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Clinical paper

The ventricular fibrillation waveform in relation to shock success in early vs. late phases of out-of-hospital resuscitation

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Abstract

Background: The amplitude spectrum area (AMSA) of the ventricular fibrillation (VF) waveform predicts shock success and clinical outcome after out-of-hospital cardiac arrest (OHCA). Recently, also AMSA-changes demonstrated prognostic value. Until now, most studies focused on early shocks, while many patients require prolonged resuscitations. We studied AMSA and its changes in relation to shock success, for both the early and later phase of resuscitation.

Methods: Per-shock VF-waveform analysis of a prospective OHCA-cohort (Nijmegen, The Netherlands). The absolute AMSA and relative AMSA-changes (ΔAMSA) were calculated from three-second VF-segments prior to defibrillation. Shocks were categorised as early (#1–3) or late (#4–8). Shock success was defined as return of organised rhythm.

Results: Shock success was 46% for early (131/286) and 52% for late shocks (85/162), p = 0.18. Early shock success varied from 23% to 70% with increasing quartiles of AMSA (p-trend<0.001). For late shocks, there also was an association with AMSA, with a narrower range in shock success from 43% to 68% (p-trend = 0.04). Higher values of ΔAMSA were associated with shock success in the early, but not in the later phase.

Conclusion: AMSA relates to shock success during the entire resuscitation, but associations were most apparent for early shocks. AMSA-changes were also associated with shock success, but only in the early phase of resuscitation. In an era of smart defibrillators, absolute AMSA and relative changes hold promise for studies on early guidance of resuscitation, whereas additional studies are warranted to further characterize shock prediction in the later phase.

Keywords: Out-of-hospital cardiac arrest, Ventricular fibrillation, Waveform analysis, Amplitude spectrum area

Introduction

Ventricular fibrillation (VF) is the first observed rhythm in ±30% of all out-of-hospital cardiac arrests (OHCAs)[1], with dismal survival despite achieved improvements in the chain of care.[2–4] Appreciating that defibrillation of so-called "coarse" VF is more likely to be successful than of "fine" VF, the VF-waveform has become a topic of increasing interest to predict and improve outcomes.[5–7] In this context, the amplitude spectrum area (AMSA) has been introduced as a quantitative measure, based on a combination of frequency and amplitude characteristics.[8]

Several OHCA-studies demonstrated the potential of AMSA, in that it predicts both shock success and survival with good neurological

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outcome.[9,10] Currently, a randomised trial is running, investigating shock timing with an AMSA-guided 'smart defibrillator', with prolonged chest compressions and delayed defibrillation if AMSA is considered too low.[11]

More recently, changes in AMSA have been studied as well. Given the correlation of AMSA with coronary perfusion and myocardial energy levels, an increasing AMSA might reflect an improvement of the myocardial metabolic state.[12–14] Recent analyses on human data confirmed that increases of AMSA are associated with favorable outcome.[9,15]

In follow up on data for first defibrillation attempts, recent studies suggested that AMSA also predicts favorable outcome when obtained beyond the first shock delivery.[6,16] This is of specific interest, given that 40–50% of all VF-patients need more than three defibrillation attempts.[17–19] However, most information on AMSA, and particularly its changes, has been derived from studies restricted to the early phase of resuscitation, predominantly in cohorts with on average two shocks per patient.[6,9,15,16] At present, little information is available on how AMSA evolves over a longer period of resuscitation, and how these changes relate to shock success.

In view of the above, we aimed to improve our understanding of the VF-waveform and its association with shock success over a long period of resuscitation. In a cohort of prolonged resuscitations, we therefore assessed AMSA and AMSA-changes in relation to shock success for both the early and late phase of resuscitation.

Methods

Study population

From our prospective OHCA-registry (Nijmegen, The Netherlands) we studied all adult (≥18 years), non-traumatic arrests with VF as first observed rhythm, with at least one defibrillation attempt.[18] To ensure comparability of the included shocks, we excluded patients who received AED-shocks prior to arrival of the emergency medical services (EMS). Hence, we solely included patients who received their first shock by EMS-personnel. Further exclusion criteria were the absence of either paddle ECG-recordings or shock outcome data. Given the observational design, written informed consent was not necessary to obtain according to the Dutch Act on Medical Research involving Human Subjects.

Emergency medical services

The Nijmegen area (Gelderland-Zuid) has a population of about 530,000 residents and covers 1040 square kilometres, including urban, suburban and rural areas. The EMS-system is activated by calling 112. Paramedics give instructions to the caller to initiate basic life support, and at least one ambulance is dispatched to the scene. CPR-delivery was performed by EMS-personnel according to the prevailing guidelines at the time of arrest. At the time of our registry, our hospital participated in a randomised trial, in which the protocol dictated 3-minute CPR-intervals.[20] Although data on CPR-quality was not systematically scored, EMS-personnel were trained intensively, and there was strict feedback on CPR-quality. A mechanical chest compression device (Autopulse®) was part of the standard EMS-equipment, but not routinely used.

Data acquisition

Demographic and arrest characteristics were collected using EMS and hospital records, according to the Utstein style definitions, except for sustained return of spontaneous circulation (ROSC), which was defined as ROSC followed by hospital transport.[21] Electrocardiogram (ECG, sample frequency 125 Hz) and transthoracic impedance (TTI) data were recorded with defibrillator paddles. All patients were treated with the same defibrillator (Lifepak12, PhysioControl, Redmond, USA), with identical signal processing characteristics (e.g. built-in filters). Biphasic shocks were manually delivered in a standard sequence of 200-360-360 Joule. ECG and TTI-data were visualised with Codestat (V7.0, PhysioControl, Redmond, USA) and exported to Matlab compatible files for signal analysis.

VF-waveform analysis

VF-waveform analysis was performed with Matlab (R2014b, Mathworks, Natick, USA). We performed a per-shock analysis, i.e. an investigation in which we focused on individual shock outcomes. In this analysis, we studied the VF-waveform at subsequent measurement points (analyses of all first shocks, second shocks, third shocks, etc.). We prospectively specified a minimum number of 10 analysable shocks per measurement point during the resuscitation. VF-waveform segments were selected, visually free of (chest compression) artefacts and as close as possible, but with a maximum of 30 s, prior to the shock. Signals were pre-processed with a fourth-order Butterworth bandpass filter with cutoff frequencies of 2–48 Hz. A three-second interval of VF was used for calculation of the AMSA.

Calculation of AMSA

A discrete fast Fourier transform was performed on all 376 data points for conversion to the frequency domain. In analogy to previous reports, AMSA was calculated from the obtained frequency spectrum, as the summed product of individual frequencies and their corresponding amplitudes over an interval from 4 to 48 Hz.[7,10] A more detailed description of the AMSA can be found in Supplement File 1. Furthermore, we calculated the relative difference of AMSA compared to the previous shock delivery (e.g. the relative change of AMSA between the first two shocks is calculated as $\Delta\text{AMSA} = \frac{\text{AMSA shock2}}{\text{AMSA shock1}}$).

Study groups

Shocks were categorised as either shocks in the early phase, or the late phase of resuscitation. Dichotomisation was performed as follows:

- Early shocks: Shocks earlier than the median number of shocks in our population.
- Late shocks: Shocks later than, or equal to, the median number of shocks in our population.

End point and aim of the study

The primary end point was shock success, defined as return of organised rhythm (ROOR), i.e. at least 2 QRS-complexes within 5 s, within 60 s after shock delivery.[22] We analysed AMSA and ΔAMSA in relation to shock success, for the early and late phase of resuscitation respectively.

Statistics

Categorical data were reported as numbers (percentages). Continuous variables were analysed for Gaussian distribution and reported as

means ± standard deviations or medians (interquartile ranges, IQR), whichever appropriate. Continuous values of AMSA and ΔAMSA were reported as medians (IQR) and compared between successful and unsuccessful shocks using the Mann Whitney U test. VF-characteristics were subsequently divided into quartiles and compared in relation to shock success using Chi-square tests for trend. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS (Version 25, IBM, Armonk, USA).

Results

Dataset

In total, we performed VF-waveform analysis on 448 shocks, in a group of 139 OHCA-patients with VF as first observed rhythm. Baseline characteristics of the study population are reported in Table 1; Supplement File 2 depicts in- and exclusion criteria. Mean age was 63 ± 14 years and 71% was male. Of all patients, 39% had a public arrest, 60% received bystander-CPR and in 76% the arrest was witnessed.

Shock characteristics

The median number of shocks per patient was 4 [2–7]. Consequently, shocks 1–3 were regarded as the "early phase", whereas fourth and later shocks were regarded as the "late phase" of resuscitation. Of the 448 shocks, 48% was successful (216/448). A total of 286 analysed shocks was delivered in the early phase of resuscitation, of which 46% was successful (131/286), compared to 162 shocks in the late phase, of which 52% (85/162) was successful, p = 0.18.

Table 1 – Baseline characteristics of the study population.

VF-waveform cohort	
Patient characteristics	
Age (years)	63 ± 14
Male gender	98 (71)
Arrest characteristics	
Public location arrest	53 (39)
Witnessed arrest	97 (76)
Bystander	93 (73)
EMS	4 (3)
Bystander CPR	79 (60)
Response time (minutes)	8 (5–10)
Number of EMS shocks	4 (2–7)
Amiodarone	63 (55)
Adrenaline	95 (82)
Outcome characteristics	
Any ROSC during resuscitation	81 (60)
Sustained ROSC	61 (45)
Survival to discharge	32 (24)

Values are reported as means ± standard deviations, medians (interquartile ranges), or n (%). In some cases, baseline characteristics were missing and reported for less than 139 patients: public location (n = 136), witnessed arrest (n = 128), bystander CPR (n = 131) response time (n = 111), number of EMS-shocks (n = 138), amiodarone (n = 115), adrenaline (n = 116), any ROSC (n = 136), sustained ROSC (n = 137) and survival to discharge (n = 132). EMS = emergency medical services; CPR = cardiopulmonary resuscitation; ROSC = return of spontaneous circulation.

Amplitude spectrum area: early vs. late phase of resuscitation

Median AMSA of all shocks in the early phase was 9.2 mVHz [6.2–13.3], and higher prior to successful vs. unsuccessful shocks (11.3 mVHz [7.8–15.9] vs. 8.1 mVHz [5.1–11.1], $p < 0.001$, Table 2). The proportion of shock success was 23% in shocks of the lowest AMSA-quartile and increased across quartiles to 70% in the highest AMSA-quartile (p-trend <0.001, Fig. 1).

The median AMSA of all shocks in the late phase was 7.6 mVHz [5.8–12.0]. There was a trend towards a higher AMSA prior to successful vs. unsuccessful shocks (8.6 mVHz [6.0–12.3] vs. 6.8 mVHz [5.5–11.0], p = 0.07, Table 2). The proportion of shock success ranged between 43% and 68% among AMSA-quartiles (p-trend = 0.04, Fig. 2). AMSA-values in relation to shock success over the course of resuscitation can be found in Fig. 3 and Supplement File 3.

AMSA-changes: early vs. late phase of resuscitation

The median ΔAMSA of all shocks in the early phase was 1.06 [0.90–1.35], and higher for successful vs. unsuccessful shocks (1.16 [0.94–1.42] vs. 1.02 [0.84–1.25], p = 0.03, Table 2). The proportion of shock success ranged between 40% and 65% among ΔAMSA-quartiles (p-trend = 0.03, Fig. 1).

The median ΔAMSA in the late phase was 0.93 [0.77–1.11], without significant differences between successful and unsuccessful shocks (p = 0.48, Table 2). The proportion of shock success did not differ significantly among ΔAMSA-quartiles (p-trend = 0.48, Fig. 2).

Discussion

In this cohort of prolonged resuscitations, we demonstrated that the association between AMSA and ΔAMSA with shock success differs between the early and late phase of resuscitation. In concordance with previous reports, restricted to the first few shocks, we found significant associations between AMSA, ΔAMSA and shock success. Contrastingly, in the later phase of resuscitation, AMSA-changes showed no association. The observed association between absolute AMSA-values and shock success in this later phase were less consistent and require further study, also with regard to the predictive value. In an era of smart defibrillators, our data support future studies on AMSA-guided resuscitative efforts during the first few shocks. For later shocks, additional initiatives are eagerly awaited to further characterize determinants of shock success.

Previous studies

Animal studies

Animal studies have provided a unique study design to address the prognostic value of the VF-waveform, and it has repeatedly been shown that a higher AMSA is related to favourable defibrillation outcome.[23,24] Studies on the course of AMSA report decreasing AMSA-values with increasing time delay, and a positive effect of CPR on the VF-waveform.[25] Interestingly, in a porcine study comparing a CPR-first resuscitation strategy with a conventional shock-first strategy, subsets with CPR showed improved VF-characteristics and higher shock success rates.[26] It should be noted that experimental studies focused on VF in the early phase of cardiac arrest, hampering comparisons with our analyses in the late phase.[23–26]

Table 2 – The amplitude spectrum area (AMSA) in relation to shock success (return of organised rhythm).

VF-waveform in relation to shock success : Early vs. late phase of resuscitation

	Shock success	No shock success	p-value
All shocks			
AMSA	9.7 (7.0–14.0)	7.5 (5.3–11.1)	<0.001
Δ AMSA	0.98 (0.86–1.23)	1.00 (0.79–1.17)	0.25
Shocks 1–3			
AMSA	11.3 (7.8–15.9)	8.1 (5.1–11.1)	<0.001
Δ AMSA	1.16 (0.94–1.42)	1.02 (0.84–1.25)	0.03
Shocks 4–8			
AMSA	8.6 (6.0–12.3)	6.8 (5.5–11.0)	0.07
Δ AMSA	0.92 (0.78–1.07)	0.95 (0.76–1.13)	0.48

Shocks were divided in early shocks (shocks 1–3, N = 286) and late shocks (shocks 4–8, N = 162). Both pre-shock AMSA and the ΔAMSA (relative change of AMSA compared to previous shock) were reported. Values were reported as medians (interquartile ranges). VF = ventricular fibrillation.

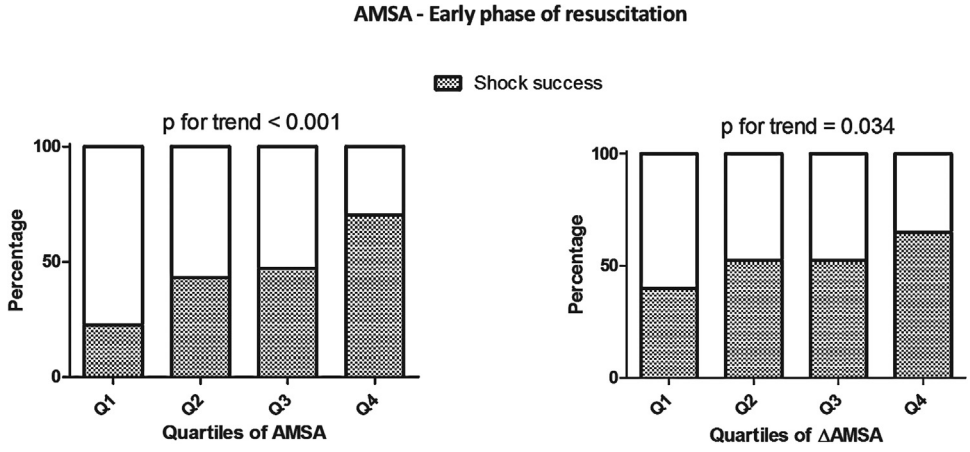

Fig. 1 – AMSA in the early phase of resuscitation. Quartiles of the amplitude spectrum area (AMSA, left) and the relative change in AMSA (ΔAMSA, right) in relation to shock success (return of organised rhythm), for the first three shock deliveries.

Fig. 2 – AMSA in the late phase of resuscitation. Quartiles of the amplitude spectrum area (AMSA, left) and the relative change in AMSA (ΔAMSA, right) in relation to shock success (return of organised rhythm), for shocks later than the third.

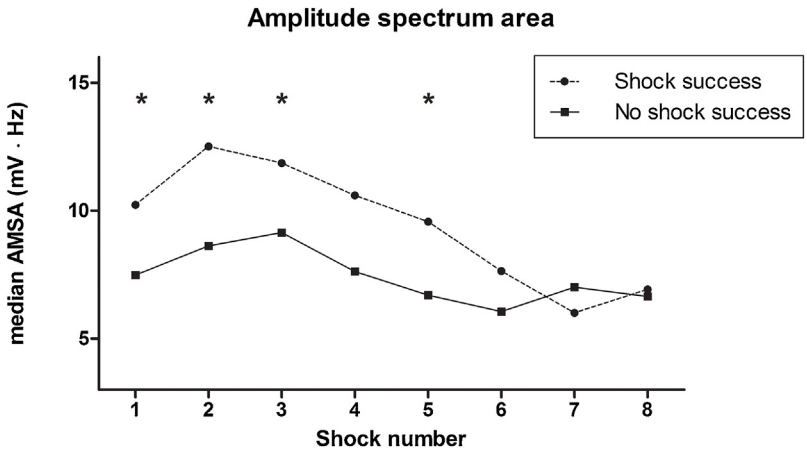

Fig. 3 – Per-shock analysis of the amplitude spectrum area (AMSA) in relation to shock success (return of organised rhythm); * $p < 0.05$.

Human studies

A previous study investigated the VF-waveform in relation to individual patient outcomes, using the averaged AMSA over the entire resuscitation. In this OHCA-cohort, with a median of 2 shocks, the averaged AMSA was a strong predictor of survival.[16] In addition, several studies reported per-shock analyses with specific focus on the impact of the AMSA beyond the first shock.[5,6,27] In a relatively small study on these so-called "subsequent shocks", the AMSA demonstrated good discriminative abilities for shock success, in that study defined as ROOR or asystole.[27] The two largest studies to date pertain to resuscitations with an average of two shocks, and distinguished between first and later shocks. It was demonstrated that AMSA is predictive for shock success in both the first as well as in later shocks.[5,6] However, the abovementioned studies did not address the possibility that the observed associations between AMSA and shock success may have been primarily driven by the first few shocks.

In our cohort of prolonged CPR-attempts, we observed that AMSA-values became lower over time. From a physiological point of view, this is plausible, as the AMSA is as a proxy for myocardial metabolic state which deteriorates in the later phase.[13,28] Another potential factor that may cause lower AMSA-values compared to the first two shocks, may be the administration of amiodarone (55%), which has previously shown to decrease frequency characteristics of VF.[29] Our observations that AMSA-values of successful shocks in the late phase were lower than in the early phase of resuscitation, may relate to these factors. Interestingly, previous literature also describes lower cut-off values for AMSA to predict outcome of subsequent shocks (9.2 mVHz), as compared to first defibrillation attempts (10.2 mVHz).[5] Although the exact mechanisms of lowering AMSA values over the course of resuscitation require further investigation, the observed differences between early and late phases may have pragmatic implications for the use of AMSA-guided shock delivery.

Waveform changes

Despite a growing interest on absolute AMSA-values and outcome, evidence on the impact of ΔAMSA is limited and restricted to the early phase. A study on OHCA-patients (1993) firstly described the association of increasing VF-amplitude with survival after VF cardiac arrest.[30]

A more recent study on the course of AMSA showed that increases between the first three shock attempts are independently associated with defibrillation success.[9] Although the latter study was restricted to the first three shocks in a population with very high survival rates, the results are in line with our observations.

Other recent studies on the course of AMSA suggested that predictive models for defibrillation success improve when ΔAMSA-measures are accounted for.[15,31] Notably, these studies incorporated resuscitations with a median of 1–2 shocks per patient, and the described AMSA-changes therefore mainly involved early shocks. Our findings on AMSA-changes during the first shocks corroborate with these studies, supporting the hypothesis that increasing VF-coarseness is a sign of improving myocardial metabolic state in the early phase of resuscitation.

To our knowledge, data on waveform changes after the third shock are scarce, and reports on how AMSA evolves over time are also limited. Our results indicate that VF-waveform characteristics develop from "coarse" to "fine" VF during the course of a resuscitation, and that ΔAMSA is not associated with shock success in the later phase of cardiac arrest. As opposed to the early phase– in which an increase in AMSA seems to reflect an improving metabolic state and thus better chances of shock success – the VF-waveform in later phases of resuscitation is typically characterised by a more varying course. Factors such as refibrillation, periods of ROSC and the total arrest time vary greatly among patients with prolonged resuscitations. This may affect the VF-waveform and undermine the use of AMSA and its changes as a determinant of shock success. Moreover, there remains uncertainty about the impact of underlying heart disease on the VF-waveform and its implications with regard to shock outcome.[29,32–35] Underlying etiology might impact a priori chances of shock success, thereby potentially influencing the relation between AMSA-measures and shock success, especially in later phases of resuscitation.

Implications

For the early phase of the resuscitation, our findings corroborate with previous work and support the rationale for further study on

AMSA-guided resuscitation efforts, now that smart defibrillators are available.[11]

Our observations with regard to the impact of AMSA and its changes over time, imply that it seems worth investigating whether other factors may be of importance for shock success in the later phase. Importantly, the observed AMSA for successful shocks in the later phase was lower than in the early phase. Operative protocols may therefore require altered cut-off values of AMSA during prolonged resuscitations. Pragmatically, further study in a larger cohort is warranted to confirm our findings and to assess the predictive value of AMSA for shock success in the late phase of resuscitation.

Future studies should also further investigate until what time point the association between AMSA and shock success is still present. We now used an arbitrary threshold of four shocks, based on the median, to define the early and late phase. However, our data suggest that the association is no longer present after shock 5/6. Rather than an early and a late phase, future studies may define a phase where shock success depends on AMSA, and a phase where the impact of AMSA is less apparent. In this "later phase", other factors may contribute to improve current shock success prediction models. One potential factor may be incorporation of information of the success of the previous shock.[31,36] With increasing shock attempts, the discriminative value of AMSA seems to become lower, while combining the AMSA with success of the previous shock results in higher diagnostic accuracy.[36] Appreciating that the majority of VF-patients requires prolonged resuscitations, additional efforts are warranted to better elucidate potential key factors for shock success of later defibrillation attempts.

A last point of specific interest, is the technical derivation of AMSA. Several factors complicate interstudy interpretation of AMSA-values. First, different defibrillators have different built-in filter settings. Second, signal processing protocols vary among studies. Third, methodologies to derive and calculate the AMSA are not uniform in different studies. In an era of increasing interest in AMSA-guided resuscitation, a uniform approach is to be preferred, as it would facilitate interstudy comparisons and implementation in 'smart defibrillators'.

Limitations

This prospective registry is of modest sample size and analyses were restricted to patients with analysable VF data and known shock outcome. Of note, no baseline differences between in- and excluded patients were observed. In the context of our modest sample size, it should be noted that this study on prolonged resuscitations reports on associations between AMSA-measures and shock success. For further optimization of operative protocols, larger data sets are warranted to define AMSA cut-offs that predict shock success in later phases of resuscitation.

In addition, we prospectively defined shock success as ROOR, in line with previous work at the time of our study design.[22,37,38] Notably, ROOR does not always imply restored circulation, and might in some cases represent pulseless electrical activity. Although the ROOR-definition potentially affects AMSA-values, a stricter definition of shock success (>40/min) yielded similar results (Supplement Files 4, 5).[39]

Finally, we did not systematically score CPR-quality, and although there was strict feedback in the vast majority of patients, it is uncertain to what extent differences in quality may have impacted our findings.

Conclusion

In the early phase of VF OHCA, both a high AMSA and an increase in AMSA indicated a high likelihood of a successful defibrillation, supporting future studies on AMSA-guided shock delivery. Although less pronounced, associations between AMSA and shock success persisted in the late phase of resuscitation. Contrastingly, no associations between AMSA-changes and shock success were found in this later phase. While it should be further elucidated whether the described associations between AMSA and shock success enable shock outcome prediction in the late phase, the use of AMSA-changes seems restricted to the early phase of resuscitation.

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Conflicts of interest

Prof. de Boer is a member of the European advisory board on interventional cardiology of Medtronic. Prof. van Royen received research grants from Abbott, Biotronik, AstraZeneca and Philips, and professional fees from Abbott and Medtronic. The other authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.04.010.

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