaline and changes in HR and QRSd regardless of initial rhythm and outcome, while Skjeflo et al. stratified his population based on the outcome. Our timeline is related to the administration of adrenaline, while Skjeflo et. al. did not know when the adrenaline was administered. Despite these differences, our results point in the same direction.

## Limitations

Our ROSC definition poses a limitation to our study. Without an objective measure of circulation, we do not know with certainty whether the patient had achieved ROSC or not. Still, it is unlikely that the clinicians would interrupt chest compressions in a patient without circulation for more than one minute, and our Sankey plots demonstrate that most patients who achieve ROSC did not rearrest shortly after. Dewolf et al. investigated interruptions during CPR and found that only 4.3% were longer than 1 minute, thus adding to the validity of our definition.[26] It is difficult to estimate whether our definition over or underestimates ROSC as patients also may have palpable pulse for a shorter than one minute.

We did not formally account for informative drop-in and drop-out. Transitions in and out of PEA may cause both under- or overestimation of HR/QRSd changes during CPR, which might change group composition. A joint model would account for this, [27] but these models interpolate values to describe development over time. This may impose artificial change points. For example, a patient may present with an HR of 50 bpm 2 minutes before and 100 bpm 2 min after adrenaline administration. Interpolating missing values will create a changepoint two minutes before adrenaline when we do not know the exact changepoint. By disregarding individual trajectories, data is available throughout the

observation period preventing changes due to data curation. Still, through the Sankey plot, we could substantiate an underestimation of HR increase during the follow-up of these values.

An important limitation to our results is not including a control group for comparison; hence we can't know for sure whether the observed changes are due to adrenaline as a secular time trend cannot be excluded. Despite this, when interpreting our results in the context of Skjeflo's results, which were based on random assignment, we find it likely that the changes seen in HR are due to adrenaline.

There is uncertainty about the timing of adrenaline administration in some of the episodes, but when the uncertainty was too large the episode was excluded. Usually, we were able to narrow down when the adrenaline was administered. The well-defined timeline is however a major strength to this study, an effect must follow an intervention.

## Conclusion:

The main finding in this study of adrenaline in in-hospital cardiac arrest was an almost immediate return of spontaneous circulation from PEA after administration of adrenaline. Those who remained in PEA exhibited an increased HR two minutes after the first adrenaline dose. There were no HR changes after the second and third dose and no changes in QRSd at all.

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## Conflicts of interest

All authors state none

| | **All patients experiencing cardiac arrest (n=265)** | **All patients receiving adrenaline (n = 119)** | **Patients eligible for adrenalin analysis (n = 93)** |
|---|---|---|---|
| Male gender | 175 (66%) | 79 (66%) | 63 (68%) |
| Mean age | 70.0 years (min 22, max 97) | 71.5 | 71.7 (min 37, max 91) |
| Survived to discharge | 113 (43%) | 20 (17%) | 15 (16%) |
| | | | |
| | **All cardiac arrest episodes (n = 280)** | **Cardiac arrest episodes receiving adrenaline (n = 120)** | **Episodes eligible for adrenaline analysis (n= 93)** |
| Initial rhythm<br>• PEA<br>• VF/VT<br>• Asystole<br>• Unknown | <br>92 (33%)<br>128 (46%)<br>43 (15%)<br>17 (6%) | <br>66 (55%)<br>21 (18%)<br>31 (25.5%)<br>2 (1.5%) | <br>51 (55.5%)<br>14 (15.2%)<br>26 (28.2%)<br>1 (1.1%) |
| Witnessed collapse | 237 (85%) (20 with unknown status) | 95 (79%) (12 with unknown status) | 69 (75%) (11 unknown) |
| Occurred in units with continuous monitoring | 152 (54%) | 58 (48%) | 45 (50%) |
| Cardiac etiology | 164 (59%) (45 with uncertain etiology) | 53 (44%) (23 with uncertain etiology) | 42 (46%) (20 with uncertain etiology) |
| Number of episodes with ROSC | 177 (67%) (5 put on mechanical circulation) | 45 (37.5%) (5 put on mechanical circulation) | 35 (38%) (1 to ECMO) |

Table 1: Overview of the study population

| | HR slope (95% CI) | | QRSd slope (95% CI) |
|---|---|---|---|
| First dose: | | | |
| • -2 to 0 min | -3.0 (-9.3, 3.3) | | 9.8 (-2.3, 22) |
| • 0 to 2min | 9.5 (3.6, 15)[a,b] | | -1.8 (-13, 9.4) |
| • 2 to 4 min | -3.3 (-12, 5.1)[c] | | -5.1 (-22, 11) |
| Second dose | | | |
| • -2 to 0min | 2.5 (-5.7, 11) | | -6.8 (-20, 6.7) |
| • 0 to 2min | 2.7 (-4.8, 10) | | 0.43 (-12, 13) |
| • 2 to 4 min | -6.4 (-17, 4.5) | | -10 (-28, 7.1) |
| Third dose | | | |
| • -2 to 0 min | -6.0 (-16, 3.6) | | 6.7 (-5.7, 19) |
| • 0 to 2 min | 2.8 (-5.4, 11) | | -8.5 (-19, 2.2) |
| • 2 to 4 min | -3.0 (-17, 11) | | 8.1 (-11, 27) |

Table 2: Overview of HR and QRSd slopes in conjunction with the first, second and third adrenaline dose. For the plots, see Figure 2

a: Statistically significant change in slope with p-value = 0.002

b: Statistically significant change in trend compared to foregoing segment, p-value = 0.025

c: Almost statistically significant change in trend compared to foregoing segment, p-value = 0.05

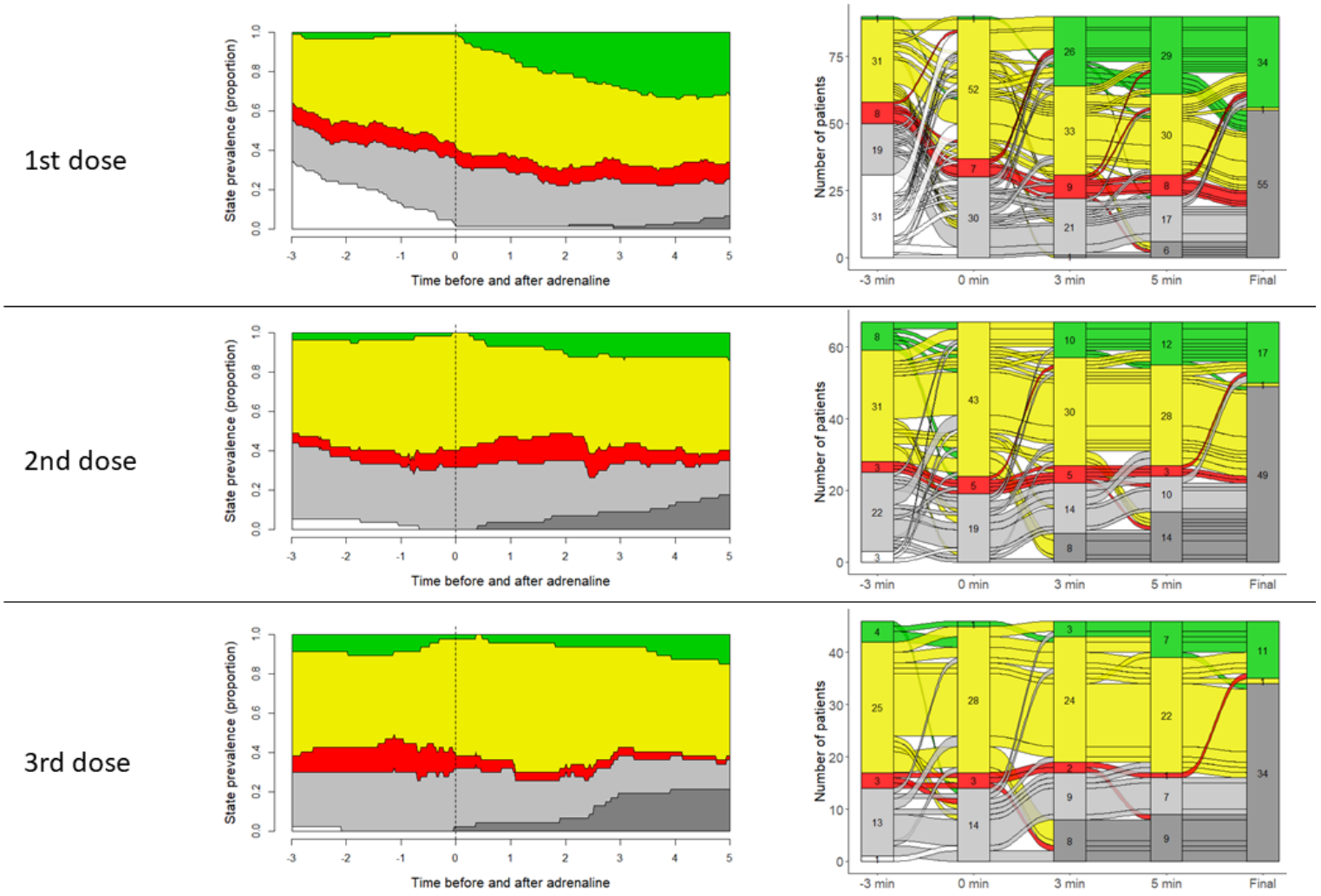


Figure 1: Prevalence and Sankey plots illustrating changes in clinical states before and after the administration of the first, second and third dose of adrenaline. ROSC (green), PEA (yellow), VF/VT (red), Asystole (gray), declared dead (dark gray), about to arrest (white)

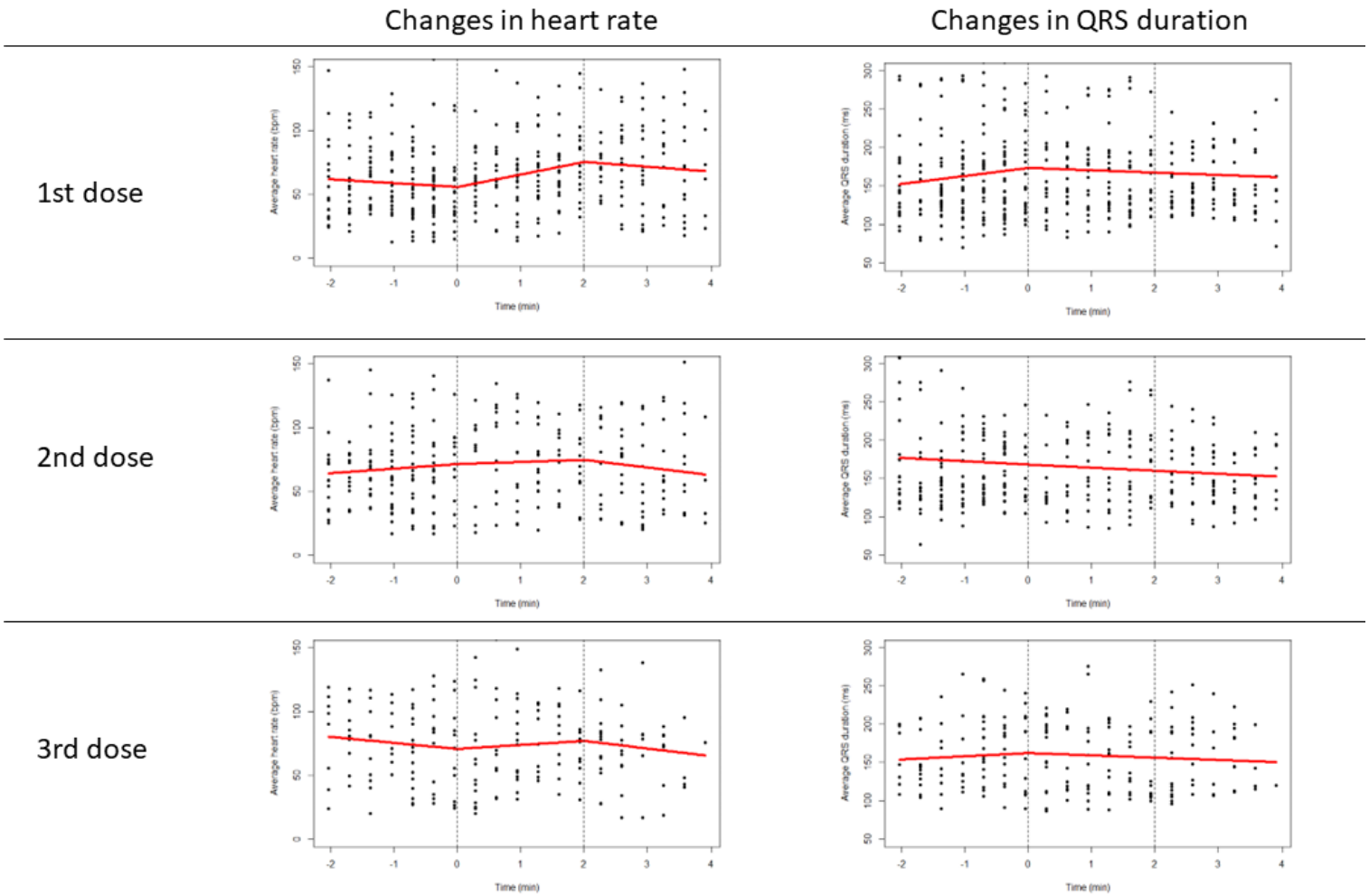


Figure 2: Linear piecewise splines (red line) showing development of HR and QRSd 2min before and 4 min after administration of the first, second and third adrenaline dose. We only observed a significant change in HR after the first dose.

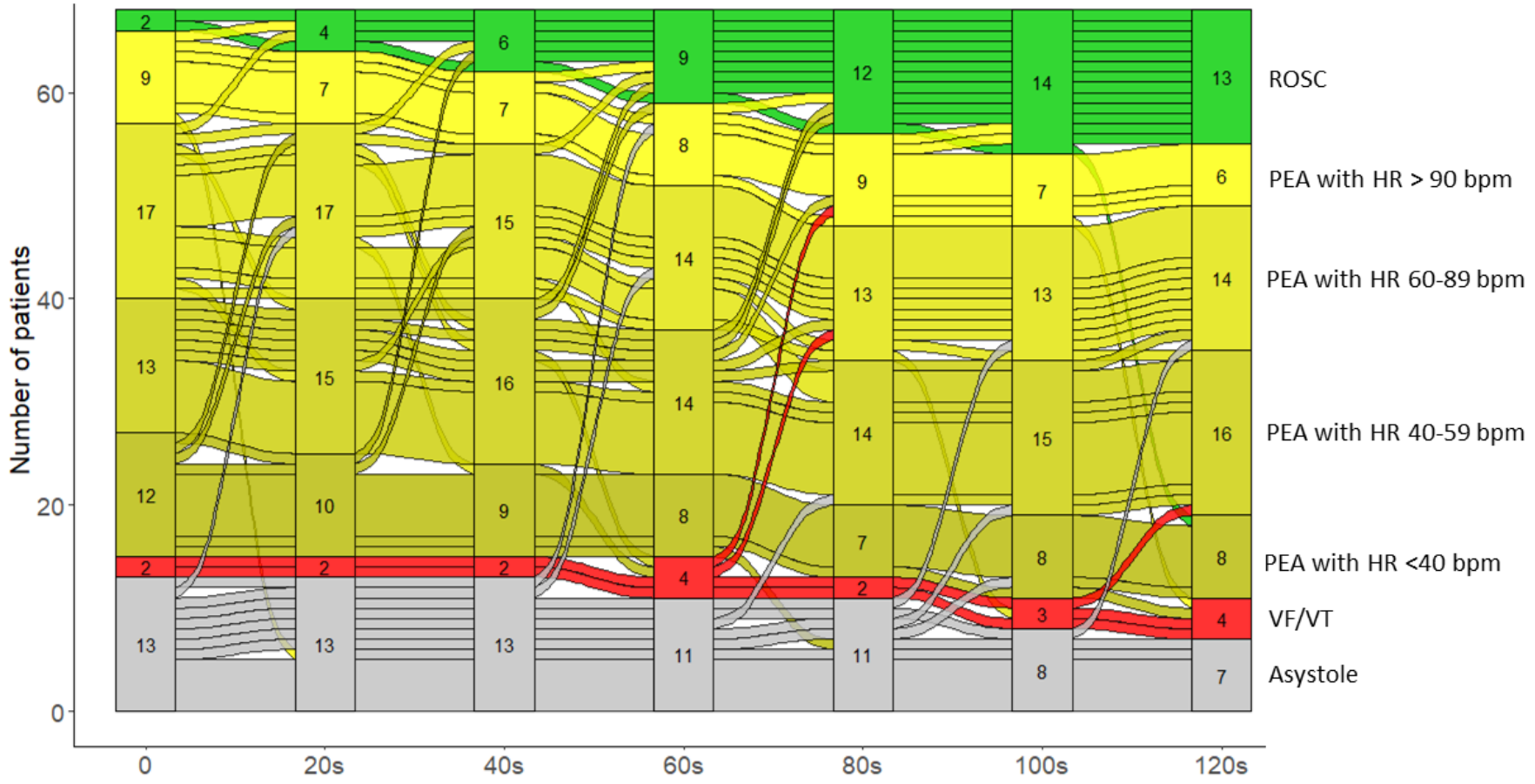


Figure 3: Sankey plot showing flow between states two minutes after administration of the first dose of adrenaline. PEA with HR > 90 bpm experience the highest rate of transitions to other states.

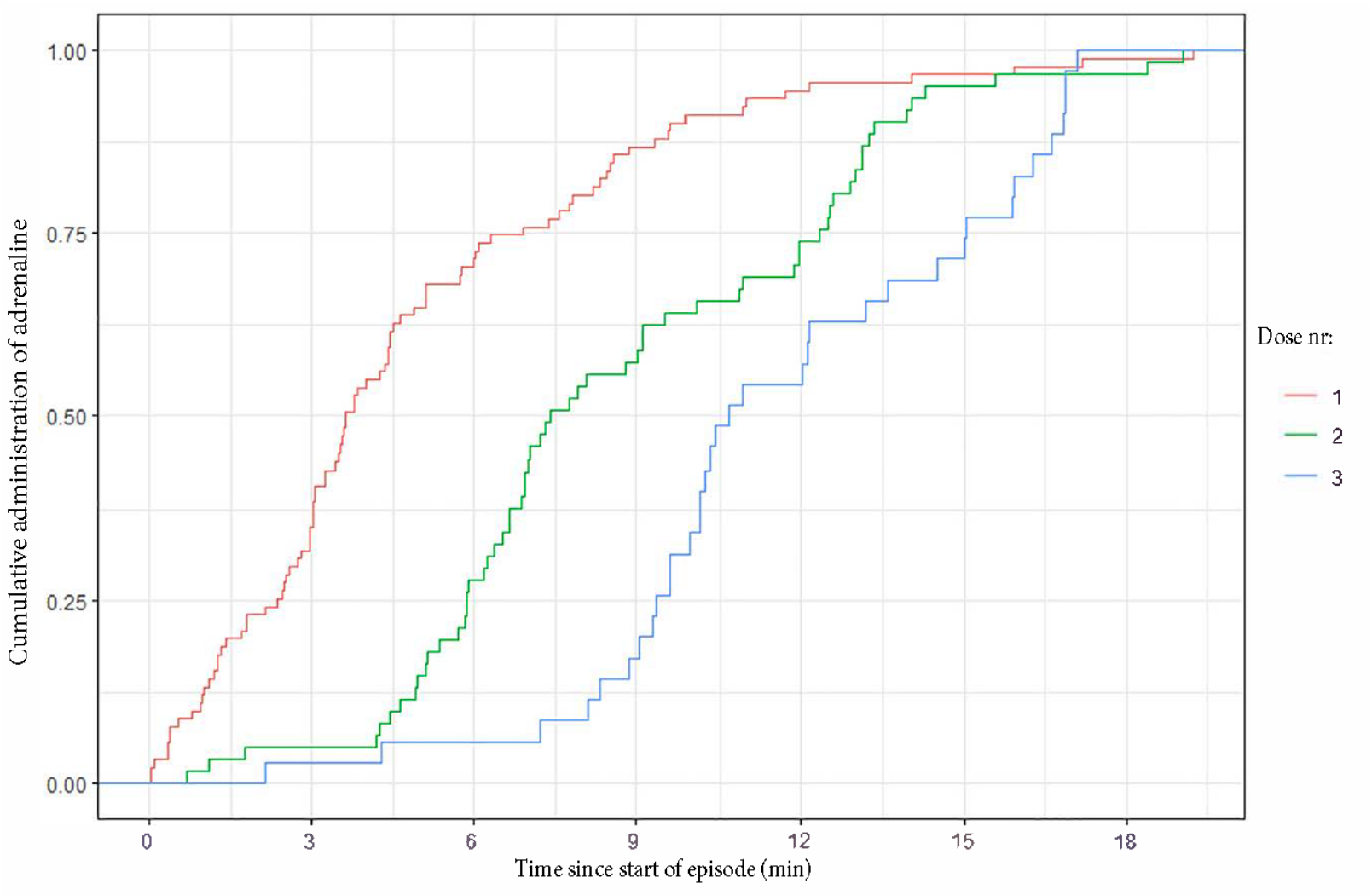


Figure 4: Cumulative administration of the first, second and third dose of adrenaline. There is approximately a 3 min delay between the first and second and second and third dose which corresponds to Norwegian recommendations. Approximately 75% receive their first dose within 6 min.

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Supplementary material

**Process of annotating arrest rhythms (Copied from:**

**Pulseless Electrical Activity in In-Hospital Cardiac Arrest – A crossroad for decisions; by Norvik et al. 2022**

**Heart rate and QRS duration as biomarkers predict the immediate outcome from Pulseless Electrical Activity; by Norvik et al. 2023)**

Defibrillators recorded ECG, chest compressions and ventilations during CPR. Data were recorded using HeartStart MRx-defibrillators (Philips Medical Systems, Andover, Massachusetts, USA), Zoll M series (Zoll Medical Corporation, Chelmsford, Massachusetts, USA), LIFEPAK 20 (Physio-Control, Redmond, USA) and LIFEPAK 1000 (Physio-Control, Redmond, USA). All events were manually assessed and annotated using a custom-made graphical application in MATLAB (version R2020a).

The start of an episode was defined when regularly performed chest compressions were identified. The initial arrest rhythm was determined based on clinical records (monitored CA) or arrest rhythm during the first pause in chest compressions.

Chest compressions were detected as fluctuations either in the transthoracic impedance (TI) signal acquired by the defibrillation pads, or in the compression depth signal recorded by the CPR assistance pad. Due to the noise generated by chest compressions, the ECG was only evaluated during chest compression pauses. ASY was defined as no measurable cardiac electrical activity, or a rhythm with QRS-like complexes slower than 12 complexes/min; corresponding to a “flat” line on a monitoring scope (see also “limitations”). PEA was defined as an organized rhythm with frequency >12 QRS/min lasting less than 1 min before being interrupted by compressions. VF and VT were categorised by their unique morphologies. ROSC was defined as an organized rhythm lasting > 1 min without signs of chest compressions. Sustained ROSC was declared if spontaneous circulation lasted longer than 20 min; in the statistical model the patient was still considered at risk for relapse during that period. We defined a new episode if a new cardiac arrest ensued in the same patient beyond

20 min. For patients declared dead, death was defined at the last chest compression or defibrillation attempt. PEA was classified into four categories as described in the introduction.

HR and QRSd were determined for all available QRS complexes of every PEA segment by the first author (AN). Start of QRS was defined as a sudden upwards or downwards deflection from a stable baseline. The end of QRS was defined at the J-point, i.e. first part of deflection on the terminal upstroke or downstroke of the QRS. [15] In cases where the J-point could not be defined, the end was defined where the downstroke of the R-wave or the upstroke of the S-wave crossed the baseline. Cases with an unclear J-point were reviewed with an electrophysiologist for adjudication (JPL). HR in beats per minute (bpm) was determined by dividing 60000 by the RR-time in milliseconds (i.e., time from one R-wave to the next).