Effects of Cardiopulmonary Resuscitation on Predictors of Ventricular Fibrillation Defibrillation Success During Out-of-Hospital Cardiac Arrest

Trygve Eftestøl, PhD; Lars Wik, MD, PhD; Kjetil Sunde, MD, PhD; Petter Andreas Steen, MD, PhD

Background—Early defibrillation is considered the most important factor for restoring spontaneous circulation in cardiac arrest patients with ventricular fibrillation. Recent studies have shown that, after prolonged ventricular fibrillation, the rates of return of spontaneous circulation (ROSC) and survival are improved if defibrillation is delayed so that CPR can be given first. To examine whether CPR improves myocardial readiness for defibrillation, we analyzed whether CPR causes changes in predictors of defibrillation success calculated from the ventricular fibrillation waveform.

Methods and Results—ECG recordings were retrieved for 105 patients from an original study of 200 patients receiving CPR or defibrillation first. Altogether, 267 CPR sequences from 77 patients were identified on which the effect of CPR could be evaluated. Five predictors of ROSC (spectral flatness measure, energy, centroid frequency, amplitude spectrum relationship, and estimated probability of ROSC) were determined from a spectral analysis of the ventricular fibrillation waveform immediately before and immediately after each of the 267 sequences. CPR increased spectral flatness measure, centroid frequency, and amplitude spectrum relationship ($P<0.05, P<0.001, P<0.01$). In an analysis of the effect of the duration of CPR, the probability of ROSC and amplitude spectrum relationship showed a positive change for CPR sequences lasting $>3$ minutes ($P<0.001, P<0.05$).

Conclusions—During resuscitation from ventricular fibrillation, changes in the predictors calculated from the ventricular fibrillation waveform indicated a positive effect of CPR on the myocardium. (Circulation. 2004;110:10-15.)

Early defibrillation is considered by many experts to be the most important factor for return of spontaneous circulation (ROSC) and survival in patients with ventricular fibrillation (VF). Immediate defibrillation as soon as a defibrillator is made available is therefore advocated in the guidelines for cardiopulmonary resuscitation (CPR).

Whether CPR is performed before attempted defibrillation also influences outcome. CPR before defibrillation decreases by at least 50% the magnitude of reduction in survival associated with passage of time from collapse. In 2 recent prehospital studies, the rates of ROSC and survival increased even when defibrillation was withheld on purpose until the ambulance personnel had given CPR for 1.5 minute or 3 minutes in patients with ambulance response times of $>4$ to 5 minutes. Although it was previously thought that CPR was capable only of slowing the deterioration of the myocardial milieu, it would appear that CPR can improve the situation in a myocardium with depleted levels of high-energy phosphates and severe acidosis so that it will respond more favorably to a defibrillation attempt.

The probability for achieving ROSC ($P_{\text{ROSC}}$) after a defibrillation attempt can be predicted from analysis of the VF waveform. For example, we have previously reported that in patients with $>25\%$ probability to achieve ROSC with a defibrillation attempt, this probability was more than halved after a 20-second episode without CPR. If CPR can improve the chance of ROSC as found in 2 previous studies, this might also be reflected in changes in the VF waveforms. This has previously been shown in animal experiments. Therefore, the present analysis evaluates VF waveforms during periods of CPR in ECGs taken from patients in the study by Wik et al. We used previously published predictors of defibrillation success to quantify waveform changes. Because their predictive capabilities vary and not all of them have been reported on with human data, this aspect was evaluated in a separate data set.

Methods

Data Collection

Data were collected from a recently published randomized controlled trial from Oslo, Norway, in which defibrillation was delayed in half the patients to allow 3 minutes of CPR to be given. Approval for this study was obtained through the Regional Committee for Research Ethics. We used the ECG, impedance measurements between the defibrillator pads, and defibrillator log data registered in LifePak12 defibrillators (Medtronic Physio-Control), together with clinical data.
resuscitation data according to the Utstein style. The defibrillator data were transferred from the defibrillators into the CODE-STAT SUITE Data Management System (Medtronic Physio-Control) in the EMS office by the paramedics after a completed CPR episode. The clinical resuscitation data were registered in a database (FileMaker Pro). Data extracted from the defibrillator were linked to clinical data by matching date, time, and case number.

Figure 1 shows the flow of patients from those who participated in the original study to those who participated in the present analysis. Of the 200 patients in the original study, we were able to link defibrillator and resuscitation data for 105 patients. The lack of such linkage in half the cases was due mainly to the fact that transferal of the defibrillation data to the CODE-STAT SUITE system was not a required step in the protocol for the original study. Furthermore, the CODE-STAT SUITE system was unavailable for significant periods, and in some cases, another type of defibrillator (Heartstart 3000, Laerdal Medical) was used. The data were analyzed with MATLAB (The Mathworks Inc) and R (R Development Core Team, R Foundation for Statistical Computing).

To ensure reliable evaluation of the ECG signals, a short 4-second VF period without CPR was required to avoid artifacts. Such periods without CPR occur mostly when the ECG is analyzed. We identified all periods in which VF (pre-CPR) was followed by a sequence of continuous CPR and then VF again (post-CPR). Our definition of a continuous CPR sequence was a sequence with no pauses between compressions of >5 seconds. (All patients were intubated with no pause in compressions to ventilate.) For this purpose, we used a graphical user interface showing the ECG tracings and impedance measurements at the same time. Artifacts in the ECG and changes in the impedance tracings induced by CPR were used to determine when it was provided. We were able to identify and extract 267 paired pre-CPR and post-CPR VF waveforms without CPR-induced artifacts (Figure 2) for further analysis from 77 of the 105 patients. There was a much larger number of compression sequences in the original material, but only 267 started and ended with VF. (Many started with asystole or pulseless electrical activity after a defibrillation attempt.) Table 1 gives more details about the number of patients in the original study groups, the distributions into subgroups of response times, and ROSC/no-ROSC outcomes for the original study. Similar numbers are given for the patient material included in the final number of compression sequences analyzed in this study.

Calculating and Evaluating Predictors of ROSC

The ECG predictors mostly used characterize coarseness, frequency, or complexity of the VF waveform or a combination of these. In the present study, this is done with the help of Fourier transforms. These transforms are widely used in signal processing and related fields to analyze the frequencies contained in a sampled signal such as the ECG and in essence decompose or separate the ECG into sinusoids of different frequencies that sum to the original waveform. The transform identifies the different frequency sinusoids and their respective amplitudes. Five previously studied predictors characterizing different aspects of the VF waveform were used in this study. Before these predictors were calculated, the amplitude and corresponding frequency of each of the frequency components of the signals were computed with Fourier transform applied. The predictors were as follows. The amplitude spectrum relationship (AMSA) emphasizes the high-frequency characteristics of the waveform by computing the sum of each frequency component amplitude weighted by the corresponding frequency. Centroid frequency (CF) quantifies the frequency characteristics of the waveform by computing the frequency corresponding to the point of mass in the spectrum. CF emphasizes the low-frequency content of VF. Spectral flatness measure (SFM) characterizes the waveform complexity computed as the ratio of the geometric mean and arithmetic mean of the spectrum. Signal segment energy (ENRG) expresses the coarseness of the VF waveform computed as the area under the spectrum. The estimated $P_{\text{ROSC}}$ expresses the probability of patient resuscitability through a combination of several predictors.

To compute the predictors, the fast Fourier transform was first derived from 4 seconds of ECG (3 seconds for AMSA). The end point of the pre-CPR VF segment was immediately before start of the CPR sequence; the starting point of the corresponding post-CPR VF
The number of measurements per patient varied from a minimum of 1 to a maximum of 14, the total sum of measurements \( \sum_{i=1}^{77} M_i = 267 \). In the further statistical analysis, \( y_i \) is regarded as the response variable. Furthermore, covariates \( x_{ijk} \), \( k = 1, \ldots, 3 \), were determined according to the duration of the compression sequence

\[
y_{ij} = y_{\text{post}ij} - y_{\text{pre}ij},
\]

where \( \Delta t_{\text{dur}} \) is the duration in minutes.

To be able to relate CPR-related changes in the predictors to resuscitability, we also evaluated their predictive capability in discriminating between ROSC and no-ROSC defibrillation outcomes. In a previous study, we analyzed the predictive capability of SFM, ENRG, CF, AMSA, and \( P_{\text{ROSC}} \) were computed. This was done for all the pre- and post-CPR VF pairs (125 Hz, 12-bit resolution). The duration of each CPR sequence used (in minutes) was also computed. Thus, for patient \( i \), \( i = 1, \ldots, 77 \), \( M_i \) predictor measurements of pre- and post-CPR VF pairs were computed and denoted by \( y_{\text{pre}ij} \) and \( y_{\text{post}ij} \) (1 of the 5 predictors described above). The change in the predictor value resulting from the compression sequence was computed as

\[
y_{ij} = y_{\text{post}ij} - y_{\text{pre}ij},
\]

**Statistical Analysis**

To analyze the effect of varying durations of the CPR sequences on each of the predictors, the predictor value changes, \( y_{ij} = y_{\text{post}ij} - y_{\text{pre}ij} \), were grouped according to CPR sequence duration (0 to 1, 1 to 2, 2 to 3, and 3 to 4 minutes). This was analyzed by applying the technique of generalized estimating equations (GEE) with the predictor value changes, \( y_{ij} \), as the response variable and the duration of the corresponding CPR sequence \( (x_{ij}, k = 1, \ldots, 3) \) as covariates. GEE was used to evaluate mean change in predictors within 0 to 1 minute, 1 to 2 minutes, 2 to 3 minutes, and 3 to 4 minutes and is presented as mean (SD). The compression sequence durations were tested for mean level equal to 0, and all the other groups were compared with this level. GEE also accounts for possible statistical dependence between measurements originating from the same patient.

Classifier performance results are presented as the mean (SD) of the cross-validated sensitivities, specificities, true positive rate, true negative rate at 95% sensitivities, and the area under the ROC curve for each predictor. The ROC analysis was achieved by evaluating classifiers with sensitivities fixed at values from 0 to 1 in steps of 0.05. Statistical significance was considered to be at the \( P<0.05 \) level.

**Results**

In the original study, 200 patients were randomized to either CPR or defibrillation first. Mean time from collapse to ambulance arrival was 12.0 minutes (95% CI, 10.7 to 13.4) and 11.7 minutes (95% CI, 10.7 to 12.7) for the CPR and defibrillation first groups, respectively, and additional time to first defibrillation was 3.8 minutes (95% CI, 3.4 to 4.2) and 1.9 minutes (95% CI, 1.6 to 2.2). ROSC was achieved in 102 patients (51%), and 37 (19%) were discharged from hospital.

The changes caused by different compression sequence durations in the present study are shown for all predictors in Figure 3. Table 2 summarizes the results from the GEE analysis of these changes.

**TABLE 1. Material Used in the Study**

<table>
<thead>
<tr>
<th>Group</th>
<th>Ambulance Response Time</th>
<th>≤5 min</th>
<th>&gt;5 min</th>
<th>≤5 min</th>
<th>&gt;5 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients from original study (n=200)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No ROSC</td>
<td>Standard</td>
<td>18 (46)</td>
<td>34 (62)</td>
<td>19 (48)</td>
<td>27 (42)</td>
</tr>
<tr>
<td></td>
<td>CPR First</td>
<td>23 (56)</td>
<td>21 (38)</td>
<td>21 (52)</td>
<td>37 (58)</td>
</tr>
<tr>
<td>ROSC</td>
<td>Standard</td>
<td>10 (50)</td>
<td>20 (62)</td>
<td>12 (52)</td>
<td>16 (53)</td>
</tr>
<tr>
<td></td>
<td>CPR First</td>
<td>10 (50)</td>
<td>12 (38)</td>
<td>11 (48)</td>
<td>14 (47)</td>
</tr>
<tr>
<td>Patients with ECG tracings on computer (n=105)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No ROSC</td>
<td>Standard</td>
<td>7 (54)</td>
<td>14 (64)</td>
<td>11 (55)</td>
<td>15 (60)</td>
</tr>
<tr>
<td></td>
<td>CPR First</td>
<td>6 (46)</td>
<td>5 (36)</td>
<td>9 (45)</td>
<td>10 (60)</td>
</tr>
<tr>
<td>ROSC</td>
<td>Standard</td>
<td>27 (61)</td>
<td>50 (81)</td>
<td>38 (54)</td>
<td>54 (60)</td>
</tr>
<tr>
<td></td>
<td>CPR First</td>
<td>17 (39)</td>
<td>12 (19)</td>
<td>33 (46)</td>
<td>36 (40)</td>
</tr>
</tbody>
</table>

Values are n (%).

Patients either were defibrillated immediately and received 1 minute of CPR between defibrillation series (standard) or received 3 minutes of CPR before first defibrillation attempt and between defibrillation series (CPR first).
minutes at same level, except with AMSA showing a further significant increase for durations $>3$ minutes ($P<0.05$).

$P_{\text{ROSC}}$ was not significantly changed by compression sequences of 0 to 1 minute, but it changed positively as a result of compression sequences of 1 to 2 minutes ($P<0.05$) and showed an even clearer positive change for CPR sequences lasting $>3$ minutes ($P<0.001$).

ENRG showed no significant changes, except for a negative change for durations of 2 to 3 minutes ($P<0.05$). In the separate data set, the different predictors showed variability in predictive capability as illustrated by the predictor box plots for ROSC and no-ROSC (Figure 4). The resulting validation sensitivities (fixed at 0.95), corresponding specificities, true positive rates, true negative rates, and area under the ROC curve are shown in Table 3. SFM has poor predictive capability with an ROC area of 0.49 (SD, 0.08). ENRG and CF perform better with ROC areas of 0.71 (SD, 0.05) and 0.67 (SD, 0.05), respectively. Results were significantly better with AMSA and $P_{\text{ROSC}}$ with ROC areas of 0.77 (SD, 0.05) and 0.86 (SD, 0.02), respectively. The sensitivity and specificity for SFM, ENRG, and CF (Table 3) corresponded well with our previously published results.

**Discussion**

The present results suggest that the VF waveform in human cardiac arrest can improve with CPR and that the changes appear more prominent for CPR lasting $>3$ minutes. Four of 5 waveform-based predictors of defibrillation success improved with CPR, whereas 2 improved significantly with CPR lasting $>3$ minutes. It is interesting that these 2 predictors, AMSA and $P_{\text{ROSC}}$, also were the most powerful predictors of ROSC. There was no sign of deterioration in the VF waveform during CPR, which counters the previous general hypothesis that CPR is capable only of slowing the deterioration of the myocardial milieu.

These findings agree with the clinical results from the study from which the ECG data were taken. Although there was no significant difference in outcome with or without 3 minutes of CPR before the first shock, only a trend to better results with CPR first, the results were significantly better with CPR first for patients with an ambulance response time $>5$ minutes. Similarly, Cobb et al reported that survival was higher in patients in whom defibrillation was delayed to give CPR, and this positive effect was seen in patients with a response interval of $>4$ minutes.

The results are also consistent with previously published animal data. In a porcine model, the median frequency (CF correspondent) improved with CPR with no significant change in the amplitude (ENRG correspondent). In other pig models, both Marn-Pernat et al and Povoas et al reported that AMSA improved with CPR. Marn-Pernat et al demonstrated that both AMSA and ROSC increased with an increased duration of CPR. Berg et al also pointed out that 2 to 3 minutes of CPR was superior to 1 minute in terms of resuscitability. This was also demonstrated by a study by

<table>
<thead>
<tr>
<th>TABLE 2. Change in Predictor Values for Different Durations of CPR Sequences Compared With Duration of 0 to 1 Minute (Tested Versus No Change)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of Compression Sequence, $t_{\text{fav}}$</strong></td>
</tr>
<tr>
<td><strong>0–1 min, Level of $y_j$</strong></td>
</tr>
<tr>
<td><strong>Predictor</strong></td>
</tr>
<tr>
<td>SFM</td>
</tr>
<tr>
<td>ENRG</td>
</tr>
<tr>
<td>CF</td>
</tr>
<tr>
<td>AMSA</td>
</tr>
<tr>
<td>$P_{\text{ROSC}}$</td>
</tr>
</tbody>
</table>

*Values are mean (SD).

‡$P<0.001$; †$P<0.01$; *$P<0.05$. For 0 to 1 minute, significant difference from zero change. For other groups compared with level of $y_j$ at durations of 0 to 1 minute for same predictor.
Achleitner et al.\textsuperscript{21} in which VF mean frequency (CF correspondent) was shown to correlate significantly with the coronary perfusion pressure during compressions in pigs, whereas VF mean amplitude (ENRG correspondent) demonstrated no such correlation. Finally, Kolarova et al.\textsuperscript{22} recently concluded that improved outcome after prolonged untreated VF in rats may result from strategies that provide chest compressions before defibrillation and avoid early and repetitive defibrillation attempts. In their model, 6 minutes of CPR gave the best ROSC and survival results, and they found a progressive increase in a variant of AMSA and mean amplitude (ENRG correspondent) with a compression duration that correlated significantly with the chance of ROSC.

Results of the present study indicate that 3 minutes of CPR was superior to CPR of a shorter duration. Although this finding was significant only for AMSA and $P_{\text{ROSC}}$, these were the best predictors of ROSC; the poorer predictors did not show any time dependency. It is worth noting that $P_{\text{ROSC}}$ is the result of a multivariate combination of spectral predictors, including SFM, ENRG, CF, and peak power frequency, which therefore all affect the behavior of $P_{\text{ROSC}}$. ENRG showed a negative change for compression sequences of 2 to 3 minutes’ duration and no change otherwise and might be the reason why $P_{\text{ROSC}}$ did not change significantly for the whole data set in the present study. It should also be noted that there are 3 severe negative outliers for ENRG in the 2-to-3-minute-duration group (Figure 3). In the porcine study by Berg et al.,\textsuperscript{8} AMPL behaved similarly to ENRG with no changes resulting from CPR. That some predictors showed positive changes for all durations but not $P_{\text{ROSC}}$ could, in addition to the effect of ENRG on $P_{\text{ROSC}}$, be explained by the fact that the other predictors were poorer predictors of ROSC than $P_{\text{ROSC}}$. Thus, positive changes in these predictors might be of less clinical significance.

What clinical implications can be drawn from the present results? First, they support the suggestions from the outcome studies by Cobb et al.\textsuperscript{3} and Wik et al.\textsuperscript{4} that CPR done by professionals can improve the chance for ROSC and ultimate survival of patients with prolonged cardiac arrest and significantly deteriorated myocardium. This study also indicates that CPR periods of 3 minutes might be better for the myocardium than shorter periods. Finally, together with the studies showing rapid deterioration of the myocardium in even a few seconds without CPR after a cardiac arrest,\textsuperscript{10} it gives the important message that periods without CPR (for ECG analysis, defibrillation charging, pulse checks, intubation attempts, etc) should be kept to a minimum. This is frequently not the case clinically.\textsuperscript{19}

The present study has limitations. Compression sequences from only 77 of the 200 patients in the original study were included. Ninety-five patients were excluded because ECG records were lacking (a random occurrence), whereas 28 patients did not have CPR periods with VF both immediately before and after the CPR. The distribution of outcome and ROSC, however, was not different between the subgroup of 77 patients and the original 200 patients (Table 2). In the GEE analysis, only covariates for duration of the sequences were included in the model. In similar modeling, time from the start of the episode was included but did not contribute significantly to any of the predictors. Different models for correlation structure in repeated measurements were tried without altering the conclusion. Because $P_{\text{ROSC}}$ was reevaluated from the same dataset on which its predictive capability was developed, this could potentially cause a slight bias, but it cannot be lower than the originally reported sensitivity of 92% and specificity of 42% of the optimal predictor\textsuperscript{13} from which it was derived.\textsuperscript{17} The conclusion in this study is therefore not in any way affected by this. $P_{\text{ROSC}}$ was developed

<table>
<thead>
<tr>
<th>Predictor</th>
<th>SFM</th>
<th>ENRG</th>
<th>CF</th>
<th>AMSA</th>
<th>$P_{\text{ROSC}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>1.00 (0.00)</td>
<td>0.87 (0.04)</td>
<td>0.91 (0.11)</td>
<td>0.95 (0.05)</td>
<td>0.96 (0.05)</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.01 (0.02)</td>
<td>0.19 (0.05)</td>
<td>0.22 (0.05)</td>
<td>0.40 (0.07)</td>
<td>0.51 (0.05)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>0.10 (0.01)</td>
<td>0.11 (0.01)</td>
<td>0.11 (0.01)</td>
<td>0.15 (0.01)</td>
<td>0.18 (0.02)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>- - (- -)</td>
<td>0.93 (0.01)</td>
<td>0.96 (0.04)</td>
<td>0.99 (0.01)</td>
<td>0.99 (0.01)</td>
</tr>
<tr>
<td>Area under ROC curve</td>
<td>0.49 (0.08)</td>
<td>0.71 (0.05)</td>
<td>0.67 (0.05)</td>
<td>0.77 (0.05)</td>
<td>0.86 (0.02)</td>
</tr>
</tbody>
</table>

Values are mean (SD).
with the use of data from another type of defibrillator, which might cause inconsistencies. The input values of $P_{\text{ROC}}$ also have a restricted range, causing extreme values to be rejected in a few cases. As in all clinical studies in which chest compressions are performed manually, we had no control over quality; compression not performed optimally as in controlled, experimental laboratory studies may reduce the overall results.

We conclude that during resuscitation from VF in humans, there was no sign that the myocardium deteriorated during CPR. In fact, the VF waveform indicated a positive effect of CPR on the myocardium.

Acknowledgments
This work was supported in part by the Center for Information and Communication Technology, Norwegian Air Ambulance, Laerdal Foundation for Acute Medicine, and Anders Jahre’s Foundation. The computer software for transferring the ECG tracings to ASCII-coded files was kindly provided by Medtronic Physio-Control, Redmond, Wash. We thank the paramedics, Mona Monsen, and the physicians of Oslo EMS for their work over the years. We also thank Jan Terje Kvaløy for help on statistical issues.

Disclosure
Dr Wik is a member of the Medical Advisory Board of Medtronic Physio Control and Philips. Dr Steen is a board member of Laerdal Medical AS, the manufacturer of the Heartstart 3000 defibrillator used in part of this study. Dr Eftestøl was a part-time employee of Laerdal Medical during the years 1995 to 2000. Laerdal Medical had no influence on the writing of this article.

References
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