Original Article

Validation of spectral energy for the quantitative analysis of ventricular fibrillation waveform to guide defibrillation in a porcine model of cardiac arrest and resuscitation

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Background: The amplitude spectrum area (AMSA), a frequency-domain ventricular fibrillation (VF) waveform metric, can predict successful defibrillation and the return of spontaneous circulation (ROSC) after defibrillation attempts. We aimed to investigate the validation of Spectral Energy for the quantitative analysis of the VF waveform to guide defibrillation in a porcine model of cardiac arrest and compare it with the AMSA metric. In addition, we sought to determine the effects of epinephrine and cardiopulmonary resuscitation (CPR) on AMSA and Spectral Energy.

Methods: Sixty male domestic pigs weighing 35 to 45 kg were involved in this study. VF was initially untreated for 10 min followed by 6 min of CPR. Epinephrine was administered to the animals after 2 min of CPR. After the CPR, a single 120-J biphasic shock was applied to the animals. AMSA and Spectral Energy values were measured every minute from the electrocardiogram (ECG) to defibrillation. Receiver operating characteristic (ROC) curves were calculated for both the Spectral Energy and AMSA methods.

Results: Spectral Energy and AMSA values gradually decayed during untreated VF in all the animals. However, after the application of CPR and epinephrine, Spectral Energy and AMSA values were significantly increased in animals which were later successfully defibrillated, but did not increase in animals in which defibrillation was unsuccessful. The ROC curves showed that the Spectral Energy and AMSA methods possessed similar levels of sensitivity and specificity in predicting defibrillation success ($P<0.001$).

Conclusions: Both the Spectral Energy and AMSA methods accurately predict successful defibrillation. Moreover, increases in the value of either Spectral Energy or AMSA after application of CPR and epinephrine may also predict successful defibrillation.

Keywords: Cardiopulmonary resuscitation (CPR); cardiac arrest, ventricular fibrillation (VF); defibrillation; amplitude spectrum area (AMSA)

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Introduction

Although incidence of ventricular fibrillation (VF) as a presenting rhythm are decreasing, it is still the initial rhythm of 19.5% of adult out-of-hospital cardiac arrest cases in the United States (1). Despite the fact that electrical defibrillation performed at an early stage is the best treatment for VF, research has shown that the number of defibrillation attempts should be minimized and that attempts with a low probability of return of spontaneous circulation (ROSC) should be delayed to allow for additional cardiopulmonary resuscitation (CPR) (2,3). Since defibrillation interrupts CPR that improve myocardial blood flow during VF, it may increase the severity of ischemic injury to organs and ineffective, unsuccessful, and repeated high-energy electrical shocks may damage myocardial function (4,5).

Recent studies have focused on optimizing the defibrillation timing during VF to improve the success of defibrillation (6,7). VF electrocardiograms (ECGs) are correlated with downtime and the myocardial metabolic state, and studies have shown that the quantitative waveform measures (QWM), non-invasive measurements derived from ECG characteristics (such as frequency and amplitude), can potentially predict defibrillation success and optimize defibrillation timing (7,8). The amplitude spectrum area (AMSA) is one of the waveform parameters that is calculated by the weighted area under the frequency spectrum, and is generally considered one of the most accurate predictors for successful defibrillation (9-12).

Although the mechanisms of the relationship between QWM and defibrillation success are not currently understood, clarifying the correlation between myocardial energy and the VF waveform metric may shed some light on the process (13). Prior research has suggested that a decrease in the VF waveform frequency is due to the loss of intramyocardial adenosine triphosphate concentration. A higher AMSA value has also been demonstrated to reflect higher myocardial energy stores that are more likely to aid in the successful progression of defibrillation to a perfusing rhythm (14,15). Various VF analysis strategies based on VF ECG traits such as frequency (AMSA), slope (median slope), or amplitude (Spectral Energy) have been investigated to optimize the timing of defibrillation and improve the outcome of VF (16-18). The power spectrum of a VF ECG might provide more details about the myocardial-consumed energy and could indirectly reflect the degree of myocardial metabolic activity during the VF process. In this study, we assessed the accuracy of the Spectral Energy method for predicting the success of defibrillation and compared it with the AMSA method to test the hypothesis that the Spectral Energy and AMSA methods have a similar ability to predict the success of defibrillation. In addition, we sought to determine the effects of epinephrine and CPR on AMSA and Spectral Energy.

Methods

Sixty male domestic pigs weighing 35 to 45 kg were involved in this study. All animal experiments were performed in accordance with the Animal Research: Reporting of *In Vivo* Experiments guidelines (19). The protocol was approved by the Institutional Animal Care and Use Committee of the Tang Wanchun Laboratories of Emergency & Critical Care Medicine at Sun Yat-sen Memorial Hospital, Sun Yat-sen University.

Animal preparation

Animals were fasted overnight but given free access to water. Anesthesia was initiated by an intramuscular injection of ketamine (20 mg/kg), followed by an intravascular injection of sodium pentobarbital (loading dose, 30 mg/kg). An additional dose of sodium pentobarbital (maintain dose, 8 mg/kg) was injected if animals awakened or showed signs of restlessness, and was repeated at intervals of approximately 1 h if necessary. The minimum time between the start of VF and last loading pentobarbital administration is at least 2 and 1 h for the last maintain administration. A cuffed endotracheal tube was introduced into the trachea and a VELA ventilator (CareFusion, California, US) was used with a tidal volume of 10 mL/kg body weight, a peak flow below 40 L/min, and 0.21 FiO_2. A capnometer module of a BeneView T5 patient monitor (Mindray, Shenzhen, China) was used to measure end-tidal carbon dioxide pressure ($ETCO_2$). Respiratory frequency was adjusted as necessary to maintain an $ETCO_2$ between 35–45 mmHg. Body temperature was maintained at 37.5±0.5 ℃ throughout the entire experiment with the aid of a cooling/warming blanket (HGT-200II, Hokai Medical Instruments Corporation, Zhuhai, China). For the measurement of aortic pressure, a 6-F catheter was inserted into the thoracic aorta through the right femoral artery. A 7-F four-chambered Swan-Ganz catheter (774HF75 Swan-Ganz TD Catheter, Edwards Lifesciences Corporation, Irvine, CA, USA) was advanced from the

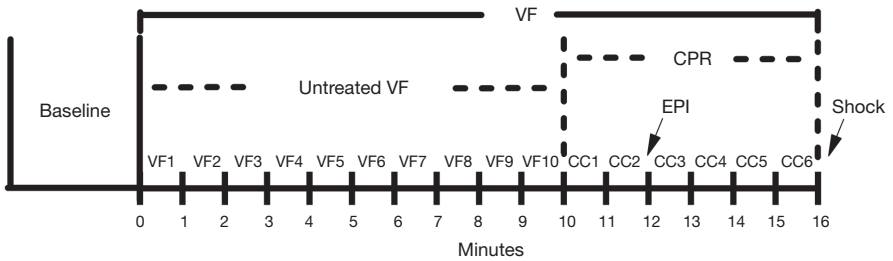

Figure 1 Experimental timeline. Baseline, baseline measurements; VF, ventricular fibrillation; CC, chest compression; CPR, cardiopulmonary resuscitation; EPI, administration of epinephrine; Shock, defibrillation.

right femoral vein into the right atrium for measurement of right atrium pressure.

Experimental procedures

Fifteen min prior to the induction of VF, baseline measurements were obtained. VF was induced by a 2-mA alternating current through the pacing catheter in the right ventricular endocardium. Mechanical ventilation was discontinued after the onset of VF. After untreated VF was sustained for 10 min, two researchers initiated a two-person CPR algorithm of basic adult life support, as recommended by the 2015 American Heart Association (AHA) guidelines (20). The researchers provided high-quality CPR with 100 to 120 compressions per minute, allowing complete chest recoil and minimum interruption. The compression depth was ~25% of the anteroposterior diameter of the thorax. A feedback device (M-Series, Zoll medical corporation, Chelmsford, MA, USA) was used to monitor the rate and depth of chest compressions. Pure oxygen was delivered with a breathing bag linked to the endotracheal tube at a compression-ventilation ratio of 30:2. CPR was maintained for a total of 6 min. Two min after initiation of CPR, epinephrine at a dose of 20 μg/kg was administered to the animals. Six min after initiation of CPR, a single 120-J biphasic shock (M-Series, Zoll Medical Corporation, Chelmsford, MA, USA) was applied to terminate VF. If a rhythm with a mean aortic pressure of >50 mmHg persisted for an interval of 5 mins or more, it was regarded as ROSC. This timeline is shown in *Figure 1*.

General measurements

Hemodynamic data and ECG were continuously measured and recorded through a data acquisition system supported by Windaq hardware/software (Dataq Instruments Inc., Akron, OH, USA). The coronary perfusion pressure (CPP) was digitally computed from the differences in time-coincident diastolic arterial pressure and right atrium pressure.

Spectral energy and AMSA methods

The experimental data was reviewed to assess the accuracy of the Spectral Energy method for predicting the success of defibrillation, and then compared with the AMSA method. ROSC was regarded as the sign of defibrillation success. MATLAB 2014a (The Mathworks, Natick, MA, USA) was used for all analysis. The one-second electrocardiographic lead II recordings that immediately preceded the first electrical shock were analyzed for each measurement. The success of defibrillation was recorded. ECG recordings during pauses in chest compressions were processed using a bandpass filter between 4 and 48 Hz to eliminate the high frequency noise produced by the power line and myoelectrical activity. Then, the one-second ECG segment was transformed from the time to the frequency domain using the Fast Fourier Transform. The Spectral Energy was calculated according to the following equation: $\text{Spectral Energy}=\sum A_i^2$, where A_i is the amplitude corresponding to the i^{th} frequency f_i in the ECG. The AMSA value of each one-second ECG segment was also calculated according to the equation: $\text{AMSA} = \sum A_i \cdot f_i$. In this study, the same frequency band between 4 and 48 Hz was analyzed for both methods. *Figure 2A,B,C,D,E,F,G,H* shows the process by which the Spectral Energy and AMSA values were calculated, where the subplots from *Figure 2* show a one-second ECG segment in the 1st min (8th min) of the untreated VF phase, the amplitude spectrum, the calculated AMSA spectrum, and the Spectral Energy spectrum.

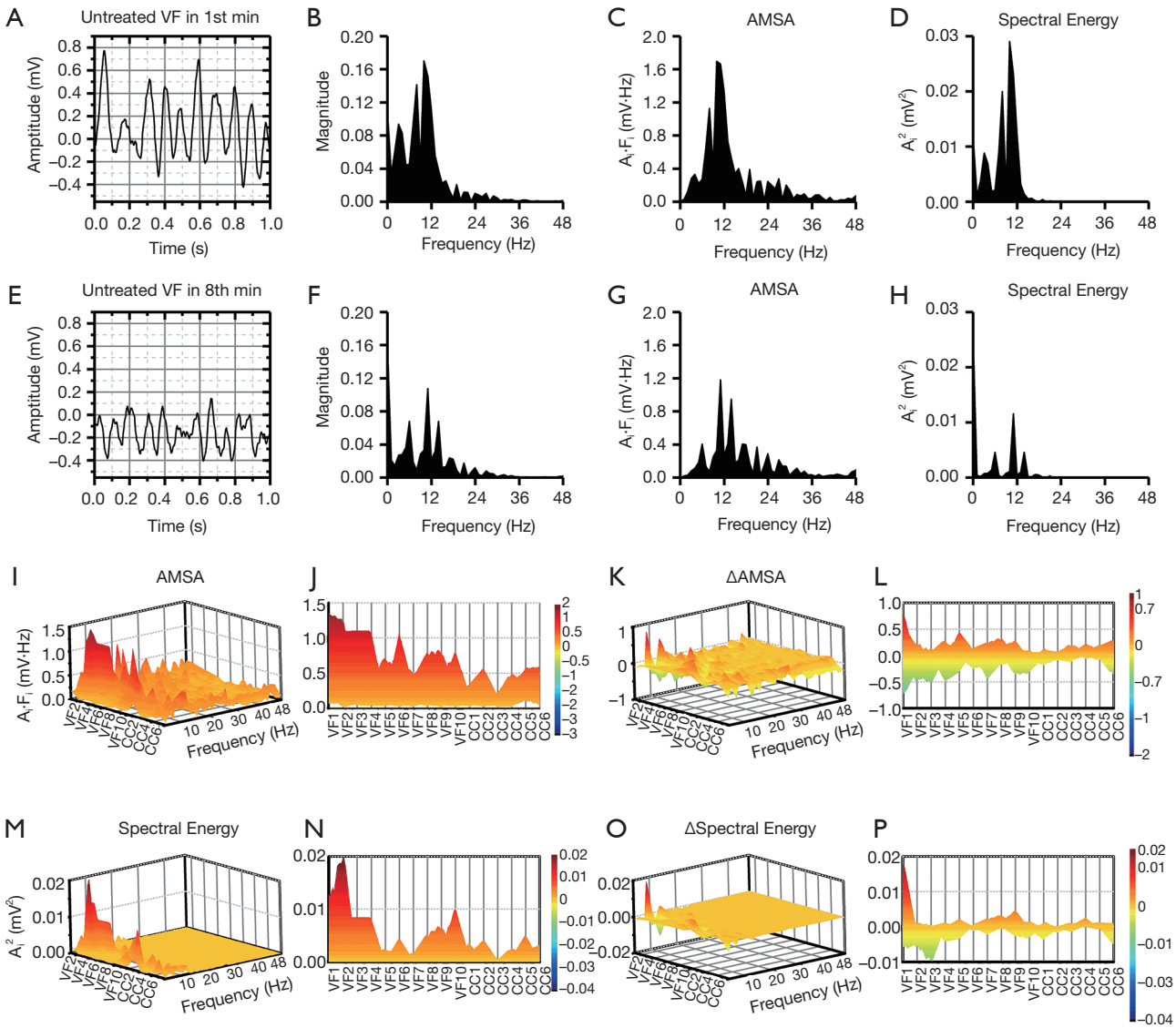

Figure 2 Schematic of Spectral Energy and AMSA methods. (A,B,C,D,E,F,G,H) Calculation of the Spectral Energy and AMSA values based on the one-second ECG segment in the 1st and 8th min of the untreated VF phase; (I,J,K,L,M,N,O,P) comparisons of changes in the Spectral Energy and AMSA values during untreated VF and CPR in heat maps. VF, ventricular fibrillation; CC, chest compression; AMSA, the amplitude spectrum area; ECG, electrocardiogram; CPR, cardiopulmonary resuscitation.

Statistical analyses

Sample size was at least 60 animals with α=0.05, two-tailed and a power of 80%. Power analysis was done to calculate the sample size using PASS 11 software (NCSS, Kaysville, UT, USA) before the study. Animals were categorized into two groups: Group R, where the animal's single defibrillation was successful; and Group N, where the animal's single defibrillation failed. The AMSA and Spectral Energy values were calculated for samples in each group. Continuous variables were shown as mean ± standard deviation (SD) if data was normally distributed. If data was not normally distributed, a median (25th, 75th percentiles) were shown. Normal distribution was confirmed by the Kolmogorov-Smirnov test. Comparisons between time-based measurements within each group were performed with one-way analyses of variance. Differences of AMSA or Spectral Energy between CC1 to CC6 and VF10 were

Table 1 Baseline physiological information and selective hemodynamics during cardiopulmonary resuscitation

Parameters	Group R	Group N
Sample, n	29	31
Weight, kg	39.5±2.9	38.7±1.5
Core temperature, ℃	37.5±0.6	37.8±1.2
Heart rate, beats/min	125±22	130±26
Mean artery pressure, mmHg	120±14	125±18
Right atrium pressure, mmHg	4.8±1.3	5.3±1.5
End-tidal CO_2, mmHg	40±2	43±4
CPP at 1st min, mmHg	15±4	16±7
CPP at 3rd min, mmHg	42±13#	25±11
CPP at 5th min, mmHg	29±9#	14±8

values are presented as mean ± SD; Group R, animals in Group R achieved first defibrillation success; Group N, animals in Group N failed to achieve first defibrillation; #, P<0.05 *vs.* Group N. CPP, coronary perfusion pressure; SD, standard deviation.

calculated, which were defined as ΔAMSA and ΔSpectral Energy, respectively. For example, at the CC1 timepoint, the value of ΔAMSA is the AMSA value of CC1 minus the AMSA value of VF10. Next, the ΔAMSA and ΔSpectral Energy values of Group R were compared with Group N. Finally, receiver operating characteristic (ROC) curves were generated for the Spectral Energy and AMSA methods. The areas under the ROC curves (AUCs) were calculated for both methods and compared using a two-tailed Z-test implemented in MedCalc 15 software (MedCalc Software, Mariakerke, Belgium) (21). The MedCalc 15 software was also used to calculate 95% CIs (two-tailed) for AMSA and Spectral Energy values at CC6. For all analyses, P<0.05 was considered to be statistically significant.

Results

Among the 60 animals included in this observational study, successful defibrillation was achieved for 29 (48%), and failed in 31 (52%). Accordingly, Group R and Group N were composed of 29 and 31 animals, respectively. There were no significant differences in baseline physiologies between both Groups R and N (*Table 1*). Although no obvious difference in the CPP at 1st min was observed between both groups, CPPs at 3rd and 5th min were significantly greater in Group R (*Table 1*). As shown in *Figure 3*, the AMSA and Spectral Energy values decayed over time during untreated VF (18.44±4.23 *vs.* 6.32±1.77 mV/Hz, P<0.001; 75.61±14.65 *vs.* 13.17±4.69 mV^2, P<0.001). Although the AMSA and Spectral Energy values of the animals in Group R increased after the implementation of CPR and epinephrine (6.29±2.30 *vs.* 8.37±2.36 mV/Hz, P=0.001; 11.68±5.45 *vs.* 16.91±5.72 mV^2, P=0.001), no changes in ECG were observed in animals from Group N (*Figure 4*). The ΔAMSA and ΔSpectral Energy of Group R were significantly higher than Group N after two min of CPR (1.26±3.97 *vs.* –0.53±1.85, P<0.05, 3.54±4.92 *vs.* –2.07±5.13, P<0.05), as shown in *Figure 5*.

The AUCs of the AMSA and Spectral Energy methods at CC3, CC4, CC5, and CC6 were 0.76 *vs.* 0.74, 0.78 *vs.* 0.81, 0.81 *vs.* 0.82, and 0.81 *vs.* 0.88, respectively (*Figure 6*). Both methods were significantly predictive of outcome (P<0.01 in all cases). The prognostic characteristics of both methods in terms of sensitivity and specificity were similar, and the ROCs of both methods at each timepoint showed no significant differences (*Table 2*). There were no significant differences in the ROCs between different timepoints of both methods. The cut-off values of the AMSA and Spectral Energy methods at CC6 were 6.95 and 10.21, respectively. The CI of AMSA values at CC6 is (2.46, 11.68) while the CI of Spectral Energy values is obtained as (1.97, 30.44).

Discussion

In the present study, it was found that Spectral Energy and AMSA values decreased over time during untreated VF. As shown in *Figure 3*, after ten min of untreated VF, AMSA values decreased from 18.44±4.23 to 6.32±1.77 mV/Hz, while Spectral Energy values decreased from 75.61±14.65 to 13.17±4.69 mV^2. However, increases in the mean Spectral Energy and the mean AMSA values after the application of CPR and epinephrine were observed in successfully resuscitated animals, in contrast to non-responsive animals, indicating that this change in AMSA and Spectral Energy over time is an indicator of a good outcome. Moreover, the Spectral Energy and AMSA methods had a similar ability to predict the success of defibrillation.

The results of recent studies have shown that Spectral Energy is one of the characteristic patterns of the VF ECG signal that can be used to estimate the duration of VF (16). It can be seen in heat maps (*Figure 2*) that the main components of Spectral Energy and AMSA are in the low frequency band, in which the dominant frequencies of Spectral Energy are concentrated in the range of 5 to 20 Hz, while the dominant frequencies of AMSA are concentrated from 5 to 25 Hz. These results were

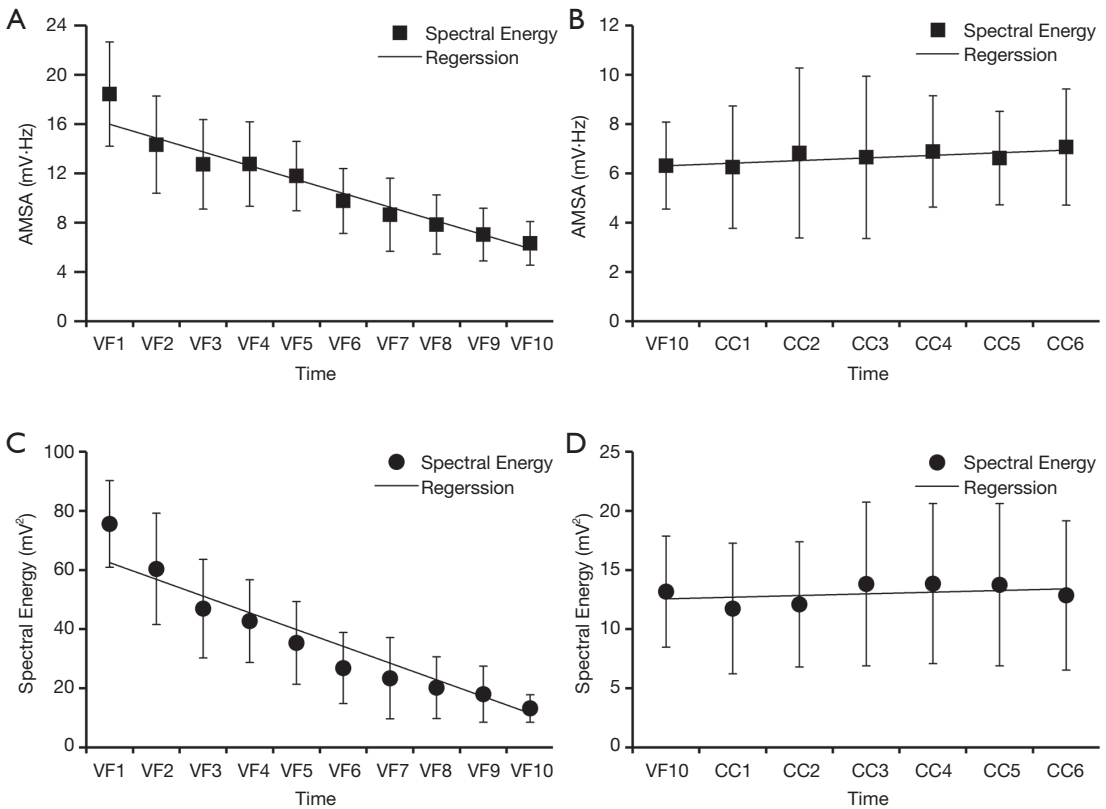

Figure 3 Values and regression lines of Spectral Energy and AMSA during untreated VF and CPR phases. AMSA, the amplitude spectrum area; VF, ventricular fibrillation; CC, chest compression; CPR, cardiopulmonary resuscitation.

consistent with the characteristic of AMSA. Since AMSA is frequencies sensitive, high frequency components with low amplitude may have an impact on AMSA values (22). However, it has been suggested that filtering out frequency components with low amplitude improves performance of AMSA method (23). Therefore, Spectral Energy method which is high amplitude dominant may have an inherent advantage. Both AMSA and Spectral Energy values showed a significant decline during VF. From a physiological point of view, the metabolic level of the heart during VF is typically in a downward trend (24). The observed declines in AMSA and Spectral Energy during untreated VF are consistent with a downward metabolic trend in the myocardium.

During VF, if no rescue measures such as CPR or defibrillation are applied, the energy of cardiomyocytes gradually decays until exhaustion, and the depletion of myocardial energy during VF has been shown to correlate with QWM (13,14). In this study, the Spectral Energy and AMSA values decreased during the untreated VF phase in a time-dependent manner. Both the Spectral Energy and AMSA values in the successfully defibrillated animals increased again when CPR and epinephrine were applied, but no responses to CPR and epinephrine were observed in animals in which defibrillation failed. Previous research has also shown that AMSA increases after effective CPR (25) and its value is associated with the concentration of adenosine triphosphate (3,14). The Spectral Energy method, which could indirectly reflect myocardial metabolic activity, might also serve as a predictive indicator for effectiveness of CPR, revealing whether the myocardial blood flow has been effectively improved. However, all animals in the present experiment were also administered epinephrine during resuscitation. For this reason, it is difficult to distinguish the effects of CPR from epinephrine. The effect of repeated epinephrine doses on AMSA values was described in a study by Wagner *et al.*, but this prior study did not compare the differences between a relative Group R and Group N (26). In their trials, there was no statistical difference in AMSA values calculated from animals that received epinephrine versus animals that did not receive epinephrine. In our

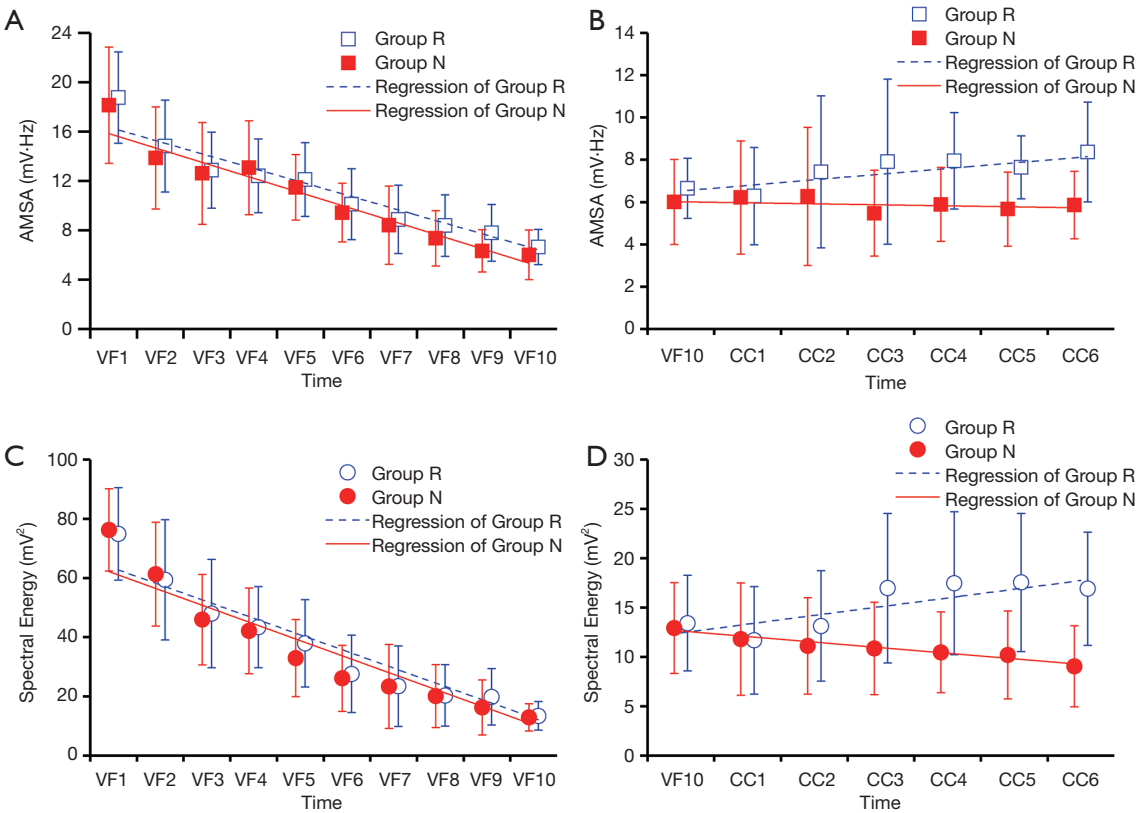

Figure 4 Comparisons of values and regression lines of Spectral Energy and AMSA during untreated VF and CPR phases between animals whose initial defibrillation was successful or failed. Group R, animals in Group R achieved first defibrillation success; Group N, animals in Group N failed to achieve first defibrillation. AMSA, the amplitude spectrum area; VF, ventricular fibrillation; CC, chest compression; CPR, cardiopulmonary resuscitation.

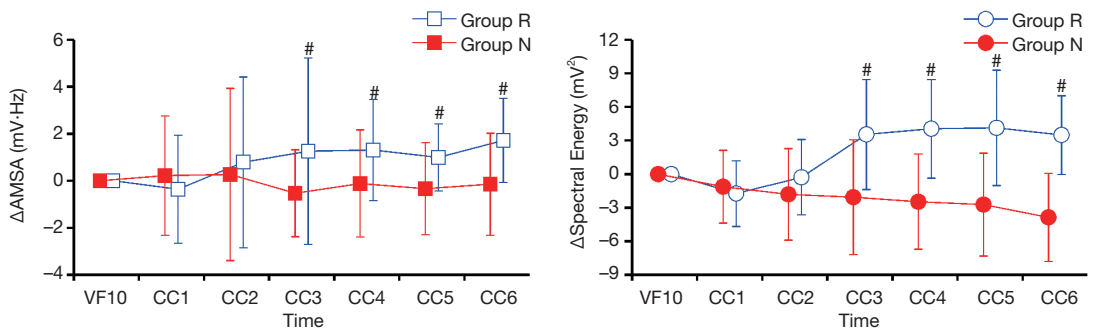

Figure 5 Comparisons of ΔAMSA and ΔSpectral Energy between animals whose initial defibrillation was successful or failed. #, P<0.005 *vs.* Group N. ΔAMSA, differences in AMSA between CC1 to CC6 and VF10; ΔSpectral Energy, differences in Spectral Energy between CC1 to CC6 and VF10. AMSA, the amplitude spectrum area; VF, ventricular fibrillation; CC, chest compression.

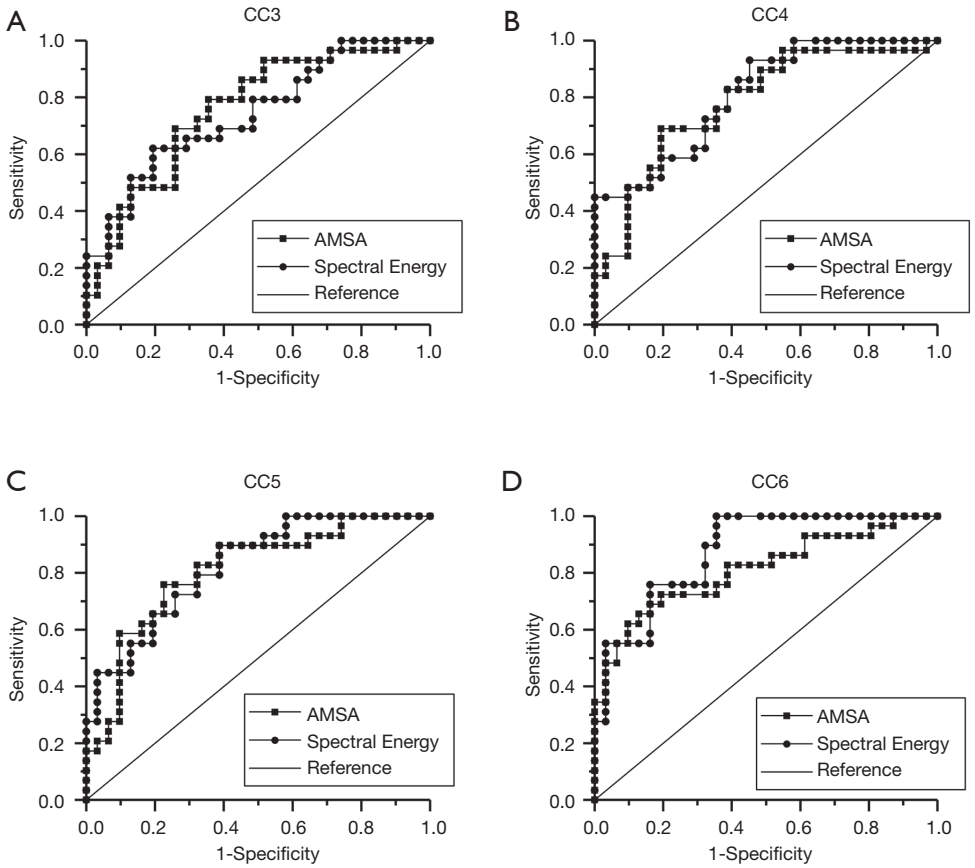

Figure 6 ROC analysis of the AMSA and Spectral Energy methods. AMSA, the amplitude spectrum area; CC, chest compression; ROC , receiver operating characteristic.

Table 2 Comparison of ROC curves between AMSA and Spectral Energy methods.

Epoch	Method	AUC	Comparison with a null curve, P	Comparison between two ROCs, P
CC3	Spectral Energy	0.74	0.002	0.80
	AMSA	0.76	0.0006	
CC4	Spectral Energy	0.81	0.0001	0.63
	AMSA	0.78	0.0002	
CC5	Spectral Energy	0.82	0.0001	0.80
	AMSA	0.81	0.0001	
CC6	Spectral Energy	0.88	0.0001	0.35
	AMSA	0.81	0.0001	

ROC, receiver operating characteristic; AMSA, the amplitude spectrum area; CC, chest compression; AUC, areas under the ROC curve.

study, the ΔAMSA and ΔSpectral Energy of Group R were always greater than zero after two min of CPR where epinephrine was administered, which means that the Spectral Energy and AMSA values in animals which were successfully defibrillated significantly increased. In contrast, the ΔAMSA and ΔSpectral Energy values of Group N were smaller than zero, and were significantly less than Group R. These results suggest that epinephrine is effective and important for long-term resuscitation, in line with the 2015 AHA guidelines (20). Furthermore, we speculate that the values of AMSA or Spectral Energy from ECG may be suitable guides to predict the effect of CPR on outcomes. For example, during resuscitation, if AMSA or Spectral Energy values increase after the implementation of CPR and epinephrine, a subsequent defibrillation may produce a better result versus a case in which AMSA or Spectral Energy values decrease after implementation. Moreover, the possibility of successful defibrillation can be predicted by analyzing the change in Spectral Energy or AMSA after the initiation of CPR.

We also found that higher Spectral Energy and AMSA values were correlated with defibrillation success. As previously demonstrated, AMSA effectively predicted the success of defibrillation and the possibility of ROSC (5,27-29). Thus, the Spectral Energy method could also be a valuable parameter for predicting the outcome of defibrillation (16). The ROC curve results further confirmed the ability of the Spectral Energy method to predict successful defibrillation. Among all the QWM used to determine the timing of defibrillation, AMSA is generally considered one of the most accurate predictors for successful defibrillation (9,15), and the predictive sensitivity and specificity values between Spectral Energy and AMSA were similar. Therefore, the Spectral Energy method could be an alternative predictor for successful defibrillation. Since the formula of Spectral Energy is consistent with the signal energy theory of signal processing, it may be beneficial to predict successful defibrillation using Spectral Energy method.

There were several limitations to our study. First, this is a relatively small animal study, and a study with a larger sample number should also be performed. In addition, the species difference between pigs and humans should be noted, and thus further work is needed to validate our findings for human cardiac arrest. Second, the VF waveform segment collected during ventilations was analyzed in this study, which did not include chest compressions. Nevertheless, only one-second ECG segments were used, a pause which was acceptable and had little effect on the quality of CPR. Third, all animals in this experiment were administered epinephrine during resuscitation. Experiments with a control group that does not receive epinephrine should be conducted in the future. Fourth, the investigation was an observational animal study. Ideally, we would further explore the ability of the threshold value in the Spectral Energy method to optimize the defibrillation time and predicting the possibility of ROSC in a prospective randomized controlled trial.

Conclusions

Both the Spectral Energy and AMSA methods accurately predict the success of defibrillation. Moreover, increases in the value of either Spectral Energy or AMSA after application of CPR and epinephrine may also predict successful defibrillation.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The protocol was approved by the Institutional Animal Care and Use Committee of the Tang Wanchun Laboratories of Emergency & Critical Care Medicine at Sun Yat-sen Memorial Hospital, Sun Yat-sen University (P1610).

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