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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.

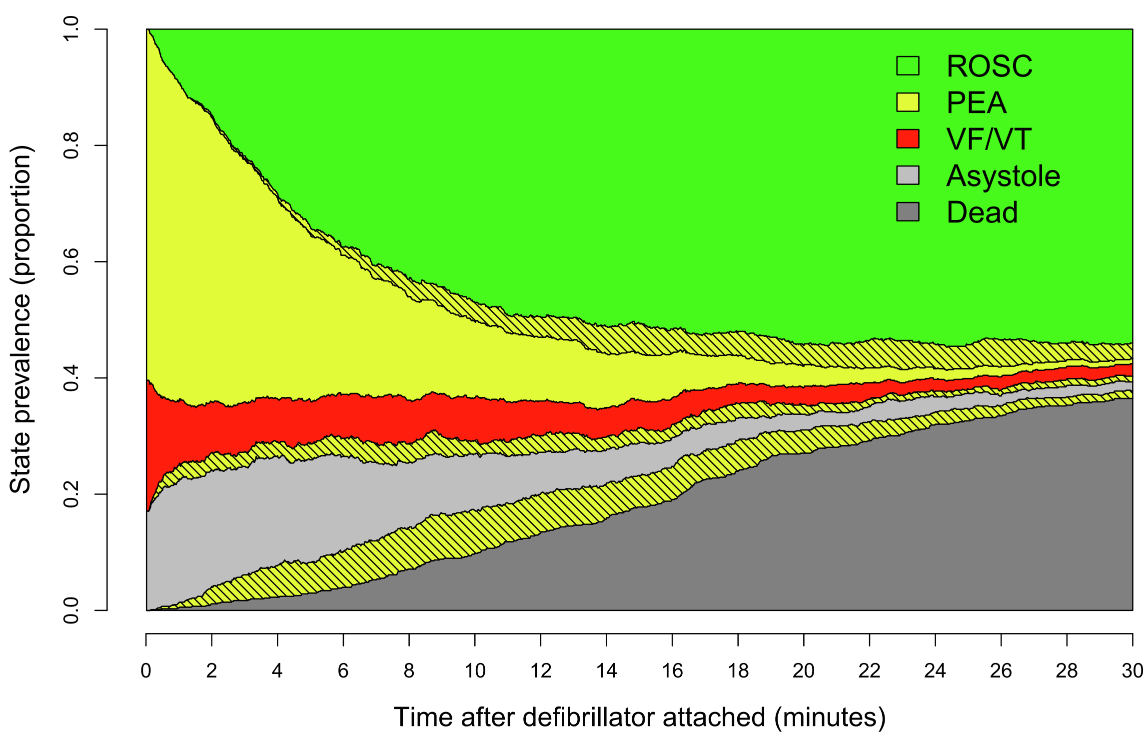

Fig. 1 – The running prevalence of clinical states during the first 30 minutes of resuscitation. The secondary PEA states are line-shaded and placed under their respective states of origin. For example, PEA_{ASY} is plotted between ASY (light grey) and Dead (dark grey). All clinical states except "Dead"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

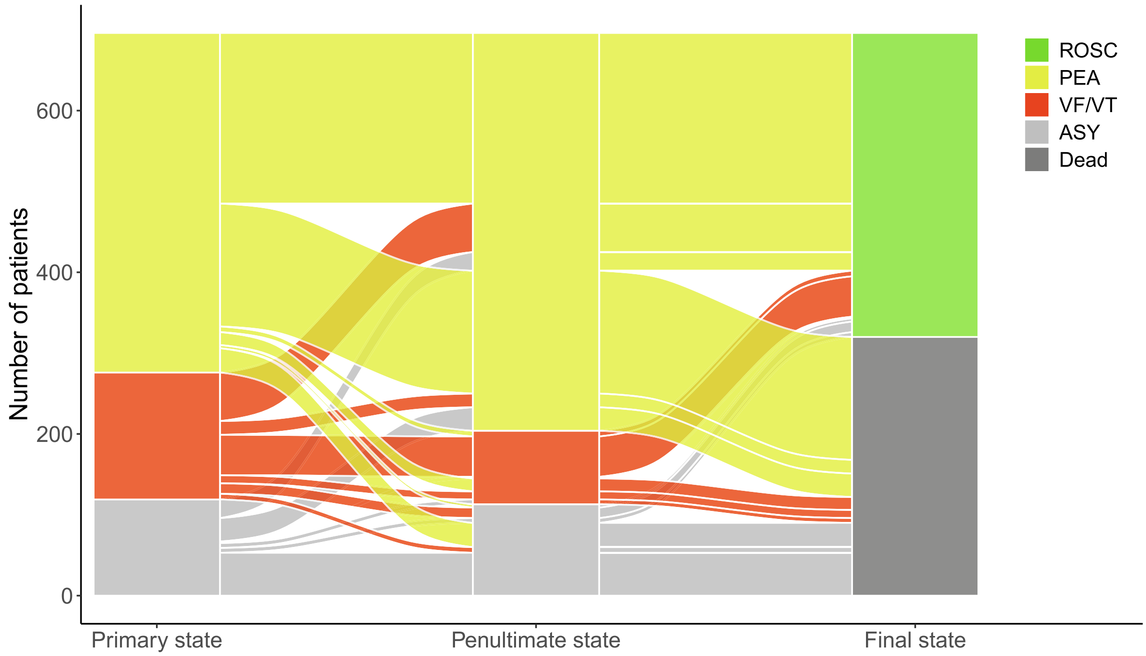

Fig. 2 – The "flow" of patients from their primary clinical state via the penultimate state to their final state. Approximatley half of the patients with primary VF/VT who achieved ROSC went through PEA. Approximatley of patients with initial ASY who achieved ROSC went through PEA.

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

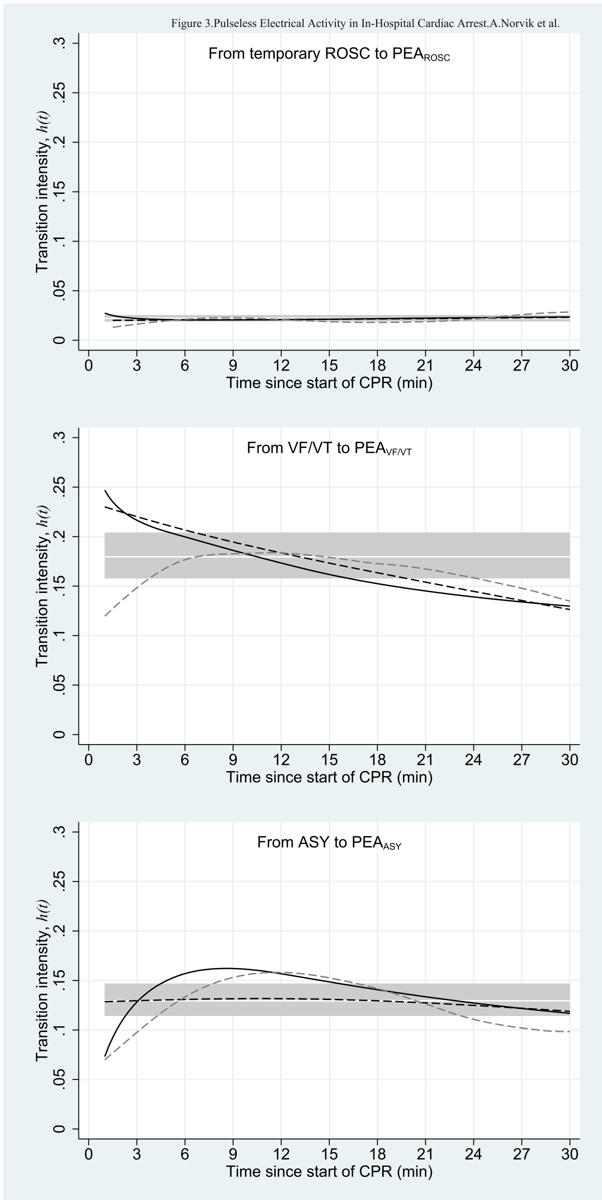

Fig. 3 – The transition intensity functions to PEA during the first 30 min of resuscitation, from temporary ROSC, VF/VT and ASY. Interrupted lines [- - -] show non-parametric estimates (grey: differentiated cumulative intensity; black: b-splines). Continuous lines. [___] show the parametric estimates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

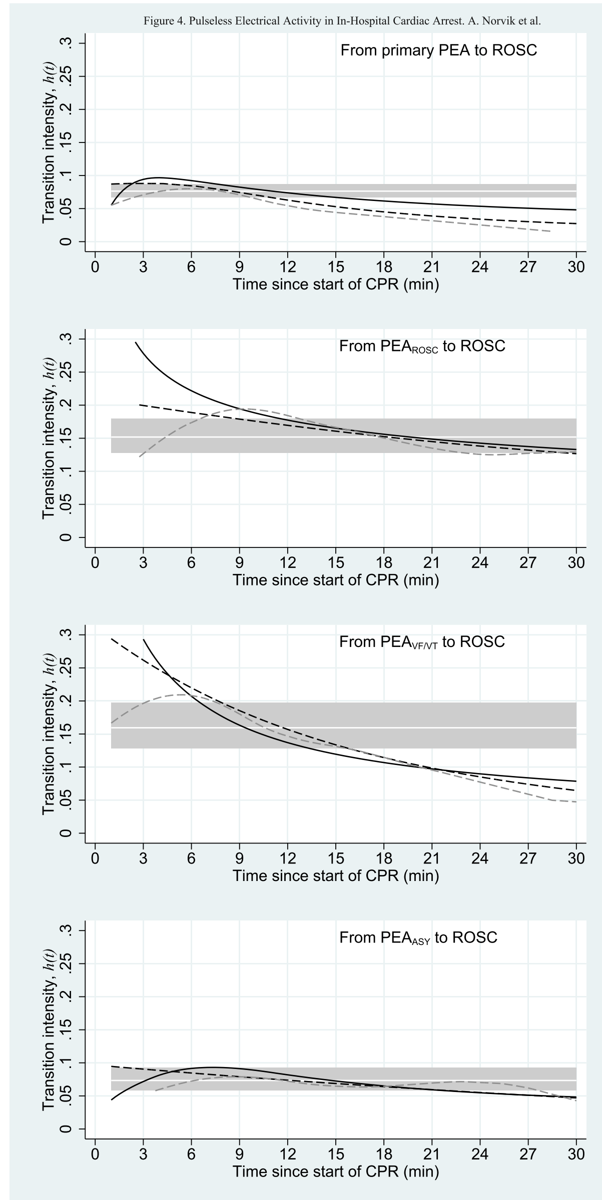

Fig. 4 – The transition intensity functions to ROSC during the first 30 min of resuscitation, from primary PEA, from PEA after temporary ROSC, PEA after VF/VT, and PEA after ASY. Interrupted lines [- - -] show non-parametric estimates (grey: differentiated cumulative intensity; black: b-splines). Continuous 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.

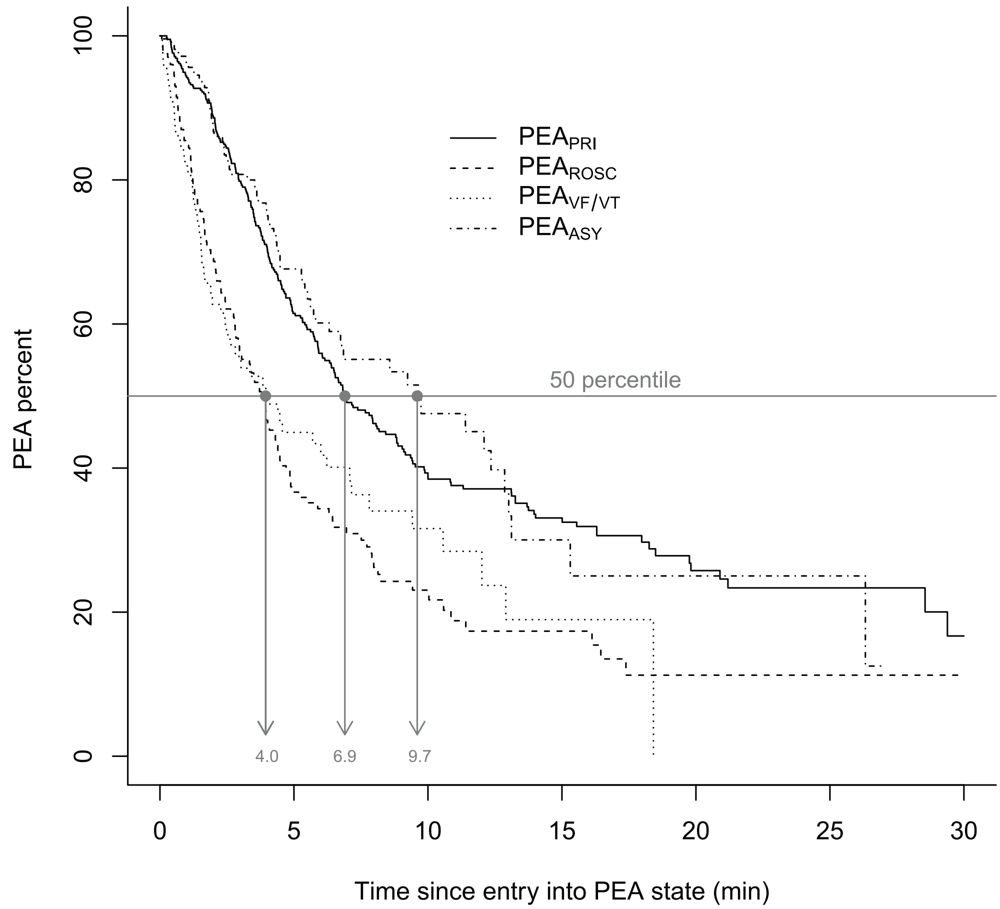

Fig. 5 – Observed sojourn times in the four PEA states.

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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