Time in Recurrent Ventricular Fibrillation and Survival After Out-of-Hospital Cardiac Arrest

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Background—Current resuscitation guidelines (2005 guidelines [G2005]) accelerate ventricular fibrillation (VF) recurrence. We investigated whether patients resuscitated under G2005 spend more time in VF and have better survival rates than patients treated under the 2000 guidelines (G2000).

Methods and Results—We analyzed continuous ECG recordings of out-of-hospital cardiac arrests prospectively collected from January 2006 to January 2008. Patients treated according to G2000 (n = 282) or G2005 (n = 240) with VF as initial rhythm were included. We measured the total time a patient was in recurrent VF (the sum of all intervals from each onset of recurrent VF to each next successful shock) and the time a patient was in initial VF (time interval from rescuer arrival to first effective shock). The primary outcome measure was neurologically intact survival to discharge. The median time in recurrent VF was 2.7 minutes (quartile 1 to 3, 0.4 to 9.0 minutes) under G2000 versus 4.0 minutes (quartile 1 to 3, 0.2 to 11.6 minutes) under G2005 (P = 0.03). Median time in initial VF was 2.7 minutes (quartile 1 to 3, 1.7 to 4.3 minutes) versus 3.9 minutes (quartile 1 to 3, 2.3 to 6.5 minutes), respectively (P < 0.001). Increased time in recurrent VF was significantly associated with decreased neurologically intact survival in both G2000 use (odds ratio, 0.92; 95% confidence interval, 0.87 to 0.97; P = 0.001) and G2005 use (odds ratio, 0.94; 95% confidence interval, 0.90 to 0.99; P = 0.02). Neurologically intact survival decreased significantly with increasing time in initial VF under G2000 (odds ratio, 0.86; 95% confidence interval, 0.74 to 0.99; P = 0.04). This observation was nonexistent in patients treated under G2005. Neurologically intact survival was 29% (82 of 282) under G2000 versus 27% (65 of 240) under G2005 (P = 0.61).

Conclusions—With G2005, the time in recurrent VF remains associated with worse outcome. Studies of immediate defibrillation for recurrent VF are warranted. (Circulation. 2010;122:1101-1108.)

Key Words: cardiac arrest • defibrillation • outcomes research • resuscitation • ventricular fibrillation

Ventricular fibrillation (VF) is common in patients with out-of-hospital cardiac arrest (OHCA), varying from 18% to 63% of all cases.12 About half of these patients have VF recurrence within the first 2 minutes after successful VF conversion; 74% of the patients have VF recurrence sometime during prehospital care.4 Although the effect of time in VF until the first defibrillation on survival is well documented,5,6 the effect of the cumulative time in recurrent VF on survival is not well established. One study found the number of VF recurrences to be negatively associated with survival,7 but these findings were not confirmed by another study.8 A study that investigated the effect of the duration of VF during resuscitation efforts found an inverse correlation to the probability of return of spontaneous circulation.9

Clinical Perspective on p 1108

The current guidelines for cardiopulmonary resuscitation issued in 2000 (G2000) advised performing postshock rhythm analysis before continuing CPR for a minute.12,13 We found that the first few chest compressions after defibrillation cause VF recurrence, which arises sooner after the shock under resuscitation G2005 than under G2000.14

The purpose of this study was to investigate whether the patients treated according to G2005 spend more time in VF than patients treated according to G2000 and to determine whether both the time in VF resulting from protocolized CPR before the first effective shock and the time in recurrent VF are associated with decreased survival.

Methods

Setting
The Dutch province of North Holland has a population of 2.4 million people and covers 2671 km2, including both urban and rural communities. Medical emergency calls are immediately transferred after a countershock, regardless of shock success.10,11 Guidelines for cardiopulmonary resuscitation issued in 2000 (G2000) advised performing postshock rhythm analysis before continuing CPR for a minute.12,13 We found that the first few chest compressions after defibrillation cause VF recurrence, which arises sooner after the shock under resuscitation G2005 than under G2000.14

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to the regional emergency medical services (EMS) dispatch center. When suspecting a cardiac arrest, the EMS dispatcher sends out 2 ambulances of a single tier.15 All EMS paramedics are qualified to perform advanced life support according to the guidelines of the European Resuscitation Council16 and are equipped with a manual defibrillator (LIFEPAK 12, Physio Control, Redmond, Wash). Two of the 3 regions (Amsterdam and Kennemerland) also dispatch a first responder equipped with an automated external defibrillator (AED; LIFEPAK 500/LIFEPAK 1000, Physio Control). These first responders are firefighters or policemen trained in basic life support and AED use.

Data Collection
Between January 1, 2006, and January 1, 2008, we prospectively collected data on all patients in whom resuscitation was attempted by EMS personnel during an OHCA of suspected cardiac cause. Arrests were considered noncardiac if the EMS rescuers or the physicians at the hospital could identify a noncardiac origin such as trauma, drowning, drug overdose, asphyxia, exsanguination, or any other unequivocal noncardiac condition. We analyzed EMS guideline use via defibrillator recordings of the continuous ECG and impedance signals. Our guideline classification protocol of the ECGs has previously been published.17 Continuous ECGs were classified as G2000 or G2005. In summary, ECGs classified according to the G2000 protocol show a 15:2 compression:ventilation ratio, 1-minute CPR cycles, and postshock rhythm analysis. ECGs classified according to the G2005 protocol show an initial CPR period of 2 minutes, a 30:2 compression:ventilation ratio, 2-minute CPR cycles, and immediate CPR resumption after a shock without rhythm analysis. All shocks and CPR cycles were individually classified. The same guideline needed to be applied for at least 75% of all shocks and CPR cycles. All analyses that did not fulfill any guideline criteria were classified as indeterminate. Patients were included if they had VF as the initial rhythm and if the use of G2000 or G2005 could be determined from the ECG. The G2005 was gradually implemented from the publication of Dutch translation guidelines in March 23, 2006, until early May 2007, when >80% of cases were resuscitated according to G2005.17

Data Sources
After each resuscitation attempt, EMS paramedics routinely downloaded and sent the continuous ECG and impedance recordings from their manual defibrillators to the study center by modem. Study personnel, who visited the AED site shortly after the cardiac arrest, collected the AED ECG and impedance recording. The clock times of the AED recordings were synchronized with the laptop used to download the ECGs. We merged the LIFEPAK AED recordings with those of the manual defibrillator to obtain 1 consistent timeline of the data from both defibrillators. Other AED brands were excluded from this analysis because the clock synchronization was not always possible. The ECGs were stored and analyzed with dedicated software (Code Stat Reviewer 7.0, Physio Control). Data items about the resuscitation were collected according to the Utstein recommendations.18 The Medical Ethics Review Board of the Academic Medical Center, Amsterdam approved the study and gave a waiver for the requirement of (written) informed consent.

ECG Analysis
All shocks were annotated automatically in the ECGs and analyzed for shock success. A successful shock was defined as VF termination for at least 5 seconds by defibrillation regardless of the subsequent rhythm and was read from the ECG. Two researchers individually annotated the moment of VF recurrence after the each successful shock.14 This annotation was based on the ECG of the AED and/or the ECG of the manual defibrillator. We eliminated CPR artifacts from the ECG using filtering software (Physio Control),19 which allowed determination of the onset of VF recurrence during CPR. The initial time in VF was the time interval from EMS arrival to first effective shock; the total time in recurrent VF was the sum of all intervals from each onset of recurrent VF to each next successful VF conversion. If an episode of recurrent VF was not successfully terminated, the case was excluded from analysis. These patients were not transported and left at home while still in VF.

Follow-Up
Survival was verified by contacting the hospital of admission and confirmed in the civic registry. Patients who survived to admission were surveyed after the resuscitation attempt by contacting the hospital department. We retrieved data on the use of therapeutic hypothermia and neurological outcome at discharge from the hospital charts estimating the cerebral performance category: 1=good cerebral performance, 2=moderate cerebral disability, 3=severe cerebral disability, 4=coma or vegetative state, and 5=death. A cerebral performance category score of 1 or 2 was classified as favorable neurological status.20

Statistical Analyses
We examined the association between neurologically intact survival and the time in VF. The primary analysis focused on the time in recurrent VF. The association between neurologically intact survival and the time in VF from EMS arrival to first effective shock is presented as a secondary analysis. Thirty-day neurologically intact survival in relation to time in VF was analyzed by logistic regression analysis per guideline use in single-variable analyses. Next, we analyzed 30-day neurologically intact survival according to the prognostic factors age, sex, bystander CPR, witnessed collapse, location of the collapse, biphasic defibrillation, percentage of time CPR was given, time interval from emergency call to EMS arrival, and year of the arrest with single-variable logistic regression. Single-variable significance was accepted if $P<0.10$. Survival according to time in VF was then analyzed by logistic regression with adjustments for significant correlates of survival. We also included variables that differed significantly between groups. We tested for interaction between survival and time in VF between the guidelines used with a likelihood ratio test. Neurologically intact survival was estimated with the Kaplan-Meier method and compared by use of the log-rank test.

Descriptive statistics are reported as mean (SD), median (25th to 75th percentile), or number (percent) as indicated. Comparisons of continuous variables were made with t tests; the Mann-Whitney U test was used when discrete variables were compared; the $\chi^2$ test was used when binary variables were compared. All statistical tests were 2 tailed, and a value of $P<0.05$ was considered statistically significant. All statistics were performed with SPSS (version 16.0 for Mac, SPSS Inc, Chicago, Ill).

Results
Inclusion and Treatment Characteristics
During the study period of 24 months, 1748 patients had an OHCA of cardiac origin, of whom 833 had VF as the initial rhythm (Figure 1). Of these patients, 311 were treated according to G2000 and 263 were treated according to G2005. The ECGs of 282 and 240 patients, respectively, were analyzed. The patient and resuscitation characteristics are shown in Table 1. There was a statistically significant overrepresentation of men treated under G2000. A biphasic defibrillator was used more often under G2005. The other characteristics were not statistically significantly different between the 2 groups.

Table 2 shows the procedure and outcome characteristics according to guideline use. When using G2005, rescuers took a median of 1.2 minutes longer after arrival to successfully defibrillate a patient ($P<0.001$). VF recur in 229 of 282 patients (81%) treated under G2000 and in 182 of 240 patients (76%) treated under G2005 ($P=0.14$). Patients
treated according to G2005 spent a median of 1.3 minutes longer in recurring VF (4.0 versus 2.7 minutes; \(P = 0.03\)).

**Guideline Use and Survival**

Overall survival to discharge was 32% (91 of 282; 95% confidence interval [CI], 27 to 38) in patients with an OHCA treated according to G2000 versus 30% (71 of 240; 95% CI, 24 to 35) in patients with an OHCA treated according to G2005 (\(P = 0.51\)). Neurologically intact survival was 29% (82 of 282; 95% CI, 24 to 34) versus 27% (65 of 240; 95% CI, 21 to 33), respectively. The 282 patients with an OHCA treated according to G2000 showed no significant difference in neurologically intact survival rate compared with the 240 patients in OHCA treated according to G2005, as shown in an unadjusted Kaplan-Meier analysis (log-rank \(P = 0.73\); Figure 2). For patients admitted to the intensive care unit, there were no appreciable differences in hypothermia therapy (81% [109 of 135] of cases under G2000 versus 88% [103 of 117] of cases under G2005; \(P = 0.12\)).

**Time in VF and Survival**

Neurologically intact survival decreased with increased time in recurrent VF and with an increasing number of VF recurrences (Figure 3). The influence of an increased time in recurrent VF on neurologically intact survival did not differ significantly between the use of G2000 (odds ratio [OR], 0.94; 95% CI, 0.90 to 0.98; \(P = 0.004\)) and the use of G2005 (OR, 0.95; 95% CI, 0.91 to 0.98; \(P = 0.007\)). The association between recurrent VF and neurologically intact survival was unaltered after adjustment for possible confounding (under G2000: OR, 0.92; 95% CI, 0.87 to 0.97; \(P = 0.001\); under G2005: OR, 0.94; 95% CI, 0.90 to 0.99; \(P = 0.02\); Table 3).

Figure 4 shows the neurologically intact survival rates by the time from EMS arrival to the first effective shock. We found that the time from EMS arrival to the first effective shock was associated with decreased survival only in patients treated according to G2000 (OR, 0.84; 95% CI, 0.72 to 0.97; \(P = 0.02\); Table 3). This relation was absent in patients treated according to G2005 (OR, 0.98; 95% CI, 0.93 to 1.05; \(P = 0.62\)). These ORs were statistically significantly different (\(P = 0.03\), test for interaction). When adjusted for possible confounding by age, sex, percentage of CPR given, location of the collapse, biphasic defibrillation, time from emergency call to EMS arrival, and year of the arrest, the association between increased time in initial VF and survival remained significant for patients treated according to G2000. A combined analysis showed that the association between neurologically intact survival and the time in recurrent VF was independent of the time in initial VF (data not shown).
The main finding of our study is that the total time in recurrent VF was associated with decreased survival. Survival rates did not differ significantly between patients treated according to G2000 and those treated according to G2005. When comparing the time in VF between the 2 guidelines, we found that the use of G2005 was associated with increased time in initial VF and an increased time in recurrent VF. The increased time to first effective shock was associated with decreased survival when G2000 was applied but not when G2005 were applied. The time in recurrent VF was associated with decreased survival with both G2000 and G2005 use. The increased time in recurrent VF under G2005 use appears to be in part to early refibrillation, occurring in

**Discussion**

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![Figure 2. Kaplan-Meier survival curve. If patients were treated according to G2000, 29% of the 282 patients survived with a cerebral performance category score of 1 or 2; if patients were treated according to G2005, 27% of the 240 patients survived with a cerebral performance category score of 1 or 2.](image)

![Figure 3. The 30-day neurologically intact survival rates by the time in recurrent VF and number of VF recurrences. The linear association is significant for 30-day neurologically intact survival and both the time in recurrent VF (P<0.001) and number of VF recurrences (P<0.001).](image)
the first few compressions when CPR is resumed after defibrillation, which happens sooner after the shock in G2005 than in G2000. It is also due in part to the elimination of stacked shocks and extension of the CPR period between shocks, which combine to place a longer period of CPR between defibrillation attempts. Both the conversion of the first episode of VF and the consecutive episodes were prolonged because of the elimination of a postshock rhythm check under G2005. An unsuccessful shock could not be recognized until a full 2 minutes of CPR had been done.

Effect of Guideline Use on Survival

The major protocol changes were the initiation of 2 minutes of CPR before the first shock, 1 shock instead of the stacked shocks, and the emphasis on continuous CPR.

All paramedics applying G2005 had recently been trained in the new protocol, including extensive refreshing of their CPR skills, whereas those applying G2000 had received training at least a year before the resuscitation. Recent training leads to better performance in the field. During the training of the new protocol, the importance of optimal chest compressions was emphasized. It is possible that this recent training could be an incentive for rescue personnel to better focus on technique and performance during the new protocol time period. Therefore, one would expect the patients treated with G2005 to have better outcome. However, our data show similar survival rates under the 2 guidelines, which are in accordance with the findings of a recently published randomized clinical trial and an observational study on the impact of G2005 compared with G2000 on resuscitation outcome. One observational study in which AEDs were programmed according to G2005 that also had historic controls showed an improvement in survival. In this study, however, only the first-tier responders treated the patient according to the G2005 protocol; they resuscitated the patient for 5 minutes with an AED before paramedics took over resuscitation efforts using G2000. Taking these factors into consideration, it is likely that the improvement could also have been due to a nonspecific Hawthorne effect or other temporal developments. The randomized study also found significant improvements in outcome over time but no improvements when the 2 guidelines were compared.

Effect of Recurrent VF on Survival

In support of the data we present, a randomized clinical trial showed that the time in VF recurrence is greater with G2005 than with G2000. However, a relation between the time in VF and survival was not investigated.

According to our data, it is desirable to end recurrent VF as soon as possible because survival decreases with every minute that the next shock is postponed. Experimental work is inconclusive about whether it would be better, during
resuscitation from cardiac arrest, to terminate VF quickly when it recurs or to ignore it and continue CPR. The deleterious metabolic effect of VF on the myocardium has been demonstrated previously; whereas ATP and glycogen rapidly decrease, glucose-6-phosphate and lactate levels increase.\textsuperscript{26} Administration of epinephrine during VF, which is advised every 3 minutes by resuscitation advanced life support guidelines, increases myocardial adenosine 3',5'-cyclic monophosphate concentrations and induces an even higher oxygen consumption.\textsuperscript{27} However, other experimental work has shown better resuscitation outcome when CPR is done during VF than during pulseless electric activity.\textsuperscript{28}

The results of the present study indicate either that time spent in recurrent VF itself is detrimental to survival or that time in recurrent VF is a marker for patients who are less likely to survive because of their underlying pathology. Further research is needed to determine which is the case.

Effect of Initial Time in VF on Survival
Work by Cobb et al\textsuperscript{29} and Wik et al\textsuperscript{30} suggested that delaying the first defibrillation by 3 minutes of chest compressions improved survival when EMS had a response time interval of >4 to 5 minutes. The benefit of CPR before the first defibrillation has not been confirmed in other randomized trials.\textsuperscript{31,32} In addition, a large randomized multicenter study by the Resuscitation Outcomes Consortium National Institutes of Health trial on CPR first and defibrillation first was discontinued before completion of enrollment on the grounds of futility; there was no statistical likelihood that a significant difference between the 2 groups could be obtained (http://www.nih.gov/news/health/nov2009/nhlbi-06.htm). Our study showed that survival outcome was not influenced by whether the patient first received CPR with a delay in defibrillation or was defibrillated immediately when EMS arrived on scene after a median of 9 minutes. However, delaying the initial shock without performing CPR does decrease survival rates, as our data show for patients with a delayed initial defibrillation when treated with G2000.

Implications for the Guidelines
The changes to the guidelines were based on limited evidence. The increase from a 15:2 to a 30:2 compression:ventilation ratio was based on animal data\textsuperscript{33–35} and a mathematical model.\textsuperscript{36} There were no published human or animal studies comparing a single-shock protocol with a 3-stacked-shock protocol for treatment of VF. Shortly after the guidelines were published, a porcine model showed increased survival when stacked shocks were replaced by single shocks, allowing more chest compressions and shorter preshock pauses.\textsuperscript{37} The expectation based on that evidence was that outcome would be improved by the constellation of protocol changes that G2005 implemented, yet the only randomized test of this had neutral results.\textsuperscript{23} Our finding in the present study may account at least in part for the lack of an outcome benefit; the G2005 group patients, in addition to receiving more CPR, also spend more time in VF. This additional time in VF may have counteracted the putative benefit of increased CPR, with a neutral net effect on outcome.

Our findings suggest that it may be beneficial to treat VF rapidly when it recurs, although it would presumably be best to do so without interrupting chest compressions. New methods are being developed to identify a shockable rhythm without interrupting chest compressions.\textsuperscript{38–40} With this technique, the patient could be defibrillated immediately when VF recurs. The use of chest compression devices could allow compressions to continue through defibrillation with perhaps a need to time the shock relative to the compression. Hands-on defibrillation would also allow chest compressions during the administration of a shock.\textsuperscript{41,42}

Limitations
Our study was not a randomized trial but a prospective observation cohort. Therefore, we cannot exclude the possibility that survival differences between the 2 guidelines were masked by changes over time in other factors that influence survival. Nevertheless, we did not observe substantial differences in influential baseline characteristics between the 2 groups.

Thirteen percent of cases with VF as initial rhythm could not be included in the analysis for technical reasons. The baseline characteristics and survival rates of patients whose ECG could not be analyzed were similar to those of patients analyzed in this study (data not shown). Therefore, selection bias is not a likely explanation for the findings in our study.

The movement artifacts of CPR in the ECG render precise annotation of the moment of VF recurrence difficult. However, in our previous study, the difference between the observations of the 2 researchers was <1 second in 96% of cases.\textsuperscript{14}

Conclusions
The use of G2005 is associated with longer-lasting initial VF and longer-lasting recurrent VF. Although the increased time in initial VF is not associated with decreased survival, the time in recurrent VF is. New studies that compare immediate defibrillation for recurrent VF with the current G2005 protocol are warranted.

Acknowledgments
We are greatly indebted to the dispatch centers and regional ambulance services of Amsterdam Agglomeraties, Kennemerland and Noord-Holland Noord; the Amsterdam, Amstelveen, and Haarlemmermeer fire brigade; Kennemerland and Texel police; Schiphol airport; and Meditaxi for their contribution to the data collection. We greatly appreciate M. Hulleman, E. Landman, and R. van der Meer for their excellent data management and secretarial assistance. We thank all the students of the University of Amsterdam who helped collect the data of the AEDs on site.

Sources of Funding
This study was supported by a grant from Physio Control Inc, Redmond, Wash, and the Netherlands Heart Foundation, grant 2009R013.

Disclosures
Dr Fred Chapman is a full-time employee of Physio Control Inc (Redmond, Wash), which designs and manufacturers medical devices. The other authors report no conflicts.
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CLINICAL PERSPECTIVE

Ventricular fibrillation (VF) frequently recurs after initial defibrillation for out-of-hospital cardiac arrest. To minimize interruptions in chest compressions during cardiopulmonary resuscitation, the 2005 resuscitation guidelines (G2005) advise immediate resumption of cardiopulmonary resuscitation for 2 minutes after a shock, regardless of shock success. Resuscitation guidelines 2000 (G2000) advised a postshock rhythm analysis before resuming cardiopulmonary resuscitation for only 1 minute. Because chest compressions sometimes reinduce VF, we investigated whether patients resuscitated under G2000 spend more time in VF and whether time in VF is related to neurologically intact survival. Patients treated under G2000 and G2005 were compared. Considering the time to initial defibrillation shock, time in initial VF was associated with worse outcome for G2000 but not for G2005. Time with cardiopulmonary resuscitation increased from an average of 60% under G2000 to 74% under G2005. For recurrent VF, under G2005, rescuers delayed repeat defibrillation, and patients spent a longer time in recurrent VF. A longer cumulative duration of recurrent VF was associated with worse outcome. Neurologically intact survival was similar in both guidelines groups. Thus, the additional time in recurrent VF with G2005 may offset the putative benefit of increased cardiopulmonary resuscitation, with a neutral net effect on outcome. Studies of immediate defibrillation for recurrent VF to reduce recurrent VF duration are warranted.
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Circulation. 2010;122:1101-1108; originally published online August 30, 2010; doi: 10.1161/CIRCULATIONAHA.110.958173

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