ECG changes during resuscitation of patients with initial pulseless electrical activity are associated with return of spontaneous circulation

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ABSTRACT

Background: Pulseless electrical activity (PEA) is a frequent initial rhythm in cardiac arrest, and ECG characteristics have been linked to prognosis. The aim of this study was to examine the development of ECG characteristics during advanced life support (ALS) and cardiopulmonary resuscitation (CPR) in cardiac arrest with initial PEA, and to assess any association with survival.

Methods: Patients with in-hospital cardiac arrest with initial PEA at St. Olav Hospital (Trondheim, Norway) over a three-year period were included. A total of 2187 combined observations of QRS complex rate (heart rate) and QRS complex width for the duration of ALS were determined from defibrillator recordings from 74 episodes of cardiac arrest.

Results: Increasing heart rate and decreasing QRS complex width during ALS was significantly more prevalent in patients who obtained return of spontaneous circulation compared to patients who were declared dead.

Conclusion: Changes in ECG characteristics during ALS in cardiac arrest presenting as PEA are related to prognosis. An increase in heart rate was observed in the last 3–6 min before ROSC was obtained.

Introduction

In-hospital cardiac arrest (IHCA) has been reported to occur in 1–5 per 1000 admissions [1]. The initial rhythm may be ventricular fibrillation (VF), pulseless ventricular tachycardia (VT), pulseless electrical activity (PEA) or asystole. PEA is the presenting rhythm in 25–42% of IHCA, and survival to hospital discharge for this subgroup has been reported to vary between 3 and 19% [2–6]. The proportion of cardiac arrest patients presenting with PEA has increased during the last decades, whereas the proportion of patients presenting with VF/VT has decreased [4,7,8].

In a previous study of IHCA with initial PEA, we found that most patients had wide initial QRS complexes and slow heart rates, but we found no association of initial ECG characteristics with aetiology or survival [9]. Previous studies on out of hospital cardiac arrest (OHCA) have reported conflicting results regarding the association between initial heart rate and QRS width and subsequent survival. While some studies report increased survival with higher heart rates and narrower QRS complexes, others report no such association [10–13]. An animal study on post-defibrillation PEA demonstrated increased likelihood of return of spontaneous circulation (ROSC) with higher initial heart rates and narrower QRS complexes [14]. While these studies investigated the impact of ECG characteristics at one time point, the dynamic nature of ECG development during advanced life support (ALS) and cardiopulmonary resuscitation has not yet been studied.

The aim of this study was to describe the development of ECG characteristics during ALS in patients with initial PEA, and to examine whether ECG characteristics were associated with ROSC.

Materials and methods

Adult patients (> 18 years) who experienced in-hospital cardiac arrest at St. Olav University Hospital (Trondheim, Norway) and received ALS by the hospital emergency team between January 2009 and January 2012 were prospectively included in the study. Details regarding the hospital and the collection of data have previously been described [3,15].
Electrocardiographic characteristics

ECG and impedance signal data were collected from LifePack 20 and LifePack 1000 defibrillators (Physio-Control, Redmond, USA) as well as Zoll M-series defibrillators (Zoll Corporation, Chelmsford, MA, USA). Defibrillator files were analysed using the software MATLAB (R2014b, Math Works Inc., Natick, MA). Type of heart rhythms, QRS widths, and heart rates were evaluated during pauses in chest compressions for any reason (including end of efforts), or when ROSC was obtained.

The annotation of clinical state along the time axis (PEA, VF/VT, asystole, ROSC and declaration of death) has been described in a previous publication [3]. Briefly, PEA was defined as the presence of organized complexes exceeding 12 per minute, but not constituting VT or ROSC. To visualize, we further subdivided according to QRS width and rate as in the publication by Bergum et al. [9]; rates under 60/min were classified slow, rates between 60 and 100 were classified normal, and rates above 100/min were classified fast. QRS widths below 120 milliseconds (ms) were considered normal and QRS widths > 120 ms were considered wide. ROSC was defined as an organized rhythm without evidence of compressions along with clinical information suggesting ROSC either during the episode or at end of the episode.

The QRS width was defined as the interval between the initial deflection from the baseline towards the Q- or R-wave and the beginning of the ST-interval on the ECG. The QRS end-point was marked off where a clear break from the high frequency changes of the QRS complex (depolarization), towards the lower frequency change of the ST-interval (repolarization) was observed. In cases with no obvious transition from the QRS to the ST-interval, the point where the ECG tracing crossed the baseline towards the T-wave was marked off as the QRS end-point.

During analysis of ECG tracings, the exact points of measurement were labelled on each trace, both for reproducibility and to enable assessment by one of the co-authors (JPL) (Fig. 1). Two to three QRS complexes were measured at each pause in compressions, as determined from the impedance signal. Single complexes that differed substantially from neighbouring complexes with respect to morphology were disregarded. Heart rates were calculated from the intervals between the beginnings of measured QRS complexes.

Statistical analysis

We calculated Pearson’s correlation coefficient between heart rate and QRS width. Development and consequences of ECG characteristics during the course of ALS were investigated in the following ways:

First, we fitted additive models [16] to smooth and visualize the development of the outcome variables heart rate and QRS width over the entire duration of ALS, and for the last 12 min of ALS before ROSC or termination of ALS efforts. We fitted separate models according to whether ROSC was achieved or not. As observations were nested within patients, a mixed effects model in which each patient is assigned an individual offset (known as “random intercept”) was used. We expected that measures closer in time would be more similar than measures further apart and therefore allowed for autocorrelated residuals. This improved model fit.

Second, we plotted the values of QRS width and heart rate during ALS onto a two-dimensional (2D) plane. We constructed bivariate vectors of the change in mean heart rate and QRS width from the first 15 s to the last 15 s of each episode to illustrate the development from start to end of ALS. If asystole had occurred at the very end of the episodes, we used the values from the last preceding measurements during PEA. We tested the null hypothesis of no change using multivariate analysis of variance (MANOVA) [17].

Finally, we investigated the effects of heart rate and QRS width as continuous predictor variables on the cumulative intensity of transition from PEA to ROSC, using Aalen’s additive regression model for time-to-event data [18].

The software R version 3.4.0 [19] and the R packages nlme, gmodels, mgcv and timereg were employed for the statistical analysis. We considered a p value < 0.05 to indicate statistical significance.

Ethics

The Regional Committees for Medical and Health Research Ethics approved the study. Informed consent was obtained from surviving patients, or from the next-of-kin if required. The study is registered at clinicaltrials.gov (NCT00920244).

Results

One hundred and fourteen adult patients with IHCA and an initial rhythm of PEA were included. Of these, 40 were excluded because of missing defibrillator files (n = 28), lack of consent (n = 5), illegible defibrillator file (n = 6), and ROSC before recording started (n = 1), leaving 74 episodes of IHCA for analysis. The data set included a total 2187 combined observations of QRS width and rate.

Table 1 shows demographic and clinical data, stratified on whether or not ROSC was achieved or not. In nine episodes, the defibrillator file was incomplete because the recording stopped before the end of ALS. Four of these were in the ROSC group, five in the no-ROSC group. Median duration of ALS was 6 min in the ROSC group (interquartile range: 3.7–12.8 min). Median duration of resuscitation was 13 min in the group without response to ALS (interquartile range: 8.3–24.4 min). Nine of the included patients (12%) survived to discharge.

Fig. 2 illustrates the changing prevalence of the different clinical states (ROSC, PEA, VF/VT, Asystole, and death) over time. The figure shows that wide-slow PEA rhythms dominated initially, and that almost all ROSC occurred before 21 min of ALS.

Fig. 3 shows the development of mean QRS width and rate during ALS, according to ROSC/no ROSC for the last 12 min before ROSC, or before the end of ALS efforts, by the additive mixed models. The development of heart rate and QRS width was different in patients obtaining ROSC compared to in patients with no response to ALS. In the ROSC group, a marked rise in heart rate started to occur at about 3–6 min prior to ROSC. The development of QRS width was more linear, with a gradual decrease in the ROSC group. In patients without response to ALS, both heart rate and QRS width were essentially unchanged or slightly decreased and increased, respectively, towards the end of ALS efforts. Plots of the predicted mean heart rates and QRS widths for the full duration of ALS from the beginning are provided in figure 1 in Supplementary material, the differences between the groups

Fig. 1. Example ECG and impedance signal with QRS start/stop marked by red “+”. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
are similar from this viewpoint, at least for the first 20 min of ALS. These estimates are increasingly uncertain with time as the number of patients still receiving ALS declines rapidly.

A bivariate scatterplot of heart rate and QRS width is given in Fig. 4. The scatterplot shows considerable variation in the individual responses at the beginning, during, and at the end of ALS. The arrows illustrate that the patients’ ECG courses were fundamentally different depending on whether the patients obtained ROSC at the end of IHCA or not. Both the ROSC and non-ROSC groups started out with an average heart rate slightly below 60/min and an average QRS width of about 160–180 ms. Those who obtained ROSC moved towards an increased heart rate and a narrow QRS, while those without any response had no change in heart rate and the QRS width increased (MANOVA: p < 0.001).

Increasing heart rate increased the intensity of transitions from PEA to ROSC significantly during the first 18 min of ALS (Aalen’s additive model, p < 0.01). A graphical representation of this finding is provided as an e-supplement (e-figure 2 in Supplementary material). Reduced QRS complex width (not shown) had the same effect (p < 0.01) but entering both variables into the model did not improve fit substantially since they by nature are highly correlated (Pearson’s r = −0.41, p < 0.01).

Discussion

This study is, to our knowledge, the first to describe the development of ECG characteristics during ALS in in-hospital cardiac arrest with pulseless electrical activity as the initial rhythm.

Our main finding is that changes in ECG characteristics during ALS are strongly associated with the probability of ROSC. We observed increasing heart rate and narrowing of the QRS complexes during ALS among those with ROSC, with an accelerated change towards ROSC. In particular, an increase in heart rate was observed in the last 3–6 min before ROSC appeared. Different perspectives consistently indicate that the ROSC group developed increased heart rates and decreased QRS widths during ALS compared to the patients without response.

We have modelled the development of heart rate and QRS with for the last 12 min of ALS efforts. This ensures that data from all patients contribute to the model, and that the precision of the estimates improves close to the event of interest. The bivariate plot disregards the time dimension, but clearly shows the joint development of heart rate and QRS from start to end of ALS. Finally, the continuing “loss” of patients under observation over the course of ALS requires a proper way to handle time-varying covariates and censoring; here Aalen’s additive

| Demographics According to Etiology and ROSC group. |
|---------------------------------|---------------------------------|
|                                  | ROSC (n=50)                      | No ROSC (n=50)                  |
| Age, median (IQ-range)          | 65 (60–80)                      | 78 (68–84)                     |
| Males, n (%)                    | 25 (76)                         | 22 (54)                        |
| Department, n (%)               |                                 |                                |
| Ward                            | 12 (36)                         | 28 (68)                        |
| CCU                             | 13 (39)                         | 9 (22)                         |
| ED                              | 5 (15)                          | 2 (5)                          |
| Other                           | 1 (3)                           | 2 (5)                          |
| ICU                             | 2 (6)                           | 0 (0)                          |
| Admission cause, n (%)          |                                 |                                |
| Cardiac                         | 12 (36)                         | 15 (37)                        |
| Pulmonary                       | 8 (24)                          | 10 (24)                        |
| Surgical                        | 7 (21)                          | 5 (12)                         |
| Infectious diseases             | 2 (6)                           | 5 (12)                         |
| Other Internal Medicine         | 0 (0)                           | 3 (7)                          |
| Other                           | 4 (12)                          | 3 (7)                          |
| Arrest cause, n (%)             |                                 |                                |
| Cardiac                         | 11 (33)                         | 15 (37)                        |
| Hypoxic                         | 13 (39)                         | 5 (12)                         |
| Pulmonary Embolism              | 4 (12)                          | 4 (10)                         |
| Hypovolaemic                    | 1 (3)                           | 6 (15)                         |
| Sepsis                          | 0 (0)                           | 3 (7)                          |
| Other                           | 3 (9)                           | 4 (10)                         |
| Unknown                         | 1 (3)                           | 4 (10)                         |

CCU: Coronary Care Unit. ED: Emergency Department. ICU: Intensive Care Unit.

Changes in heart rate and QRS width are negatively correlated in general, but the development was different both regarding magnitude and time. This suggests that the development in one variable does not fully explain the change in the other, and may yield food for thought. Several studies have highlighted the fact that IHCA results from a combination of acute illness, underlying comorbidities, and gradual clinical deterioration over time [20–23]. Metabolic derangement of the myocardium may lead to changes in substrate availability and affect ionic concentrations and currents. This may cause slower pacemaker activity, reduced conduction velocity and delayed myocardial depolarization, leading to slower heart rates and wider QRS complexes.

Fig. 3. Development of heart rate (left) and QRS width (right) for the last 12 min of ALS, i.e the last 12 min before sustained ROSC (green) or before ALS efforts were stopped (grey), according to the additive mixed effects model. Dots are placed every three minutes. Dashed lines: 95% confidence intervals. (ms: milliseconds. min: minutes. ROSC: return of spontaneous circulation\(^*\)). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 4. Bivariate Plot of Heart rate vs QRS width. The arrows are vectors from beginning to end for the ROSC (green) and no-ROSC groups (grey). The green ellipses represent the 50, 75 and 90% coverage areas for the ROSC-group end estimate. For visualization, we assigned instances of VT/VF a heart rate of 320/minute and a QRS width of 50 milliseconds; and instances of asystole were assigned a heart rate of 10/minute and a QRS width of 400 milliseconds. (ms: milliseconds, min: minutes.). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
The mechanism is not well known, but tissue acidosis and increased potassium concentrations may be part of the common pathophysiologic pathways in patients with PEA [26,27]. The baseline values in this study were slow heart rates and wide QRS complexes. The change in the ROSC group towards higher heart rates and narrower QRS complexes represent a move towards more normal values, perhaps because ALS efforts at least partially restored normal physiology in the heart. The different pattern of change in heart rate and QRS width suggest that the mechanisms underlying each variable may differ somewhat, and the potential clinical utility may also be different. It is possible that the QRS width narrows slightly before heart rate rises as the myocardial condition improves, and that this change is actually a prerequisite for heart rate increase and ROSC.

The goal of this study was first and foremost to describe the general development of heart rate and QRS width during ALS, thus clinical application of the results to any individual patient may be premature. With this caveat in mind, it does seem that patients with gradual narrowing of QRS complex width during ALS has a better chance of achieving ROSC, while sudden increases in heart rate may indicate that ROSC is about to occur. The predictive value of these variables with respect to ROSC development in the individual may possibly be analysed further via Bayesian methods.

In the setting of ongoing ALS, the heart rate is more easily monitored than the QRS width. In this study, almost all transitions to ROSC had occurred by about 20 min of ALS, but a few patients attained ROSC later than that. After 20 min an increase in heart rate may be seen as a positive prognostic factor, prompting continued efforts, rather than abandoning ALS efforts, especially if the QRS width has narrowed from the outset.

In three OHCA studies examining PEA characteristics, of which one was published more than 25 years ago and two more recently, similar initial heart rates but narrower initial QRS widths were found when compared to the results in our study [10–13]. None of these studies have examined the dynamics of the ECG-characteristics during ongoing ALS. The proportion of initial PEA in OHCA is usually lower than found in our and other in-hospital studies, while the proportion of asystole is usually higher. This is perhaps to be expected due to the natural increasing transition from PEA (and VF/VT) to asystole with time [8,28,29].

Limitations

This is a single-centre study with relatively few PEA episodes, potentially limiting the generalizability of our results. The demographics are nevertheless similar to a large ICRA study from the United Kingdom [30].

Some uncertainty applies to the measurement of QRS width, both due to the lack of an existing uniform definition of QRS interval endpoint, and due to a sometimes aberrant appearance of ECG complexes found in this study. To address this uncertainty, a consistent approach to assess ECG complexes was applied to all electrocardiograms, and an experienced electro-cardiologist (JPL) was consulted in difficult cases.

Conclusion

Changes in ECG characteristics during ALS in cardiac arrest with pulseless electrical activity was related to prognosis. A move towards more normal ECG characteristics with increased heart rate and narrowing of the QRS during ALS efforts was found to be more prevalent in patients obtaining ROSC compared to patients who were declared dead at end of resuscitation efforts. A significant increase in heart rate was observed in the last 3–6 min before ROSC appeared.

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Conflict of interest statement

Gunnar Waage Skjeflo, Trond Nordsæth, Jan Pål Loennechen, Daniel Bergum and Eirik Skogvoll all declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.resuscitation.2018.03.039.

References


