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Original Contribution

Amplitude screening improves performance of AMSA method for predicting success of defibrillation in swine model☆

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ABSTRACT

Purpose: A novel amplitude screening method, termed Optimal Amplitude Spectrum Area (Opt-AMSA) with the aim of improving the performance of the Amplitude Spectrum Area (AMSA) method, was proposed to optimize the timing of defibrillation. We investigated the effects of the Opt-AMSA method on the prediction of successful defibrillation when compared with AMSA in a porcine model of ventricular fibrillation (VF).
Method: 60 male domestic pigs were untreated in the first 10 min of VF, then received cardiopulmonary resuscitation (CPR) for 6 min. Values of Opt-AMSA and AMSA were calculated every minute before defibrillation. Linear regression was used to evaluate the correlation between Opt-AMSA and AMSA. Receiver Operating Characteristic (ROC) analysis was conducted for the two methods and to compare their predictive values.
Results: The values of both AMSA and Opt-AMSA gradually decreased over time during untreated VF in all animals. The values of both methods of defibrillation were slightly increased after the implementation of CPR in animals that were successfully resuscitated, while there were no significant changes in either method in those who ultimately failed to resuscitate. The significant positive correlation between Opt-AMSA and AMSA was shown by Pearson correlation analysis. ROC analysis showed that Opt-AMSA (AUC = 0.87) significantly improved the performance of AMSA (AUC = 0.77) to predict successful defibrillation ($Z = 2.27$, $P < 0.05$).
Conclusion: Both the Opt-AMSA and AMSA methods showed high potential to predict the success of defibrillation. Moreover, the Opt-AMSA method improved the performance of the AMSA method, and may be a promising tool to optimize the timing of defibrillation.

1. Introduction

Ventricular fibrillation (VF) is typically the primary rhythm of cardiac arrest [1,2]. Currently, the most effective treatment to terminate VF is electrical defibrillation [3]. However, repetitive unsuccessful defibrillations may damage the myocardium due to high energy levels released by defibrillation. Therefore, the total number of defibrillation attempts should be minimized [2,4,5].

To improve defibrillation success rates, several methods based on electrocardiograms (ECGs) are undertaken to optimize the timing of defibrillation. The Amplitude Spectrum Area (AMSA) is one of the common predictors of the success of defibrillation [6-8], and is proven to be one of the most accurate [9-11].

There are many advantages of the AMSA method, including a high AUC value and high correlation with coronary perfusion pressure (CPP) [12]. The AMSA method is based on a wide frequency range from 4 Hz to 48 Hz, which might introduce electromyograms (EMGs) and other factors into its calculation [13]. Therefore, we hypothesized that there are some interferences mixed with an effective ECG signal. It may benefit the optimization of defibrillation timing to filter out irrelevant information.

Motivated by this, we introduced a new method we named Optimal Amplitude Spectrum Area (Opt-AMSA) to improve the performance of AMSA and to better predict the success of defibrillation. In the present retrospective porcine study, we compared the effectiveness and accuracy of AMSA and Opt-AMSA to predict successful defibrillation.

☆ The work was performed at Tang Wanchun Laboratories of Emergency & Critical Care Medicine, Guangzhou, China.

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Table 1
Prediction performance of Opt-AMSA with different amplitude thresholds.

Threshold, mV	AUC	*P*, AUC = 0.5
0.01	0.81	<0.01
0.015	0.81	<0.01
0.02	0.81	<0.01
0.025	0.83	<0.01
0.03	0.82	<0.01
0.035	0.87	<0.01
0.04	0.85	<0.01
0.045	0.86	<0.01
0.05	0.86	<0.01
0.055	0.82	<0.01
0.06	0.83	<0.01
0.065	0.82	<0.01
0.07	0.80	<0.01
0.075	0.77	<0.01
0.08	0.77	<0.01
0.085	0.78	<0.01
0.09	0.79	<0.01
0.095	0.79	<0.01
0.1	0.75	<0.01

Opt-AMSA, the Optimal Amplitude-spectral area; AUC, areas under the ROC curve.

2. Methods

A total of 60 male domestic pigs weighing 40 ± 5 kg were included in this retrospective study. All animal experiments were 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. All animal experiments were conducted from November 2015 to November 2017.

2.1. Animal preparation

Animals were fasted overnight and had free access to water. Anesthesia was initiated with intramuscular injection of ketamine (20 mg/kg), followed by intravascular injection of sodium pentobarbital (30 mg/kg). A dose of sodium pentobarbital (8 mg/kg) was injected to maintain anesthesia after approximately 1 h if animals were awake or showed uneasiness. A cuffed endotracheal tube was inserted into the trachea using a VELA ventilator (CareFushion, California, US) with a tidal volume of 10 mL/kg body weight, a peak flow of <40 L/min, and 0.21 FiO_2. The end-tidal carbon dioxide pressure ($ETCO_2$) was measured using the BeneView T5 patient monitor's capnograph module. The respiratory frequency was adjusted as necessary to maintain an $ETCO_2$ between 35 and 45 mmHg. Throughout the experiment, animals' body temperature was maintained at 37.5 ± 0.5 °C with the aid of a cooling/warming blanket (HGT-200II, Hokai Medical Instruments, Zhuhai, China).

2.2. Experimental procedures

Baseline measurements were obtained via the right ventricle endocardium 15 min before the induction of VF with a 2 mA alternating current through the pacemaker catheter. Mechanical ventilation was stopped after the onset of VF. Before starting the resuscitation procedure, the pacemaker catheter was removed to avoid damage to the

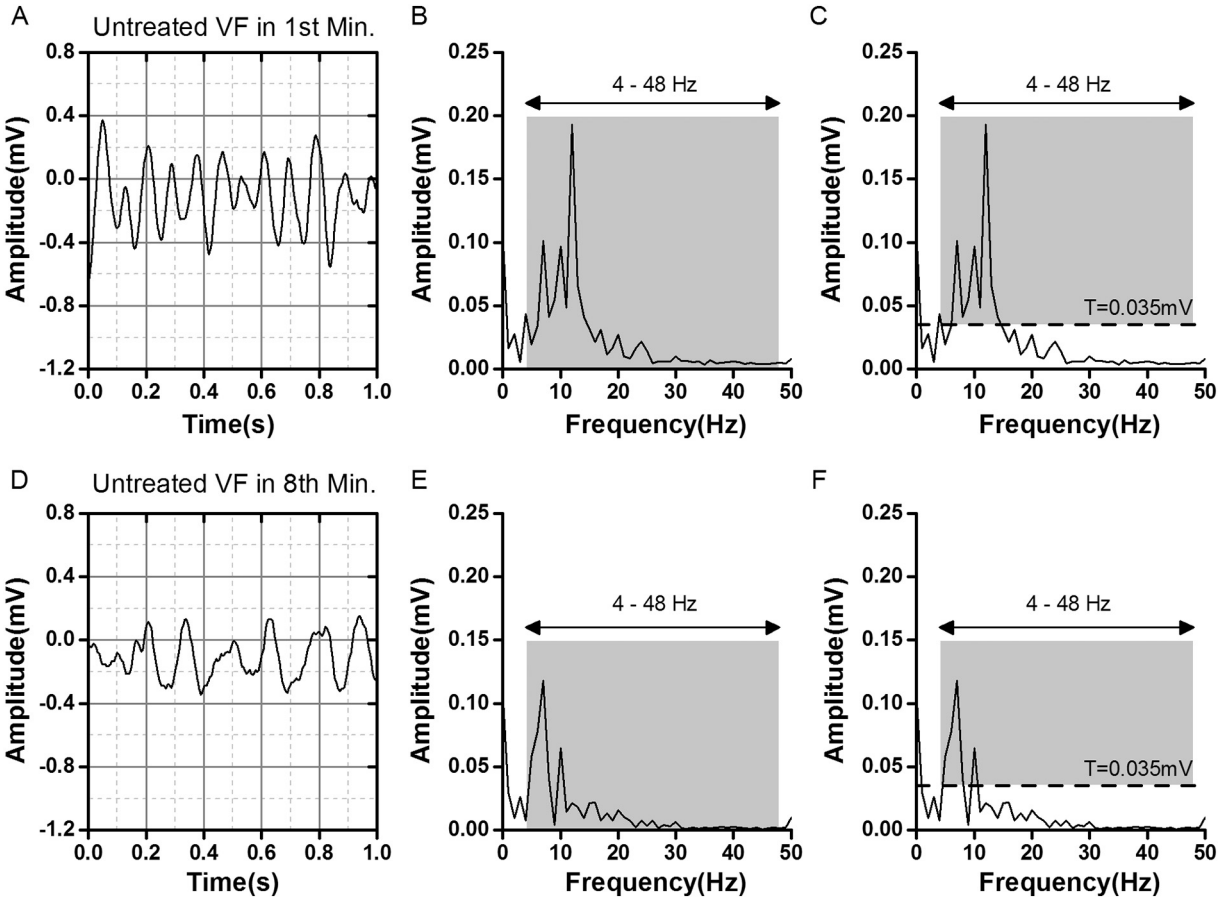

Fig. 1. The schematic of the Opt-AMSA method. (A) time domain waveform example of untreated VF in the first minute, (B) corresponding frequency domain waveform after FFT, (C) calculation of Opt-AMSA with frequency components in the shadow, (D) time domain waveform example of untreated VF in the eighth minute, (E) corresponding frequency domain waveform after FFT, (F) select frequency components used to calculate Opt-AMSA. Opt-AMSA, the Optimal Amplitude-spectral area; VF, ventricular fibrillation; FFT, fast Fourier transform; T, amplitude threshold.

heart during chest compressions. After 10 min of untreated VF, two researchers started a two-person CPR algorithm of basic adult life support according to the 2015 American Heart Association guidelines [14]. The precordial compression was maintained for 6 min. After 2 min of CPR, a dose of 20 μg/kg epinephrine was administrated to the animals. Six minutes after CPR, a single 120-J biphasic shock (M-Series, Zoll Medical, Chelmsford, MA, USA) was used to attempt to terminate the VF [9,12]. When a rhythm with mean aortic pressure > 50 mmHg lasted for 5 s or longer, it was considered successful defibrillation [15-18]. After successful resuscitation, mechanical ventilation was initiated with 100% inspired oxygen for 30 min, then the oxygen was reduced to 50% for the following 30 min, and then was decreased to 21%. The first 2 h following resuscitation were monitored.

2.3. General measurements

A data acquisition system supported by Windaq hardware/software (Dataq Instruments Inc., Akron, OH, USA) was used to continuously record all hemodynamic data. The CPP was calculated digitally based on the differences in time-coincident diastolic arterial pressure and right atrial pressure.

2.4. Opt-AMSA method, AMSA method

We reviewed the data recorded in the animal experiment to assess the predictive ability of the Opt-AMSA method and compared it with the AMSA method. MATLAB 2016b software was used to carry out the analyses. The one-second electrocardiographic lead II recordings before the first electrical shock were analysed (a total number of 60 recordings), with a sampling rate of 300 Hz. For both the Opt-AMSA and AMSA methods, all one-second segments were converted to frequency domain through fast Fourier transform (FFT) and the segments from 4 Hz to 48 Hz were used.

The AMSA value of each segment was calculated according to the following equation: AMSA $= \sum A_i \cdot f_i$, where A_i is the amplitude corresponding to the i^{th} frequency f_i in the ECG [8]. The Opt-AMSA value was calculated according to the following equation: Opt - AMSA $= (\sum A_i \cdot f_i)/n$, where A_i is the amplitude corresponding to the i^{th} frequency component f_i, A_i is greater than a threshold T, and n is the number of A_i whose value is greater than or equal to T. Only the frequency component f_i which had an amplitude exceeding the threshold T was considered in the calculation of the Opt-AMSA method. The threshold T was set as 0.035 mV according to the Receiver Operating Characteristic (ROC) analysis shown in Table 1. Prediction performance of different amplitude threshold T was tested and the best performance was obtained when T was equal to 0.035 mV. The schematic of the Opt-AMSA method is shown in Fig. 1.

2.5. Statistical analyses

The animal samples were subdivided into two groups based on their defibrillation outcomes, including Group R, whose first defibrillation was successful, and Group N, whose first defibrillation failed. Comparisons between Group R and Group N for each of method were performed

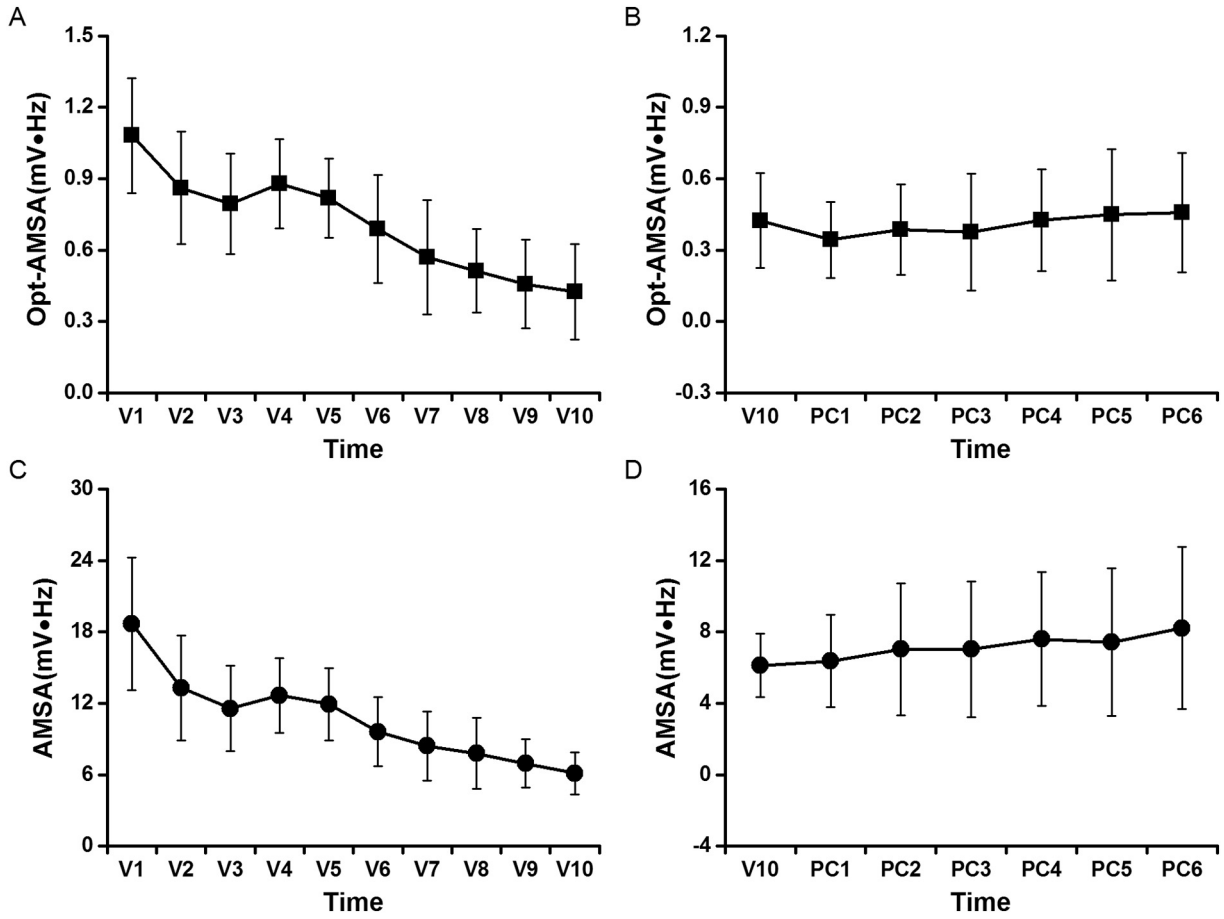

Fig. 2. Changes in values of Opt-AMSA and AMSA per minute during untreated VF and CPR phases. Opt-AMSA, the Optimal Amplitude-spectral area; AMSA, the Amplitude-spectral area; V, ventricular fibrillation; PC, precardiac compression.

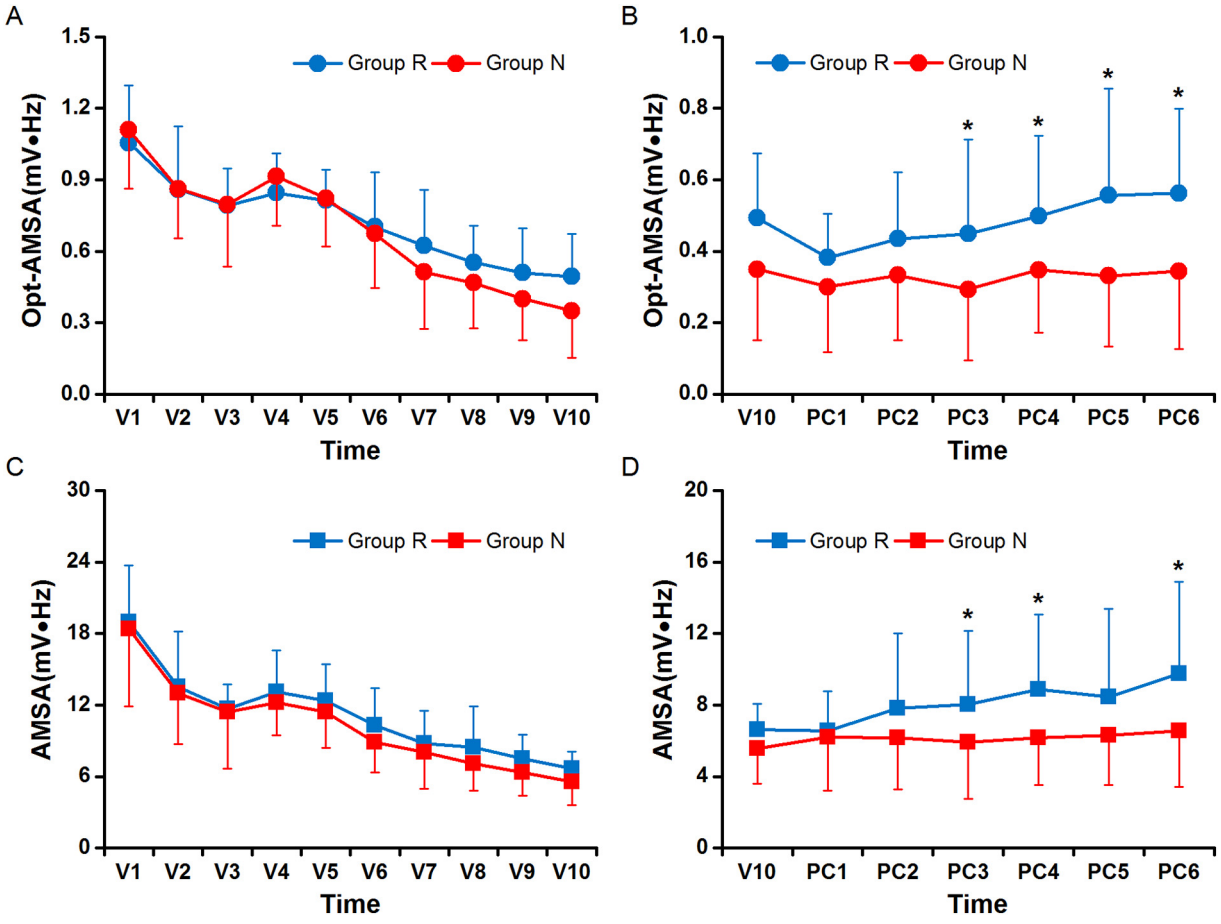

Fig. 3. Comparisons of values of Opt-AMSA and AMSA during untreated VF and CPR phases between animals whose initial defibrillation was successful or failed. Opt-AMSA, the Optimal Amplitude-spectral area; AMSA, the Amplitude-spectral area; V, ventricular fibrillation; PC, precardiac compression; Group R, animals whose initial defibrillation was successful; Group N, animals whose initial defibrillation failed.

with one-way analyses of variance (one-way ANOVA). The correlation coefficient was calculated to show the two methods' relationship through the Pearson correlation analysis. Also, ROC curves and areas under the ROC curves (AUCs) were used to evaluate the effectiveness of both Opt-AMSA and AMSA methods. Their resulting AUCs were compared using *Z*-tests. For all analyses, $P < 0.05$ was considered to be statistically significant.

3. Results

Among the 60 animal samples included in this retrospective study, successful first defibrillation was achieved for 29 (48%), while the other 31 (52%) failed to resuscitate. Fig. 2 shows the decrease in value of each method over time during untreated VF. Fig. 3 shows the increase in value of Group R, in each method, after the implementation of CPR. The comparison between Group R and Group N using the Opt-AMSA method shows significant differences in PC3(the third minute during precardiac compression, same as below), PC4, PC5, and PC6, while the

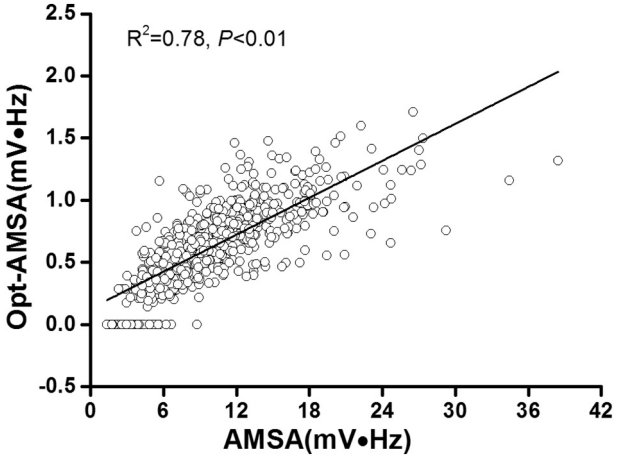

Fig. 4. Assessment of linear association among Opt-AMSA and AMSA methods. Opt-AMSA, the Optimal Amplitude-spectral area; AMSA, the Amplitude-spectral area.

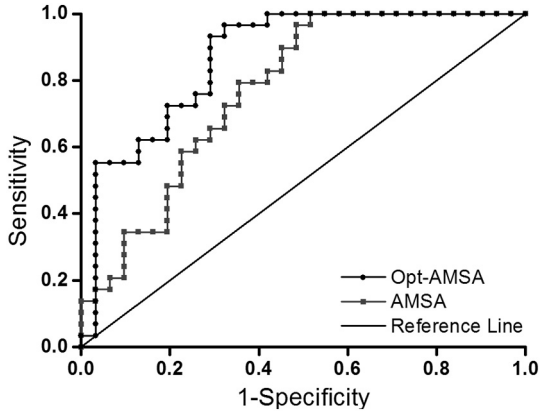

Fig. 5. ROC curve of Opt-AMSA and AMSA methods. Opt-AMSA, the Optimal Amplitude-spectral area; AMSA, the Amplitude-spectral area.

Table 2
Prediction performance between AMSA and Opt-AMSA with different cut-off value selection methods.

Method	Criteria	Cut-off value	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
AMSA	Yuden Index	8.94	100	48.39	64.44	100	73.33
	Maximum of sensitivity * Specificity	12.65	79.31	64.52	67.64	76.92	71.67
	Minimum of distance to corner	12.65	79.31	64.52	67.64	76.92	71.67
Opt-AMSA	Yuden Index	0.73	96.30	64.00	74.28	94.11	80.76
	Maximum of sensitivity * Specificity	0.79	81.48	76.00	78.57	79.17	78.84
	Minimum of distance to corner	0.79	81.50	76.00	78.57	79.17	78.84

differences using the AMSA method is statistically significant only in PC3, PC4, and PC6, as shown at the same figure. Fig. 4 shows the high correlation between Opt-AMSA and AMSA values. Fig. 5 shows the comparison of ROC curves between the Opt-AMSA and AMSA methods. The AUC of Opt-AMSA was higher than the AUC of AMSA, which were 0.87 and 0.77 respectively, with a significant statistical difference between them ($Z = 2.27$, $P < 0.05$). With a cut-off value of 0.73, the sensitivity and specificity of Opt-AMSA was 96.3% and 64%, with a positive predictive value (PPV) of 74.28%, a negative predictive value (NPV) of 94.11% and an accuracy of 80.76%. With a cut-off value of 8.94, AMSA method resulted in a sensitivity of 100% and a specificity of 48.39%. Simultaneously, the PPV, NPV and accuracy of AMSA method were 64.44%, 100% and 73.33%. The prediction performance between these two methods is shown in Table 2.

4. Discussion

Clinical and animal experiments have confirmed that a higher AMSA reflects higher myocardial energy and a higher probability of a successful defibrillation. In the present study, we proposed a new Opt-AMSA method for predicting the success of defibrillation. We found that Opt-AMSA maintains the same trend as AMSA over time. We also demonstrated that the Opt-AMSA method is highly correlated with AMSA, which is based on frequency domain. According to the analysis of ROC curves, both methods exhibited good performance in predicting the success of defibrillation. However, their resulting AUCs showed that Opt-AMSA demonstrates a much better performance than AMSA.

It has been demonstrated that AMSA has an optimal combination of sensitivity and specificity and will not be invalidated by chest compressions [16,19-24]. However, as we hypothesized, our proposed Opt-AMSA method can still improve over the original AMSA method through feature extraction. As shown in Table 1, when the amplitude threshold T is low, most frequency components are included in the calculation of Opt-AMSA. In these circumstances, the AUC values of Opt-AMSA are slightly higher than AMSA. With the increase of amplitude threshold in the Opt-AMSA method (i.e. more frequency components below the threshold are excluded), the AUC value of Opt-AMSA is generally increased. We conjecture that those frequency components with low amplitude potentially cause interference and are likely filtered out during the exclusion process, which may be the reason for the increase of AUC values. When the amplitude threshold is >0.035 mV, the AUC value of Opt-AMSA begins to deteriorate. This may be because the vast majority of frequency components are filtered out, including those that are critical to judgement.

The balance between sensitivity and specificity of the Opt-AMSA method should also be considered. Using different criteria for cut-off selections will result in different cut-off values, and hence different sensitivities and specificities [25]. Using the by the Youden index method, we obtain the optimal cut-off value of Opt-AMSA with an amplitude threshold of 0.035mV is 0.73mV · Hz, which leads to a sensitivity of 96.30% and a specificity of 64.00%. The second cut-off selection method is selecting the point on the ROC curve where sensitivity is closest to specificity as the cut-off value. The third optional criterion is selecting the point on the curve which is closest to the left-upper corner [26-30]. In this experiment, the cut-off values promoted by the last two criteria were coincidentally equal. All three methods have an accuracy of about 80%. The prediction performance including PPV and NPV among these different cut-off value selection methods is shown in Table 2. Researchers can choose one of those cut-off values according to the purpose of their experiments.

In this study, the Opt-AMSA and AMSA values decreased during the untreated VF phase in a time-dependent manner. Both the Opt-AMSA and AMSA values in the successfully defibrillated animals increased again when CPR was applied, but no responses were observed in animals that ultimately failed to defibrillate. Therefore, we speculate that the values of Opt-AMSA or AMSA from an ECG have similar ability to predict the success of defibrillation while CPR was applied.

Although current research has confirmed the ability of AMSA to predict defibrillation success, AMSA is still not widely used in clinical settings. The Opt-AMSA method improves upon the AMSA method, and is a more successful predictor than AMSA [22-24]. Therefore, Opt-AMSA is a method with potential for a clinical application.

Complying with current guidelines, in-hospital cardiac arrest patients should be defibrillated as early as possible. But for patients with out of hospital cardiac arrest, to increase the success of defibrillation, it was assumed that defibrillation should be applied after a period of CPR and Opt-AMSA rises to higher value.

In this study, there are some limitations. First, all VF waveform segments in this study did not include the chest compression period. Chest compressions may cause interference and influence the performance of predictors. Second, since only the one-second ECG recordings were used, the effect of Opt-AMSA under other data lengths has not been validated. Third, the real conditions of human patients in a clinical setting couldn't be totally indicated by a healthy porcine model. Finally, it is still unknown whether the Opt-AMSA method is practical to human defibrillation.

5. Conclusion

Both the Opt-AMSA and AMSA methods show high potential to predict the success of defibrillation. The Opt-AMSA method improves the performance of the AMSA method, and provides a promising tool to optimize the timing of defibrillation.

Competing interests

The author declares that there are no competing interests regarding the publication of this manuscript.

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