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Clinical paper

Factors affecting the course of resuscitation from cardiac arrest with pulseless electrical activity in children and adolescents

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Abstract

Background: Although in-hospital pediatric cardiac arrests and cardiopulmonary resuscitation occur >15,000/year in the US, few studies have assessed which factors affect the course of resuscitation in these patients. We investigated transitions from Pulseless Electrical Activity (PEA) to Ventricular Fibrillation/pulseless Ventricular Tachycardia (VF/pVT), Return of Spontaneous Circulation (ROSC) and recurrences from ROSC to PEA in children and adolescents with in-hospital cardiac arrest.

Methods: Episodes of cardiac arrest at the Children's Hospital of Philadelphia were prospectively registered. Defibrillators that recorded chest compression depth/rate and ventilation rate were applied. CPR variables, patient characteristics and etiology, and dynamic factors (e.g. the proportion of time spent in PEA or ROSC) were entered as time-varying covariates for the transition intensities under study.

Results: In 67 episodes of CPR in 59 patients (median age 15 years) with cardiac arrest, there were 52 transitions from PEA to ROSC, 22 transitions from PEA to VF/pVT, and 23 recurrences of PEA from ROSC. Except for a nearly significant effect of mean compression depth beyond a threshold of 5.7 cm, only dynamic factors that evolved during CPR favored a transition from PEA to ROSC. The latter included a lower proportion of PEA over the last 5 min and a higher proportion of ROSC over the last 5 min. Factors associated with PEA to VF/pVT development were age, weight, the proportion spent in VF/pVT or PEA the last 5 min, and the general transition intensity, while PEA recurrence from ROSC only depended on the general transition intensity.

Conclusion: The clinical course during pediatric cardiac arrest was mainly influenced by dynamic factors associated with time in PEA and ROSC. Transitions from PEA to ROSC seemed to be favored by deeper compressions.

Keywords: Cardiopulmonary resuscitation (CPR), Paediatric resuscitation, Return of spontaneous circulation (ROSC), Ventricular fibrillation, Ventricular tachycardia (VT), Pulseless electrical activity (PEA), Additive regression, Dynamic course

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Introduction

Immediate resuscitation care provided to victims of cardiac arrest consists of chest compressions, ventilations, defibrillation and administration of intravenous (IV) medications.[1] Although in-hospital pediatric cardiac arrests and cardiopulmonary resuscitation occur $>$15,000/year in the US,[2] few studies have assessed which factors affect the course of resuscitation in these patients. Notably, the clinical course from start to end of resuscitation may be tortuous and unpredictable. In children, this involves transitions between five possible clinical states, i.e. asystole, Pulseless Electrical Activity (PEA, including severe bradycardia with insufficient perfusion), Ventricular Fibrillation (VF), pulseless Ventricular Tachycardia (pVT) and Return of Spontaneous Circulation (ROSC). PEA is a frequent initial state in children.[3,4] For ultimate survival, ROSC should be achieved as quickly as possible, while avoiding subsequent deterioration into VF/pVT, asystole or PEA. We have previously described the general dynamic characteristics of CPR in children and adolescents, by quantifying the state transition intensities (or "transition rates") over time during CPR.[4] In this prior work, simple simulation suggested that the prevalence of sustained ROSC might rise substantially if the PEA to ROSC transition intensity was doubled and the intensity of PEA recurrence from ROSC was halved. To clarify how such desirable changes might come about, we considered the succession of clinical states during resuscitation. The aim of this study was to investigate how the transition intensities from PEA to ROSC, deterioration from PEA into VF/pVT, and recurrence of PEA from ROSC might depend on fixed factors (e.g. age, etiology), time-varying factors (e.g. CPR quality), and dynamic time-varying factors that accumulate information over the course of CPR.

Materials and methods

Resuscitation episodes at the Children's Hospital of Philadelphia (CHOP) were prospectively registered between 2006 and 2013. Details on data collection and study conduct have been published previously.[4,5] The Institutional Review Board (IRB) at CHOP approved the study (IRB 16-012813), and this secondary analysis was approved by the Regional Ethics Committee in Norway (REK N-2016/712).

Defibrillators recorded chest compression depth and rate using an integrated accelerometer and force detector.[6] The ventilation rate was estimated based on changes in thoracic impedance.[7] CPR process data (compressions, ventilations) were revised and rhythms were annotated along the episode time axis by two of the authors (TN, ES) using a customized graphical data annotator developed in the software Matlab (The Mathworks, Natic, MA, USA) by the University of the Basque Country, Bilbao, Spain. ROSC was annotated when an organized ECG rhythm was observed in an interval of at least 1 min without chest compressions. Start of the episode was defined when the defibrillator was attached, and an ECG and/or compression signal with sufficient quality was observed. The observations were split into non-overlapping, successive 5-second time intervals for statistical time-to-event analysis.

Statistical analysis

We employed Aalen's non-parametric additive regression model,[8] parametric exponential regression, and Cox' proportional hazards model to investigate how covariates affected the intensity of state transitions over time. Covariates, also known as factors, predictors or independent variables, were entered univariately in the models for the transition intensities between PEA and ROSC, between PEA and VF/pVT, and for the transition from ROSC back to PEA. For each patient, a data point with updated values of all covariates was calculated every 5 s for the time dependent models (see Appendix A). The following covariates were included: CPR variables for the previous 3 min (i.e. mean compression depth/rate, ventilation rate), patient characteristics (weight, age, gender) and etiology of the arrest. Likewise, dynamic covariates that accumulated information about the course of CPR were considered, such as time in PEA until the time point of analysis, time in ROSC until the time point of analysis and total rate of transitions until the time point of analysis.

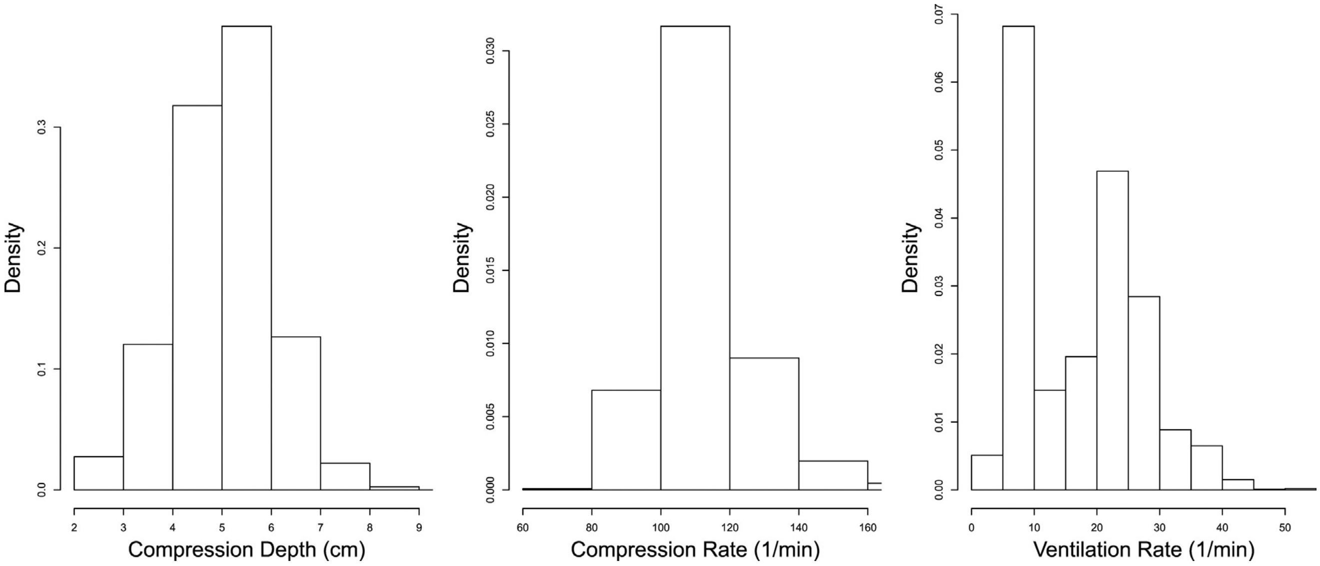

Fig. 1 – Histograms and summaries of CPR quality metrics during resuscitation in PEA. Mean compression depth (median 5.1 cm, interquartile range 4.4–5.7 cm), mean compression rate (median 113/min, interquartile range 105–119/min), mean ventilation rate (median 18.4/min, interquartile range 6.9–24.6/min).

The basic procedure for Aalen's additive regression model[8] estimates cumulative regression coefficients over time. Thus, the effect of the covariates at different time points can be visualized. The method allows for both time dependent effects and time dependent covariates. By differentiating and smoothing the cumulative intensity it is also possible to obtain direct estimates of the regression coefficients (i.e. the transition intensity itself) as a function of time,[9] although these might be prone to bias towards zero at the boundaries. If the effect is fairly constant over time, an average regression coefficient may be calculated.[10] The average coefficient summarizes the change in intensity by a one-unit change in the covariate.

Aalen's model was run from start until 30 min, 45 min, and 87 min; corresponding to the 75th, 85th and 100th percentile of episode durations. Because of some estimation instabilities caused by the low number of observations we report the estimates at 45 min. The exponential and Cox models were run to the end of 87 min. We investigated the propensity towards deeper compressions by other patient or fixed event characteristics in a logistic regression model. All analyses were performed using the software R version 3.5.3[11] including using the package 'flexsurv' for the Cox- and parametric models.[12] A *P*-value less than 0.05 was considered statistically significant.

Results

Demography and observed state transitions

We analyzed a subgroup from the previous study[4] in which PEA or ROSC (temporary or sustained) occurred; 67 cardiac arrest episodes in 59 patients. The episodes lasted for a median of 14 min (range 1–87 min, interquartile range 4–29 min). Median patient age was 15 years (interquartile range 11–17 years), median weight 48 kg (interquartile range 31–55 kg), and 48% were female. In 66% of patients, the arrest was attributed to an acute respiratory event. There were 52 transitions from PEA to ROSC in 35 episodes, 23 recurrences of PEA from ROSC in 12 episodes, and 22 transitions from PEA to VF/pVT in 16 episodes. In 27 episodes (40%), sustained ROSC was achieved.

CPR and treatment variability

The histograms in Fig. 1 show the distribution of CPR quality metrics along with quantitative summaries calculated for every 5-s period of PEA. The effects of covariates for the clinical state transitions considered are summarized numerically and graphically in the following subsections.

Obtaining ROSC from PEA

The cumulative intensity and the intensity function describing the PEA to ROSC transition is shown in Fig. 2. The estimated average baseline intensity was approximately 0.07 per minute. Thus, a patient in PEA at any time had an estimated probability of roughly 7% to obtain ROSC per minute of ongoing CPR.

Transitions from PEA to ROSC were favored by deep chest compressions ($p = 0.049$), as shown in the cumulative intensity plot of Fig. 3 (left). The effect was estimated as 0.018 transitions per cm per minute (blue line), meaning that a 1 cm increase in compression depth from 5.1 cm (average depth) to 6.1 cm increased the transition intensity from 0.070 to 0.088, a 25% increase in intensity. The Cox model suggested an intensity ratio of 1.32 ($p = 0.06$); i.e. a 32% increase. As seen in figure 3, the effect of compressions was roughly constant over time and on closer inspection it was more pronounced beyond the highest quintile of 5.7 cm (not shown). We did not observe any association between the propensity towards deeper compressions and other patient or fixed event characteristics.

No CPR quality variables other than depth had measurable effects on transition intensity from PEA to ROSC. Rather, the only important

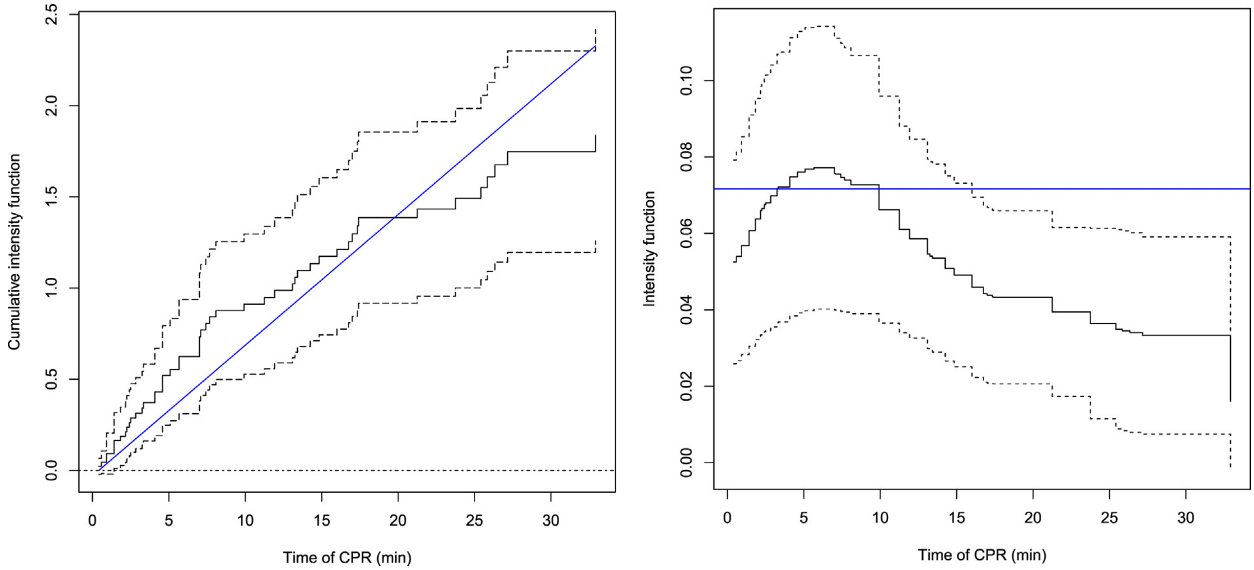

Fig. 2 – *Left*: Cumulative PEA to ROSC transition intensity vs. time of CPR in minutes, according to Aalen's additive regression model run from start until 45 min. Each step indicates the time point when a patient does transit from PEA to ROSC, the size of the step depend on how many patients were at risk for this transition. The blue line is a weighted mean slope representing the intensity; estimated as 0.07 transitions/minute. *Right*: The PEA to ROSC transition intensity (the derivative of the cumulative intensity) vs. time of CPR, the blue line is drawn at an intensity of 0.07/min. Dotted grey lines indicate 95% confidence intervals. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

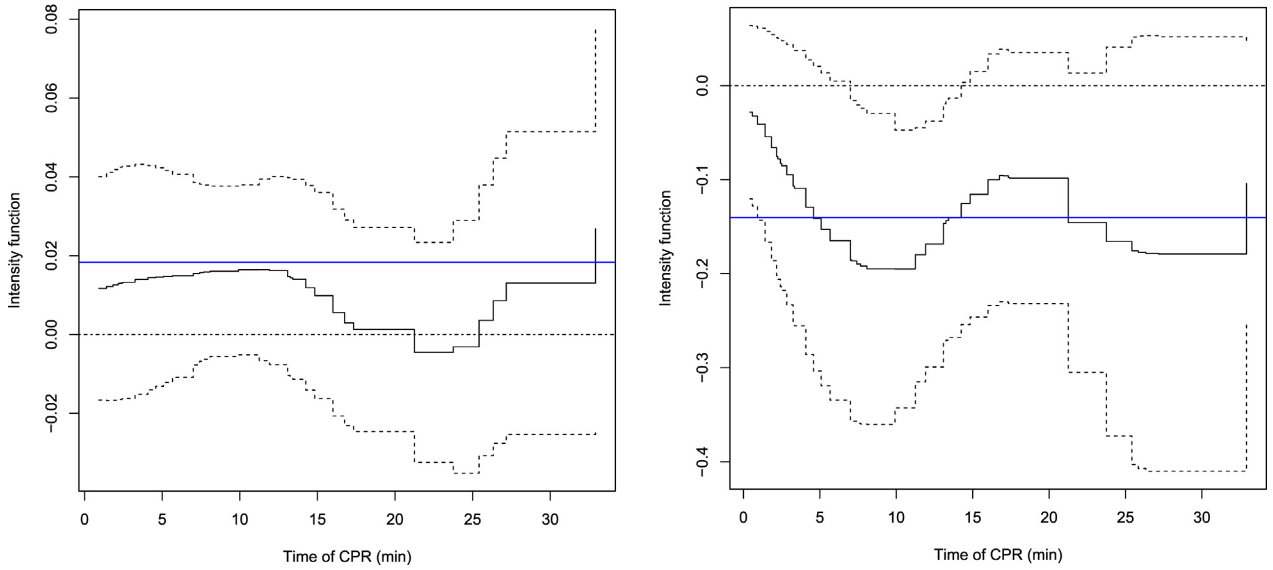

Fig. 3 – The effect of two covariates on the PEA to ROSC transition intensity. Left: "Mean chest compression depth during the last 3 min" vs. time of CPR, estimated as about 0.018 transitions/cm and min (blue line). Right: "Prevalence of PEA in the previous 5 min" (a dynamic covariate) vs. time of CPR, reaching a plateau of about −0.14 per unit and min after 7 min of CPR (blue line). Dotted lines indicate 95% confidence intervals (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

covariates were those that accumulate dynamically during CPR. As shown in Fig. 3 (right), the PEA prevalence in the five previous min was highly significant ($p = 0.001$), with an estimate of -0.14 transitions per minute and unit that reached a plateau at 7 min of CPR. This means that 7 min into CPR, an average increase of 0.1 in the prevalence of PEA from 0.59 (the mean prevalence) to 0.69 would reduce the transition intensity by 0.014 (0.1 * 0.14) from 0.070 to 0.056. And if no response had been observed at that time, the expected PEA to ROSC intensity would drop by 0.057 (0.41 * 0.14) to 0.013; i.e. a 1.3% chance of obtaining ROSC from PEA per minute of CPR. Deepening compressions by 1 cm would mitigate this marginally by increasing the intensity by 0.018, to 0.03.

The prevalence of ROSC in the five previous min had an effect of the same magnitude but in the opposite direction, with an intensity estimate of 0.13 per minute and unit. Finally, the 5-min average transition intensity of 1.25 transitions per minute was highly significant ($p < 0.001$). The latter can be considered a measure of overall "instability" (i.e. all transitions to and from the states) so observing any transition during the last 5 min (which on average equals 0.2 per min) will increase the intensity of the PEA to ROSC transition by 0.2 * 1.25 = 0.25/min, or about three times the baseline intensity.

PEA recurrence from (temporary) ROSC

The baseline intensity for PEA recurrence from ROSC was 0.20, meaning that the probability of PEA to recur was about 20% every minute for patients in ROSC. No patient-fixed (weight, gender, etiology) nor any treatment related covariates influenced the rate of PEA recurrence. The only significant dynamic covariate was the average transition intensity.

Deterioration into VF/pVT

The baseline intensity for deterioration into VF from PEA was low (about 0.03) and associated with a presenting shockable rhythm, age, weight, the proportion spent in VF/or in PEA (and ROSC) the last 5 min (with opposite signs). In addition, dynamic covariates that reflect "instability" (e.g. the transition intensity, DC shock indicator, etc.) were significant.

Discussion

In this study of pediatric in-hospital cardiac arrest, we found that dynamic variables that captured the patients' response during CPR (e.g. cumulative time in PEA or ROSC) had the strongest effect on the intensities of transitions between clinical states. Among the CPR quality variables analyzed, only deeper chest compressions favored the transition from PEA to ROSC. Information on other clinical interventions that may have prevented or led to the recurrence of PEA after ROSC (such as epinephrine dosing) was unfortunately not available for analysis.

Similar results were observed in a cohort of adult out-of-hospital cardiac arrest (OHCA) patients investigated earlier by Kvaløy and co-workers using the same statistical method.[10] The observed transition intensities in the present study were similar to those observed in the out-of-hospital study, although a higher observed PEA to VF/pVT intensity in the adult cohort may reflect a higher prevalence of ischemic heart disease. Internal, dynamic covariates like time in PEA had similar effects in both studies. Thus, this dynamic model appears to capture essential quantitative aspects of the course of CPR, in settings as different as pediatric in-hospital arrest and adult out-of-hospital cardiac arrest.

The strong effect of dynamic covariates (e.g. the proportion of time spent in PEA) suggests that it is important to closely monitor the patient's response during CPR. If the patient had spent a substantial time in PEA at 5–10 min of resuscitation we found the probability of obtaining ROSC from PEA to be very low, and deep compressions would not make much difference. Thus, the clinician may need to consider more invasive rescue strategies beyond conventional CPR at this time, such as extracorporeal membrane oxygenation (ECMO) – CPR, or different therapeutic

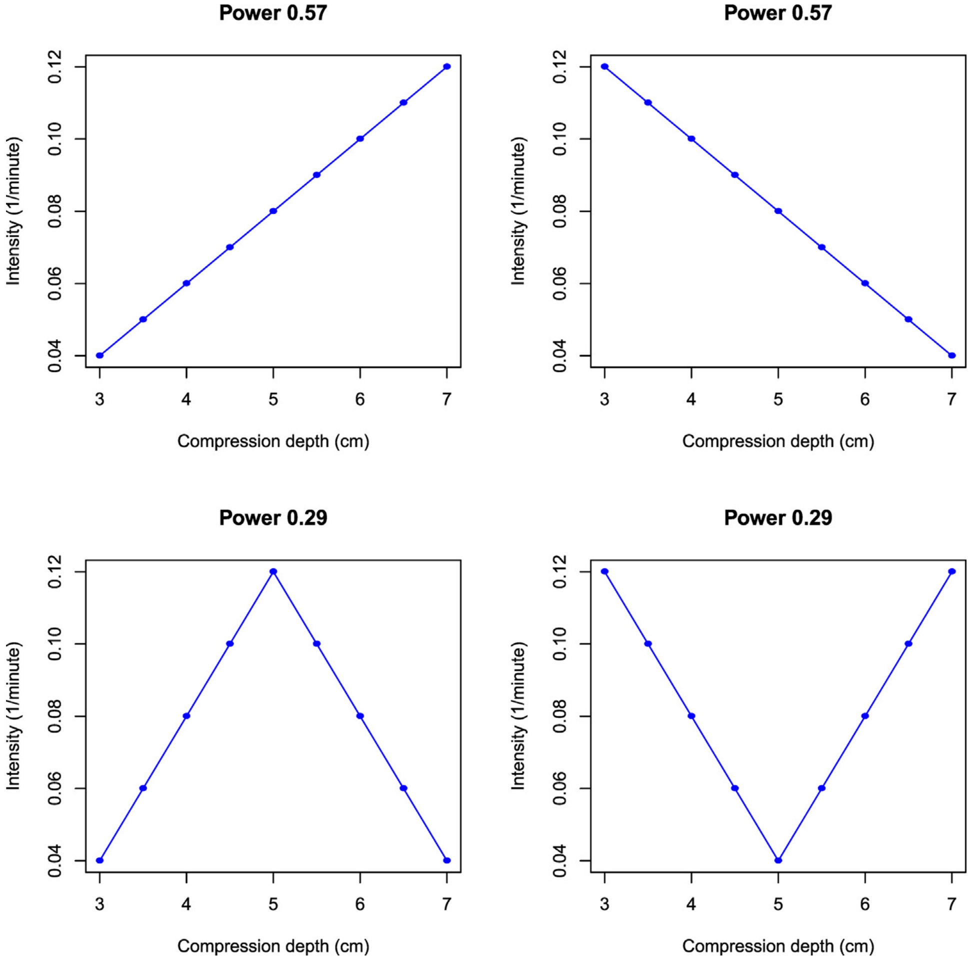

Fig. 4 – Four possible hypothetical relations between chest compression depth and PEA to ROSC transition intensity, used for simulation using the exponential distribution. *Upper left*: increasing intensity with increasing depth; *lower left*: Inverse U-shaped relation with highest intensity at 5 cm.

strategies (e.g. thrombolytic therapy for pulmonary embolism-associated cardiac arrests in adolescents).[13]

The transition intensity from PEA to ROSC increased markedly beyond 5.7 cm of compression depth; this nearly significant effect was reasonably constant over the course of CPR. It is further noteworthy that the apparent threshold of 5.7 cm is higher than the current AHA recommendation for young children, likely due to our population being comprised mainly of adolescents. In a previous analysis of CPR quality in this same cohort, AHA-compliant compressions (i.e. >51 mm) during the first 5 min of CPR was associated with 24-h survival.[14] Kramer-Johansen et al.[15] found an OR of 1.6 for sustained ROSC per 10 mm increase in chest compression depth in adults, consistent with our observations of a 25% relative increase in the rate of obtaining ROSC from PEA with deeper compressions.

Limitations and strengths of the study

While the distribution of CPR quality related variables seems representative, the low number of observed transitions limits the power for this non-parametric analysis to detect small effects of CPR quality change. This is further elaborated in the Appendix A. The distinction between PEA and temporary ROSC is difficult and relies partially on subjective interpretation of the limited clinical data available. Regarding the effect of deeper compressions, we acknowledge the possibility of a spurious (false positive) finding due to multiple testing, and this finding should be independently corroborated. The low sample size also caused the p-value for the effect to vary between 0.05 and 0.1 depending on the length of analysis (between 30 min and the extreme of 87 min). One may speculate whether the observed effect of compressions might be confounded with some favorable patient characteristics or with treatment given, but we have no evidence to suggest this.

A strength of this study is that the entire course of CPR was analyzed and not only the first minutes. Furthermore, the longitudinal design allows for proper consideration of the temporal and thus possibly causal relationship between CPR metrics and patient response, and dynamic covariates incorporates information about the individual course of CPR.

Conclusion

The clinical course during pediatric cardiac arrest was mainly influenced by dynamic factors associated with time in PEA and ROSC, rather than by CPR or patient-fixed variables. Transitions from PEA to ROSC were possibly favored by deeper compressions.

Conflict of interest

None.

Appendix A

A.1 Data and covariate structure

The following is a 30-s-long excerpt from one episode, illustrating the data structure including some of the time-dependent covariates:

ts	te	mCD	mCR	from	to	msD3e	pPEA5	dtROSC
115	120	5.355	116.94	4	4	4.79	1.00	0
120	125	5.380	118.22	4	4	4.81	1.00	0
125	130	NA	NA	4	5	4.82	1.00	1
130	135	NA	NA	5	5	NA	0.96	0
135	140	NA	NA	5	5	NA	0.93	0
140	145	NA	NA	5	5	NA	0.90	0
145	150	NA	NA	5	5	NA	0.87	0

ts, start point (in s since start of resuscitation) of the present 5-s time interval; te, end point of the time interval; mCD, mean chest Compression Depth observed in the current 5-s interval; mCR, mean chest Compression Rate (1/min) observed in the current 5-s interval; from, clinical state at the start of interval; to, clinical state at the end of interval (here 4 = PEA, 5 = ROSC); msD3e, mean compression depth the previous 3 min in current state (since entering the state); pPEA5, prevalence of PEA the last 5 min, dtROSC, indicator of whether a transition into transient ROSC state (the current state) occurred during the time interval; NA, not available. A narrative of this data excerpt is as follows: the patient had PEA (4 = PEA) at 115 s, with a change to ROSC (5 = ROSC) at 130 s that then prevailed. In the 5-s interval preceding the transition, mean compression depth was about 5.4 cm, but on average 4.8 cm when extending the analysis backwards for a maximum of 3 min. This is presumably more relevant for the observed transition than the instantaneous 5-s measurement. Similarly, the prevalence of PEA during the last 5 min was 1.00 (100%) until the change in clinical state, after which it declined. Chest compression variables were (obviously) not recorded after ROSC had ensued.

A.2 Covariates considered

The following table shows all covariates and their units of measurement considered in the univariate analysis using Aalen's additive regression.

Fixed covariates
Age (years)
Weight (kg)
Gender (1/0)
Respiratory etiology (1/0)
Initial VF/pVT (1/0)
CPR quality covariates
Mean compression depth the previous 3 min in current state (cm)
Mean compression rate the previous 3 min in current state (min^{-1})
Mean compression duty cycle the previous 3 min in current state (proportion)
Mean compression rate the previous 3 min in current state (min^{-1})
Chest compressions in the episode (proportion)
Chest compressions the previous 5 min (proportion)
Dynamic covariates
Current state entered by a DC shock (1/0)
Asystole the previous 5 min (proportion)
VF/pVT the previous 5 min (proportion)
Pulseless electrical activity the previous 5 min (proportion)
Spontaneous circulation the previous 5 min (proportion)
Time in current state (s)
Average state transition rate (min^{-1})
Average previous 5 min state transition rate (min^{-1})
Average DC shock rate (min^{-1})
Average previous 5 min DC shock rate (min^{-1})

A.3 Power analysis

With a null hypothesis of no relation between compression depth and transition intensity, the power of 50 observations to detect an alternative hypothesis of a monotone (i.e. strict increasing or decreasing) relation between compression depth varying between 3 and 7 cm and transition intensity was found by simulation to be slightly less than 60%. Detecting a more complex alternative relationship like an "inverted U" is harder and the power is about half this value. Fig. 4 shows simulation results for such patterns. A power of 90% would require about 120 observations for the monotone pattern, and about 200 observations for the more complex ones.

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