Ventricular Fibrillation Scaling Exponent Can Guide Timing of Defibrillation and Other Therapies

James J. Menegazzi, PhD; Clifton W. Callaway, MD, PhD; Lawrence D. Sherman, MD; David P. Hostler, PhD; Henry E. Wang, MD; Kristofer C. Fertig, BS; Eric S. Logue, BS

Background—The scaling exponent (ScE) of the ventricular fibrillation (VF) waveform correlates with duration of VF and predicts defibrillation outcome. We compared 4 therapeutic approaches to the treatment of VF of various durations.

Methods and Results—Seventy-two swine (19.5 to 25.7 kg) were randomly assigned to 1 of 9 groups (n=8 each). VF was induced and left untreated until the ScE reached 1.10, 1.20, 1.30, or 1.40. Animals were treated with either immediate countershock (IC); 3 minutes of CPR before the first countershock (CPR); CPR for 2 minutes, then drugs given with 3 more minutes of CPR before the first shock (CPR-D); or drugs given at the start of CPR with 3 minutes of CPR before the first shock (Drugs+CPR). Return of spontaneous circulation (ROSC) and 1-hour survival were analyzed with χ² and Kaplan-Meier survival curves. IC was effective when the ScE was low but had decreasing success as the ScE increased. No animals in the 1.30 or 1.40 groups had ROSC from IC (0 of 16). CPR did not improve first shock outcome in the 1.20 CPR group (3 of 8 ROSC). Kaplan-Meier survival analyses indicated that IC significantly delayed time to ROSC in both the 1.3 (P=0.0006) and the 1.4 (P=0.005) groups.

Conclusions—VF of brief to moderate duration is effectively treated by IC. When VF is prolonged, as indicated by an ScE of 1.3 or greater, IC was not effective and delayed time to ROSC. The ScE can help in choosing the first intervention in the treatment of VF. (Circulation. 2004;109:926-931.)

Key Words: fibrillation • heart arrest • defibrillation • cardiopulmonary resuscitation

Sudden cardiac death claims 600 to 1000 lives per day in the United States, and survival rates are dismal.1–3 Current therapy for the treatment of cardiac arrest is prescribed by the guidelines established by the American Heart Association, known as Advanced Cardiac Life Support (ACLS).4 Electrical defibrillation is the only ACLS intervention that is associated with good outcomes, but the effectiveness of this intervention decreases dramatically over several minutes.3 Defibrillation is also not an innocuous therapy.5–7 Human clinical experience in treating ventricular fibrillation (VF) demonstrates that the conventional use of electrical therapy results in 58% of patients being shocked into pulseless electrical activity (PEA) or asystole.8 There is also evidence that patients who have postcountershock PEA and asystole are less likely to survive to hospital discharge than patients whose primary ECG rhythms are asystole or PEA.9

A growing body of evidence suggests that performing other interventions before electrical therapy may improve defibrillation success.10–15 Cobb et al14 produced the first human clinical study to show that CPR before defibrillation results in improved survival to hospital discharge. In this population-based study of 1100 cases of out-of-hospital VF, a 90-second bout of CPR was delivered before the first defibrillation attempt. The rate of survival to hospital discharge went from 24% to 30% when patients were treated with CPR before defibrillation. The difference was even more pronounced in patients in whom the VF duration was estimated before defibrillation. The difference was even more pronounced in patients in whom the VF duration was estimated to be >4 minutes (ie, a benefit from CPR was not seen in patients whose downtime was known to be brief).

This study was corroborated by a prospective, randomized clinical trial by Wik et al.15 In this study, defibrillation was performed either immediately or after 3 minutes of CPR. Overall, 15% of the patients who were defibrillated immediately survived to hospital discharge, whereas 22% of those who had CPR first survived (although this difference was not statistically significant). However, when the response interval was known to be >5 minutes, the group that was treated with CPR before defibrillation had a 22% rate of survival to hospital discharge, compared with 4% of patients who were shocked first.

Defibrillation is most effective when used very early in the course of VF, and pretreatment before defibrillation may im-prove success when VF is prolonged. The duration of VF is rarely known, especially in the out-of-hospital setting. Therefore, it would be beneficial if information contained in the ECG signal could be used to guide the use of electrical therapy. We recently reported on a quantitative descriptor of the VF waveform morphology, the scaling exponent (ScE).16–19 It is highly

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926
correlated with the duration of VF. The values of the ScE begin low and gradually increase as the duration of VF progresses. It has also been shown that the ScE can be used to predict defibrillation success in human out-of-hospital cardiac arrest.

The aim of the present study was to compare 4 different therapeutic approaches to the treatment of VF of various durations. We hypothesized that when VF is of brief and moderate duration, immediate countershock (IC) would be an effective first intervention, but that when VF is prolonged, IC would be an ineffective treatment. We hypothesized that when VF is of moderate duration, CPR before the first countershock would not be beneficial. We also hypothesized that when VF is prolonged, pretreatment with CPR and drugs would produce superior defibrillation outcomes and superior rates of return of spontaneous circulation (ROSC) and 1-hour survival compared with IC. We tested the supposition that the ScE could be used to differentiate VF that would be best treated by IC from that which would be best treated by other interventions before shocking.

Methods

The University of Pittsburgh Institutional Animal Care and Use Committee approved this investigation.

Animal Preparation

Seventy-two mixed-breed domestic swine of either sex (ranging in mass from 19.5 to 25.7 kg; Whippo Farms, Enon Valley, Pa) were prepared in a standard fashion and then randomly assigned to 9 experimental groups. We sedated the animals with intramuscular ketamine (10.0 mg/kg) and xylazine (4.0 mg/kg). We then acquired intravenous (IV) access via a peripheral ear vein. We established a surgical plane of anesthesia using a rapid IV infusion of 1.10% chloralose (40 mg/kg) and maintained this with a continuous infusion of the same (10 mg · kg⁻¹ · h⁻¹). Depth of anesthesia was verified by use of an electroencephalographic bispectral index monitoring system (BIS, Aspect Medical Systems, Inc.).

We intubated the swine orotracheally and ventilated them with room air using a volume-cycled ventilator (Harvard Apparatus). Ventilation was begun at a tidal volume of 15 to 20 mL/kg, a ventilatory rate of 12 to 16 breaths per minute, and an inspiration-to-expiration ratio of 40%. Ventilation was adjusted to maintain eucaopia (end-tidal carbon dioxide, 35 to 45 mm Hg), measured with a side-stream capnometer (LifePak 12, Medtronic Physio-Control, Inc). We measured core body temperature by placing an esophageal probe (Bi-Temp Temperature Monitor, Respiratory Supply Products, Inc) into each animal’s esophagus.

We then secured 3 surface electrodes configured to correspond to a standard lead II ECG and monitored this continuously. Electrodes were connected to a DAM-50 wide-band-pass differential amplifier, which provided a 10-fold amplification near the chest. The signal was then passed to signal-conditioning units (National Instruments, SC 2345 and SCC AI07). Here, the signal was amplified 200-fold and was passed to the PC6024E NI-DAQ board (National Instruments) in a Dell, Pentium 3-based computer.

After a surgical depth plane of anesthesia was established, we induced neuromuscular paralysis with pancuronium (4 mg initial bolus IV with additional 2 mg boluses as needed). We then placed arterial and venous introducers (9F) in the right femoral artery and vein and placed micromanometer-tipped pressure catheters (Millar Instruments) into the ascending aorta and right atrium. Arterial and venous pressures were also monitored continuously with the same data acquisition system as used to record the ECG. These data were acquired digitally at a sampling rate of 1000 points per second with a commercially available software package (Chart, v.3.5/s, ADInstruments). We analyzed an arterial blood gas as soon as arterial access was established (ABL 3, Radiometer). We repeated this any time ventilator settings were changed and just before the induction of VF to establish physiological stability of the preparation. We induced VF by transthoracically delivering a 3-second, 60-Hz, 100-mA AC current.

ScE Calculation

We have previously described the methodology used to calculate the ScE in detail. The ScE estimates the fractal self-similarity dimension of the VF signal and is calculated by modification of a method developed by Higuchi. In brief, the ScE corresponds conceptually to the morphology of the VF waveform. Coarse VF, of brief duration, will produce low values of the ScE (starting at 1.07 at 10 seconds). As the VF progressively deteriorates to a finer appearance over time, the ScE increases (to values on the order of 1.20 at 5 minutes and 1.40 at 12 minutes of VF). After 20 minutes of VF, the values of the ScE are in the 1.70 to 1.80 range. Asystole produces an ScE that approaches 2.0.

Experimental Groups

Once the preparation was completed, we assigned the animals to 1 of 9 experimental groups (8 animals per group) in a block-randomized fashion. All animals were shocked into VF as described above and were left untreated until the VF had reached a predetermined ScE.

The predetermined ScE values represented VF of brief (ScE = 1.10), moderate (ScE = 1.20), and prolonged (ScE = 1.30 and 1.40) duration. At each of these experimental starting points, a group was treated with IC. Thus, 4 groups had IC as their first therapeutic intervention (group identifiers of 1.10 IC, 1.20 IC, 1.30 IC, and 1.40 IC). These 4 groups were treated with up to 3 consecutive counter-shocks, according to whether the postshock ECG rhythm remained VF, before other therapies were begun. One of the groups whose ScE starting value was 1.20 was first treated with 3 minutes of CPR before the first countershock (group identifier of 1.20 CPR). Two of the prolonged-VF groups, one at an ScE value of 1.3 and the other at a value of 1.40, were first treated with 3 minutes of CPR, followed by the administration of a study drug cocktail (40 U vasopressin, 0.10 mg/kg epinephrine, and 1.0 mg propranolol) and 2 additional minutes of CPR before the first countershock (group identifiers of 1.30 CPR-D and 1.40 CPR-D). Thus, these groups had a 5-minute delay from the time they reached the ScE starting point until they received their first countershock. The 2 other prolonged-VF groups were treated with immediate administration of the same drug cocktail together with 3 minutes of CPR before the first countershock (group identifiers of 1.30 Drugs+ICP and 1.40 Drugs+CP). These 2 groups had a 3-minute delay until the first countershock. The timing and initial therapeutic interventions are shown in Figure 1. Once the first countershock was given, standardized care was provided for all experimental groups. The standardized interventions and post-ROSC care are shown in Figure 2.

To ensure the fairest possible comparisons, and in an attempt to isolate the effects of the shock-first approach, we gave the 3-drug cocktail to animals in the IC and 1.20 CPR groups starting at 2 minutes after the last failed countershock as CPR continued.

All countershocks were given at a fixed dose of energy (150 J) and with an impedance-compensating, truncated exponential biphasic defibrillation waveform (LifePak 12, Medtronic Physio-Control). We standardized CPR in all groups by use of an oxygen-driven mechanical resuscitation device (Thumper, Michigan Instruments).

Any animal in which a pulse was not restored and maintained had resuscitative interventions continued for 20 minutes beyond the start of the first experimental intervention. Any animal surviving for 1 hour was euthanized with a rapid IV injection of 40 mEq of KCl. Thus, the experimental end points were either 1-hour survival after attaining ROSC or 20 minutes of failed resuscitation beginning from the time the target ScE had been reached.

Countershock Outcomes

The primary dependent variable in this experiment was the outcome of the first countershock. We classified these outcomes as being either successful or unsuccessful. We defined a successful shock as...
one that resulted in either ROSC (defined as an organized ECG with an arterial systolic pressure of ≥80 mm Hg sustained for ≥1 minute continuously) or restoration of organized electrical activity (PEA). We defined unsuccessful shocks as those in which VF was not terminated (ie, postshock rhythm remains VF) or the ECG rhythm changed to asystole. Rhythm classification was performed immediately after the amplifier desaturated after the countershock, which takes ~5 seconds. We also determined the time from the beginning of the resuscitation (defined as the time the animals reached the ScE starting point) to the time the first sustained ROSC was established. Finally, we recorded the proportions of successful first shocks (which included shocks 1 to 3 before other interventions) and the proportions of animals attaining ROSC and 1-hour survival.

### Statistical Analyses

We calculated descriptive statistics (reported as mean and SD) for all baseline characteristics. Baseline characteristics were compared by ANOVA. We compared dichotomous variables with 2-tailed Fisher’s exact tests and χ². We constructed Kaplan-Meier survival curves to compare the times from the start of the resuscitation to establishment of ROSC between groups. We censored all animals that did not achieve ROSC after 20 minutes of resuscitative efforts. To account for the relatively small sample sizes, we formally compared times to ROSC using the Peto-Peto test. A per-comparison probability value of 0.05 was considered significant for all comparative statistics. To minimize the number of animals used in this study, we made the a priori decision to perform interim survival analyses when 8, 12, and 16 animals per group were successfully randomized. Because of the large number of groups in this series, we also made the a priori decision to terminate the study if the survival analyses comparing the prolonged-VF groups attained statistical significance. We performed statistical analyses using StatExact Version 4.0.1 (Cytel Software Corporation) and Stata version 7.0 (Stata Corp).

### Results

The baseline characteristics (weight, sex distribution, temperature, end-tidal CO₂, arterial blood gases, and systolic and diastolic blood pressures) were mathematically similar for all groups. The times required for the VF signal to reach the target ScE value, the duration of VF until delivery of the first countershock, and the average number of shocks delivered are summarized in the Table.

### Times and Numbers of Countershocks

<table>
<thead>
<tr>
<th>Group</th>
<th>Time to Target ScE</th>
<th>Time to First Countershock</th>
<th>Total No. of Countershocks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 IC</td>
<td>1.20 (1:11)</td>
<td>1.23 (1:15)</td>
<td>1.1 (0.13)</td>
</tr>
<tr>
<td>1.2 IC</td>
<td>4.50 (0:29)</td>
<td>4.52 (0:33)</td>
<td>2.5 (1.3)</td>
</tr>
<tr>
<td>1.2 CPR</td>
<td>4.42 (1:49)</td>
<td>7.45 (1:55)</td>
<td>3.6 (2.4)</td>
</tr>
<tr>
<td>1.3 IC</td>
<td>9.36 (3:08)</td>
<td>9.41 (3:13)</td>
<td>9.4 (5.5)</td>
</tr>
<tr>
<td>1.3 CPR-D</td>
<td>10.09 (3:05)</td>
<td>15.08 (3:05)</td>
<td>4.3 (3.1)</td>
</tr>
<tr>
<td>1.3 Drugs + CPR</td>
<td>10.33 (3:12)</td>
<td>13.32 (3:12)</td>
<td>2.4 (2.4)</td>
</tr>
<tr>
<td>1.4 IC</td>
<td>13.10 (2:24)</td>
<td>13.10 (2:25)</td>
<td>6.9 (2.8)</td>
</tr>
<tr>
<td>1.4 CPR-D</td>
<td>12.17 (3:57)</td>
<td>17.17 (3:57)</td>
<td>5.3 (4.0)</td>
</tr>
<tr>
<td>1.4 Drugs + CPR</td>
<td>11.40 (1:56)</td>
<td>14.42 (1:56)</td>
<td>4.4 (1.9)</td>
</tr>
</tbody>
</table>

Times are reported as mean (SD) in minutes and seconds. Shocks are reported as mean (SD).
attained at any time during the resuscitation, and numbers of
animals surviving to the 1-hour end point are presented in
Figure 3. Results of the Kaplan-Meier survival analyses are
presented in Figures 4 through 6.

In the IC groups, the proportion of first-shock success de-
creased as VF became more prolonged, with 88% (7 of 8) in
the 1.10 IC group, to 63% (5 of 8) in the 1.20 IC group, to 0% (0 of
16) in the 1.30 IC and 1.40 IC groups. In the groups in which VF
was prolonged, no animal in the 1.30 IC group, 0 of 8 (0%) had
successful first shocks compared with 7 of 8 (88%) successful
first shocks in both the 1.30 CPR-D and 1.30 Drugs+CPR
groups ($\chi^2=16.8, 2 \text{ df}, P=0.0002$). No animal in the 1.40 IC
group (0 of 8, 0%) had successful first shocks, whereas 4 of 8
(50%) in the 1.4 CPR-D group and 5 of 8 (63%) in the 1.4
Drugs+CPR group did ($\chi^2=7.47, 2 \text{ df}, P=0.024$).

When VF was brief to moderate, ROSC on the first 1 to 3
shocks occurred in 6 of 8 (75%) of the 1.10 IC animals, 0 of
8 (0%) of the 1.20 IC animals, and 2 of 8 (25%) of the 1.20
CPR animals. The 5 successful first shocks in the 1.20 IC
group were all PEA that later responded to CPR and drug
administration. When VF was prolonged (1.30 and 1.40), no
animals that had IC first (0 of 16) attained ROSC on the first
1 to 3 shocks, compared with 11 of 16 (69%) of the CPR-D
animals ($P=0.001$) and 12 of 16 (75%) of the Drugs+CPR
animals ($P=0.001$).
ROSC at any time during the resuscitation occurred in 8 of 8 (100%) of both the 1.10 IC and 1.20 IC groups and 5 of 8 (63%) of the 1.20 CPR group. When VF was prolonged, ROSC occurred in 7 of 8 (88%) of both the 1.3 CPR-D and Drugs+ICP groups, and 8 of 10 (100%) of both the 1.3 IC group and in 7 of 8 (88%) of both the 1.3 CPR-D and Drugs+ICP groups (χ²=4.2, 2 df, P=0.12). Sustained ROSC occurred in 5 of 8 (63%) of the 1.3 IC group and in 7 of 8 (88%) of the 1.4 Drugs+CPR group, and 7 of 8 (88%) of the 1.4 Drugs+CPR group (χ²=4.26, 2 df, P=0.11).

One-hour survival occurred in 8 of 8 (100%) of both the 1.10 IC and 1.20 IC groups and 5 of 8 (63%) of the 1.20 CPR group. One-hour survival was achieved in 4 of 8 (50%) of the 1.3 IC group and in 7 of 8 (88%) of both the 1.3 CPR-D and Drugs+CPR groups (χ²=4.0, 2 df, P=0.14). One-hour survival was maintained in 2 of 8 (25%) of the 1.4 IC group, 3 of 8 (38%) of the 1.4 CPR-D group, and 5 of 8 (63%) of the 1.4 Drugs+CPR group (χ²=2.4, 2 df, P=0.30).

When VF was of brief (ScE of 1.10) to moderate (ScE of 1.20) duration, Kaplan-Meier survival curves show that IC produced ROSC sooner than when there was a delay to the first shock to perform CPR (P=0.008). Contrary to current therapy, Kaplan-Meier survival analyses indicated that when the ScE was 1.30 at the start of resuscitation, IC actually delayed the time to achieve ROSC compared with the 2 other treatment groups (P=0.0006). This was also true when Kaplan-Meier curves were plotted for the 1.4 groups, again indicating that IC delayed ROSC compared with the CPR-D and Drugs+CPR groups (P=0.005).

Discussion

The likelihood of success for a countershock is highly dependent on the degree of organization of the VF in the ECG signal and the duration of VF. This level of organization can be quantified by the ScE, which is also highly correlated with the duration of VF and is predictive of shock outcome. We have demonstrated here that when VF is of brief to moderate duration (as indicated by an ScE of 1.10 and 1.20), IC is effective in successfully terminating VF. We did not observe an added benefit to preceding the first shock with CPR when VF was of moderate duration. This finding is consistent with previous findings in swine and humans. The ScE may be useful in differentiating which patients may be best treated with IC from those who would benefit from having some CPR first, ie, an ScE of 1.20 would indicate immediate shock.

The most important finding of the present study is that when VF is prolonged (as indicated by an ScE of 1.30 and 1.40), IC was the least effective of the 3 therapeutic strategies studied. In fact, the Kaplan-Meier survival analyses make it clear that even when 3-minute and 5-minute delays to the first countershock are built into the resuscitation scheme, ROSC is still achieved earlier than when the first intervention is a defibrillation attempt. No animal in either of the 2 prolonged-VF IC groups had ROSC after any of the initial 1, 2, or 3 countershocks. These failed countershocks made the animals more difficult to resuscitate, as evidenced by the more prolonged resuscitation times, increased number of shocks, and fewer animals surviving 1 hour. Failed shocks in prolonged human VF often produce PEA or asystole, and Niemann et al have shown that patients who are shocked into PEA/asystole are less likely to survive to hospital discharge than patients whose initial ECG rhythm is PEA or asystole. Because being shocked into asystole decreases a patient’s odds of survival, rescue shocks that have a high likelihood of failing should be avoided.

There are several important limitations to our study. First, we used immature swine that we presumed to be free of cardiovascular disease. Obviously, the results seen in swine have not always translated to similar benefits in humans. However, we are encouraged by the fact that when standardized ACLS care is used in this model, very human-like results are produced. Another limitation lies in the fact that we induced VF suddenly with an AC current and used the ScE as a surrogate marker for VF duration. Thus, we were unable to examine whether the capability of the ScE to guide therapy would be affected by changes other than duration of VF (for example, if the VF were induced or accompanied by an ischemic insult). Other studies suggested by the present findings could include exploration into whether pharmacological manipulation of the ScE would alter the predictive capabilities of the ECG waveform.
Conclusions
VF of brief to moderate duration, as indicated by an ScE of \( \leq 1.20 \), is effectively treated by IC. Delaying the first countershock to perform CPR when VF can be identified as of brief or moderate duration may not be beneficial. When VF is prolonged, as indicated by an ScE of \( \geq 1.3 \), IC was the least effective of the treatment strategies studied and significantly delayed the eventual ROSC in animals achieving pulses. The ScE may provide useful information in deciding which initial treatment to use in the treatment of VF.

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References
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