Utility of the Ventricular Fibrillation Waveform to Predict a Return of Spontaneous Circulation and Distinguish Acute From Post Myocardial Infarction or Normal Swine in Ventricular Fibrillation Cardiac Arrest

Julia H. Indik, MD, PhD; Daniel Allen, BS; Michael Gura, MS; Christian Dameff, MS; Ronald W. Hilwig, DVM, MS, PhD; Karl B. Kern, MD

Background—In cardiac arrest, the ventricular fibrillation (VF) waveform, particularly amplitude spectral area (AMSA) and slope, predicts the return of spontaneous circulation (ROSC), but it is unknown whether the predictive utility differs in an acute myocardial infarction (MI), prior MI, or normal myocardium and if the waveform can distinguish the underlying myocardial state. We hypothesized that in a swine model of VF cardiac arrest, AMSA and slope predict ROSC after a shock independent of substrate and distinguish an acute from nonacute MI state.

Methods and Results—MI was induced by occlusion of the left anterior descending artery. Post MI swine recovered for a 2-week period before induction of VF. VF was untreated for 8 minutes in 10 acute MI, 10 post MI, and 10 control swine. AMSA and slope predicted ROSC after a shock independent of myocardial state. For AMSA >31 mV-Hz, the odds ratio was 62 (P≤0.001) compared with AMSA <19 mV Hertz. For slope >3.1 mV/s, odds ratio was 52 (P≤0.001) compared with slope <1.8 mV/s. With chest compressions, AMSA and slope were significantly lower for acute MI swine compared with control swine, whereas in post MI swine the waveform characteristics were similar to control swine. In particular, for an AMSA >33.5 mV-Hz, the sensitivity to identify an acute from nonacute (control or post MI) state was 83%.

Conclusions—In a swine model of VF cardiac arrest, AMSA and slope predict ROSC independent of myocardial substrate. Furthermore, with chest compressions, the VF waveform evolves differently and may offer a means to distinguish an acute MI. (Circ Arrhythm Electrophysiol. 2011;4:337-343.)

Key Words: cardiopulmonary resuscitation ■ myocardial infarction ■ heart arrest ■ ventricular fibrillation ■ defibrillation

Out-of-hospital cardiac arrest is estimated at 295,000 cases per year in the United States, with 23% caused by ventricular fibrillation (VF) or other initially shockable rhythm.1,2 In a study of patients ages 50 to 79 years,3 two-thirds of cardiac arrest patients had preexisting heart disease, with one-third having a prior myocardial infarction (MI). In an autopsy study of sudden cardiac death victims, an active coronary lesion (active thrombus and/or disrupted plaque) was seen in 57%, with acute MI identified by the presence of coagulation necrosis of myocytes, present in 21%4 and healed, nonacute MI present in 41%. Patients under the age of 50 years have also been demonstrated to have extensive coronary artery disease on autopsy.5 Furthermore, acute MI with acute coronary occlusion is present in survivors but may not be evident on a postresuscitation ECG,6,7 which has prompted the recommendation that survivors of cardiac arrest be immediately taken to the cardiac catheterization laboratory.8

Clinical Perspective on p 343

It is unclear if the optimal timing of defibrillation and chest compressions is altered in the presence of an acute MI or preexisting coronary disease or heart failure. We have previously shown in a swine study that survival with good neurological outcome is improved by delivering defibrillation first, before the onset of chest compressions in acute myocardial ischemia9 but not in normal myocardium.10 For VF of short duration, <4 minutes, the myocardium is physiologically regarded as being in the “electric phase,” in which defibrillation is highly likely to restore a perfusing rhythm and therefore the optimal intervention is immediate shock.11 In a swine study of VF of short duration, the optimal intervention was defibrillation in either an acute MI or normal myocardium.12 When untreated VF is prolonged beyond 4 minutes and up to about 10 minutes, the myocardium is described as being in the circulatory phase,11 and in this phase the characteristics of the VF waveform, including parameters based on frequency and amplitude such as amplitude spectral area (AMSA) and slope, have shown good promise as predictors for achieving a return of spontaneous circulation (ROSC) in human and animal studies.13-21 However, it is unclear whether the predictive ability of AMSA and slope to achieve ROSC is affected by the underlying myocardial substrate, such as the...
presence of an acute MI, a prior MI without acute ischemia, or normal myocardium. Furthermore, survival of cardiac arrest hinges on not only care during resuscitation but also care in the postresuscitation period, including emergent cardiac catheterization for acute MI. Because the postresuscitation ECG may not reflect an acute coronary occlusion, other means to identify these patients are needed, in particular if immediate coronary catheterization resources are not available. The VF waveform itself may also help guide this assessment and the triage of patients to emergent cardiac catheterization.

The present study examines the effect of acute or prior MI on the prediction of ROSC based on waveform and whether the waveform can itself reflect the underlying myocardial substrate. In a swine study of VF cardiac arrest we investigate 3 underlying myocardial substrates, an acute MI with acute occlusion of the left anterior descending (LAD) artery, a prior, nonacute, MI, and normal noninfarcted myocardium. We hypothesized that regardless of underlying myocardial substrate that AMSA and slope would predict ROSC and that the evolution of AMSA and slope during resuscitation would distinguish an acute MI from a nonacute MI state.

Methods

Experimental protocols follow the guidelines of the American Physiological Society and were approved by the University of Arizona Institutional Animal Care and Use Committee. Anesthesia and instrumentation were performed by a protocol that is standard in our laboratory. In brief, anesthesia was induced using 5% isoflurane in 100% oxygen delivered by a nose cone, followed by endotracheal intubation. Mechanical ventilation was used a mixture of room air and in 100% oxygen delivered by a nose cone, followed by endotracheal intubation. Mechanical ventilation was used at a rate of 12 respirations per minute and tidal volume of 15 mL/kg, as used before the induction of VF. Mechanical ventilation was assumed at a rate of 12 respirations per minute and tidal volume of 15 mL/kg, as used before the induction of VF. Manual chest compressions were provided at a metronome-guided rate of 100 compressions per minute if a perfusing rhythm was not immediately obtained after the shock, and ventilation with oxygen was commenced at a rate of 10/min. ROSC was defined as an unassisted pulse with a peak systolic aortic pressure >50 mm Hg and a pulse pressure of at least 20 mm Hg, lasting for at least 1 minute. After 2 minutes of chest compressions, rhythm was reanalyzed with a ten-second “hands-off” interval to allow for an artifact-free period for the off-line data analysis of the VF waveform, described below. Two minutes of uninterrupted chest compressions followed each defibrillation shock and was continued if there was pulseless electrical activity. Resuscitation was continued until ROSC was obtained, or efforts were terminated if ROSC was not achieved by 25 minutes. ROSC was assigned to a particular defibrillation shock if it occurred by the end of the 2-minute postshock chest compression interval. Resuscitation time was defined as time from the first defibrillation shock. All shocks were of 150 J. Epinephrine (0.02 mg/kg) was administered intravenously immediately after the first shock if a perfusing rhythm was not obtained and repeated every 3 minutes until ROSC was obtained, for a total of 3 doses.

Data Analysis

The VF signal immediately preceding each defibrillation shock, taken from the 10-second hands-off interval, was analyzed in an 8.2-second interval to determine AMSA and slope, as previously described. AMSA was calculated as the summed product of the VF signal immediately preceding each defibrillation shock. Slope can be thought of as reflecting the product of median frequency and overall amplitude. Thus AMSA and slope measure very similar information from the VF waveform, one from the frequency domain (AMSA) and one from the time domain (slope). 

Statistics

Data are presented as mean±SD. A Kruskal-Wallis rank test was performed for comparisons of baseline weight and hemodynamics among the 3 groups of swine.

Logistic regression was performed to determine factors that predicted ROSC, and factors tested were AMSA, slope, MI state (acute, post MI, and control), and resuscitation time, starting with the first shock. In multivariate analyses, AMSA and slope were not tested together because these parameters are highly colinear because they measure very similar information from the VF waveform. In this investigation, the correlation coefficient between AMSA and slope was 0.95. Analysis of factors for the prediction of ROSC included all shocks. The cut-points for slope and AMSA were based on tertiles, which were prespecified. This choice was made to allow for the potential nonlinearity in its association with the outcome of ROSC. The number of bins (tertiles) was chosen so that there would be an ample (of order at least 20) data points within each bin. Logistic regression was also used to assess whether AMSA or slope could predict an acute MI versus nonacute (control or post MI) status. Differences in AMSA and slope among the 3 groups of swine (control, acute MI, and post MI), were assessed by linear regression. Generalized linear mixed models were used to account for correlations within an individual animal due to multiple shocks (ie, multiple measurements of the waveform), using random effects. A receiver operator characteristic (ROC) curve analysis was performed to determine sensitivity and specificity for AMSA and slope to predict
Results

A total of 30 swine were studied (10 acute MI, 10 post MI, and 10 control). Baseline characteristics (weight, right atrial pressure, heart rate, systolic aortic pressure, and cardiac output) were similar in all groups of swine before the induction of VF (Table 1).

VF occurred spontaneously in 3 acute MI swine and was induced electrically in the remaining 7, with VF induced in 1 animal at 6 minutes after plug placement because of hypotension. A total of 33 shocks were delivered to acute MI swine, 25 shocks to post MI swine, and 18 shocks to control swine. All control swine achieved ROSC by the second shock, and 2 control swine achieved ROSC with the first shock alone. Two acute MI swine did not achieve ROSC. VF recurred after ROSC had been initially achieved in 2 acute MI swine: 1 at 27 minutes post ROSC, and another animal at 15 minutes and again at 25 minutes. One acute MI animal achieved ROSC within 2 minutes of the first shock. All post MI swine achieved ROSC by the third shock. One post MI animal refibrillated after first achieving ROSC but achieved ROSC again after an additional 10 minutes of resuscitation.

The time course of the waveform characteristics during resuscitation including outcome of each shock for each animal in each group is shown in Figure 1 for AMSA and Figure 2 for slope. AMSA and slope were predictive of ROSC after a shock (Table 2). The highest tertile of AMSA (>31 mV-Hz) had an odds ratio for achieving ROSC of 62 (95% confidence interval [CI], 7.0 to 550; \( P<0.001 \)) compared with the lowest tertile (<19 mV-Hz), with the middle tertile (19 to 31 mV-Hz) having an odds ratio of 10 (95% CI, 1.2 to 89; \( P=0.04 \)). The area under the ROC curve was 0.88. For an AMSA of 32 mV-Hz, the sensitivity to predict ROSC was 68%, with a specificity of 88%, positive predictive value of 76%, and negative predictive value of 82%. The highest tertile of slope (>3.1 mV/s) had an odds ratio for achieving ROSC of 52 (95% CI, 5.9 to 450; \( P<0.001 \)) compared with the lowest tertile (slope <1.8 mV/s). The middle tertile of slope (from 1.8 to 3.1 mV/s) had an odds ratio for achieving ROSC of 12 (95% CI, 1.4 to 105; \( P=0.02 \)) compared with the lowest tertile of slope. An ROC analysis gave an area under the curve of 0.89, and for a slope of 3.1 mV/s, the sensitivity to predict ROSC was 68%, with a specificity of 83%, positive predictive value of 70%, and negative predictive value of 82%.

Resuscitation time was not predictive of ROSC (\( P=NS \)). MI status was predictive for achieving ROSC. Acute MI swine had an odds ratio of 0.26 (95% CI, 0.08 to 0.87; \( P=0.03 \)) compared with control swine, and post MI swine
had an odds ratio of 0.53 (95% CI, 0.16 to 1.8; \( P = 0.009 \)) for achieving ROSC compared with control swine. In a multivariable analysis of MI status compared with slope, the presence of acute MI remained a weak but significant independent predictor (\( P = 0.02 \)). The highest tertile of slope was highly significant as an independent predictor of ROSC, with \( P < 0.001 \), and the middle tertile of slope, with \( P = 0.009 \). For MI status compared with AMSA, the presence of an acute MI also remained a weak but significant independent predictor (\( P = 0.04 \)). The highest tertile of AMSA was highly significant as an independent predictor of ROSC, with \( P < 0.001 \), with the middle tertile significant, with \( P = 0.015 \).

Waveform characteristics measured before the first shock were similar between acute MI, post MI swine, and control swine (Figure 3). Before the first shock, acute MI swine had an AMSA of 15.7 ± 7.3 mV-Hz compared with 13.5 ± 2.9 mV-Hz for post MI swine and 15.1 ± 6.4 mV-Hz for control swine (\( P = 0.04 \)). Before the first shock, slope was 1.5 ± 0.8 mV/s for acute MI swine compared with 1.2 ± 0.4 for post MI swine and 1.5 ± 0.7 mV/s for control swine (\( P = 0.002 \)). However, after the initiation of chest compressions, AMSA was larger for post MI and control compared with acute MI animals (Figure 3). Before second or higher shocks, AMSA was significantly lower for acute MI swine, 28 ± 9 mV-Hz, compared with control swine, 45 ± 9 mV-Hz (\( P = 0.001 \)), whereas AMSA in post MI swine, 38 ± 9 mV-Hz, was similar to control swine (\( P = 0.18 \) for post MI compared with control). Before second and higher shocks, slope was 2.8 ± 1.0 mV/s for acute MI swine compared with 4.4 ± 1.1 mV/s for control swine (\( P = 0.002 \) for acute MI compared with control), whereas for post MI swine, slope was 3.5 ± 0.9 mV/s (\( P = 0.06 \) for post MI compared with control).

Waveform characteristics were also predictive of whether an acute MI was present compared with a nonacute MI (post MI or control) state, after the initiation of resuscitation (measured before second or later shocks). AMSA was predictive of whether an acute MI was present (\( P = 0.001 \)), with an area under the ROC curve of 0.85. For AMSA \( > 33.5 \) mV-Hz, the sensitivity to identify an acute MI state (fraction of shocks from acute MI swine correctly classified as coming from acute MI swine) was 83%, with a specificity (fraction of shocks from nonacute MI swine that are correctly classified as coming from nonacute MI swine) of 78%, with a positive predictive value of 79% and negative predictive value of 82%. Slope was also predictive for the presence of an acute MI versus a nonacute MI (control or post MI) state, \( P = 0.006 \), with area under the ROC of 0.75. For slope \( > 3.3 \) mV/s, the sensitivity to identify an acute MI state

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>( P ) Value</th>
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<td>Resuscitation time</td>
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*Compared with lowest tertile.
†Compared with control swine.

Table 2. Univariate Logistic Regression Analysis for the Prediction of ROSC

Figure 2. Evolution of slope over resuscitation time for control (A), acute MI (B), and post MI (C) swine. The outcome of each shock for each animal (\( n = 10 \) for each group shown as a connecting line for each animal) is shown by type of marker: open circle indicates VF; black filled circle, ROSC; gray triangle, pulseless electric activity followed by refibrillation; and black circle with inner white dot, transient perfusing rhythm without ROSC followed by refibrillation.
was 65%, with a specificity of 65%, positive predictive value of 65%, and negative predictive value of 65%.

Discussion
The present investigation finds that in a swine model of VF cardiac arrest, AMSA and slope are predictive of achieving ROSC regardless of myocardial state, but the waveform characteristics evolve differently in acute MI once resuscitation (ie, chest compressions) is commenced. In untreated VF, waveform characteristics were similar in acute MI, post MI, and control swine. However, after the initiation of resuscitation, namely chest compressions, AMSA and slope were significantly lower in acute MI swine, and both AMSA and slope could distinguish an acute MI status. For AMSA (33.5 mV-Hz, the sensitivity to correctly identify an acute MI was 83%, and for a slope (3.3 mV/s, the sensitivity to identify an acute MI was 65%.

Differences in the evolution of the VF waveform according to myocardial state may be related to alterations in the underlying electrophysiological substrate. Optical mapping studies have demonstrated that VF is maintained by the formation of rotors that propagate wave fronts that fragment in surrounding tissues creating successive wavelets, referred to as fibrillatory conduction. Alterations in sodium and potassium membrane currents, as can occur in ischemic and nonischemic myocardium, can modify how rotors form and how fibrillatory conduction proceeds. Dominant frequency and number of singularity points have been studied by optical mapping in isolated hearts and shown to be slower in ischemia and heart failure.

Characteristics of the VF waveform have been studied for their ability to predict ROSC after a shock in both human and animal studies, but with variable reported predictive power. As a result, it has remained unclear if waveform parameters are sufficiently useful as a threshold to decide whether to deliver a shock or continue chest compressions. There is further uncertainty as to whether different thresholds may apply, based on the underlying myocardial substrate.

We have previously demonstrated in a swine model of VF arrest that AMSA and slope predict ROSC in second and later shocks regardless of the presence or absence of an acute MI, compared with normal swine. A more clinically relevant comparison is the inclusion of preexisting coronary disease with prior MI, which is modeled in the present study. We find that in a multivariable analysis of VF waveform and myocardial status that the VF waveform, AMSA, or slope remains highly predictive of achieving ROSC, whereas myocardial status (acute MI versus control) is weakly predictive of the outcome of a shock. The presence of a post MI status compared with control was not predictive of ROSC after a shock. Our work implies that the VF waveform is the most important factor to account for in an algorithm to decide when to shock.

Nonetheless, it has been demonstrated in human and swine studies that VF waveform parameters are affected by myocardial substrate and by chest compressions. In swine studies during untreated VF, VF frequency characteristics had an altered time course in different myocardial substrates (acute MI, post MI, and normal myocardium), whereas AMSA and slope were similar among these substrates. Treatment with chest compressions, however, does alter the VF waveform, as studied in normal swine and human studies. After the initiation of chest compressions in swine in which VF was induced by balloon occlusion of the LAD, animals with the deflated catheter remaining in place in the LAD had a lower value of AMSA compared with animals in which the balloon catheter was withdrawn.
A differential effect of chest compressions (or other resuscitation interventions), depending on myocardial status, may explain the results reported from an analysis of cardiac arrest victims in Norway, where median slope and AMSA were depressed in patients with an acute MI compared with nonacute MI states, although in that study there was considerable overlap in waveform between patients with and those without an acute MI. We find in this swine study that although AMSA and slope are similar in untreated VF in control, acute, and post MI, they evolve differently once resuscitation, in particular, the delivery of high-quality chest compressions, is commenced. Although overlap in the VF waveform remains between myocardial substrates (Figure 3), we have found that after the initiation of resuscitation, an AMSA >33.5 mV-Hz has a sensitivity of 83% to detect an acute MI from nonacute (control or post MI) state and for slope >3.1 mV/s a sensitivity of 65%. This work would imply that the VF waveform responds differently to well-performed resuscitation interventions according to the underlying myocardial state.

The present study has implications for optimizing postresuscitation care. Both acute and prior nonacute MI are important etiologies for cardiac arrest, as identified both in autopsy data and survivors. In particular, the postresuscitation ECG may not indicate the presence of an acute MI from an acute coronary stenosis. In 435 patients resuscitated from VF cardiac arrest who underwent immediate coronary angiography from the PROCAT registry, a significant coronary lesion was identified in 58% of patients who did not show ST-segment elevation on a postresuscitation ECG and that successful coronary intervention improved hospital survival regardless of the findings on a postresuscitation ECG. In that registry, the most frequent culprit lesion was in the LAD artery. Patients with an acute MI resuscitated from VF arrest are recommended to be taken immediately to the cardiac catheterization laboratory. If laboratory facilities are not immediately available, the patient may require transport to a facility with cardiac catheterization availability. The present study has shown that waveform characteristics respond differently to chest compressions, based on whether an acute or nonacute MI state is present, and suggests that it may be possible to identify patients who are not having an acute MI and who would otherwise not require emergent cardiac catheterization. Along with other markers of acute MI that may or may not be present, such as substantially elevated cardiac enzymes or wall motion abnormalities, as well as the postresuscitation ECG, the waveform evolution during resuscitation may be very useful adjunctive information for the triage of patients to the cardiac catheterization laboratory.

**Limitations**

There are limitations inherent in animal studies and their applicability to human cardiac arrest. In particular, resuscitation in this model is performed with high-quality chest compressions with minimal interruptions, whereas in human cardiac arrest, chest compressions are performed by lay personnel only 20% to 40% of the time or with a shallow depth and long interruptions for other interventions such as endotracheal intubation by emergency personnel, and for which survival is substantially improved if such interruptions in chest compressions are avoided. Therefore, the usefulness of examining the change in the VF waveform to predict myocardial state in human arrest may be lost if chest compressions are not performed well. In the present study, epinephrine is given within the first minute of the onset of chest compressions, and we have not addressed which of these resuscitation interventions, compressions or epinephrine, are of greatest importance for the differential changes in VF waveform, based on myocardial state. Further animal and human studies are needed to determine if changes in VF waveform can predict myocardial state in a prospective fashion and whether decisions to shock or continue compressions, based on the VF waveform, can result in an earlier restoration of a perfusion rhythm and improved survival.

We also induced VF in acute MI animals electrically if it did not occur spontaneously by 15 minutes after placement of the plug in the LAD to avoid large variation in total ischemic time. One study has suggested that resuscitation outcome, including number of shocks and time to achieve ROSC, is different in acute MI animals that achieve VF spontaneously versus electrically. In our study, 3 animals in the acute MI group achieved VF spontaneously within 15 minutes of ischemic time, and we cannot assess whether the method of achieving VF is a factor in either resuscitation outcome or change in VF waveform.

**Conclusions**

In a swine model of cardiac arrest caused by VF, we find that AMSA and slope predict the ROSC after the initiation of resuscitation interventions including chest compressions, regardless of the presence of an acute or prior MI or normal myocardium. AMSA and slope evolve differently in these myocardial substrates and may offer a method to distinguish an acute MI.

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**Disclosures**

None.

**References**


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**CLINICAL PERSPECTIVE**

Ventricular fibrillation and pulseless ventricular tachycardia are the initial rhythm in about one-quarter of cardiac arrests. Although the performance of effective chest compressions with minimal to no interruptions is well known to be a critical component in resuscitation, the optimal duration of chest compressions before defibrillation shocks is unclear. It is unknown if the timing of shocks and chest compressions should be the same for patients with acute myocardial infarction (MI) as those with a history of MI, or even those without any cardiovascular disease. Furthermore, it is recognized that patients with acute MI resuscitated from cardiac arrest caused by ventricular fibrillation may not show ST-segment elevation, complicating decisions of whether to send patients for emergent cardiac catheterization once a perfusing rhythm has been restored. This investigation explores the evolution of the ventricular fibrillation waveform parameters of amplitude spectral area and slope in acute MI, post MI, and control swine. We find that amplitude spectral area and slope predict the restoration of a perfusing rhythm after a shock independent of the underlying myocardium, and furthermore with well-performed chest compressions, amplitude spectral area at a threshold of 33.5 mV-Hz showed a sensitivity of 83% to distinguish an acute from a nonacute MI state.
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