Available online at www.sciencedirect.com

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

Rhythm characteristics and patterns of change during cardiopulmonary resuscitation for in-hospital paediatric cardiac arrest

Trond Nordseth[a,b,*], Dana E. Niles[c], Trygve Eftestøl[d], Robert M. Sutton[c], Unai Irusta[e], Benjamin S. Abella[f], Robert A. Berg[c], Vinay M. Nadkarni[c], Eirik Skogvoll[b,g]

[a] Department of Emergency Medicine and Prehospital Services, St.Olav Hospital, Trondheim, Norway
[b] Department of Circulation and Medical Imaging, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, NO-7491, Trondheim, Norway
[c] Department of Anesthesiology and Critical Care Medicine, The Children's Hospital of Philadelphia, Philadelphia, USA
[d] Department of Electrical Engineering and Computer Science, University of Stavanger, Stavanger, Norway
[e] Department of Communications Engineering, University of the Basque Country, Bilbao, Spain
[f] Center for Resuscitation Science, University of Pennsylvania, Philadelphia, USA
[g] Department of Anaesthesia and Intensive Care Medicine, St.Olav Hospital, Trondheim, Norway

Abstract

During paediatric cardiopulmonary resuscitation (CPR), patients may transition between pulseless electrical activity (PEA), asystole, ventricular fibrillation/tachycardia (VF/VT), and return of spontaneous circulation (ROSC). The aim of this study was to quantify the dynamic characteristics of this process.

Methods: ECG recordings were collected in patients who received CPR at the Children's Hospital of Philadelphia (CHOP) between 2006 and 2013. Transitions between PEA (including bradycardia with poor perfusion), VF/VT, asystole, and ROSC were quantified by applying a multi-state statistical model with competing risks, and by smoothing the Nelson-Aalen estimator of cumulative hazard.

Results: Seventy-four episodes of cardiac arrest were included. Median age of patients was 15 years [IQR 11–17], 50% were female and 62% had a respiratory aetiology of arrest. Presenting cardiac arrest rhythms were PEA (60%), VF/VT (24%) and asystole (16%). A temporary surge of PEA was observed between 10 and 15 min due to a doubling of the transition rate from ROSC to PEA (i.e. 're-arrests'). The prevalence of sustained ROSC reached an asymptotic value of 30% at 20 min. Simulation suggests that doubling the transition rate from PEA to ROSC and halving the relapse rate might increase the prevalence of sustained ROSC to 50%.

Conclusion: Children and adolescents who received CPR were prone to re-arrest between 10 and 15 min after start of CPR efforts. If the rate of PEA to ROSC transition could be increased and the rate of re-arrests reduced, the overall survival rate may improve.

Keywords: Cardiac arrest, Cardiopulmonary resuscitation (CPR), Intensive care, Paediatric resuscitation, Resuscitation, Return of spontaneous circulation, Ventricular fibrillation, Ventricular tachycardia (VT), Pulseless electrical activity (PEA), Asystole

* Corresponding author.
E-mail address: trond.nordseth@ntnu.no (T. Nordseth).

https://doi.org/10.1016/j.resuscitation.2019.01.006
Received 25 September 2018; Received in revised form 5 December 2018; Accepted 3 January 2019

Introduction

A paediatric patient in cardiac arrest will receive numerous medical interventions in an effort to bring the child back to life. Depending on age, comorbidity and the underlying cause of arrest, these interventions may impose several cardiac rhythm changes and hopefully the return of spontaneous circulation (ROSC). During resuscitation, the patient may occupy and transition between four possible clinical states: pulseless electrical activity (PEA), asystole, ventricular fibrillation /–tachycardia (VF/VT) or ROSC.[1] In addition, the term 'bradycardia with poor perfusion' in paediatric patients refers to insufficient perfusion due to a very low heart rate, a pre-arrest physiologic state that is also treated with CPR.[2,3]

We have previously demonstrated that there is great variability in how adult patients with cardiac arrest respond to resuscitation efforts with respect to transitions between these clinical states.[1,4] In a randomized study, intravenous adrenaline (epinephrine) increased the rate of transitions from PEA to ROSC, from PEA to VF/VT and from ROSC to VF/VT in patients with initial PEA, compared to patients that did not receive adrenaline.[5] It is reasonable to assume that the underlying cause of arrest may influence such transitions as well. In children, the aetiology may be more diverse than among adults, in whom coronary artery disease and cardiac failure dominates.[6] Quantifying the transition rates between clinical states is a way of describing the overall response to paediatric CPR, and may provide further insight into the pathophysiology of cardiac arrest in paediatric patients. In order to assess the course of clinical state transitions in cardiac arrest for research purposes, it is required that a defibrillator is attached to the patient and that the ECG and CPR delivery recordings are downloaded after the event.[7] In a study that assessed the relationship between survival and the quality of cardiopulmonary resuscitation (CPR), one of few such datasets containing defibrillator files in paediatric cardiac arrest was systematically collected.[8]

The main aim of this study was to analyse how paediatric patients responded to CPR and defibrillation with respect to transitions between PEA, VF/VT, asystole and ROSC during resuscitation.

Material and methods

Study setting and population

The Children's Hospital of Philadelphia (CHOP) is a tertiary care hospital with 516 inpatient beds. Paediatric patients > 1 years of age with cardiac arrest in the Emergency Department (ED) or Intensive Care Unit (ICU), between October 2006 and September 2013, were previously included in a study of compression depth and survival.[8] The Institutional Review Board (IRB) at CHOP assessed that further IRB oversight was not required for the data analysis performed in the current study (IRB 16-012813). The study was approved by the Regional Ethics Committee in northern Norway (REK N-2016/712).

Data collection and -handling

Quantitative CPR data was collected and recorded with HeartStart MRx-defibrillators with the Q-CPR option (Phillips Medical Systems, Andover, Massachusetts, USA). Defibrillator files were downloaded within 24 h after each event. The software Q-CPR Review (Version 2.1.0.0, Laerdal Medical, Stavanger, Norway) was used to facilitate the initial extraction. All channels including ECG, impedance and compression depth signal data were further processed applying the software MATLAB R2016b (The Mathworks, Natick, MA, USA), and visualized in a customized graphical user interface (GUI) developed by two study investigators (TE, UI). Other study investigators (TN, ES) assessed and classified the ECG-rhythm recorded by the defibrillators attached during resuscitation. The compression depth channel and the impedance (when depth was not available) were used to detect chest compressions, and to identify pauses in chest compressions in order to assess the ECG rhythm undisturbed by compression artefacts.[9] Rhythms were further confirmed by inspecting the ECG in the customized GUI during compressions, after a CPR artefact filter was applied.[10,11]

The patients were classified along the time axis to be either in VF/VT, PEA, asystole or ROSC. The annotation process has been described in previous publications.[1,4] Some patients were classified by the resuscitation team to have 'bradycardia with poor perfusion' as the presenting rhythm treated with CPR. Physiologic data that could help assess the degree of circulatory failure were not systematically registered by the defibrillators (e.g. arterial waveform, end-tidal CO2), and these patients were therefore classified as having PEA to simplify analysis. ROSC was suspected in patients with prolonged pauses in chest compressions (>1 min) and clinical documentation suggesting ROSC. Patients who obtained ROSC during resuscitation but later had a relapse to another clinical state before end of efforts were classified with temporary ROSC (tROSC). At the end of resuscitation efforts, the patients were classified with sustained ROSC (sROSC) or as having been declared dead. The underlying cause of arrest, broadly categorized as respiratory or non-respiratory, was determined by the clinical team involved and recorded in an Utstein style template.

Statistical analysis

Statistical analyses and the visualization of the distribution and development of clinical states over time were performed with the software R (version 3.5.0, R Development Core Team, Vienna, Austria), with the additional packages 'mvna','msm', 'flexsurv' and 'TraMineR'.[12–16]

The observed time between the different state transitions (time-to-event) were analysed applying a multi-state model, which is a generalization of the commonly used survival models to more than two states.[17] For instance, a patient may transition from PEA to either VF/VT, ROSC, or asystole.[1,4] A multi-state model allows patients to move between several clinical states while taking such 'competing risks' into account.

We used two statistical measures commonly applied in multistate models to describe the dynamic nature of the process. First, the Nelson-Aalen estimator of the *cumulative hazard* of specific state transitions (i.e. events) over time.[18] Second, and of direct interest, is the instantaneous *hazard rate* of transitioning from one state to another, corresponding to the derivative of the Nelson-Aalen estimator. Continuous hazard rates for all relevant transitions were estimated using smoothing splines implemented in the R-package 'flexsurv'.[16,19] This approach was chosen instead of demonstrating constant transition rates, as constant rates make biologically less sense with respect to the deteriorating physiologic state over time in patients receiving CPR. To illustrate their interpretation and importance, we undertook a simple simulation of the hypothetical effect of doubling the beneficial transition rate from PEA to ROSC and halving the less beneficial rate of relapse from ROSC to PEA. Summary data

are presented as medians with interquartile range (IQR) or range, as appropriate.

Results

There were 89 episodes of cardiac arrest occurring in 78 individual patients included in the original study. Among these, 74 of the episodes for 65 individual patients had a recording of the ECG and impedance signal with sufficient quality to be included in the current analysis. Five patients had two episodes and two patients had three episodes of cardiac arrest. Fifty percent of the patients were female. Median age was 14.7 years (IQR 10.4–17.0), with range 21 months to 23 years. Median weight was 45 kg (IQR 31–58 kg). A respiratory aetiology was considered the main cause of arrest in 46 of the episodes (62%). PEA was the most frequent presenting cardiac arrest rhythm (38%) followed by VF/VT (24%), pulseless bradycardia (22%), and asystole (16%). The observed numbers of state transitions during resuscitation are presented in Table 1. There were 231 state transitions with a median of two per episode (IQR 1–4, range 1–23). Transitions to and from PEA were the most frequent.

A high-resolution picture of the changing prevalence of clinical states over time is demonstrated in Fig. 1. The prevalence of VF/VT decreased rapidly while PEA dominated. There was a "surge" of PEA between 10 and 15 min, due to a temporary increase in the rate of relapse from temporary ROSC to PEA. There was no net recruitment of sustained ROSC past 30 min of resuscitation efforts. The prevalence of clinical states stratified on the initial rhythm is demonstrated in Supplementary Fig. S 1.

The smoothed hazard rates for transitions between PEA, ROSC, VF/VT and asystole are demonstrated in Fig. 2. The corresponding plots of the Nelson-Aalen estimators are demonstrated in Supplementary Fig. S2. For three of the specific transitions, constant rates were reported instead of smoothed rates due to the low number of observations. There was an initial high transition rate from PEA to ROSC. In patients with initial VF/VT, transitions to ROSC and to PEA both represent successful defibrillations; the latter rate peaked early and then declined. The rate of re-arrests, i.e. transitions from ROSC to PEA, peaked in intensity at about 12 min.

The hazard rate roughly corresponds to the one-minute probability of transition from one state to another when hazard rates are low. For instance, from inspection of the curve one can see that a patient with ROSC at 5 min has a probability of 12% to relapse into PEA in the following one minute (hazard rate starting at 0.12). At about 12 min into resuscitation, the hazard rate had risen to about 0.23, implying a higher probability of relapse. These transitions and the corresponding rate estimates describe the basic response to resuscitation. One may better understand their interpretation and importance by exploring how different values for key transition rates

Table 1 – The distribution of 231 clinical state transitions during the first 45 min of CPR in 74 episodes of paediatric cardiac arrest. Rows indicate from and columns indicate to which states the transitions took place.

Transitions from	Transitions to					
	ROSC	PEA	VF/VT	Asystole	Death	Total
ROSC	–	23	6	0	0	29
PEA	52	–	22	16	24	114
VF/VT	6	32	–	9	4	51
Asystole	0	15	5	–	17	37

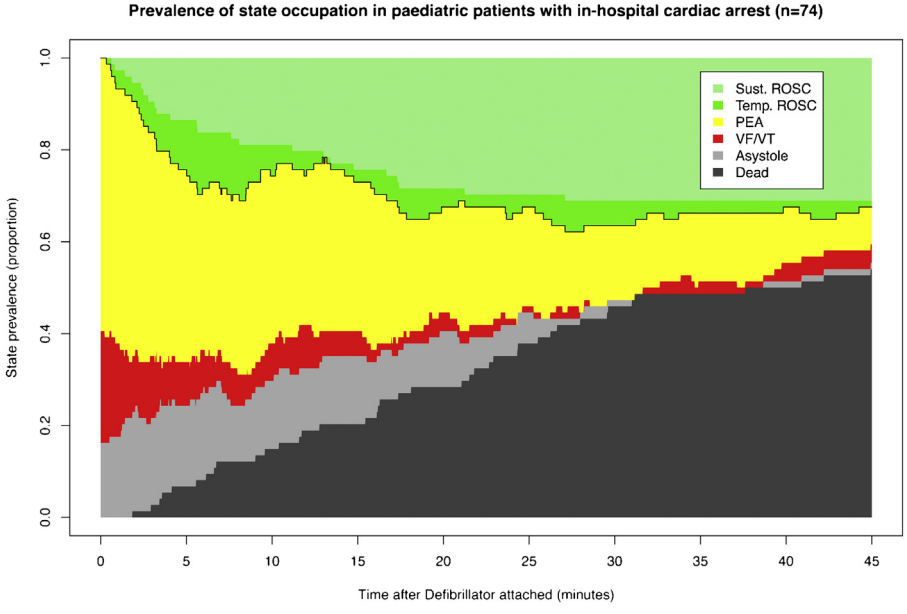

Fig. 1 – Plot of the prevalence of state occupation with time in paediatric patients with in-hospital cardiac arrest receiving CPR (n = 74). The proportion of patients at any time occupying the different states can be read of the y-axis. Sust.ROSC — sustained return of spontaneous circulation (light green); Temp.ROSC — temporary ROSC (green); PEA — pulseless electrical activity (yellow); VF/VT — ventricular fibrillation or —tachycardia (red) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

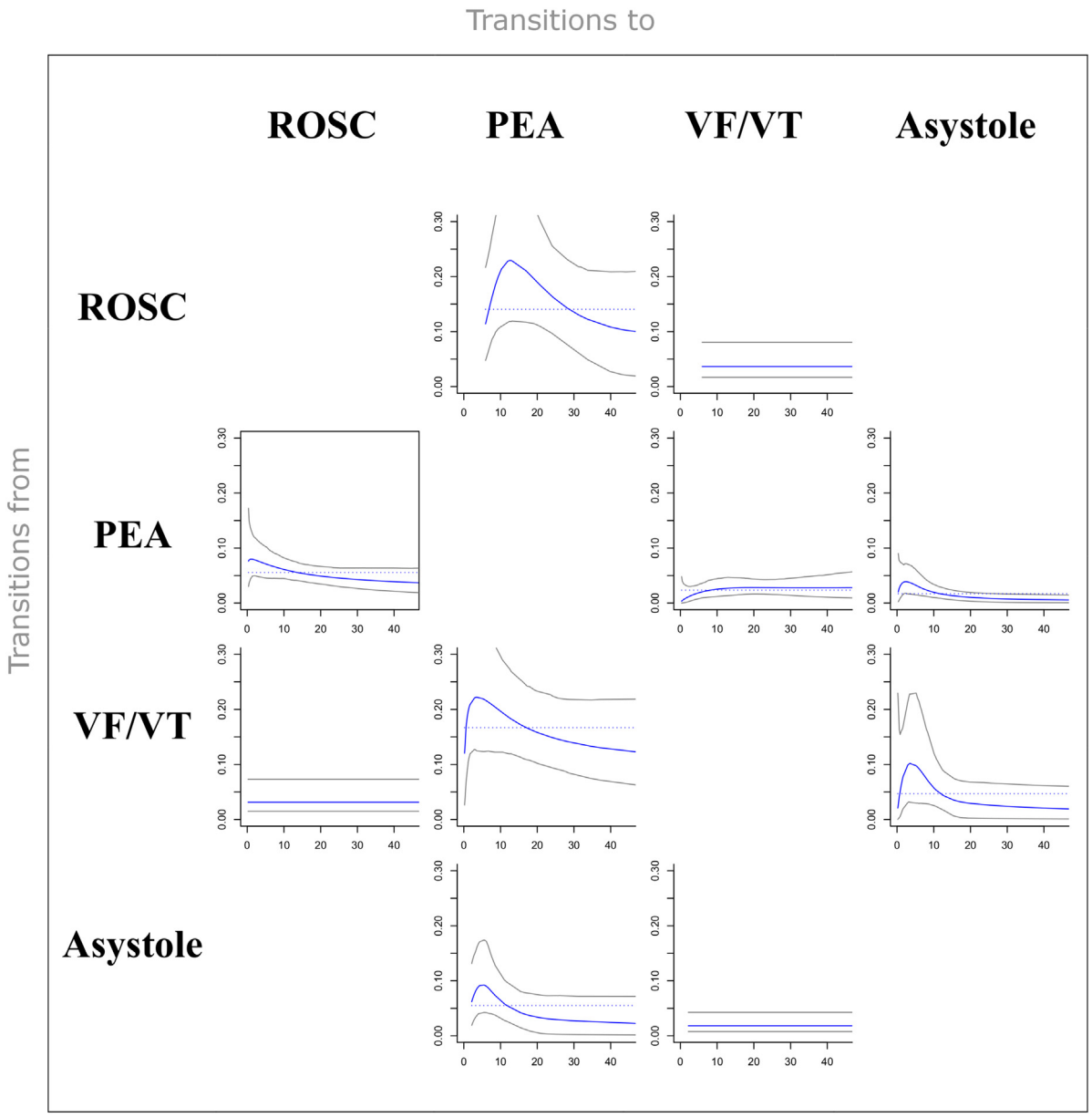

Fig. 2 – Plot of hazard rates for state transitions between the clinical states of ROSC, PEA, VF/VT and asystole (blue lines) with associated 95% confidence intervals (grey lines). For transitions with very few observations, only constant (average) rates could be estimated. Rows indicate from and columns indicated to which state the state transitions took place. An additional dotted blue line shows the corresponding average (constant) rates. No transitions between ROSC and asystole were observed. ROSC — return of spontaneous circulation; PEA — pulseless electrical activity; VF/VT — ventricular fibrillation or —tachycardia (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

can change patient outcome. Fig. 3A demonstrates the simulated expected prevalence of clinical states over time using (for simplicity) the time-constant transition rates found in the study. The model captures most of the essential features of the current observed process in Fig. 1. In Fig. 3B, the results of doubling the PEA to ROSC transition rate from 0.06 to 0.12, and halving the ROSC to PEA relapse rate from 0.12 to 0.06 is demonstrated. In this simulated case, the prevalence of sustained ROSC at 30 min would rise substantially, from 28% to approximately 50%.

Discussion

This is, to our knowledge, the first study to describe and quantify the dynamic features of physiologic responses to CPR and defibrillation in children and adolescents during in-hospital cardiac arrest. We observed several important clinical features of resuscitation in these age groups, both with respect to the state prevalence and with respect to the rate of state transitions with time.

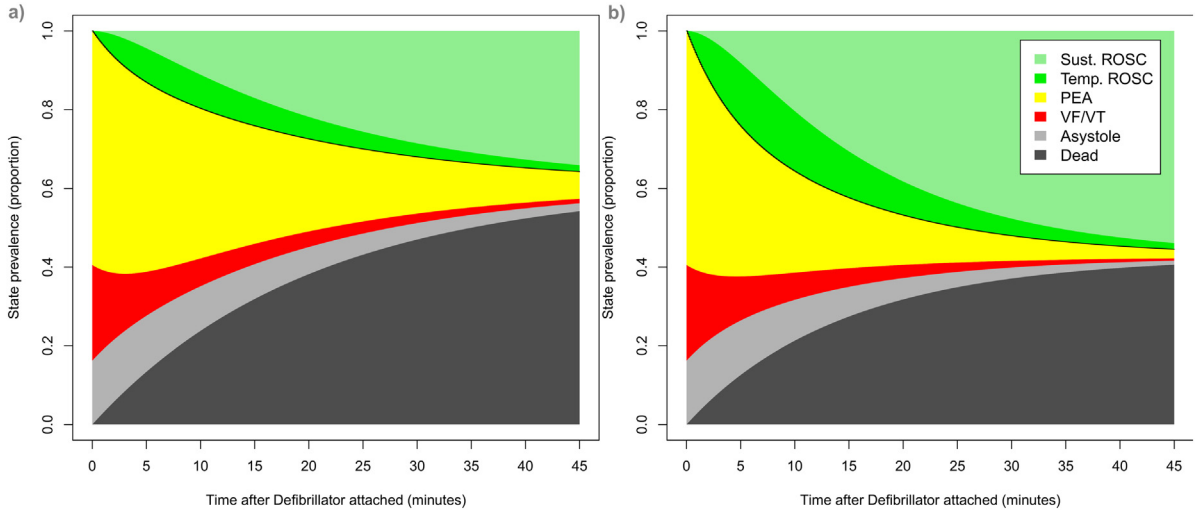

Fig. 3 – Plot of state prevalence based on the time-constant hazard rates found in the study is demonstrated in panel a). The results of a simulated increase in the PEA to ROSC transition rate and halving of ROSC to PEA transition rate is demonstrated in panel b). Sust.ROSC — sustained return of spontaneous circulation (light green); Temp.ROSC — temporary ROSC (green); PEA — pulseless electrical activity (yellow); VF/VT – ventricular fibrillation or –tachycardia (red) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

After the first 5–7 min of resuscitation efforts, nearly one in four patients had obtained ROSC. Quantitatively, we observed that the rates of re-arrest from ROSC to PEA peaked in intensity shortly after 10 min. Thus, the resuscitation team should be aware of the possible risk of losing ROSC when this is first obtained; and focus on preserving sufficient circulation of blood by optimizing ventilation, the use of inotropic drugs / vasopressors and fluid treatment — depending on the physiologic state of the patient and the most probable aetiology of arrest. The early recognition of a reversible cause of arrest has been demonstrated to be associated with better survival in adult in-hospital arrest.[20] An adult study of out-of-hospital cardiac arrest (OHCA) found that re-arrests were more common among patients with initial VF/VT. However, the low number of patients in our cohort does not justify further comparisons based on the initial rhythm.[21]

Although nearly 25% of the paediatric patients had an initial rhythm of VF/VT, the proportion of patient being in VF/VT at any time point after 5–7 minutes of CPR was quite low (<5%). Few patients with initial asystole or PEA developed secondary VF/VT. Samson et al. found a lower proportion of patients with initial VF/VT (10%) in a larger cohort of patients with paediatric cardiac arrest, but the median age was lower (4 years) in their study.[22] In Samson's study, the proportion of VF/VT at any time was 37% in children >8 years of age. Thus, the high proportion of adolescents in our cohort may explain the higher proportion of initial VF/VT observed. Some patients were >18 years of age, as they received continuous follow-up at CHOP beyond the paediatric period for medical reasons.

We found an asymptotic prevalence of sustained ROSC of 30% at 45 min after start of CPR. In a previous study of in-hospital adult cardiac arrest using similar methodology, the proportion of patients with ROSC at 45 min was 45%.[4] In a study of 64,399 adult patients with in-hospital cardiac arrest, Goldberger and co-workers found the asymptotic prevalence of sustained ROSC at one hour to be 48.5%.[23]

For patients with initial asystole, nearly 80% were still in asystole after 8–9 min of CPR efforts. This suggests that frequent rhythm assessments of paediatric patients with initial asystole are less important in the initial phase of resuscitation, similar to adults.[24]

The patients were included over a 7-year period (2006–2013) and the 24-h survival was much lower in the first part of the study (< 20%) compared to the last part of the study (60–80 %).[8] During the same period, compliance with the American Heart Association (AHA) compression depth recommendation increased from less than 20% to nearly 80%. The institution implemented and studied an intensive post-cardiac arrest debriefing program during our data collection period, which may have contribute to both the improved CPR quality and outcomes.[25] The increased quality of CPR observed in the study period may have affected several of the transitions observed in this material. We have not investigated any possible relationship between the state transitions and CPR quality, nor with other time-dependent factors or patient covariates. Such an analysis has so far only been done in adults with OHCA.[26] We believe it is particularly useful to investigate which factors favour the PEA to ROSC transition and the ROSC to PEA transition. If suitable interventions could respectively double and halve these transitions rates, one would expect a doubling of the prevalence of sustained ROSC at an earlier time, which may result in better long-term outcomes.

Limitations

A major limitation in our study is that the definition of ROSC was based on the assumption that prolonged periods of pauses in chest compression pauses was due to ROSC, along with clinical documentation suggesting that the patient had experienced ROSC. Ideally, continuous measurements of end-tidal CO_2 and/or arterial pressure would more accurately identify ROSC, but these types of measurements were not available in our study. The applied methodology necessitates that a defibrillator is attached to the patient during resuscitation efforts. Any periods of CPR given (and rhythm changes experienced) before the defibrillator was attached was not possible to observe. Rhythm assessments were made during pauses

in chest compression to avoid compression artefacts disturbing the ECG signal. Thus, state transition may have occurred during periods of chest compression and may have influenced the precision with respect to the timing of the state transitions. Study investigators (TN, ES) made the annotations retrospectively with limited access to the clinical information in the patient records, partly due to IRB regulations. We based the classification of sustained ROSC or death at end of efforts on the available clinical documentation. The overall low number of patients included limited the amount of data available, specifically for transitions that were more infrequent in the dataset (e.g. ROSC to VF/VT). This limits the generalizability of the findings. Finally, the estimates of continuous hazard rates in time intervals where there were relatively few observations may not be robust. However, they provide more information than assuming merely time-constant average rates.

Conclusion

A quantification of the physiologic response to CPR and defibrillation in children and adolescents with in-hospital cardiac arrest has been described in this study. Paediatric patients were prone to re-arrest between 10 and 20 min after start of CPR efforts. Simulation demonstrated that higher rates of early ROSC along with lower rates of re-arrests could improve the overall survival rate substantially.

Conflict of interests

The authors have no conflicts of interest to report.

Authors UI received funding from the Spanish Ministerio de Economía y Competitividad, project TEC2015-64678-R jointly with the Fondo Europeo de Desarrollo Regional (FEDER) and from the University of the Basque Country (UPV/EHU) through project GIU17/31. Otherwise departmental funding only.

Acknowledgment

The authors wish to thank Professor Jan Terje Kvaløy at The University of Stavanger (Norway) for valuable comments with respect to the statistical analysis.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.01.006.

REFERENCES

1. Skogvoll E, Eftestol T, Gundersen K, et al. Dynamics and state transitions during resuscitation in out-of-hospital cardiac arrest. Resuscitation 2008;78:30–7.
2. Walsh CK, Krongrad E. Terminal cardiac electrical activity in pediatric patients. Am J Cardiol 1983;51:557–61.
3. Donoghue A, Berg RA, Hazinski MF, et al. Cardiopulmonary resuscitation for bradycardia with poor perfusion versus pulseless cardiac arrest. Pediatrics 2009;124:1541–8.
4. Nordseth T, Bergum D, Edelson DP, et al. Clinical state transitions during advanced life support (ALS) in in-hospital cardiac arrest. Resuscitation 2013;84:1238–44.
5. Nordseth T, Olasveengen TM, Kvaloy JT, Wik L, Steen PA, Skogvoll E. Dynamic effects of adrenaline (epinephrine) in out-of-hospital cardiac arrest with initial pulseless electrical activity (PEA). Resuscitation 2012;83:946–52.
6. Wallmuller C, Meron G, Kurkciyan I, Schober A, Stratil P, Sterz F. Causes of in-hospital cardiac arrest and influence on outcome. Resuscitation 2012;83:1206–11.
7. Eftestol T, Thorsen KA, Tossebro E, Rong C, Steen PA. Representing resuscitation data-Considerations on efficient analysis of quality of cardiopulmonary resuscitation. Resuscitation 2009;80:311–7.
8. Sutton RM, French B, Niles DE, et al. American Heart Association recommended compression depths during pediatric in-hospital resuscitations are associated with survival. Resuscitation 2010;2014(85):1179–84.
9. Ayala U, Eftestol T, Alonso E, et al. Automatic detection of chest compressions for the assessment of CPR-quality parameters. Resuscitation 2014;85:957–63.
10. Irusta U, Ruiz J, de Gauna SR, Eftestol T, Kramer-Johansen J. A least mean-square filter for the estimation of the cardiopulmonary resuscitation artifact based on the frequency of the compressions. IEEE Trans Biomed Eng 2009;56:1052–62.
11. Aramendi E, Ayala U, Irusta U, Alonso E, Eftestol T, Kramer-Johansen J. Suppression of the cardiopulmonary resuscitation artefacts using the instantaneous chest compression rate extracted from the thoracic impedance. Resuscitation 2012;83:692–8.
12. R Core Team. R: a language and environment for statistical computing. R foundation for statistical computing. . http://www.r-project.org/.
13. Allignol A. Package 'mvna'. Nelson-Aalen estimator of the cumulative hazard in multistate models. http://cran.r-project.org/web/packages/mvna/.
14. Jackson C. Multi-state models for panel data: the msm package for R. J Stat Software 2011;38.
15. Gabadinho A, Ritschard G, Muller NS, Studer M. Analyzing and visualizing state sequences in R with TraMineR. J Stat Software 2011;40.
16. Amdahl, J. https://cran.r-project.org/web/packages/flexsurvcure/index.html. 2018.
17. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med 2007;26:2389–430.
18. Aalen OO, Borgan O, Gjessing HK. Survival and event history analysis. Springer; 2008. p. 69–130.
19. Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat Med 2002;21:2175–97.
20. Bergum D, Haugen BO, Nordseth T, Mjolstad OC, Skogvoll E. Recognizing the causes of in-hospital cardiac arrest—a survival benefit. Resuscitation 2015;97:91–6.
21. Salcido DD, Sundermann ML, Koller AC, Menegazzi JJ. Incidence and outcomes of rearrest following out-of-hospital cardiac arrest. Resuscitation 2015;86:19–24.
22. Samson RA, Nadkarni VM, Meaney PA, et al. Outcomes of in-hospital ventricular fibrillation in children. N Engl J Med 2006;354:2328–39.
23. Goldberger ZD, Chan PS, Berg RA, et al. Duration of resuscitation efforts and survival after in-hospital cardiac arrest: an observational study. Lancet 2012;380:1473–81.
24. Nordseth T, Edelson DP, Bergum D, et al. Optimal loop duration during the provision of in-hospital advanced life support (ALS) to patients with an initial non-shockable rhythm. Resuscitation 2014;85:75–81.
25. Wolfe H, Zebuhr C, Topjian AA, et al. Interdisciplinary ICU cardiac arrest debriefing improves survival outcomes*. Crit Care Med 2014;42:1688–95.
26. Kvaloy JT, Skogvoll E, Eftestol T, et al. Which factors influence spontaneous state transitions during resuscitation? Resuscitation 2009;80:863–9.