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AMPLITUDE SPECTRUM AREA AS A PREDICTOR OF SUCCESSFUL DEFIBRILLATION: THRESHOLD VALUES ANALYSIS IN A LARGE DATABASE OF OUT-OF-HOSPITAL CARDIAC ARREST TREATED BY DC-SHOCK

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AMPLITUDE SPECTRUM AREA AS A PREDICTOR OF SUCCESSFUL DEFIBRILLATION: THRESHOLD VALUES ANALYSIS IN A LARGE DATABASE OF OUT-OF-HOSPITAL CARDIAC ARREST TREATED BY DC-SHOCK

OVERVIEW

Introduction

Cardiac arrest represents a dramatic event that can occur suddenly and often without warning signs. Cardiopulmonary resuscitation (CPR), including chest compression often in conjunction with electrical defibrillation, has the potential to obtain return of spontaneous circulation (ROSC). However, CPR is likely to be successful only if it is instituted within 5 min after the heart stops beating [1–3]. Ventricular fibrillation (VF) is the primary rhythm in many cases of human cardiac arrest, and defibrillation by electric countershock represents the treatment of choice for this otherwise lethal arrhythmia. VF duration remains a main determinant of countershock success. When the interval between estimated VF onset and delivery of the first shock is <5 min, the likelihood is that an immediate defibrillation attempt will be successful [4–6]. When the duration of untreated VF is >5 min, both human and animal studies demonstrate that initial CPR with chest compression prior to delivery of an electrical shock improves the likelihood of ROSC [7–10]. During cardiac arrest,coronary blood flow ceases, accounting for progressive and severe energy imbalance. Intramyocardial hypercarbic acidosis is associated with depletion of high-energy phosphates and correspondingly severe global myocardial ischaemia [11, 12]. The ischaemic left ventricle (LV) becomes contracted [13], ushering in the so-called “stone heart” syndrome [14, 15]. After the onset of contracture, the probability of successful defibrillation is remote. Early CPR that restores coronary perfusion pressure (CPP) and myocardial blood flow delays onset of ischaemic myocardial injury and facilitates defibrillation [16].

VF is characterised by three time-sensitive electrophysiological phases: (1) the electrical phase, of 0–4 min; (2) the circulatory phase, of 4–10 min; (3) the metabolic phase, of >10 min. During the electrical phase, in which VF (Type I) waves are mostly of high amplitude and more frequent, immediate defibrillation is likely to be successful. As ischaemia progresses, the success of attempted defibrillation diminishes without CPR. This phase is characterised by transition to slow VF wavelets during accumulation of ischaemic metabolites in the myocardium. Type II VF often fails defibrillation attempts because of its re-entry and recurrence due to the loss of capability of restoring the electrophysiologic stability within the myocardium. In the metabolic phase, there is no likelihood of successfully restoring a perfusing rhythm [17].

More than 50% of all patients initially resuscitated from cardiac arrest subsequently die before leaving the hospital [18–20], and the majority of these deaths are due to impaired myocardial function [21].

The severity of postresuscitation myocardial dysfunction is at least in part related to the magnitude of the electrical energy delivered during defibrillation [22, 23]. Increases in defibrillation energy are associated with decreased postresuscitation myocardial function [22, 24]. It is therefore important to have noninvasive and real-time monitoring that predicts whether or not shock will obtain ROSC.

Current resuscitation methods are limited in part by the lack of practical and reliable real-time monitoring of the efficacy of CPR interventions and timing for the defibrillation attempt. Electrocardiographic (ECG) analyses of VF waveforms represent the best noninvasive approach to guide intervention priority, namely, chest compression or defibrillation

Monitoring Effectiveness of Chest Compression and Predicting Return of Circulation

The quality of chest compression is a major determinant of successful resuscitation [25–27]. Existing and established predictors of good-quality CPR, and thereby successful resuscitation, include CPP [16, 28–30] and end-tidal carbon dioxide ($etCO_2$) [31, 32].Blood flow generated by chest compression is dependent on the pressure gradient between aortic and venous pressures [33]. CPP , defined as the difference

between simultaneously measured minimal aortic pressure and right atrial pressure during compression diastole [34-37] is significantly correlated with coronary blood flow during cardiac resuscitation and is recognized as the best single indicator of successful defibrillation [30,38,39]. Based on both experimental and clinical observations, ROSC can be predicted when CPP is maintained > 15 mmHg during chest compression [30,39,40]. Resuscitation strategies that increase CPP, including highly effective chest compression [41,42] and the use of vasopressors [[43], are reccommended as considered more effective in restoring circulation.

Expired CO_2 ($etCO_2$) is determined by the body's production of CO_2 and the relationship between minute ventilation and pulmonary perfusion. When the circulatory status is normal, pulmonary perfusion is within the physiologic ranges and $etCO_2$ is determined by minute ventilation. During cardiac arrest and CPR cardiac output is usually less than one third of normal and pulmonary flow and $etCO_2$ are dramatically reduced. $etCO_2$ is therefore an indirect indicator of pulmonary blood flow and cardiac output produced by chest compression [31,32] and has emerged as a valuable tool for noninvasive monitoring of the effectiveness and quality of chest compression during CPR [31,32,44-46]. When $etCO_2$ is > 10-15mmHg during CPR, there is a greater likelihood of successful ROSC [47-51]; however, this measurement technique is not widely available. Portable infrared capnometers can be successfully employed in prehospital settings during CPR. However, monitoring $etCO_2$ requires endotracheal intubation. Out-of hospital endotracheal intubation carries both a high failure rate and up to a 30% incidence of traumatic injury to the airway [52, 53]. Moreover, epinephrine administration during CPR causes a signicant decrease in etCO2 by increasing pulmonary shunting [54], which may cause an important misinterpretation when monitoring the effectiveness of resuscitative manoeuvres. This is in contrasts with the routine availability of ECG in conjunction with external debrillators.

Attempts to find a better predictor of ROSC have therefore focused on analysing ECG features of VF.

Analyses of ECG Features During Ventricular Fibrillation and CPR

The search for a reliable indicator of successful defibrillation obtained from analysing ECG features began more than 20 years ago. Initial approaches included measuring VF amplitude [54] first and frequency later [55]. Subsequently, to increase ECG sensitivity and specificity predictors for ROSC, more sophisticated methods of VF waveform analyses were introduced and investigated, including wavelet decomposition [56], nonlinear dynamics methods [57] and a combination of different ECG parameter analyses [58].

Earlier investigations using ECG focused on VF wavelet amplitude or voltage as a predictor of the likelihood of successful debrillation. VF voltage, or signal amplitude, is defined as the maximum peak-to-trough VF amplitude in a given time window of the ECG signal [59]. Mean VF voltage is calculated as the average over the chosen time interval. It has been established that VF amplitude declines over time and greater amplitudes are associated with correspondingly greater debrillation success [54, 60–64]. Several studies have shown that this ECG feature reflects vital-organ blood flow and in particular myocardial blood flow and energy metabolism [54, 59, 65–67]. Weaver et al. observed that patients in whom VF amplitude was >0.2 mV have a signicantly greater likelihood of resresuscitation [54]. VF voltage appeared not only as an ROSC predictor but showed utility as an indicator for timing VF duration since collapse. Amplitude measurement, however, has the disadvantage of depending on the direction of the main fibrillation vector and therefore is subject to a great interindividual variance. VF amplitude might also be modified by electrode size, location, thoracic impedance, skin condition and chest morphology.

Subsequently, it was realised that other parameters could be computed using Fourier transformation analyses in a selected ECG interval, including VF median frequency, peak power frequency, edge frequency and spectral flatness measure. The starting point for all these calculations was the power spectrum, defined as the square of Fourier amplitudes. Brown et al. [55, 65] specifically developed this technique to analyse VF voltage and frequency to obtain the so-called VF median frequency. VF median frequency served as a predictor of electrical debrillation success [55, 68]. In a porcine model of VF and CPR, a median frequency of >9.14 Hz had 100% sensitivity and 92% specificity in predicting successful defibrillation. Frequency analysis of VF wavelets and, specifically, median frequency was also correlated with CPPs in animal models and humans and therefore became the preferred ECG feature for use as predictor of CPR

outcome [55, 63, 65, 66, 69–73]. In addition, this parameter appeared as a more accurate indicator for estimating the duration of untreated VF compared with the earlier VF amplitude [65, 71, 74, 75]. To determine the best ECG feature prognosticator, several studies focused on the changes and differences of VF waveform features in relationship to cardiac arrest pathophysiology. Specifically, investigators focused on the differences between VF as a result of ischaemic heart disease, which represents the main cause of sudden death, and electrically induced VF, which represents the main experimental model employed in laboratories [76, 77]. Indik et al. [78] induced VF in swine in which acute myocardial infarction followed left anterior descending coronary artery (LAD) ligation. The study revealed that VF spectral features, such as median, mean or dominant frequency and bandwidth, were signicantly reduced compared with those derived from electrically induced VF [79]. In a different porcine model of ischaemically induced cardiac arrest through acute LAD occlusion, Ristagno et al [80] confirmed lower mean VF frequency in comparison with electrically induced VF (Fig. A).

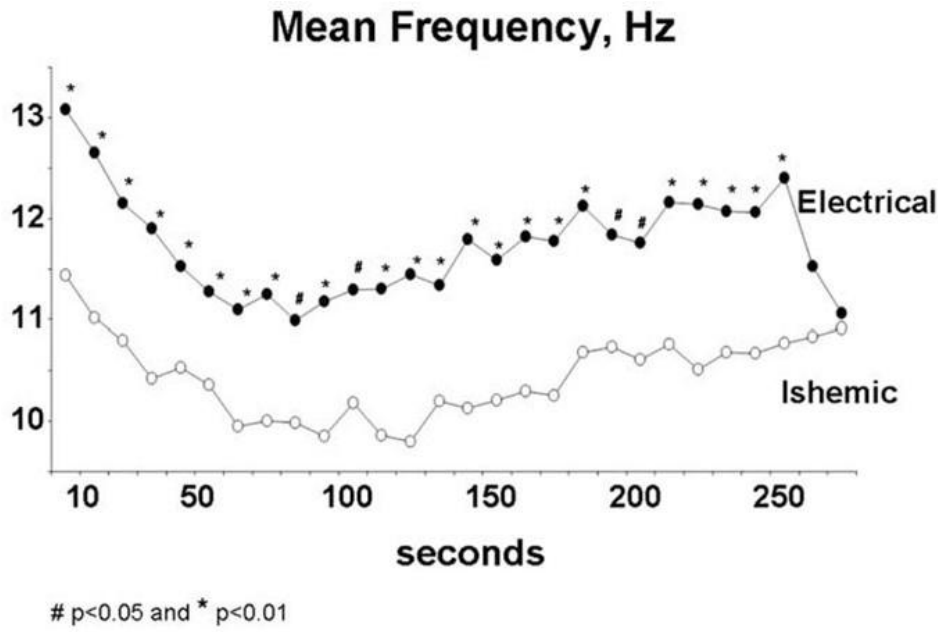

Fig. A Ventricular fibrillation (VF): mean frequency during 5 min of untreated VF. Closed circle : VF electrically induced; open circle: VF ischaemically induced

Although VF features might be different in relationship to the cause of cardiac arrest, these Authors observed that those features continuously changed during

resuscitative manoeuvres in the ischaemic VF model, as well. In particular, VF amplitude and mean frequency increased during chest compression, and such increases were representative of successful defibrillation [81, 82].

These observations provided evidence that ECG predictors of outcome are at least in part correlated to the mechanism by which VF evolves. Of more importance, relationships between VF amplitudes, frequencies and successful defibrillation are maintained in ischaemically induced VF, confirming the utility of ECG predictors of outcome.

Chest compression performed during CPR, however, interferes with ECG signal recording, affecting the extracted parameters and therefore leading to incorrect prediction of defibrillation outcomes. On the other hand, although CPR might be interrupted for an interval to allow acquisition of reliable parameters, this interruption shortens the period of vital myocardial perfusion and yields worse outcome and greater postresuscitation myocardial dysfunction [83,84]. Several filters and algorithms to reduce and eliminate ECG artefacts and noise due to chest compression or ambient interferences have been developed and successfully used [59, 63, 66, 85–87]. Among them, the wavelet-transform technique constitutes one of the most promising methods [38, 86].

Amplitude Spectrum Area (AMSA) as Predictor of Successful Defibrillation

The need for ECG analyses and for predicting successful defibrillation escalated after the introduction of automated external defibrillators (AEDs). In 1994, Noc and Bisera [64] began investigating ECG VF waveforms as predictors of successful cardiac resuscitation. Initially, they focused on the ECG indicator widely investigated at that time and specifically evaluated the possibility of using VF amplitude to predict resuscitability in a well-established rodent model of cardiac arrest and CPR. Increases in CPP during precordial compression were associated with concomitant increases in VF voltage, and greater VF voltages were observed in resuscitated animals. Moreover, greater VF voltages after initiation of cardiac resuscitation were associated with increases in myocardial creatine phosphate and significant decreases in lactate content. Accordingly, increases in VF voltage during cardiac resuscitation reflected increases in myocardial perfusion and

favourable changes in myocardial energy metabolism, with consequent greater success of cardiopulmonary resuscitation.

In 1999, the same authors [59] developed a new method of analysing VF waveform, the real predecessor of AMSA, in which mean amplitude and dominant frequency were combined. The so-called defibrillation predictor (DP) was calculated by ECG signals obtained with lead-2 monitoring and in which artefacts produced during precordial compression were removed by digital filtering. The DP was tested in a porcine model of cardiac arrest and CPR. Successfully resuscitated animals had significantly greater CPP,dominant VF amplitude, mean VF amplitude and dominant VF frequency. No animals could be resuscitated if the CPP was <8 mmHg, dominant amplitude was <0.48 mV, mean amplitude was <0.25 mV or dominant frequency <9.9 Hz independently of the duration of untreated VF. However, defibrillation attempts uniformly failed when mean amplitude was below the threshold level, even though dominant frequency would have predicted otherwise.

When mean amplitude and dominant frequency were combined, predictability was signicantly improved. Defibrillations were uniformly unsuccessful if the combination of mean amplitude and dominant frequency did not exceed the threshold values obtained in a derivation study. Mean VF amplitude in combination with mean VF frequency was expressed as a numeric score . Using stepwise multiple regression analysis, they identified a single numeric score that was established as a DP and represented by the following equation:

DP = 3.60 – 4.85 mean VF amplitude – 0.06 VF dominant frequency

This DP served as an objective, noninvasive measurement comparable to CPP for predicting successful defibrillation. The ECG predictor nevertheless served as a monitor with which there was essentially total predictability of failed defibrillation attempt. However, due to its poor positive predictive value (PPV) to predict only 20% of successful defibrillation attempts, the rudimental defibrillator predictor was later replaced by the amplitude spectrum area [38,88,89].

This ECG-derived parameter was obtained starting from conventional ECG scalar limb ECG leads. The frontal-plane lead 2 was used for VF wavelet analyses. ECG signal was continously sampled and recorded at 300 mHz and further digitized.

The signal was selected to be between 4 and 48 Hz to minimize low frequency artifacts produced by precordial compression and to exclude electrical interference of ambient noise at frequencies >48 Hz. Peak-to-trough VF amplitudes were obtained, and the average was calculated for a specific ECG interval.

The power spectrum was then obtained by squaring the amplitude of each frequency component obtained from the fast-Fourier transform of the ECG signal (Fig.B).

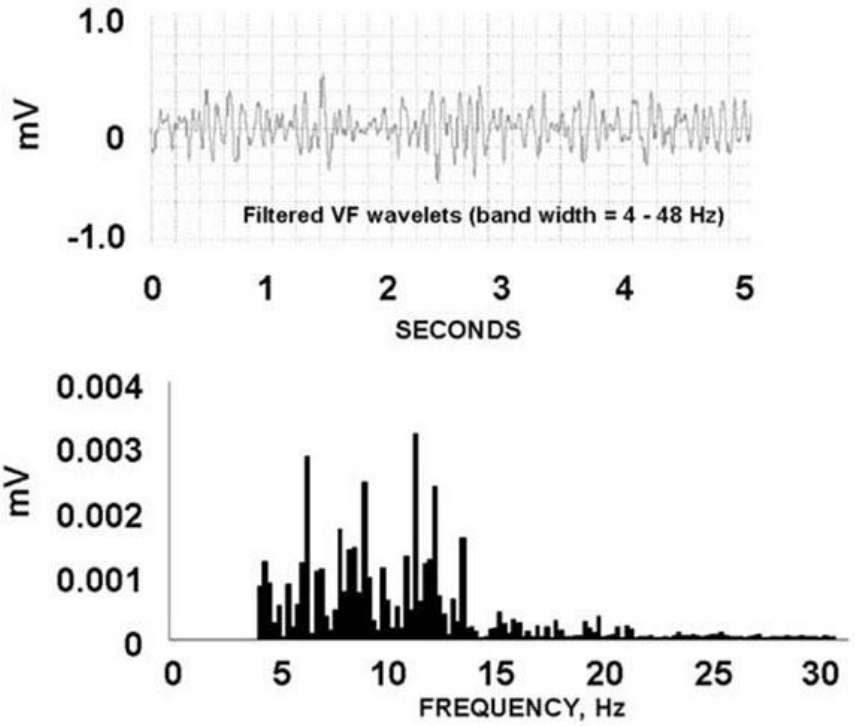

Fig B Representative example of amplitude frequency relationship and area under the curve that defines the amplitude spectrum area (*AMSA*)

The median frequency represented the frequency at which half of the power of the spectrum was above and half below and is represented by the following equation:

MF = Ó Fi x Pi / Ó Pi where Fi is the ith frequency component and Pi the relative power at Fi. AMSA was then calculated from the resulting amplitude frequency spectrum according to the following equation:

AMSA = Ó Ai x Fi where Ai is the amplitude at the ith frequency Fi.

In an initial investigation, Povoas and Bisera [38] investigated CPP obtained from arterial and right atrial pressures and VF mean amplitude, median frequency and AMSA obtained from ECG recordings from 55 domestic pigs during CPR. From these measurements,threshold values for ROSC were obtained and subsequently validated in another ten animals. CPP and mean amplitude each had a PPV of 100% but negative predictive value (NPV) of only 44% and 22%, respectively. Median frequency predicted successful defibrillation, with a PPV of 75% but an NPV of only 30%. Only AMSA yielded a more optimal combination of PPV and NPV: 86% and 85%, respectively. Among the results obtained with this new ECG parameter, the high NPV was of special interest because it was recognised that AMSA would minimise repetitive and ineffective electrical shocks during CPR.

In the same period, Pernat confirmed those results, demonstrating the capability of AMSA to optimise ventricular defibrillation timing [88] in a porcine model of cardiac arrest and resuscitation in which AMSA was highly correlated with CPP levels during CPR. The AMSA value of 21 mV-Hz predicted perfusing rhythm restoration with sensitivity and specificity >90%. AMSA NPV was 95% and statistically equivalent to that of CPP, mean amplitude and median frequency. One year later, the same authors [89] further investigated the AMSA ECG signal analysis technique to establish a threshold level that would have predicted whether an electrical shock would reverse VF in a porcine model. The investigators confirmed that an AMSA value of 21 mV-Hz had an NPV of 96% and a PPV of 78%. An AMSA value of.21 mV-Hz predicted perfusing rhythm restoration in seven of eight instances, and AMSA of 20 mV-Hz correctly predicted electrical resuscitation failure in 24 of 26 instances. It therefore became apparent that AMSA represented a method that potentially fulfilled the need for minimising ineffective and detrimental defibrillation attempts during resuscitative manoeuvres. In that investigation, AMSA values were displayed in real time for the first time and were continuously updated every 5 sec interval during CPR. AMSA was not invalidated by artefacts resulting from precordial compression. The progressive increases in AMSA observed before successful resuscitation further demonstrated that AMSA had the potential to provide an objective guide, offering better CPR quality control. Failure to increase AMSA values to near threshold levels prognosticated defibrillation failure.

The initial empirical trials identified AMSA as representing the area under the curve based on amplitude and spectral frequency as a more optimal predictor for guiding

the defibrillation attempt. The subsequent validation studies confirmed that AMSA has impressively higher specificity and PPV compared with the other predictors, maintaining sensitivity, NPV, mean amplitude, and median frequency comparable with CPP. Because AMSA was obtained during precordial compression, it fulfilled the other goal of allowing for uninterrupted precordial compression during ECG analyses. AMSA was well correlated with CPP, which is widely recognised as the gold standard for predicting successful defibrillation. Yet CPP was robust only for negative prediction. It is specificity and PPV, which are assured by AMSA, which are more likely to minimise adverse effects of repetitive high-energy shocks during CPR and the resulting postresuscitation myocardial dysfunction.

In more than 65% of the cardiac arrest events, the usual cause is an underlying acute or chronic ischaemic heart disease [90–92]. Accordingly, myocardial ischaemia and reperfusion have been involved in the triggering of malignant ventricular dysrhythmias [93, 94] and both duration and severity of myocardial ischaemia play important roles in causing myocardial cell damage [95]. Thus, VF amplitude and especially VF frequencies are different in instances of ischaemic heart disease. More recently, Indik et al. [78] confirmed these results and, more interestingly, demonstrated that AMSA values did not change importantly when VF was induced in hearts with underlying ischaemic diseases. During CPR, however, Ristagno et al proved that reduced coronary blood flow significantly affects AMSA values. AMSA was superior to CPP as an indicator of return to a perfusing rhythm after defibrillation under condition of partial occlusion of the LAD coronary artery in a porcine model of cardiac arrest and resuscitation with partial LAD occlusion of approximately 75% of the internal lumen was maintained during CPR [96] .During chest compression, CPP increased and exceeded threshold value for successful resuscitation. AMSA however, was signicantly lower in animals in which partial occlusion of the LAD was maintained during CPR. This was reflected in the greater number of electrical shocks required prior to terminating VF and in the lesser success of resuscitation. CPP is, in fact, an indirect indicator of myocardial flow produced by chest compression and represents a gradient pressure between aorta and right atrium. This gradient might be maintained even in the presence of occlusion of the coronary tree. AMSA, which is instead related to myocardial blood flow and metabolism, has been shown to be capable to substantially decrease when myocardial perfusion is reduced.

Accordingly, the quality of chest compression is a major issue [25–27]. Effectiveness of chest compressions relates to compression depth, rate and chest-wall decompression [97]. Outcomes may have been improved by assuring adequate compression depth in addition to more optimal rates of compression [98, 99]. As chest compression is usually performed without feedback, and because relatively small changes in compression depth profoundly alter haemodynamic effectiveness and outcomes, there is an increasingly recognised need for a monitor of effectiveness of chest compression [100–102]. Li and colleagues [103] therefore investigated the possibility of assessing CPR quality, especially of chest compression depth, using AMSA – which has the important advantage of being noninvasive and calculable from the universally available ECG – as part of the current practices of advanced life support. In a porcine model of VF and CPR, animals were randomised to optimal or suboptimal chest compression after VF onset. Optimal mechanical compression depth was defined as a decrease of 25% in anterior–posterior chest diameter during compression. Suboptimal compression in six animals was defined as a decrease of 17.5% in anterior–posterior chest diameter. All animals had ROSC after optimal compression. This contrasted suboptimal compressions after which no animal had ROSC. As with CPP and end tidal CO2, AMSA once again has been proven to be predictive of outcomes. Calculated AMSA values during CPR and immediately prior to defibrillation attempts were signicantly greater after optimal chest compression: the quality of chest compression was closely related to AMSA value and, in turn, to the likelihood of ROSC. As with the CPP threshold value, AMSA threshold value was achieved contingent upon compression depth such that AMSA increased progressively during chest compression and, as with CPP, predicted the likelihood of successful defibrillation. AMSA therefore was confirmed to serve as a guide to the effectiveness of chest compression and optimal timing of an electrical shock. AMSA measurement is therefore valuable to guide chest compression quality due to its capability to aid in restoring the electrical robustness of the myocardium through restoring threshold levels of coronary blood flow, as reflected by CPP. When the area under the VF amplitude spectrum curve is of insufficient magnitude, the rescuer is prompted to push harder and perhaps faster.

Current American Heart Association (AHA) guidelines suggest an interval of chest compression prior to defibrillation if the duration of untreated cardiac arrest is >4 min [104]. However in case of unwitnessed cardiac arrest, downtime is not predictable. Ristagno et al therefore hypothesized and subsequently confirmed AMSA efficacy in

identifying the duration of untreated cardiac arrest [105]. In nine domestic male pigs, VF was induced and untreated for 15 min. AMSA, more so than VF amplitude and mean frequency, was highly correlated with VF downtime and decreased over the time. Significantly lower AMSA was observed after 3 min of untreated VF. Following the 4th min, AMSA values decreased more rapidly. AMSA therefore emerged as a tool able to predict the downtime of untreated cardiac arrest and thereby a guide to better initial intervention.

Applicability of AMSA to the Clinical Scenario

The subsequent step in the evolution of AMSA as a better indicator of intervention effectiveness and defibrillation guide was confirmation of its efficacy in clinical settings. At present, in fact, chest compression creates artifacts on the ECG signal to the degree that pauses in CPR are mandatory for rhythm analysis prior to attempted de brillation [106, 107]. Substantial interruptions of chest compression have detrimental effects on the success of cardiopulmonary resuscitation [28, 84, 107], reducing the likelihood of successful defibrillation due to immediate declines in coronary perfusion [13, 84, 108]. Bisera and co-workers retrospectively applied the AMSA algorithm to human ECG recordings obtained from AEDs (automatic external defibrillators) employed in out-of-hospital cardiac arrests. The first confirmation of the capability of AMSA to predict successful defibrillation and ROSC in the clinical scenario was reported in late 2004 by Young et al. [109], and those results were recently confirmed by Ristagno et al [110].

The first study was a retrospective analysis by Young et al. [109] of ECG records of lead-2-equivalent recordings on 108 defibrillation attempts with an automated external defibrillator on 46 patients with out-of-hospital VF-related cardiac arrest. There was an impressive separation between AMSA values and successful VF conversion with ROSC. An AMSA value of 13 mV-Hz predicted successful defibrillation with a sensitivity of 91% and a specificity of 94%. This was the first evidence that the predictive value of AMSA developed in experimental models of cardiac arrest and resuscitation in pigs could be extended to humans.

In 2008, the same Authors [110] analysed a new database that included episodes of VF or ventricular tachycardia with defibrillation attempts on humans who

experienced out-of-hospital cardiac arrest. ECGs were recorded from AEDs that provided escalating biphasic shock in the sequence 120, 150, 200 j. AMSA was confirmed as a valid tool for predicting the likelihood that any one electrical shock would restore a perfusing rhythm during cardiopulmonary resuscitation in 90 men with out-of-hospital cardiac arrest. The analysis was performed on a 4.1-s interval of ECG recordings immediately preceding the delivery of defibrillatory shock. For that study, the outcome was defined as being successful if defibrillation restored an organised rhythm with heart rate > 40 bpm commencing within the 1-min postshock period and persisted for a minimum of 30 s. The outcome was considered unsuccessful if VF, ventricular tachycardia (heart rate >150 bpm), asystole or pulseless electrical activity with pauses >5 s occurred. AMSA values were significantly greater in successful versus unsuccessful defibrillation (16 mV-Hz and 7 mV-Hz, respectively; $p < 0.0001$). A threshold value of 12 mV-Hz AMSA was predictive of the success of each defibrillation attempt with a sensitivity of 91% and a specificity of 97% (Fig. C). PPV, which refers to the proportion of shocks that correctly predicted perfusing rhythm restoration, was 95%. NPV, which refers to the proportion of shocks that predicted failure and actually failed to restore a perfusing rhythm, was 97%. The results of that study were consistent with the previous retrospective analysis [108,109] of human cardiac arrest patients. A very close AMSA threshold value was calculated and a high sensitivity and specificity of this approach was confirmed. Of particular interest was that although defibrillators by different manufactures were employed in the two studies, results were consistent. This is therefore further confirmation that AMSA represents an excellent predictor of success of an electrical shock attempt, and this capability is independent of the defibrillatory energies and waveforms used. Although several limitations were clarified by the authors of those studies, such as the potential confounding variables of “hands-off time before defibrillation” that was not controlled for, and the old “three-shocks” protocol employed during that period, clinical efficacy of AMSA was confirmed.

Finally, in a study of 267 CPR sequences from 77 patients with out-of-hospital cardiac arrest, Eftestøl and colleagues [111] confirmed AMSA as one of the most powerful predictors of defibrillation success.

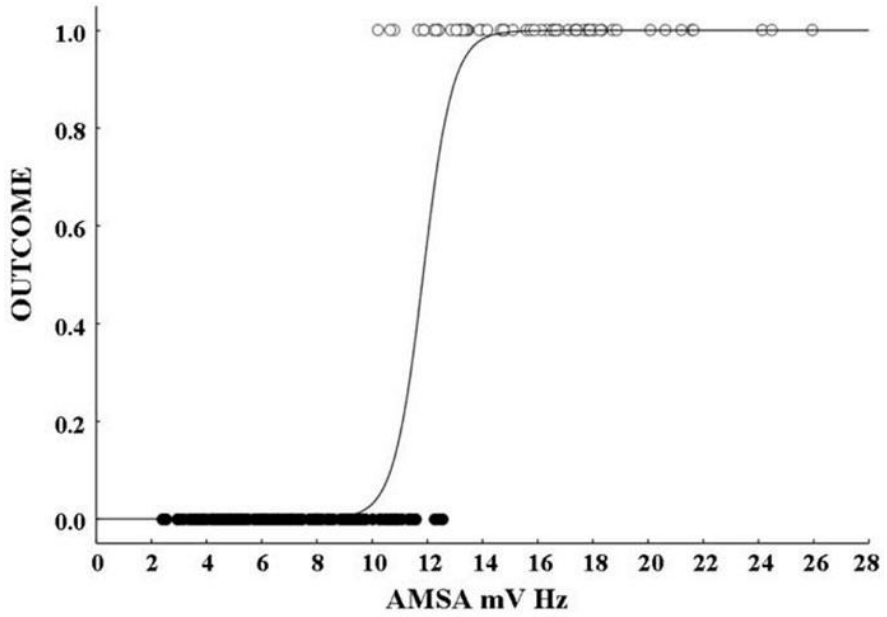

Fig. C Logistic regression representing amplitude spectrum area (*AMSA*) in relationship to defibrillation outcome

Summary

CPP and etCO2 represent useful tools for monitoring the effectiveness of chest compression and predicting CPR success. These measurements, however, are not feasible in out of-hospital cardiac arrest situations. Investigators therefore focused their attention on VF waveform morphology as a success predictor of resuscitation. Greater VF amplitude with dominant and median frequency was associated with improved outcomes. However, the challenge is to ensure high sensitivity and specificity, especially during precordial compression, to identify the ideal moment to deliver the defibrillatory shock. AMSA analysis represents an accurate predictor for successful defibrillation and is a simple parameter that can be easily obtained by a conventional surface ECG, which is part of routine practice of advanced cardiac life support. Moreover, this method has the potential advantage in that it is not invalidated by artefacts produced by chest compression and thereby can be used during CPR without detrimental interruptions of chest compression and ventilation. Experimentally, consistent evidence of AMSA validity has been proved in data from both animals and humans. Accordingly, AMSA has now emerged as a clinically applicable method derived from ECG tracing that may provide a real-time indicator for chest compression efficacy and predict defibrillation success. We therefore anticipate that the AMSA algorithm incorporated into conventional AEDs will

minimise interruption in chest compression and thus decrease the delivery of futile and detrimental electrical shocks, leading to more optimal defibrillation timing.

AIM OF THIS STUDY

The present study is the first phase of large translational clinical study. It is based on the retrospective analysis of ECG and clinical data obtained from out-of-hospital cardiac arrest (OHCA) victims in the Lombardy Region to evaluate and confirm the efficacy of AMSA as a predictor of successful defibrillation (DF) during CPR and calculate a threshold value for AMSA in this specific population. The following phase will be observational and prospective, based on a similar patient population, aiming to validate on-field the efficacy and accuracy of AMSA as a guide to RCP in OHCA. At present, prospective clinical study are still lacking.

In this phase, the following specific primary objectives will be addressed:

- To verify the relationship between pre-DF AMSA values and success of defibrillation
- To identify the threshold AMSA value capable to predict successful DF in first, second and subsequent defibrillation attempts
- To evaluate the correlations between successful DF and other classical ROSC predictor derived from ECG recording, as amplitude and rate of VF and ventricular tachycardia (VT)
- To evaluate the correlation between pre-DF AMSA value ,and vital hospital admission

EXPERIMENTAL DESIGN

Inclusion criteria

The study has been designed to enroll 1000 adult patients with non-traumatic OHCA in whom an ECG requiring defibrillation during CPR had been recorded. The

recruitment period ranged from January, 1st , 2008 to Dec 31st,2009. On-field emergency interventions by automatic external defibrillators (AED) were carried out by ambulance emergency teams of the 118 network of Regione Lombardia, based in the provinces of Bergamo, Brescia, Como, Cremona, Lecco, Lodi, Milano, Monza, Mantova, Pavia, Sondrio and Varese.

Exclusion criteria

Patients less than 18 years of age, pregnant, with traumatic OHCA or known advanced end-stage condition were excluded. Moreover, cases with inappropriate AED DF as identified by the core lab investigator (i.e. the author of the present manuscript) were excluded.

Data collection

AED stored electrograms and clinical data, which had been already stored in digital form at all operative units headquaters, were subsequently transmitted to the central database collecting center (Institute of Anesthesiology of the S. Gerardo Hospital, Monza) and subsequently sent to the Mario Negri Institute, Milan, for verification of inclusion/exclusion criteria and subsequent AMSA analysis.

AMSA analysis

AED electrograms were processed via a custom-made software based on Matlab 7.2. ECG signal was filtered in a window between 2 and 48 Hz in order to minimize low-frequency artifacts from chest compressions and exclude environmental electrical interferences at frequencies > 48 Hz. Analogic ECG signals were then digitized and converted from time to frequency domain by the fast Fourier transform technique which converts a time-related voltage variation (mV) into a frequency-related voltage variation (Hz). The resultant relationship is called “power spectrum” or amplitude/frequency spectrum. The sum of individual amplitudes and frequencies determines AMSA = $\sum Ai \cdot Fi$ where Ai is the amplitude relative to Frequency i.

A 2 sec ECG window ending at 0.5 sec before DF was analyzed and AMSA calculated, after fast Fourier transformation. In the 2 sec interval the classical waveform parameters were calculated, i.e. amplitude in mV and frequency in Hz. The *dominant amplitude* has been defined as the longest distance between two VF deflections; the *mean amplitude* as the average amplitude within the time interval. The mean and dominant

frequencies were obtained by the fast Fourier transform of the ECG signal: the *mean frequency* is the frequency value by which the spectrum is divided in two equal sectors, the *dominant frequency* is the one indicating the highest value of the power spectrum.

DF was defined as successful in the presence of spontaneous rhythm ≥ 40 bpm starting within 60 secs from the DF. DF was defined as unsuccessful if, after DF , VF, ventricular tachycardia > 150 bpm, asystole or pulseless electrical activity < 40 bpm were observed.

Statistical analysis

Threshold values of AMSA able to discriminate DF outcome were individuated and sensitivity, specificity, accuracy, positive and negative predictive values (PPV, NPV) were calculated. AMSA value was defined as the one correlated to the best balance between sensibility and specificity The area under the receiver operating characteristic (ROC) curve was measured: the area under the curve, as identified by sensibility and by the reciprocal of specificity for any variation of AMSA value, indicates the ability of AMSA in discriminating positive or negative results of DF: the discriminatory capability of the test is higher when area under the curve shifts towards 1, worse when it shifts towards 0.5

RESULTS

Electrocardiographic (ECG) data recorded by automated external defibrillators from different manufactures (Zoll, PhysioControl) were obtained from 8.419 cardiac arrest events. Zoll defibrillators were provided with accelerometers for the discrimination between electrograms and chest compression artifacts. Among these events, only VF/VT cardiac arrests receiving DFs were selected (n = 1055, 12,5%). Of such 1055 patients, 583 were males and 472 females, of mean age 68.4±12.3. Clinical data previous to the index event, beyond those considered exclusion criteria, were unknown or largely insufficient in more than 60% of cases and were therefore excluded from the present analysis.

A total of 2.442 quality DF events, including 1055 first attempts and 1.387 subsequent ones, from 1.055 out-of-hospital cardiac arrests were included in the analyses. The remaining 7364 were events of pulseless electrical activity, asystole, bradyarrhythmias for which the automated system did not indicate DF. No more than 8 inappropriate indications

and subsequent DF discharges were delivered, 3 in patients with implanted pacemaker, the other as a result of erroneous AED interpretation of spontaneous, not chest compression generated, artifacts. An AED solid memory recording with successful DF is reproduced in Fig.1, a filtered electrogram for AMSA processing in Fig 2 . A sample of resulting AMSA profile of VF in a case with successful DF is showewd in Fig.3. Consensus decision on electrogram vs artifactual nature of the recording was required in 1% of recordings, whereas consensus interpretation of the recorded arrhythmia was carried out in 18 cases. DF success rate was of 26%, 27%, and 25.2% for all, first, and subsequent DFs, respectively. AMSA was significantly greater prior to successful DFs, compared to that preceding unsuccessful ones (13.8 vs. 6.9 mV-Hz, and 13.9 vs. 6.8 mV-Hz, and 13.7 vs. 7 mV-Hz, for all, first, and subsequent DFs respectively (Figure 4). Intersection of sensitivity, specificity and accuracy curves identified a threshold value of AMSA of approximately 9.5 mV-Hz, able to predict DF outcome, with a balanced sensitivity, specificity and accuracy of 80%, for all, first, and subsequent DFs (Figure 5). Moreover, intersection of PPV and accuracy curves identified a threshold value of AMSA of approximately 15 mV-Hz able to predict a successful DF with a PPV and accuracy of 80%, for all, first, and subsequent DF attempts. AMSA values greater than 27 mV-Hz correctly predicted the success of DF with a PPV value of 100%. AMSA below 8 mV-Hz correctly predicted the DF failure with a NPV of > 95%, for all, first, and subsequent DFs. Further decreases in AMSA values below 4 mV-Hz achieved a NPV of 100%. Area under ROC curves was 0.872, 0.869, and 0.875 for all, first, and subsequent DFs, respectively (Figure 6).

AMSA prediction of successful DF and ROSC was verified in a subgroup of 628 patients with confirmed CPR outcome and hospital admission. Of them 205 (33%) were declared dead on site, 177 (28%) died during transport to hospital, 105 (17%) died in emergency room and 141 (22%) were resuscitated. AMSA mean value of resuscitated versus dead patients was significantly higher (11.93 ± 5.65 vs 7.15 ± 4.57, $p < 0.05$) (Fig 7). The non significant differences with the mean AMSA values observed general population probably reflect the differences in event number.

DISCUSSION

The present study was carried-out on a database the dimensions of which exceed those of the previously published studies, thanks to a design aimed to incorporate events and DF intervention in a densely populated area, Lombardy, with 10 million inhabitants. For this reason, raw data included all events which were initially declared of cardiac arrest on-field but a large proportion of them was probably of non cardiac origin. This explains the low proportion of cases (12,5%) in which VF or VT amenable to DF was recorded, even taking into account the fact that asystole and bradyarrhythmias form a consistent or even prevalent finding in primary cardiac arrest [90]. This study confirms the AED as a reliable and effective devices to deliver appropriate and timely DF minimizing the chest compression standstill to confirm underlying cardiac rhythm [81].

AMSA values were comparable to those of previous studies[105-109]: its position in the superior portion of the values obtained by others reflects the magnitude of the database, which entailed VF morphologies with extremely variable power-spectrum features; it is however noteworthy that only a 1,2 Hz difference was found between the mean threshold value (13.8 Hz) and the threshold of 15 Hz identifying 80% of successful DF attempts. The 13,8 Hz threshold value consistently approaches the 13 Hz value obtained in the first clinical study by Young [109]. This confirms that the power spectrum area widely included between 12-15 Hz, as it emerges from ours and other published data, consistently correlates with a perfused and viable state of the fibrillating heart which allows to predict successful DF. The presence of a small number of cases in which VT or ventricular flutter instead of VF was recorded can explain a somewhat higher threshold value: in fact, their morphologies are characterized by discrete and tall electrograms amenable to higher AMSA values. On the other hand, 8 Hz has been confirmed as a reliable threshold below which DF attempts should be withheld.

Of note is the fact that no difference was noted when recordings from devices provided with accelerometers to discriminate compression artifacts and from those not provided were compared: this confirms the reliability in the filtering settings of AMSA cutoff setup in accepting only signals of true cardiac origin, as demonstrated in previous experimental and clinical studies [112].

The comparative analysis of AMSA values and inherent ROCs demonstrated no significant differences between the first and the subsequent DF in comparison with the unsuccessful DF. This result is consistent with the fact that the perfusion and metabolic state is substantially comparable both when a single or multiple DF are needed to restore ROSC. Details of this subanalysis demonstrate that in most cases of multiple DF leading

to stable ROSC, recurrent VF after a variable period of ROSC and not persisting VF after a first of multiple DF is the case; so, electrical instability, even in the presence of restored perfusion is responsible for the need of multiple interventions as confirmed by the reproducibility of AMSA findings in the recurrent VF electrograms. This findings that the 2005 ILS guidelines raccomendations for “one single shock only”, in order to avoid damage to the heart before other interventions do not apply to cases with better metabolic and perfusion profile where subsequent DF can achieve restoration of a perfusing rhythm [110].

The findings obtained by comparing AMSA values in patients successfully resuscitated versus those of patients who died either on-field or during transport to the hospital and in the emergency room (11.93 ± 5.65 vs 7.15 ± 4.57, $p < 0.05$) consistently confirm the clinical relevance of this parameter not only as an immediate predictor of successful DF but also as an reliable prognostic indicator, at least at short term.

Study limitations

Given the experimental design, in which the amplitude of the database and the “real life” setup were preferred to precise clinical data acquisition , this study has some obvious limitations: baseline clinical condition of the patients is largely unknown; time from cardiac arrest to beginning of CPR is unknown, although AMSA values can help to discriminate non-intervention time intervals longer than 10 minutes. Viceversa, as underlying conditions where largely unknown AMSA profile discriminations between ischemic and nonischemic VF was impossible [81]. Moreover, the modality and quality of CPR was not assessed but, given the number of cases, of rescue teams involved and operational settings, it is presumable that it was variable; however, this could be a minor problem as all rescue teams were part of the 118 network and were declared proficient after an adequate and generally adopted training workup [100,101]. More importantly, the “hands off period” before DF was not taken into account [84], but its value should not be overestimated as the use of AED has been demonstrated to minimize this period [111]. However, some variability should be taken into account when considering the number of delivered DF in each patient which were decided individually decided by the paramedic in charge of the defibrillator and/or by the rescue team leader. the interruption of DF treatment after one or two failed attempts could have eliminated some theoretical possibility on successful DF and, therefore, of augmenting the positive case percentage and, consequently, modifying

the AMSA values. The same apply to the decision of early transport or on-site attempt to stabilize the clinical conditions which could have affected the outcome of the substudy population the fate of which has been analysed and compared with AMSA values.

CONCLUSIONS

In this population, probably the largest studied to date, an AMSA algorithm was capable to predict DF outcome with high accuracy, thus confirming previous experimental findings and results of smaller clinical studies. Although these database deserves further insights and analyses, its positive results opens the way to a prospective study utilizing customized defibrillators incorporating a real-time display. If, it is reasonable to expect, also this study will be successful, a new generation of AMSA guided AED could be expected for approved clinical use in the next few years.

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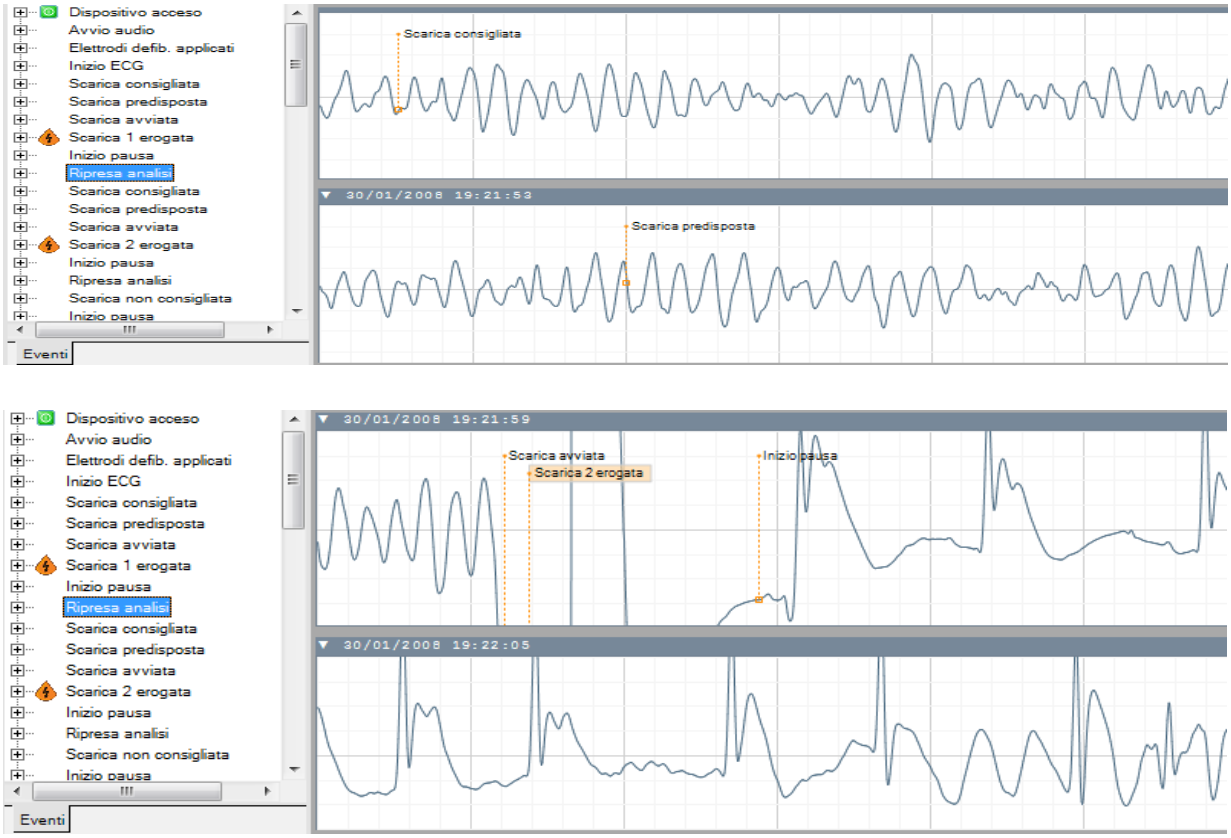


Fig. 1. Automatic external defibrillation solid memory recording of a ventricular fibrillation event successfully interrupted by DC-shock and followed by resumption of sinus rhythm with ST elevation

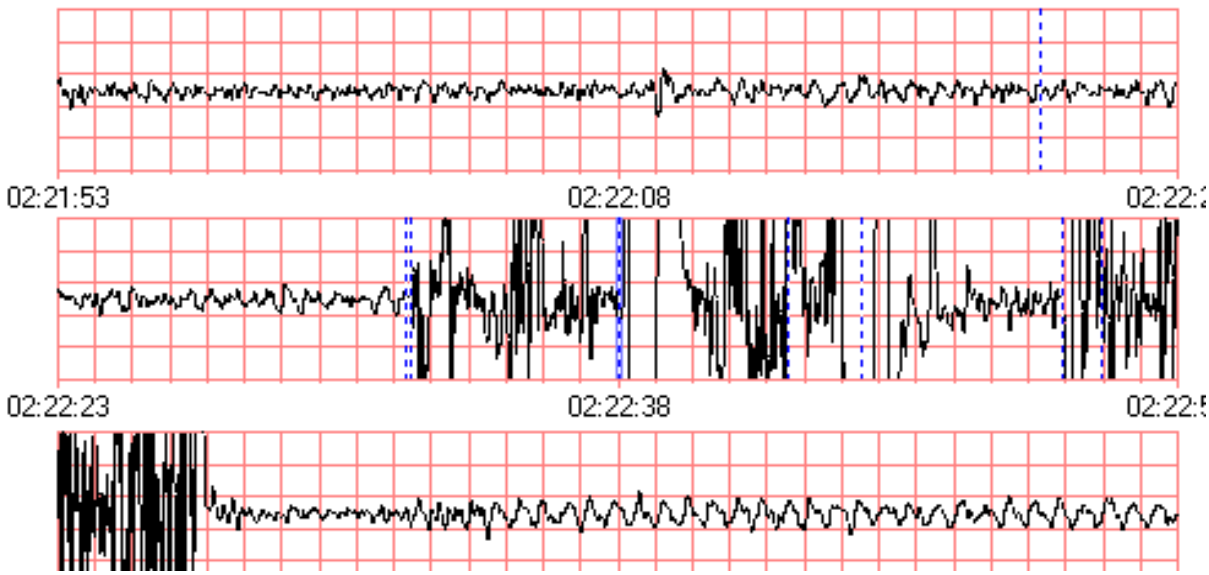


Fig.2 Filtered electrogram at 4 to 48Hz of a ventricular fibillation episode for AMSA analysis

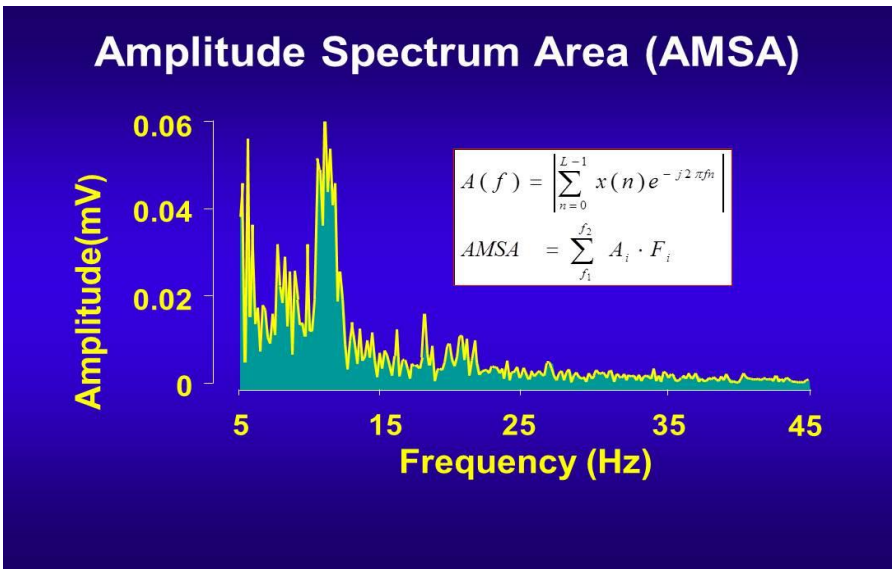
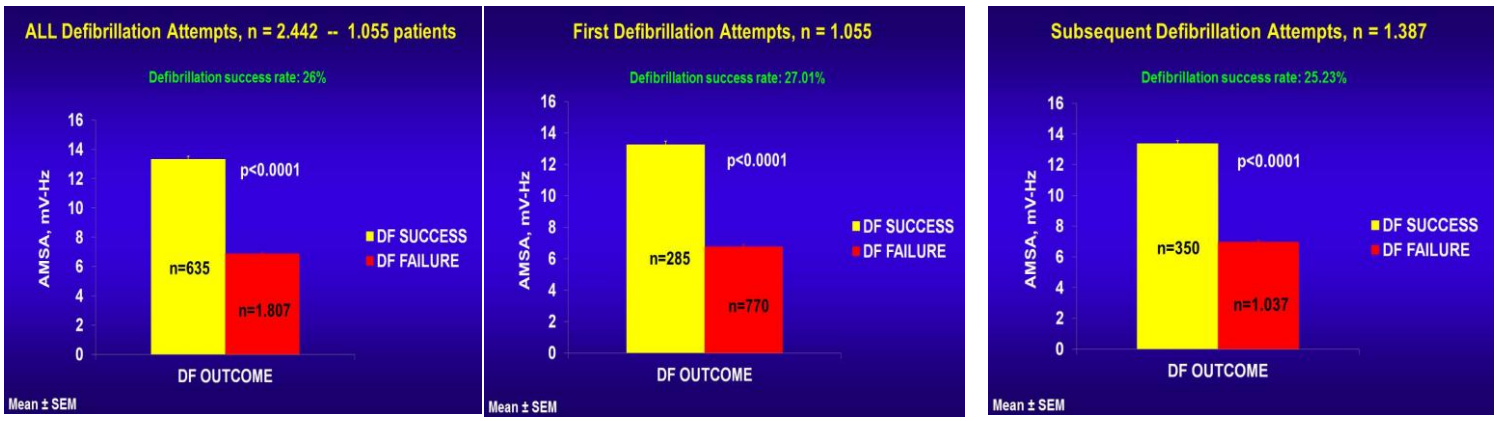
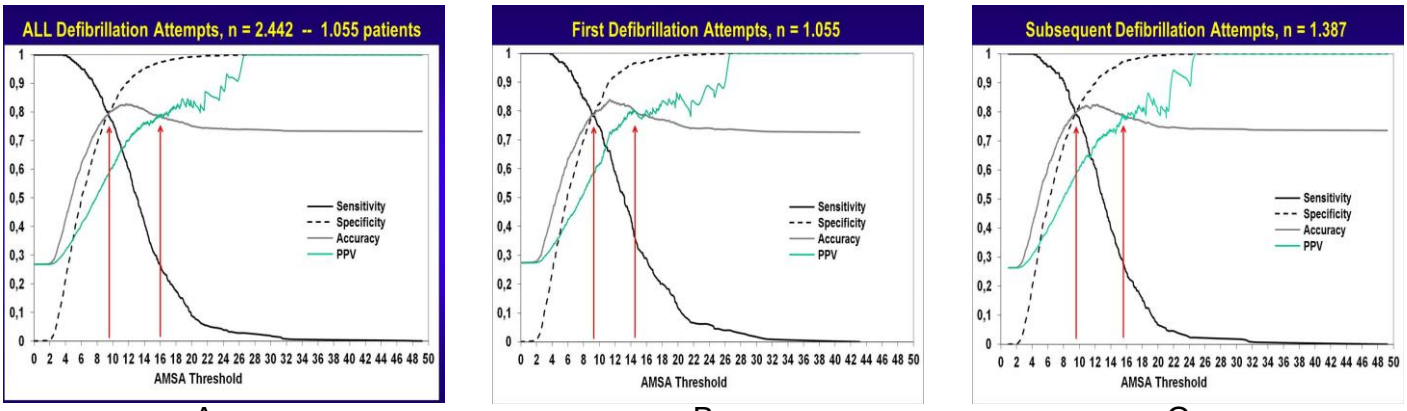


Fig. 3 Typical AMSA profile of ventricular fibrillation in a successful defibrillation event



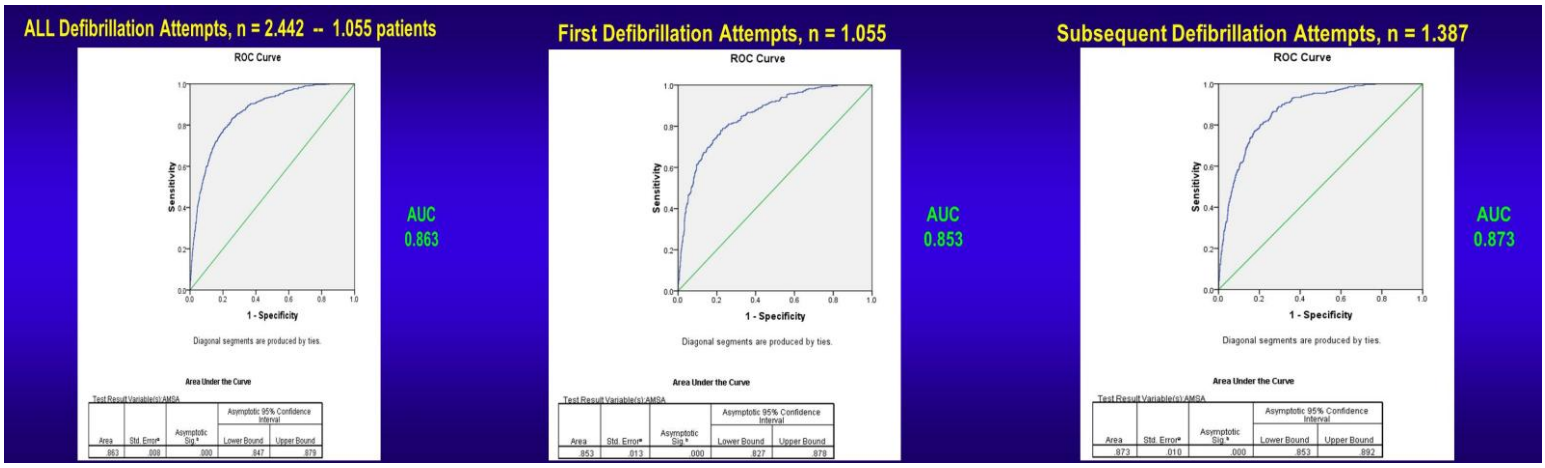
A B C

Fig. 4 AMSA values in successful and failed defibrillation in all treated events (panel A),first (panel B) and subsequent defibrillation attempts. The difference between successful and failed attempts remain stable even after subdivision



A B C

Fig. 5. Intersection of sensitivity, specificity and accuracy curves of threshold value of AMSA for all, first, and subsequent defibrillation attempts (panels A,B,C): a threshold of approximately 9.5 mV-Hz, able to predict DF outcome, with a balanced sensitivity, specificity and accuracy of 80%. No significant differences appeared when first and subsequent attempts were considered separately.



A B C

Fig. 6 Area under ROC curves for all, first, and subsequent defibrillations, respectively (panels A,B,C) did not show significant differences between total, first and subsequent successful attempt

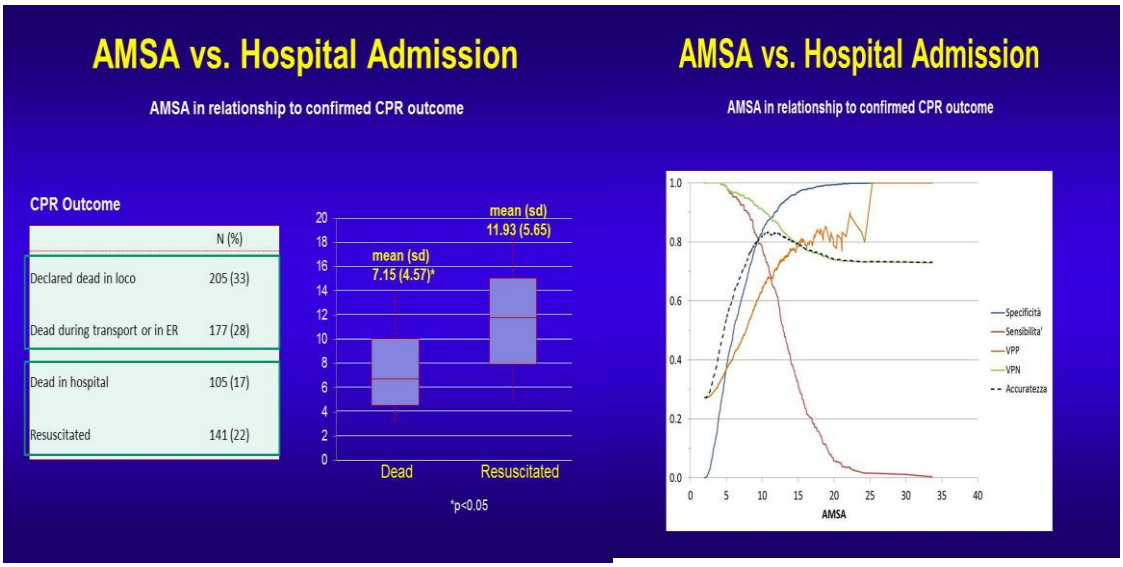


Fig. 7. AMSA value and intersection curves in a subgroup of events with confirmed CPR outcome showing significant differences between dead and resuscitated patients (p = <0.05)