Chest Compressions Cause Recurrence of Ventricular Fibrillation After the First Successful Conversion by Defibrillation in Out-of-Hospital Cardiac Arrest

Jocelyn Berdowski, MSc, MSE; Jan G.P. Tijssen, PhD; Rudolph W. Koster, MD, PhD

Background—Unlike Resuscitation Guidelines (GL) 2000, GL2005 advise resuming cardiopulmonary resuscitation (CPR) immediately after defibrillation. We hypothesized that immediate CPR resumption promotes earlier recurrence of ventricular fibrillation (VF).

Methods and Results—This study used data of a prospective per-patient randomized controlled trial. Automated external defibrillators used by first responders were randomized to either (1) perform postshock analysis and prompt rescuers to a pulse check (GL2000), or (2) resume CPR immediately after defibrillation (GL2005). Continuous recordings of ECG and impedance signals were collected from all patients with an out-of-hospital cardiac arrest to whom a randomized automated external defibrillator was applied. We included patients with VF as their initial rhythm in whom CPR onset could be determined from the ECG and impedance signals. Time intervals are presented as median (Q1-to-Q3). Of 361 patients, 136 met the inclusion criteria: 68 were randomly assigned to GL2000 and 68 to GL2005. Rescuers resumed CPR 30 (21-to-39) and 8 (7-to-9) seconds, respectively, after the first shock that successfully terminated VF (P=0.001); VF recurred after 40 (21-to-76) and 21 (10-to-80) seconds, respectively (P=0.001). The time interval between start of CPR and VF recurrence was 6 (0-to-67) and 8 (3-to-61) seconds, respectively (P=0.88). The hazard ratio for VF recurrence in the first 2 seconds of CPR was 15.5 (95% confidence interval, 5.63 to 57.7) compared with before CPR resumption. After more than 8 seconds of CPR, the hazard of VF recurrence was similar to before CPR resumption.

Conclusions—Early CPR resumption after defibrillation causes early VF recurrence.

Clinical Trial Registration—clinicaltrials.gov Identifier: ISRCTN72257677.

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Key Words: cardiopulmonary resuscitation ☑ defibrillation ☑ electrocardiography ☑ fibrillation ☑ resuscitation ☑ heart arrest

Ventricular fibrillation (VF) is common in patients with out-of-hospital cardiac arrest, varying from 18% to 63% of all cases.1,2 About half of these patients have VF recurrence within the first 2 minutes after successful VF conversion,3 and 74% of the patients have VF recurrence sometime during prehospital care.4 The number of VF recurrences during the resuscitation period is negatively associated with survival.5

Clinical Perspective on p 78

A recent animal study found a clear relation between initiation of chest compressions and the recurrence of VF.6 The current guidelines for cardiopulmonary resuscitation (CPR) issued in 2005 advise immediately resuming cardiopulmonary resuscitation for 2 consecutive minutes after a defibrillation shock to minimize CPR interruption.7,8 Guidelines for CPR issued in 2000 advised performing postshock rhythm analysis and checking for signs of life, thus delaying resumption of CPR for about half a minute.9,10

The purpose of our study was to investigate the relation between CPR resumption after the first successful VF conversion and the recurrence of VF. We hypothesize that (1) chest compressions stimulate recurrence of VF and (2) patients who are resuscitated according to the Resuscitation Guidelines 2005 and receive immediate CPR after a shock refibrillate earlier in comparison to patients who are resuscitated according to the Resuscitation Guidelines 2000 and receive delayed CPR.

Methods

Setting

The Amsterdam Resuscitation Studies (ARREST) research group prospectively collects data of all resuscitation efforts in the Dutch province North Holland, covering approximately 2671 km² and a population of 2.4 million people. The area includes both urban and rural communities. In case of a medical emergency, people dial the national emergency number, where the operator transfers the call to the regional ambulance dispatch center. When suspecting a cardiac...

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Table 1. AED Settings for Randomization

<table>
<thead>
<tr>
<th>Resuscitation Guidelines 2000</th>
<th>Resuscitation Guidelines 2005</th>
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<tbody>
<tr>
<td><strong>Preshock CPR time, s</strong></td>
<td>OFF</td>
</tr>
<tr>
<td><strong>Postshock rhythm analysis</strong></td>
<td>ON</td>
</tr>
<tr>
<td><strong>Pulse check, s</strong></td>
<td>10</td>
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<tr>
<td><strong>Time interval shock, CPR prompt, s</strong></td>
<td>32</td>
</tr>
<tr>
<td><strong>CPR time, shockable rhythm, s</strong></td>
<td>60</td>
</tr>
<tr>
<td><strong>Shock sequence</strong></td>
<td>Maximum 3 stacked shocks</td>
</tr>
<tr>
<td><strong>Energy sequence, J</strong></td>
<td>200–200–360</td>
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arrest, the ambulance dispatcher sends out 2 ambulances of a single tier. Also, the dispatcher sends out a first responder—firefighters, policemen, or a general practitioner, equipped with an automated external defibrillator (AED) (LIFEPAK 500/LIFEPAK 1000, Physio Control, Redmond, Wash). All ambulance personnel are equipped with a manual defibrillator (LIFEPAK 12, Physio Control) and qualified to perform Advanced Life Support (ALS) according to the guidelines of the European Resuscitation Council.11

The ARREST 8 trial (http://www.controlled-trials.com; trial number ISRCTN72257677) investigates whether maximizing CPR during AED usage improves outcome. All first-responder AEDs are individually randomized to 2 modes of resuscitation therapy (Table 1). In the first mode, the AED is programmed according to Guidelines 2000, in which the AED analyzes outcome after a shock and prompts to check for a pulse and to give CPR for 1 minute until the next rhythm analysis. In the second mode, the AED is programmed according to Guidelines 2005, in which the AED prompts to immediately start CPR and continue for 2 minutes after a single shock. In addition, these AEDs prompt for 15 seconds of preshock CPR. AEDs are reprogrammed after each application of the device according to a prespecified randomization list. Therefore, AED users are blinded to the AED protocol until the AED is powered on but are not blinded during AED usage.

The primary outcome of ARREST 8 is survival until admission to a hospital. The Medical Ethics Committee of the Academic Medical Center in Amsterdam approved this study and gave a waiver for the requirement of informed consent before random assignment; all surviving patients gave written consent for usage of the data. The ARREST 8 trial started June 7, 2006, and recruitment is currently ongoing. The planned enrollment is 198 patients with VF as initial rhythm in each arm of the study.

**Data Collection**

All data concerning the resuscitation were prospectively collected according to the Utstein recommendations.12 Study personnel visited the site of the AED shortly after the cardiac arrest and downloaded the electronic data recorded by the AED. Paramedics sent the electronic data recorded by their defibrillator to the data center by modem immediately after the resuscitation effort. These data were merged, stored, and analyzed with dedicated software (Code Stat Reviewer 7.0, Physio Control).

**Design of Current Analysis**

The current analysis focused on the mechanism and timing of VF recurrence in relation to CPR and uses data from the ARREST 8 trial available at September 1, 2008. Patients were included in this analysis if their initial rhythm was VF. We excluded patients to whom an incorrectly programmed AED had been attached, patients to whom an onsite AED had been attached before the AED of the first responder, patients with missing or incomplete ECG recordings, and patients who were dead on arrival. A patient was defined as dead on arrival if clinical signs of death (ie, rigor mortis, marbling, or livor mortis) were obvious. The moment of the first successful VF conversion was defined as termination of VF for 5 seconds after the shock irrespective of the subsequent rhythm and was read from the AED ECG.13 The start of CPR after the shock was visible through the impedance signal of the recording.14 If the start of CPR after the shock could not be determined from the impedance signal recorded by the AED, the patient was also excluded from the analysis.

The electric outcome of the study was recurrence of VF after the first successful VF conversion. Two researchers individually annotated the moment of VF recurrence after the first successful VF conversion. The annotations by the 2 researchers were considered to be in agreement if the difference was less than 1 second, which was the case in 94 cases (96%). In cases in which disagreement was more than 1 second, the 2 researchers annotated the time of VF recurrence by consensus. This annotation was made on the basis of the ECG of the AED or the ECG of the manual defibrillator. We eliminated CPR artifacts from the ECG by using filtering software (Physio Control),13 which allowed determination of VF recurrence onset during CPR (Figure 1). We merged the AED recordings with those of the manual defibrillator, synchronizing the clock times of both defibrillators. As shown in Figure 2, we measured 4 time intervals: from the first VF conversion to the start of CPR; from the first VF conversion to VF recurrence; from the start of CPR to VF recurrence; and from VF recurrence to the second effective conversion—this represents the time the patient was in VF after VF recurrence. The percentage of time CPR had been given during AED connection was calculated by dividing the time that CPR was given by the total time the patient was connected to the AED.

The rhythm after VF conversion but before the start of CPR and the rhythm before VF recurrence were analyzed during the 5 seconds preceding CPR initiation and VF recurrence, respectively. Rhythms were categorized as asystole or as an organized rhythm, which was defined as at least 2 QRS complexes within 5 seconds.16

**Statistical Analysis**

All time intervals were expressed as median (Q1-to-Q3). Continuous variables of patients treated with a delayed-CPR prompt and the immediate-CPR prompt were compared by means of the Wilcoxon rank sum test. Binary variables were compared between treatment groups by χ² tests. The cumulative incidence in VF recurrence in both treatment groups was assessed with the Kaplan-Meier method. We used the Gehan-Breslow test to compare treatment groups regarding time to onset of VF recurrence after successful VF conversion. We used the Kolmogorov-Smirnov test to compare treatment groups regarding time to onset of VF recurrence in regard to CPR resumption. The instantaneous hazard of VF recurrence in the first minute after the first VF conversion was calculated by dividing the total amount of VF recurrences by the person-minutes at risk. To examine whether the moment of VF recurrence was associated with the start of chest compressions over time, we separately calculated the hazard for VF recurrence for the first 2 seconds of CPR resumption, 3 to 5 seconds, 6 to 8 seconds, 9 to 30 seconds, 60 to 120 seconds, and >120 seconds after CPR resump-
tion. Corresponding confidence intervals were calculated with the Poisson distribution regression.

Analyses were based on the intention-to-treat principle: the patient was analyzed according to the programming of the AED regardless of whether the rescuer followed the resuscitation guideline prompted by the AED. Probability values were 2-sided and were based on the standard null hypothesis of no treatment difference. All analyses were performed with the use of SPSS software for Macintosh, version 16.0. All authors reviewed the manuscript and vouch for the accuracy and completeness of the data.

Results

Inclusion and Administration of CPR

During 27 months, 410 patients were connected to a randomized AED. The AEDs were programmed to resuscitation Guidelines 2000, prompting delayed CPR after a shock for 216 patients, and to resuscitation Guidelines 2005, prompting immediate CPR after a shock for 194 patients. Figure 3 shows the enrollment of patients for the current analysis. None of the patients had been attached to an AED by bystanders before the attachment of a first responder AED that was randomized for the purpose of our study. A total of 136 patients met the criteria for inclusion. There was a significant difference between the 2 study groups in the percentage of time CPR had been given and the rhythm before CPR (Table 2). Rescuers resumed CPR after the first successful VF conversion a median time of 30 (Q1, 21; Q3, 39) seconds in patients with a delayed-CPR prompt and of 8 (Q1, 7; Q3, 9) seconds in cases with an immediate-CPR prompt ($P<0.001$). None of the included patients had return of spontaneous circulation immediately after the first successful VF conversion. In all patients, CPR was resumed within 1 minute after the first successful VF conversion.

Recurrence of VF

VF recurred in 49 of 68 patients (72%) with a delayed-CPR prompt and in 49 of 68 patients (72%) with an immediate-
The cumulative incidence of VF recurrence during the first 60 seconds after the first successful VF conversion was substantially lower among patients with delayed-CPR prompt (GL2000) than among patients with an immediate-CPR prompt (GL2005) (Figure 4). The Gehan-Breslow test was statistically significant ($P = 0.001$). There was no appreciable difference in cumulative incidence after 60 seconds. VF recurred 6 (Q1, 0; Q3, 67) seconds after CPR initiation in patients with a delayed-CPR prompt (GL2000) and 8 (Q1, 3; Q3, 61) seconds after CPR initiation in patients with an immediate-CPR prompt (GL2005) (Figure 4). The Gehan-Breslow test was statistically significant ($P = 0.001$). There was no appreciable difference in cumulative incidence after 60 seconds. VF recurred 6 (Q1, 0; Q3, 67) seconds after CPR initiation in patients with a delayed-CPR prompt (GL2000) and 8 (Q1, 3; Q3, 61) seconds after CPR initiation in patients with an immediate-CPR prompt (GL2005) (Figure 4). The Gehan-Breslow test was statistically significant ($P = 0.001$). There was no appreciable difference in cumulative incidence after 60 seconds.

VF recurred 6 (Q1, 0; Q3, 67) seconds after CPR initiation in patients with a delayed-CPR prompt (GL2000) and 8 (Q1, 3; Q3, 61) seconds after CPR initiation in patients with an immediate-CPR prompt (GL2005; Kolmogorov-Smirnov $P = 0.046$; Figure 5). VF was terminated by the second successful VF conversion after a median 98 (Q1, 62; Q3, 201) seconds among patients with a delayed-CPR prompt (GL2000) and after a median 141 (Q1, 82; Q3, 245) seconds among patients with an immediate-CPR prompt (GL2005; $P = 0.07$).

The instantaneous hazard of VF recurrence per person-minute was low (0.30) between the first effective shock and the start of CPR, (Figure 6) and jumped to 4.68 in the first 2 seconds of CPR (hazard ratio [HR], 15.5; 95% confidence interval [CI], 5.63 to 57.7). The hazard decreased over time but remained elevated, with HRs of 8.1 (95% CI, 1.2 to 49.8) and 6.9 (95% CI, 1.03 to 43.5) in the next 3-second intervals, respectively. After 8 seconds, the hazard for VF recurrence was once again low (0.41).

Thirteen of the 136 included patients showed VF recurrence before CPR resumption. Of the remaining 123 patients, 48 had an organized rhythm before CPR resumption and 75 had asystole before CPR resumption (Table 2). In total, 98 patients had VF recurrence; in 85 of these, VF recurred during CPR. The 48 patients in an organized rhythm at the moment of CPR resumption, 33 (69%) had VF recurrence during CPR; of the 75 patients in asystole when CPR resumed, 52 (69%) had VF recurrence ($P = 0.95$). The
increase in the hazard of refibrillation in the first few seconds of CPR did not differ significantly between patients with an asystole before CPR resumption and patients with an organized rhythm before CPR resumption (HR, 18.0; 95% CI, 5.6 to 57.7 and HR, 11.5; 95% CI, 6.4 to 36.6, respectively). There was no significant difference in the rhythm before VF recurrence between the delayed CPR and immediate CPR groups; 32 of the 49 patients (65%) with a delayed-CPR prompt and 37 of the 49 patients (76%) with an immediate-CPR prompt had an organized rhythm before the recurrence of VF (χ², 0.78; P=0.38). The remaining patients immediately refibrillated after a single ventricular premature complex. In total, 69 (70%) of the 98 patients who refibrillated did so after an organized rhythm.

Discussion

The main finding of our study is that VF commonly recurs within the first few seconds after CPR is initiated after successful VF conversion. The hazard of VF recurrence was 15.5 times higher in the first 2 seconds of CPR relative to the time before CPR initiation. Moreover, the timing of VF recurrence relative to the start of CPR did not depend on the timing of the CPR prompt (delayed or immediate); if rescuers started CPR earlier, the patient had earlier VF recurrence as well. To our knowledge, our study is the first to demonstrate the temporal relation between the onset of chest compressions and the onset of VF recurrence in patients with out-of-hospital cardiac arrest. These findings indicate a causal relationship between the onset of manual chest compressions and the recurrence of VF after the first successful VF conversion.

An earlier retrospective observational study showed that VF recurred in 16 of 32 patients (50%) while chest compressions were administered. The authors concluded that the recurrence of VF during a postshock organized rhythm is most commonly spontaneous and unrelated to chest compressions. However, the authors did not give a precise definition of when chest compressions were associated with VF recurrence. In contrast to their findings, we found that VF is related to chest compressions. By detailed analysis of timing, we documented a burst of CPR-associated VF recurrence in the first 2 seconds after CPR resumes.

Similar to our findings, a recent animal study showed that VF recurred within the first 2 chest compressions in 4 of 8 swine. The authors showed that the electric stimulation of the ventricles by chest compressions created a long-short activation sequence leading to VF recurrence. The long-short activation sequence is a well-recognized mechanism by which VF may be initiated. Similarly, low-energy impact to the chest wall (commotio cordis) has been shown to stimulate the ventricle during the vulnerable period and cause arrhythmias as well.

Mechanical stimuli can exert delayed afterdepolarization-like effects mediated by stretch. Mechanoelectric feedback, the phenomenon by which electrophysiological changes of the heart are brought about by mechanical changes, is a potential mechanism explaining why stretch could contribute to recurrence of VF. Stretch during diastole usually leads to depolarization, resembling delayed afterdepolarization, which may reach threshold and initiate a ventricular premature beat. A completely different mechanism that could play a role in recurrence of VF is coronary reperfusion from chest compressions. Reperfusion arrhythmias are a well-known phenomenon after restoration of coronary blood flow during reperfusion therapy in acute myocardial infarction.

These arrhythmias have been described as premature beats or (slow) ventricular tachycardia, but rarely as VF. Furthermore, it has been shown in animal experiments that it takes at least 2 to 3 chest compressions for the coronary perfusion to rise substantially. Thus, reperfusion probably does not explain the sudden strong increase in hazard of VF recurrence in the first 2 seconds of CPR. Hence, we believe that a mechano-electric mechanism is the most likely explanation of the sudden increase in instantaneous hazard of VF recurrence.

Consequences for the Patient

This study demonstrates that the immediate resumption of CPR in accordance with resuscitation Guidelines 2005, while significantly decreasing postshock pause and increasing the percentage of time CPR had been administered, also causes earlier VF recurrence and a trend toward longer-lasting VF. It is not yet clear how this finding affects patient outcome; the benefit of increased CPR time and a reduced postshock pause is well documented, but the effect of longer-lasting VF is not clearly established. Preshock chest compressions for prolonged VF can “coarsen” the VF waveform and improve the rate of successful resuscitation. Experimental studies have shown that outcome is improved by limiting the preshock pause and removing the preshock pause associated with pulse or rhythm checks. Some authors have argued that even interruptions for rescue breaths are detrimental for survival rates.

From a metabolic point of view, prolonged VF is more energy-consuming than asystole. During VF, each myofibril is activated and contracts at a rate of up to 3 to 5 depolarizations per second, depleting ATP and glycogen at a high rate, and increasing glucose-6-phosphate and lactate in the myocardium. This drop in energy availability causes the heart to fatigue, resulting in little contractile force when an organized rhythm returns. Administration of epinephrine during VF, which is advised every 3 minutes by resuscitation...
ALS Guidelines, increases myocardial adenosine 3',5'-cyclic monophosphate concentrations and induces an even higher oxygen consumption. Along these lines, a recent study showed that the duration of VF during resuscitation efforts is inversely correlated to the probability of return of spontaneous circulation. We hypothesize that the high oxygen consumption of earlier VF recurrence partially defeats the increase in CPR fraction. This could explain why the application of resuscitation Guidelines 2005 has improved survival in only 1 of 2 observational studies and not in a randomized clinical trial.

More research is needed to investigate the effect of early VF recurrence during CPR on survival outcome. For example, new methods are being developed to identify a shockable rhythm without interrupting chest compressions. With these techniques, the metabolic downside of VF can be avoided if the patient is defibrillated shortly after VF recurrence instead of completing the currently recommended 2-minute CPR cycle.

Limitations
Most of the VF recurrences occurred during CPR. The movement artifacts in the ECG caused by CPR make it more difficult to precisely annotate the moment of VF recurrence. However, in 96% of cases, the difference between the observations of the 2 researchers was less than 1 second. Therefore, the filtering software cleared most uncertainty about the exact moment of VF recurrence.

Second, we could not identify the exact underlying mechanism causing VF recurrence. Although motion artifacts were sufficiently filtered to determine the onset of VF, the filtering technique did not allow analysis of a long-short sequence during CPR in all analyzed ECGs.

Third, we only evaluated the moment of the first recurrence of VF. It must be further investigated whether our findings are applicable to subsequent VF recurrences as well.

Conclusion
In out-of-hospital cardiac arrest, when CPR is reinitiated after defibrillation, the heart often refibrillates within the first few chest compressions, suggesting that chest compressions are conducive to VF recurrence in this setting. Early resumption of CPR after a defibrillation shock, as advised by the resuscitation Guidelines 2005, is associated with earlier recurrence of VF and possibly longer lasting VF. Further research is needed to determine whether the possible metabolic negative effect of VF recurrence defeats the perfusion benefit from early CPR resumption.

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Disclosures
None.

References


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**CLINICAL PERSPECTIVE**

The current guidelines (GL) for cardiopulmonary resuscitation issued in 2005 advise to immediately resume cardiopulmonary resuscitation (CPR) after a defibrillation shock by abandoning postshock rhythm analysis and checking for signs of life to minimize CPR interruption. This shortens the delay to CPR resumption by about half a minute. At the same time, the CPR cycle is extended from 1 to 2 minutes. This study analyzed the relation between CPR resumption, ventricular fibrillation (VF) recurrence, and VF duration after a first successful shock during randomized treatment with resuscitation GL2000 or GL2005. Our study demonstrated a close relation between initiation of chest compressions and recurrence of VF. In the first 2 seconds of CPR resumption, the hazard of VF recurrence was 15 times larger than before the start of CPR, regardless of the preceding rhythm or guideline used. The hazard remained increased during the first 8 seconds of CPR. VF recurred in 72% of cases in both groups. Because of earlier resumption and longer duration of CPR, the patient treated with GL2005 had VF recurrence significantly sooner and stayed in VF longer as well—a median of 40 seconds in the first CPR cycle. From a metabolic point of view, prolonged VF is more energy-consuming than asystole. This could possibly explain why the application of GL2005 did not show improved survival in all published literature. Further research is needed to determine whether prolonged VF recurrence during CPR influences survival.
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