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Optimizing the Timing of Defibrillation: The Role of Ventricular Fibrillation Waveform Analysis During Cardiopulmonary Resuscitation

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KEYWORDS

- Cardiac arrest Cardiopulmonary resuscitation
- Timing of defibrillation Ventricular fibrillation
- · Waveform analysis

Despite important advances in prevention, cardiac arrest (CA) is still a leading cause of death in many parts of the world. The principles of cardiopulmonary resuscitation (CPR) have remained fundamentally unchanged during the past 40 years. Successful resuscitation is strongly associated with several specific interventions, including early bystander CPR,^{1,2} earlier defibrillation, high quality of chest compressions,^{3,4} and immediate postresuscitation care.⁵

Ventricular fibrillation (VF), which is characterized as rapid, disorganized contractions of the heart with complex electrocardiogram (ECG) patterns, remains the primary rhythm in many instances of CA. The only reliable method of treating VF is electrical defibrillation, which was first used in humans in 1947.⁶ For every minute that passes between collapse and defibrillation, survival rates from witnessed VF decrease 7% to 10% if no CPR is provided. Even though earlier defibrillation during CPR is greatly emphasized, it is increasingly clear that not all patients in VF benefit from being treated in the same manner, as the duration of VF is a major determinant of countershock outcome.⁷ If defibrillation is undertaken when the myocardial metabolic state is compromised, success rates are lower.^{8,9} Repetitive high-energy defibrillation can also damage the already precarious myocardium.^{9–11} For these reasons, the

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ability to gain information concerning the metabolic state of the myocardium and to optimize the timing of defibrillation would be of enormous benefit in allowing therapy to be tailored to an individual heart.

IMPORTANCE OF OPTIMIZING THE TIMING OF DEFIBRILLATION

The major determinant of successful defibrillation is the duration of VF. There is evidence that when the interval between the onset of VF and the delivery of the first shock is less than 5 minutes, an immediate electrical shock may be successful.¹² However, both animal and human studies demonstrate that when the duration of untreated VF exceeds 5 minutes, initial CPR with chest compression before delivery of a defibrillation attempt improves the likelihood of restoration of spontaneous circulation (ROSC).^{13,14} However, the duration of collapse may be difficult to access, especially in out-of-hospital patients. Analysis of the VF waveform may provide a measure of VF duration. However, more direct prognostic information that could be used to determine whether a patient should receive immediate attempted defibrillation or alternate therapy such as CPR or medications would be advantageous.

The evidence is clear that the quality of chest compressions is another major determinant of successful resuscitation. Successful shocks are associated with shorter preshock pause duration and higher mean chest compression depth in the 30 seconds preceding the preshock pause.¹⁵ Established predictors of good-quality CPR therefore may be used to optimize the timing of defibrillation by predicting the success of defibrillation and thereby successful resuscitation.

On the other hand, more than 50% of patients initially resuscitated from CA subsequently die before leaving the hospital, and the majority of these deaths are due to impaired myocardial function.^{16–18} The severity of postresuscitation myocardial dysfunction has been recognized to be related, in part, to the magnitude of the total electrical energy delivered with defibrillation.¹⁹ Increases in the defibrillation energy are associated with decreased postresuscitation myocardial function.^{19,20} Optimizing the timing of defibrillation therefore may decrease the severity of postresuscitation myocardial dysfunction by reducing the numbers of failed or unnecessary shocks.

The development of a noninvasive and real-time monitoring during CPR that provides substantial information to the rescuers and allows for optimizing the timing of defibrillation is of great importance to prioritize interventions, chest compression or defibrillation, to minimize the interruption in CPR, to reduce the number of failed defibrillation attempts, and ultimately improve the final outcome.

OPTIMIZING THE TIMING OF DEFIBRILLATION

The optimal timing of defibrillation is determined by evaluating the probability of shock outcomes. If the attempted shock has a high likelihood of defibrillation success, an electrical shock should be prompted and delivered. Otherwise, unnecessary shocks should be avoided and alternate therapy such as CPR or medications, especially high-quality chest compression, should be utilized. For the purpose of optimizing the timing of defibrillation, invasive hemodynamic measurements, especially coronary perfusion pressure (CPP)²¹ and end-tidal CO₂ (EtCO₂), are employed.²²

Experimentally, in a porcine model of CA and CPR, CPP and EtCO₂ above the threshold level of 15 mm Hg have been the only predictors of successful resuscitation, other than the priority interventions of chest compression or defibrillation.^{22,23} Although the importance of CPP during CPR is clear, invasive measurements, including aortic and right atrial pressures, are available or feasible at the time of resuscitation in only a very small minority of patients in critical care settings. The use

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of $EtCO_2$ measurements is also not widely available, especially because of the need for endotracheal intubation.

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Consideration, with the intent to identify a better predictor of defibrillation and ROSC, has therefore been focused on the analyses of electrocardiographic features of VF waveforms, which is routinely available in the current automated external defibrillators (AEDs).^{24,25} The ECG recorded from the surface of the body represents the superposition of all of the electrical fields generated by each volume element of the heart.²⁶ Presumably, organization of the surface ECG has some relationship to the underlying organization of the myocardial electrical activity. VF waveforms change with time and exhibit predictable changes over time during CA and CPR (**Fig. 1**). VF waveform analysis therefore can be used to predict the probability of shock outcome, monitor the effectiveness of chest compression, optimize the timing of defibrillation, and ultimately guide CPR interventions.

OPTIMIZING THE TIMING OF DEFIBRILLATION BY VF WAVEFORM ANALYSIS

The search for defibrillation prediction features gained from VF waveforms dates back 20 years, and recently published review articles^{24,26} provide excellent overviews of various techniques developed for VF waveform analysis and the resulting information



Fig. 1. ECG waveform recorded during untreated VF in a porcine model of cardiac arrest. (*A*) 0 minute of VF. (*B*) 5 minutes of VF. (*C*) 10 minutes of VF and CPR. (*D*) 12 minutes of VF. (*E*) 15 minutes of VF. CPR was initiated from 10 minutes of VF and lasted for 5 minutes.

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Fig. 2. RMS, median frequency, dominant frequency, and AMSA during untreated VF and CPR in a porcine model of cardiac arrest. CPR was initiated from 10 minutes of VF and lasted for 5 minutes.

obtained. Approaches for optimizing timing of defibrillation include measures based on time domain methods; frequency domain methods, including wavelet-based transformation; nonlinear dynamics methods; and a combination of these methods. **Fig. 2** provides an example of some quantitative measures calculated from the ECG waveforms during untreated VF and CPR.

Time Domain Methods

Earlier investigations using ECG analysis focused on amplitude or voltage of the VF waveform as a predictor of the likelihood of successful defibrillation because this ECG feature reflected myocardial blood flow and energy metabolism.^{8,27,28} It has been

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observed that VF amplitude declines over time, and greater amplitudes, especially after an interval of CPR, are associated with correspondingly greater success of defibrillation.^{8,29–33}

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Peak-to-peak amplitude, which is defined as the maximum peak-to-peak VF amplitude in a given time window of the ECG signal, is associated with favorable resuscitation outcomes in out-of-hospital CA. Based on the study of Weaver and colleagues,⁸ the amplitude of the initial VF waveform was greatest in subjects with witnessed collapse and with shorter intervals from collapse to CPR or from collapse to rescue shock. VF amplitude greater than 0.2 mV is recognized as a predictor of significantly greater likelihood of resuscitation. For subjects with VF amplitude of lower than 0.2 mV, rescue shocks more often result in asystole rather than organized rhythms, and these subjects rarely survive to be admitted to the hospital or discharged alive from the hospital. Survival to discharge increases with amplitude of 0.3 to 0.4 mV and is best for a VF of 0.5 mV or greater.^{31,32}

Root-mean-squared (RMS) amplitude is defined as the square root of the mean of the squares of the summed VF amplitude. Initial RMS amplitude of VF is also associated with shock success, ROSC, and discharge from hospital in out-of-hospital CA patients.³⁴

Mean and median slope of the ECG waveform, which is defined as the mean and median of the slope of the VF waveform, is also used to predict the defibrillation success and ROSC. Gundersen and colleagues³³ showed that mean probability of ROSC decreases steadily for cases at all initial levels. Regardless of initial level there is a relative decrease in the probability of ROSC of about 23% from 3 to 27 seconds into such a pause by calculating the mean slope using a 2-second window from ECG. Neurauter and coworkers³⁵ reported a highest area of 0.86 under the receiver operating curve (ROC) by the median slope in the interval 10 to 22 Hz, resulting in a sensitivity of 95% and a specificity of 50% from 197 patients with in-hospital and out-of-hospital CA.

Frequency Domain Methods

Techniques to quantify the component frequencies of the VF signal have employed Fourier and wavelet transformation. Frequency domain features resulting from fast Fourier transform (FFT) analysis of the VF signal include dominant frequency, median frequency, fibrillation power, instantaneous mean frequency, frequency ratio, and amplitude spectrum analysis (AMSA), all of which have been shown to be capable of predicting countershock success.

Dominant frequency, which is defined as the highest power in the VF spectrum, is associated with defibrillation success, ROSC, and survival to hospital discharge in out-of-hospital CA patients.^{36–38} Median frequency, which is calculated as the mean of all of the contributing frequencies weighted by the power at each frequency, also serves as a predictor of the success of electrical defibrillation.^{29,39} Experimentally, a median frequency of more than 9.14 Hz has 100% sensitivity and 92% specificity in predicting the success of defibrillation.^{29,40} Median frequency also correlates with CPPs in animal models as well as human patients and therefore becomes the preferred ECG feature to be used as a predictor of outcome.^{27,36,40,41} Other recent investigations have confirmed that there is a relationship between median frequency, dominant frequency, and ROSC after rescue shocks.^{42–44}

A refinement of spectrum analysis termed amplitude spectrum analysis (AMSA), calculated as the sum of contributing frequencies weighted by the absolute values of the Fourier transform of the VF signal, has also proved its validity as a predictor for defibrillation outcomes and monitoring the effectiveness of chest compression in

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animal studies and the clinical scenario.^{25,45–47} Retrospective analysis of human ECG records, representing lead 2 equivalent recordings, confirmed the efficacy of this tool in predicting the likelihood that any one electrical shock would have restored a perfusing rhythm during CPR. AMSA values were significantly greater in successful defibrillation, compared to unsuccessful defibrillation. A threshold value of AMSA of 12 mVHz was able to predict the success of each defibrillation attempt with sensitivity and specificity of more than 91% in out-of-hospital CA patients.⁴⁸

Hamprecht and colleagues proposed that fibrillation power is an alternative method of ECG spectral analysis.⁴⁹ Defined as the contribution of VF to the power spectral density that eliminated the spectral contribution of artifacts from chest compression, fibrillation power was used to predict the countershock success and matched the established frequency and amplitude analysis both in animal and clinical studies.^{36,49}

Sherman⁵⁰ proposed a measurement termed frequency ratio, which is defined as the ratio of the power in the high-frequency band from 8 to 24 Hz compared to the power in the low-frequency band from 3 to 5 Hz. Frequency ratio was used to estimate VF duration in an animal study and the results showed that frequency ratio is an improved frequency-based measure of VF duration, with an ROC area of 0.91 at 5 minutes and 0.95 at 7 minutes of VF duration.

Recently, a joint time-frequency approach cited that instantaneous mean frequency (IMF) was used to interpret VF episodes in 204 segments obtained from 13 isolated human hearts. The results suggested that there were significant changes in the spatiotemporal evolution of the frequency. However, IMF has not been evaluated to predict defibrillation outcomes.⁵¹

Wavelet transform-based time-frequency methods provided a more accurate prediction of rescue shock success in human CA. Energy of the wavelet spectra achieved a sensitivity of 91% and a specificity of 52% for predicting ROSC in the out-of-hospital AED recordings.⁵² In another animal experiment, wavelet transform based methodology achieved an overall accuracy of 94% in successfully predicting shock outcomes.⁵³

Nonlinear Methods

VF is confirmed to be a complex nonlinear pattern formed by drifting spiral waves of electrical activity that travel across the myocardium and subsequently break down.^{54,55} Early debates about whether this chaotic nature can be measured^{56,57} have largely settled in favor of some chaotic features for VF.^{56,58,59} Analyses of the Hurst exponents and self-similarity dimensions correlate with the duration of VF, which have favored clinical applications.⁵⁶ Increased organization in the VF signal is associated with a greater likelihood of shock success. In AED recordings from 75 patients with out-of-hospital CA, the scaling exponent (ScE), which is an estimate of the fractal dimension, was associated with an increased probability of shock success, ROSC, and hospital discharge.³⁴ Subsequently, several new approaches have been proposed and their effectiveness proved in predicting defibrillation outcomes. One of these animal studies employed N(α) histograms analysis, which was demonstrated to be superior to mean VF frequency analysis.⁵⁹

Angular velocity (AV) is the angle by which an object turns in a certain time. Sherman and colleagues⁶⁰ measured the velocity of rotation of the position vector over time by constructing a flat, circular disk-shaped structure in a three-dimensional phase space. Using ScE and AV estimated probability density, VF of less than a 5-minute duration can be identified with 90% sensitivity on the basis of a single 5-second recording of the ECG waveform.

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Methods employing entropy measures have also been shown to provide more optimal prediction of ROSC after electrical shock in human VF recordings.⁵² Lever and coworkers⁶¹ examined the degree of organization of VF that was induced by electrical stimulation as opposed to occurring clinically due to ischemia or scarring from electrograms recorded by implanted cardiac defibrillators. Using autocorrelation, Shannon entropy, and Kolmogorov entropy, the study confirmed that induced VF had a greater organization than in spontaneous episodes. However, the clinical significance and utility of differences in VF waveform regularity is still unclear.

The logarithm of the absolute correlations (LAC) is a measure based on the roughness of VF waveform. LAC was assessed and compared with the previously published ScE on the ability to predict the duration of VF and the likelihood of ROSC under both experimental and clinical conditions.⁶² In a clinical study, the LAC measure was a better predictor of ROSC following initial defibrillation, as reflected by the area under ROC of 0.77 for LAC, compared to 0.57 for ScE.

Detrended fluctuation analysis (DFA), which determines the statistical selfaffinity of the VF waveform, is applied to characterize the raw ECG waveform at very short time scales during episodes of cardiac arrhythmias, with the aim to obtain global insight into its dynamic behavior in patients experiencing sudden death.⁶³ DFA demonstrated a significant difference between patients with successful and unsuccessful defibrillation in a clinical trial that included 155 out-ofhospital CA patients.⁶⁴

Other Methods

Combinations of measurements based on frequency, amplitude, or nonlinear methods may be more predictive of VF outcome than single measurements. For example, a linear combination of amplitude and frequency more accurately predicts ROSC and hospital discharge than either measurement alone.³² Greater overall accuracy for predicting ROSC in 84 cases of human VF was demonstrated with a combination of total amplitude, peak-to-peak amplitude, proportion of total power in the 2-Hz to 7-Hz range, frequency leakage, and slope of the signal when shocks were applied.⁶⁵ In out-of-hospital settings, Eftestøl and colleagues^{42,44} analyzed the ability of a linear combination of four spectral features—power, median frequency, spectral flatness, and dominant frequency—recorded by AEDs, from 883 rescue shock attempts on 156 patients.

Neural networks were used by Neurauter and coworkers for single-feature combinations to optimize the prediction of countershock success from 197 patients with in-hospital and out-of-hospital CA.³⁵ Using frequency band segmentation of human VF ECGs, several single predictive features with high area under ROC (>0.840) were identified. However, combining these single predictive features using neural networks did not further improve outcome prediction in human VF data.

A recent study used genetic programming to fit a relationship between multiple derived measures and defibrillation shock success.⁶⁶ It indicated that an optimal algorithm included amplitude, frequency, and nonlinear statistics. This algorithm has not been prospectively tested, however.

LIMITATIONS

Although VF waveform analysis provides satisfactory and encouraging results for optimizing the timing of defibrillation in both animal and clinical studies, considerable concerns still limit implementing currently available methods into clinical devices.

The first limitation involves the use of waveform analysis methods. Concerns preventing the widespread use of VF amplitude as a resuscitation guide include the

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fact that recording conditions, movement artifact, recording devices, body habitus, and electrode placement may alter measured VF amplitude,⁶⁷ even though frequency analysis to assess the VF waveform overcomes some of the problems encountered with amplitude analysis. For example, the technique is robust and less affected by external factors. The power spectra obtained by frequency analysis are similar in simultaneous surface and endocardial ECG leads. Many of the calculations can be performed despite ambient electrical noise or artifact from chest compressions,⁴³ although the best analyses are still conducted during pauses in chest compressions. There are, however, fundamental problems with FFT analysis. The technique is suitable only for analysis of stationary signals where the waveform does not change. Given the physiologic deterioration in the myocardium during CA, this assumption cannot be extended for VF. The major limitations of the nonlinear methods include the fact that these measurements are numerically intensive to calculate and that they tend to be very sensitive to filtering and noise. As a consequence, these measurements have not been easily incorporated into the present generation of clinical monitors.

The second limitation is that acute ischemic heart disease, such as is present in acute myocardial infarction (AMI) alters VF waveform features.68 Olasveengen and colleagues⁶⁹ demonstrated that AMI patients have a depressed median slope and AMSA compared to patients without AMI during CA. Lever and colleagues⁶¹ confirmed that electrically induced VF had a greater organization than that occurring spontaneously with ischemia. In addition, cardiomyopathy, autonomic dysfunction, and differences in drug therapy make it probable that VF waveform analysis will never demonstrate perfect predictive ability. Because different measurements extract slightly different information from the VF waveform, it is likely that combinations of these measurements will provide superior discriminative ability.^{32,65,66} Neurauter and coworkers³⁵ analyzed 770 ECG recordings of countershock parameters from 197 patients with CA. His study showed that a combination feature employing neural networks does not further improve defibrillation prediction in comparison with the best predictive single features. This result may indicate that an upper limit in outcome prediction using VF waveform analysis in the time and frequency domain has already been reached.

The third limitation is the small number of side-by-side comparisons of various analytical measurements. It is possible that one measurement performs better than another. Only a few papers present results from human data of direct comparisons between various methods.^{8,26,34,50} Median frequency appears to be superior to dominant frequency,²⁹ and AMSA and multiple features of wavelet decomposition appear to be superior to median frequency.⁵² Further, methods of filtered ECG features from higher ECG sub-bands, instead of features derived from the main ECG spectrum, have improved the accuracy of shock outcome prediction during CPR.⁷⁰ Nonlinear measurements, such as ScE and FDA, are superior to time domain and frequency-based methods.⁶⁴ But these comparisons merit further validations with large patient samples.

The final limitation is that all of the existing clinical research has a paucity of prospective validation. Most of the studies have developed measurements by retrospective analysis of electrocardiographic data, and only a few studies have divided the data into training and test sets^{32,50} or examined measurements prospectively.^{44,51} This lack of validation data and prospective study creates a valid risk of overestimating the performance of each measurement for analyzing human VF. Appropriate validation of each type of measurement will be important before adopting any particular analysis for clinical use.⁷¹

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SUMMARY

There is evidence that features of VF waveforms change over time. Retrospective animal and clinical studies suggest that it is possible to optimize the timing of defibrillation by predicting the success of attempted defibrillation. Higher amplitude, dominant, median and wavelet-based frequency, total fibrillation power and amplitude spectrum area, and lower indices of randomness are all associated with successful defibrillation. Combinations of these measurements may provide a greater predictive power. However, there are still no devices available that are able to analyze the VF waveform in real time and provide reliable information for optimizing the timing of defibrillation. There are no current prospective studies that have identified the optimal measurements for optimizing the timing of defibrillation to improve resuscitation outcome and long-term survival. Therefore, the value of VF waveform analysis to guide defibrillation management is still under investigation.

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