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Clinical paper

Amplitude spectrum area to predict true shock-refractory ventricular fibrillation during basic life support-treated out-of-hospital cardiac arrest

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Abstract

Aim: Refractory ventricular fibrillation (VF) is associated with decreased survival. Guideline definition of refractory VF, i.e. a VF persisting after 3 shocks, includes cases of true shock-refractory VF or recurrent VF with transient defibrillation response. Predicting true shock-refractory VF before repeated shock failure could prioritize targeted interventions to improve out-of-hospital cardiac arrest (OHCA) outcomes. We hypothesized that amplitude spectrum area (AMSA) may predict cases of true refractory VF.

Methods: ECGs recorded by automated external defibrillators were obtained from OHCA in 8 cities in Italy. A 2-second VF window before each defibrillation was analyzed to calculate Amplitude Spectrum Area (AMSA). Defibrillation success was defined by occurrence of a perfusing rhythm, while refractory VF was defined as: “pragmatic-refractory” (based on guideline definition); or within this category, as “True shock-refractory”, if VF continuously persisted over the period needed to deliver the first 3 shocks; or “refractory-recurrent”, if VF recurred after any of the first three shocks transiently terminated VF.

Results: 1646 OHCA with shockable presenting rhythm were included, 360 (22 %) of whom met the definition of pragmatic-refractory VF. Among the 360 cases of pragmatic-refractory VF, 18 % were true shock-refractory and 82 % were refractory-recurrent VF. AMSA was significantly lower in true shock-refractory VF than in refractory-recurrent VF. A lower first AMSA was associated with occurrence of true shock-refractory VF (aOR:0.81; 95 %CI: 0.73–0.88; $p < 0.0001$).

Conclusions: Lower AMSA is associated with true shock-refractory VF, a subtype associated with persistent defibrillation failure and worse long-term survival. Identifying different VF subtypes early may help guide advanced resuscitation strategies in OHCA.

Keywords: Ventricular Fibrillation (VF), Amplitude Spectrum Area (AMSA), Refractory VF, Out-of-Hospital cardiac arrest (OHCA), Recurrent VF, Defibrillation outcome prediction, VF waveform analysis

Introduction

Cardiac arrest presenting with ventricular fibrillation (VF) requires a combination of cardiopulmonary resuscitation (CPR) and prompt defibrillation to achieve return of spontaneous circulation (ROSC).¹ However, multiple defibrillations are frequently required in case of “refractory VF”, a condition pragmatically defined when VF is still

observed following three consecutive defibrillation attempts and standard advanced life support (ALS) treatments.¹ In this context, poor clinical outcome has been reported, with survival rate decreasing after each shock, and the majority of this decline occurring within the initial three shocks.² Thus, novel defibrillation strategies have been recently explored, i.e. double sequential external defibrillation (DSED) and vector change defibrillation, showing superior outcomes compared to standard defibrillation.³

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Nevertheless, a significant challenge in treating refractory VF is the potential misclassification of the “pragmatic” definition in capturing the underlying rhythm. This definition may fail to differentiate between true shock-refractory VF (e.g. continuous VF before and after each of the first three shocks) or recurrent VF (e.g. absence of VF for at-least 5 sec after any shock, followed by spontaneous rebrillation).⁴ Indeed, VF frequently recurs upon resumption of CPR after a successful shock, with the median time of VF recurrence reported to be < 30 sec in more than 50 % of instances.^{5,6} If the rhythm analysis reveals VF again, it is unclear whether VF persisted or reoccurred within the 2-min CPR cycle after a successful defibrillation, and these different conditions are often lumped together.

The incidence of true shock-refractory VF and recurrent VF exhibits variability, with recurrent VF demonstrating higher prevalence in some studies.^{6,7} Recurrent VF has been reported in more than 50 % of patients following initial termination of VF, whereas true shock-refractory VF occurs in approximately 5–20 % of patients.^{1,5,6,8,9} Outcome of these two subtypes of refractory VF differs significantly, with patients in recurrent VF having higher survival rates compared to those with true shock-refractory VF.⁴

The ability to predict true shock-refractory VF or recurrent VF prior to repeated shock failure could facilitate preemptive or tailored interventions aiming at improving patient outcome, such as earlier administration of antiarrhythmic agents, reconsideration of epinephrine use, changes in shock delivery strategy or early use of extracorporeal CPR.^{1,7,10,11} Amplitude spectral area (AMSA) is one of the most accurate VF waveform analysis algorithms to predict defibrillation outcome in out-of-hospital cardiac arrest (OHCA).^{12–14} Retrospective clinical studies have shown that AMSA varies between recurrent and shock refractory VF, with values significantly higher in recurrent than shock-refractory VF.^{15,16} Thus, the objective of the present multicenter retrospective cohort study was to investigate whether pre-shock AMSA may identify cases of true shock-refractory VF and refractory-recurrent VF in a large database of OHCA with shockable rhythm.

Methods

The study protocol was approved by the IRB of the coordinating center, San Gerardo University hospital. The study complied with the principles of the Declaration of Helsinki and the National regulations of Good Clinical Practices (Italian Ministry of Health D.Lgs. 15/07/97). IRB waived the informed consent, in accordance with Government laws regulating the use of human clinical data (D.Lgs. 196/2003, art.5, comm.4, and art.110, comm.1), being: 1. the data already collected for administrative and statistical reasons by the National Health System; 2. the study a retrospective observational analysis with no foreseeable harm expected nor changes in patients’ treatment; 3. the waiver of consent not affecting adversely the rights and welfare of the patients; and 4. the data used in accordance to National and Regional laws regulating patients’ confidentiality (D. Lgs. 196/2003, Regional law n.9, 18/07/2006, and n.7, 5/02/2010).

Data sources and study population

All cases of OHCA with a first recorded shockable rhythm (ventricular fibrillation or pulseless ventricular tachycardia) were included in the study. A database of ECG traces recorded by different automatic external defibrillators (AEDs) during pre-hospital CPR from 1646 patients enrolled in 8 city-areas in Lombardy Region, Italy between

2008–2010, was used. ECG traces were prospectively collected from the Emergency Medical Services (EMS) of each area, for administrative and statistical reasons. EMSs were coordinated by the Regional Directing Centre, “Azienda Regionale Emergenza Urgenza” (AREU), located in Milan, and all used the same electronic data management system and data validation software EMMA (EMergency Management, Beta 80 Group, Milan, Italy). ECG traces did not contain any patients’ identifiable information. ECG traces with incomplete recording (i.e. adequate pre- and post-defibrillation intervals) and/or with artefacts (i.e. due to chest compressions or pacing) were excluded from the study. Each ECG trace included in the study was then matched to the proper record in EMMA, which collects information on the pre-hospital events and patients’ identification data. More specifically, the pre-hospital data collected in EMMA and used in this study were the EMS response interval and the cause of EMS alert. Individual patients’ identification data were used, instead, to retrieve additional information for each patient from the administrative healthcare databases. Data were subsequently anonymized. In detail, “DENALI”, a regional data warehouse that organizes the administrative databases of the public funded National Healthcare System, was used, as previously reported.¹² DENALI includes data regarding vital status (survival), hospital discharge, daily pharmaceutical and outpatient claims, in the general population living in Lombardia. Patients’ data are automatically validated and updated at annual interval by an in-house software, for Regional epidemiological and research purposes. The linkage between EMMA and DENALI used a probabilistic approach on data for patients’ identification. Data about hospital discharge and pharmaceutical claims used to define comorbidities and drug treatments prior to cardiac arrest and to assess long-term outcomes were retained in DENALI.¹² Comorbidities were reported as Charlson using the Quan algorithm based on the six discharge diagnoses (international classification of diseases, ICD-9-CM) reported on each hospital discharge.^{12,17} Drug treatments, based on the World Health Organization (WHO) Anatomical Therapeutic Chemical classification, WHO-ATC, were reported.¹⁸

ECG analyses

ECG traces were recorded from the two defibrillatory pads by three different AEDs: A. ZOLL Medical Corp.; B. Philips Health System; and C. PhysioControl Inc. ECGs were recorded at different sample rates: 250 Hz for AEDs A; 200 Hz for AEDs B; and 125 Hz for AEDs C. The recorded traces were exported to Matlab 7.2 (MathWorks, Natick, MA) for further processing. ECG traces were re-sampled at 250 Hz using a polyphase filter implementation and AMSA was computed, as previously described.¹² The pre-shock AMSA value was used.

Outcomes definition

Pragmatic refractory VF was defined based on current guidelines, as a VF that was still observed after three shocks with associated 2-min CPR cycles.¹ Non-refractory VF was defined as successful defibrillation within one or two shocks without recurrence of VF. True shock-refractory VF was defined as a VF that continuously persisted over the period needed to deliver the first 3 shocks, without termination of the shockable rhythm by any of the shock attempts. Refractory-recurrent VF was defined as recurrence of VF, which could occur after a transient initial termination of VF and/or a successful defibrillation, at any time after each of the first three shock attempts. Defibrillation outcome was assessed at 5, 30, and 60 s after each shock

and immediately prior the shock administration. Defibrillation outcome was defined according to established criteria^{12,13,16} as: “successful defibrillation”, if defibrillation restored an organized rhythm with heart rate ≥ 40 beats/min commencing within 60 sec post shock; and “unsuccessful defibrillation” or failure, if any other rhythm, including VF/VT and asystole, or low heart rate < 40 beats/min, occurred.

Long-term outcomes included: sustained ROSC, defined as hospital admission following cardiac arrest recorded in DENALI; survival to hospital discharge and to 6 months, and 1 year after cardiac arrest, retrieved from the vital status records in DENALI.

Validation in AMSA trial patients

A secondary analysis of prospectively collected data from patients enrolled in the AMSA trial requiring ≥ 3 shocks was performed.¹³ Briefly, the AMSA was a small multicenter, randomized controlled clinical trial in OHCA, with the primary objective to test whether real-time AMSA analysis during CPR might predict the success of defibrillation.¹³ The study was approved by the Ethics Committee AREA 2 Milan, Italy (189_2017bis). A deferred written patient’s consent was obtained. AMSA calculation was performed by a built-in software, which acquired the ECG signal from the defibrillator pads and displayed the value during pauses for ventilations, by means of specifically modified X-Series devices (ZOLL Med. Corp.).¹⁹ Adult shockable OHCA were randomly assigned to receive either an AMSA-guided CPR or a standard-CPR. A total of 31 patients were included, 19 in the AMSA arm and 12 in the standard one. For the current sub-study, data from the 19 AMSA-CPR patients were used. Patients were categorized in pragmatic-refractory, true shock-refractory and refractory-recurrent VF, as described above. The AMSA value before the first defibrillation attempt was used to validate the results obtained from the retrospective analyses.

Statistical analysis

Descriptive statistics were reported using counts and percentages for categorical variables, mean with SD or median with Q_1 - Q_3 for

continuous variables and counting processes. Normal distribution of AMSA was investigated. Comparisons between baseline characteristics in pragmatic-refractory, non-refractory, true shock-refractory and refractory-recurrent VF was performed using Fisher or chi-square test for categorical variables or non-parametric tests for continuous or counting variables. Univariable unadjusted analysis followed by multivariable adjusted analysis with a stepwise approach was used to assess the association with occurrence of refractory VF and true shock-refractory VF, and to assess the association with outcomes of defibrillation success, sustained ROSC, survival at hospital discharge, 6 months, and 1-year after cardiac arrest. Unadjusted and adjusted: odds ratio (OR) for logistic models and hazard ratio (HR) for Cox regression models are reported with 95 % confidence intervals (CI). The discriminatory ability of AMSA for true shock-refractory vs refractory-recurrent VF was measured as area under the curve (AUC). Statistical significance was reached when the p-value < 0.05 (two-tailed). Statistical analyses were performed using STATA-14/MP (StataCorp LP, College Station, TX, USA) and GraphPad Prism 8.3.0 (GraphPad Software, San Diego, CA, USA).

Results

Study population and outcomes

A total of 1646 eligible patients with OHCA and a shockable rhythm recorded by AEDs were assessed, 27 were excluded due to ECG artifacts (Supplemental Fig. 1). Of the remaining 1619 patients with ECGs available for VF waveform analysis, 360 patients (22 %) were classified as pragmatic-refractory VF, while 1259 (78 %) as non-refractory VF (Fig. 1). Clinical characteristics and outcomes were known in 1349 patients and summarized in Table 1. In the pragmatic-refractory VF group 76.7 % of patients were male with a median age significantly lower compared to the non-refractory VF group. Patients with pragmatic-refractory VF had less active drug treatments, i.e. cardiac therapy and antithrombotic drugs, compared to non-refractory VF patients. Median EMS response interval was

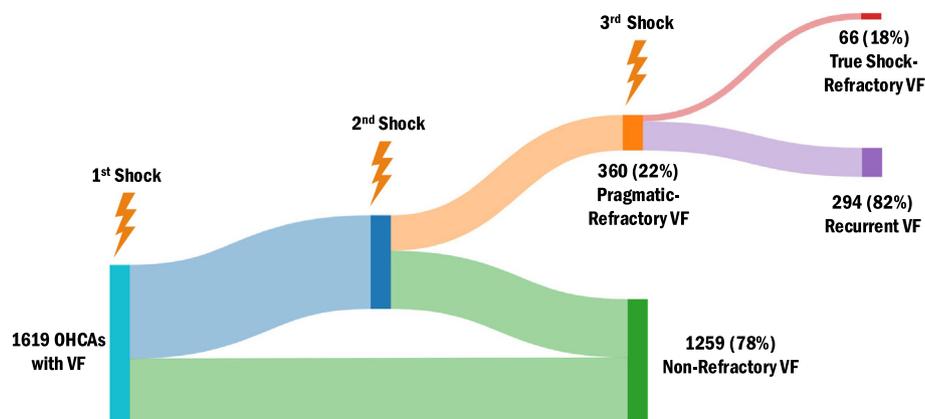


Fig. 1 – Sankey plot showing defibrillation outcome of the first three shocks. Non-Refractory ventricular fibrillation (VF) refers to cases in whom the post-shock rhythm was an organized rhythm with heart rate ≥ 40 beats/min commencing within 60 sec following one or two shocks. Pragmatic-refractory VF refers to the presence of VF after 3 shocks with associated 2-min CPR cycles, regardless of the effects of each shock. True shock-refractory VF refers to a continuously persisting VF rhythm during the first 3 shocks; refractory-recurrent VF refers to recurrency of VF after a transient termination, at any time during first 3 shocks. OHCA, out-of-hospital cardiac arrest.

Table 1 – Population characteristics non-refractory VF vs. pragmatic-refractory VF.

	Non-Refractory VF (n = 1036)	Pragmatic-Refractory VF (n = 313)	P value
Male gender	737 (71.2)	240 (76.7)	0.055
Age	70 [59–79]	67 [56–76]	0.001
Cause of EMS alert			
Medical	974 (94)	283 (90.4)	0.006
Traumatic	39 (3.8)	18 (5.8)	
Not declared	23 (2.2)	12 (3.8)	
EMS response interval	8.2 [6.3 – 10.7]	7.9 [6.1–10.5]	0.157
No. of defibrillation attempts	2 [1 – 2]	4 [4 – 6]	<0.001
Energy delivered, joule	161 [153 – 200]	157 [153 – 200]	0.003
Transthoracic impedance, Ω	81 [68 – 94]	85 [75 – 98]	<0.001
Comorbidities			
Previous myocardial infarction	148 (14.4)	44 (14.1)	0.861
Congestive heart failure	226 (21.9)	58 (18.5)	0.352
Peripheral vascular disease	89 (8.6)	34 (10.9)	0.442
Cerebrovascular disease	139 (13.5)	33 (10.5)	0.325
Chronic pulmonary disease	99 (9.6)	30 (9.6)	0.874
Diabetes mellitus	138 (13.4)	29 (9.3)	0.123
Liver disease	50 (4.9)	11 (3.5)	0.521
Renal disease	73 (7.1)	19 (6.1)	0.708
Cancer	98 (9.4)	21 (6.7)	0.278
Others	57 (5.5)	13 (4.2)	0.538
Not available	43 (4.2)	11 (3.5)	
Number of concurrent comorbidities			
0	509 (49.4)	172 (55)	0.487
1	156 (15.1)	49 (15.7)	
2	125 (12.1)	31 (9.9)	
3	98 (9.5)	27 (8.6)	
≥ 4	100 (9.7)	23 (7.4)	
Not available	43 (4.2)	11 (3.5)	
Active drug treatments			
Cardiac therapy	251 (24.2)	56 (17.9)	0.038
Antithrombotic drugs	370 (35.7)	81 (25.9)	0.002
Other antihypertensive drugs	42 (4.1)	8 (2.6)	0.399
β -blockers	214 (20.6)	56 (17.9)	0.407
Calcium channel blockers	190 (18.3)	58 (18.5)	1
Renin-angiotensin system antagonists	444 (42.9)	134 (42.8)	1
Lipid modifying agents	247 (23.9)	67 (21.4)	0.501
Selective β_2 -adrenoreceptor agonists	20 (1.9)	4 (1.3)	0.677
Number of concurrent drug treatments			
0	350 (33.8)	126 (40.3)	0.487
1	189 (18.2)	59 (18.9)	
2	165 (15.9)	49 (15.7)	
3	148 (14.3)	34 (10.9)	
4	109 (10.5)	33 (10.5)	
≥ 5	72 (7.0)	16 (5.11)	
Not available	3 (0.3)	0 (0)	
Outcome			
Defibrillation success	394 (38)	58 (18.5)	<0.001
Sustained ROSC	380 (36.7)	80 (25.6)	0.001
Survival to hospital discharge	221 (21.3)	33 (10.5)	<0.001
Six-months survival	185 (17.9)	31 (9.9)	0.003
One-year survival	174 (16.8)	27 (8.6)	0.002

Data are reported as median [Q1-Q3] or number (%).

EMS, emergency medical system; ROSC, return of spontaneous circulation.

8 min in both groups. In 58 patients with pragmatic-refractory VF, defibrillation attempts delivered by AEDs were successfully compared to 394 in the non-refractory VF group. The number of patients who achieved sustained ROSC were lower in the pragmatic-

refractory compared to non-refractory VF groups. Survival to hospital discharge, 6-months and 1-year survival were lower in the pragmatic-refractory VF group compared to non-refractory VF patients (Table 1).

AMSA and long-term outcome prediction

The median AMSA value was significantly lower in the pragmatic-refractory VF group compared to non-refractory VF patients (6.12 vs 7.74 mV-Hz; $p < 0.0001$; Fig. 2A).

AMSA, age, use of antithrombotic drugs, and presence of peripheral vascular disease were independently associated with the occurrence of pragmatic-refractory VF (Supplemental Table 1). Specifically, lower AMSA was associated with the presence of refractory VF with an adjusted OR of 0.92 (95 % CI: 0.90–0.95; $p < 0.0001$, Supplemental Table 1). Adjusted ORs for sustained ROSC and long-term outcomes are summarized in Table 2. The presence of pragmatic-refractory VF and lower AMSA values were associated with lower likelihood of sustained ROSC, survival to hospital discharge and 1-year survival.

Subtypes of refractory VFs

Of the 360 patients classified as pragmatic-refractory VF, 66 (18 %) were true shock-refractory VFs, while 294 (82 %) were refractory-recurrent VFs (Fig. 1). Clinical characteristics and outcomes were available for 57 and 256 patients respectively in the true shock-refractory and refractory-recurrent VF groups (Table 3).

In true shock-refractory VFs, 80.7 % of patients were male and the median age was 65 years, significantly lower compared to refractory-recurrent VFs ($p = 0.049$). Patients with true shock-refractory VF had higher median energy delivered compared to those with refractory-recurrent VF (200 vs. 157 J, $p < 0.0001$, Table 3). In 2 patients (3.5 %) with true shock-refractory VF, defibrillation attempts delivered by AEDs were successful—one after the sixth shock and the other after the fourteenth—compared to 56 (21.9 %) in the refractory-recurrent VF group ($p < 0.001$). The number of patients who achieved sustained ROSC were 9 (15.8 %) and 71 (27.7 %) respectively in the true shock-refractory and refractory-recurrent VF groups ($p = 0.158$). Long-term survival, i.e. 6-month and 1 year, was significantly lower in true shock-refractory VF compared to refractory-recurrent VF (0 % vs. 10.2 %, log-rank $p = 0.0069$, Table 3 and Fig. 2B).

AMSA prediction of true shock-refractory VF

The median AMSA value was significantly lower in true shock-refractory VF compared to refractory-recurrent VF (4.82 vs. 6.62; $p < 0.001$; Fig. 2C). AMSA increased during the first three shocks in both groups, showing persistently significant lower values in shock-refractory VF patients ($p < 0.01$, Fig. 2D). AMSA values significantly decrease from non-refractory VF to refractory-recurrent and true shock-refractory VF (Fig. 2E).

AMSA, age, and presence of 4 or more concurrent comorbidities, were independently associated with the occurrence of true shock-refractory VF (Table 4). Specifically, lower AMSA was associated with the presence of true shock-refractory VF compared to refractory-recurrent VF with an adjusted OR of 0.81 (95 % CI: 0.73–0.88; $p < 0.0001$, Table 4). The unadjusted AUC value for prediction of true shock-refractory VF was 0.65 (95 % CI 0.58 – 0.71, $p = 0.0002$, Fig. 2F). Among the 19 patients enrolled in the AMSA-CPR group of the AMSA trial, 9 needed three or more shocks. The AMSA value measured before the first defibrillation attempt predicted the occurrence of true shock-refractory VF with an AUC value of 0.94 (95 % CI 0.79 – 1.0, $p = 0.039$, Supplementary figure 3).

Discussion

This study enrolling a large cohort of OHCA patients with refractory VF reported variations in AMSA value between true shock-refractory and refractory-recurrent VF. Thus, the results underscore the potential use of AMSA as predictive indicator for distinguishing the refractory VF subtypes, informing more targeted defibrillation and treatment approaches.

Furthermore, this study provides critical insights regarding the association between outcome and refractory VF subtypes. Patients experiencing pragmatic refractory VF exhibited worse outcomes compared to those with non-refractory VF, with significantly lower rates of sustained ROSC, 6-month and 1-year survival in true-shock refractory VFs compared to refractory-recurrent VFs. These unfavorable outcomes were anticipated by a significantly lower pre-shock AMSA in patients with true shock-refractory VF compared to those who had refractory cardiac arrest with refractory-recurrent VF.

The incidence of true shock-refractory VF reported in this cohort is consistent with previous studies, in which it occurred in approximately 17 % of patients with OHCA receiving three consecutive standard defibrillations during resuscitation.⁴ The profound impact of true shock-refractory VF on patient outcomes underscores the critical need for a precise and early diagnosis. Indeed, this condition demonstrated a strong association with death and poor neurological outcome, likely resulting from a prolonged time to sustained ROSC and myocardial damage.^{4,7–9,20,21} In our cohort, true shock-refractory VF was associated with poorer outcome, regardless of the patients' younger age, compared to refractory-recurrent VF, indicating that the impact of this refractory VF subtype extends beyond the initial resuscitation phase, affecting the patient's overall recovery. In light of this, the identification of an early predictor of shock-refractory VF, such as AMSA, emerges as a particularly promising tool, as patients with true shock-refractory VF exhibited a lower AMSA value compared to those with refractory-recurrent VF. Identifying the type of refractory VF early during CPR has a high clinical significance to customize the upcoming defibrillation treatment, as while refractory-recurrent VF may remain responsive to conventional defibrillation, more appropriate strategies for true shock-refractory VF should be considered as alternative intervention, such as DSED or vector change.⁵

Different methodologies, with varying accuracy, have been proposed to predict refractory VF during OHCA. Lupton et al.²² used clinical information available to the EMS at the initial rhythm analysis, i.e. age, sex, witness, location, bystander interventions, initial rhythm, leading to a moderate predictive accuracy, with an AUC of 0.65. In contrast, Coult et al.¹¹ proposed a more advanced method employing an ECG signal analysis based on a machine learning algorithm, which demonstrated superior predictive performance, with an AUC of 0.85. However, it is important to note that the proposed algorithm does not distinguish between the different refractory VF subtypes, thus limiting its clinical relevance in identifying cases of true shock-refractory VF. The use of real-time AMSA from patients enrolled in the AMSA trial demonstrated promising predictive ability, showing an AUC value of 0.94. However, these results should be considered as exploratory, as they are based on a small sample size and require validation in a larger cohort. Furthermore, we acknowledge that these findings must be interpreted with caution, as signif-

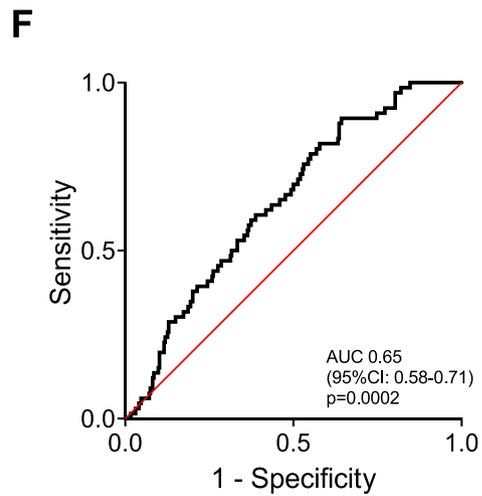
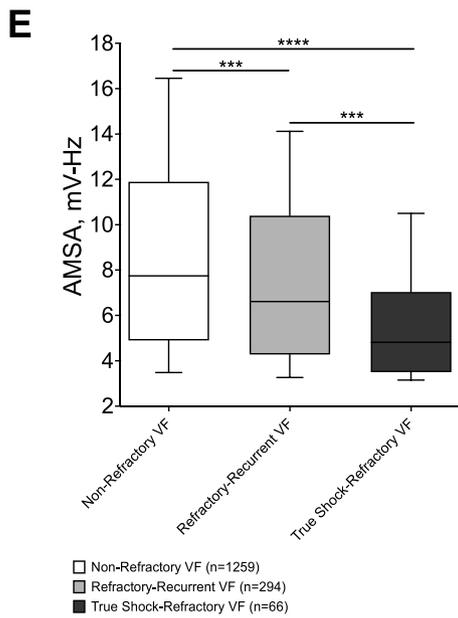
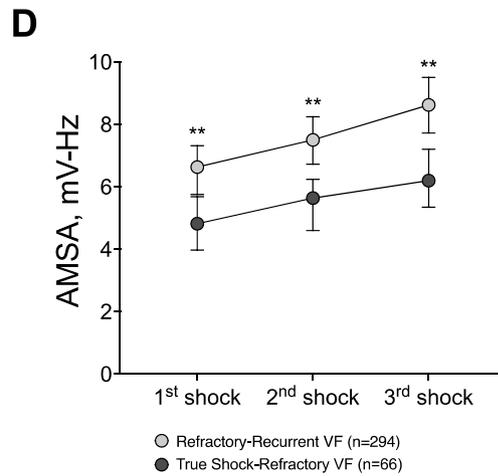
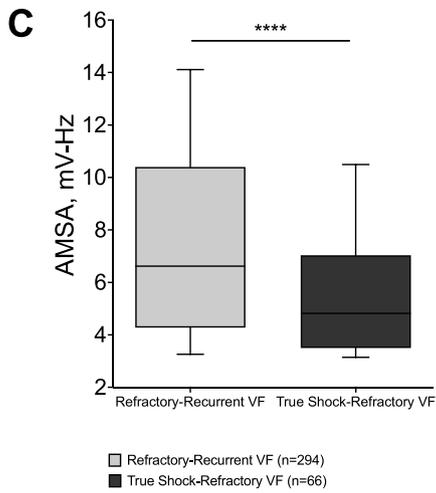
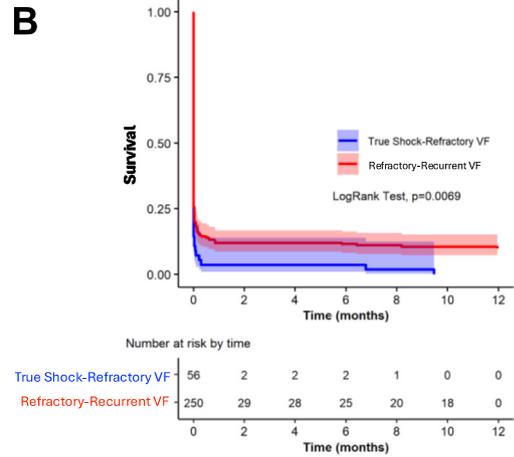
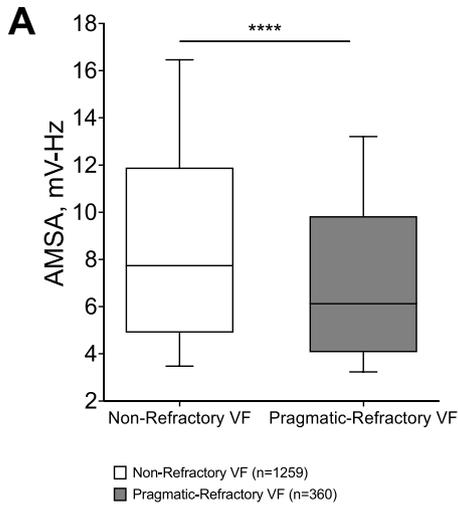


Table 2 – Multivariable logistic regression model for sustained ROSC and long-term survival.

	Sustained ROSC			Survival to Hospital Discharge			1-Year Survival		
	OR	95 % CI	P	OR	95 % CI	P	HR	95 % CI	P
Pragmatic-refractory VF	0.59	0.43–0.81	0.0012	0.43	0.28–0.65	<0.001	0.83	0.72–0.96	0.010
AMSA, mV-Hz	1.12	1.09–1.15	<0.001	1.19	1.09–1.15	<0.001	1.05	1.03–1.06	<0.001
Age, years	0.97	0.96–0.98	<0.001	1.71	1.10–2.67	0.017	0.99	0.98–0.99	<0.001
EMS response interval, min	0.93	0.90–0.97	<0.001	0.92	0.88–0.96	0.0003	0.98	0.97–0.99	0.014
Number of concurrent comorbidities: ≥ 4	–	–	.	0.307	0.146–0.646	0.002			
Renin-angiotensin system antagonists (Y vs N)	–	–	.	1.586	1.141–2.203	0.006			

icant differences in the selection of the patient population may have influenced these results. Specifically, 1) only patients with refractory VF who were randomized to the AMSA-guided CPR arm of the trial were included, which may introduce a selection bias due to the treatment algorithm that did not adhere to the standard advanced life support but was instead guided by the AMSA value (first two shocks administered with high AMSA values); 2) these individuals initially received advanced life support treatment by EMS with controlled quality of chest compression, which differs from the general cohort analyzed in this study, who received basic life support. Nevertheless, this finding underlines the utility of AMSA in identifying true-shock refractory VF and expands the potential information provided by this real-time VF waveform analysis algorithm. Indeed, AMSA has been extensively investigated over the past decades, with numerous studies consistently showing that AMSA represents the most accurate parameter to predict defibrillation outcome among several VF waveform analysis algorithms. Real-time AMSA represents a non-invasive approach to guide defibrillation during CPR that may guide the timing of defibrillation, thus preventing the delivery of futile high-energy shocks while it enables healthcare providers to distinguish between different VF subtypes. Furthermore, AMSA is an important tool for early identification of the underlying arrest etiology while the patient is in VF, showing significantly lower values in case of myocardial

infarction,^{13,23} which often accompanied refractory VF. While the prospective trial on AMSA-guided defibrillation have demonstrated feasibility, further research and larger-scale validation are required before this technology can be broadly implemented. Indeed, as AMSA technology advances, there is potential for its integration into AEDs used in public settings allowing first responders to deliver more effective defibrillations, i.e. DSED or vector change.

Limitations and future directions

Some limitations of this study should be acknowledged. First, given the retrospective nature of the study, missing data on clinical outcomes for some patients could have influenced the accuracy of the findings and the predictive value of AMSA. Second, external factors not assessed in the present study like the timing of defibrillation attempts or the presence of underlying myocardial infarction, might have influenced the AMSA values and their interpretation. Third, AEDs did not measure CPR quality, which is a crucial for AMSA, as poor chest compressions could lead to a reduced AMSA value.²⁴ Nevertheless, we noted a consistent increase in AMSA values from the first to the third shock in both the refractory-recurrent and true shock-refractory VF groups, indicating enhancement in myocardial viability due to CPR maneuvers. Additionally, we do not have information on the treatment administered by EMS physicians (such as

Fig. 2 – A) Box plots of the first pre-shock Amplitude Spectrum Area (AMSA) in non-refractory and pragmatic-refractory ventricular fibrillation (VF). **P < 0.0001 vs. Non-refractory VF. B) Kaplan-Meier survival curve for patients with refractory-recurrent and true shock-refractory ventricular fibrillation (VF). C) Box plots of the first pre-shock Amplitude Spectrum Area (AMSA) in refractory-recurrent and true shock-refractory ventricular fibrillation (VF). ****P < 0.0001 vs. refractory-Recurrent VF. D) Amplitude Spectrum Area (AMSA) in true shock-refractory and refractory-recurrent ventricular fibrillation (VF) over the first three defibrillation attempts. Mean \pm SD **P < 0.0001 vs. refractory-recurrent VF. E) Amplitude Spectrum Area (AMSA) in non-refractory, refractory-recurrent and true shock-refractory ventricular fibrillation (VF). Mean \pm SD, Kruskal-Wallis test P < 0.0001 with multiple comparison ****P < 0.001, ****P < 0.0001. F) Performance of amplitude spectrum area (AMSA) for prediction of true shock-refractory VF. Receiver operating characteristic curve (ROC) and the area under the curve (AUC) of the pre-shock AMSA value measured before the first defibrillation from the ECG of OHCA patients recorded by AEDs.**

Table 3 – Population characteristics for refractory-recurrent VF vs true shock-refractory VF.

	Refractory- Recurrent VF (n = 256)	True Shock-Refractory VF (n = 57)	p value
Male gender	194 (75.8)	46 (80.7)	0.427
Age	68 [58–77]	65 [50–71]	0.049
Cause of EMS alert			
Medical	233 (91)	50 (87.7)	0.733
Traumatic	9 (3.5)	3 (5.3)	
Not declared	14 (5.5)	4 (7.0)	
EMS response interval	7.7 [6.1–10.0]	9.0 [6.2–10.9]	0.206
No. of defibrillation attempts	4 [4–6]	4 [3–5]	0.101
Energy delivered, joule	157 [153–200]	200 [157–300]	<0.0001
Transthoracic impedance, Ω	85 [73–98]	83 [72–99]	0.767
Comorbidities			
Previous myocardial infarction	38 (14.8)	6 (10.5)	0.535
Congestive heart failure	47 (18.4)	11 (19.3)	0.709
Peripheral vascular disease	28 (10.9)	6 (10.5)	0.729
Cerebrovascular disease	29 (11.3)	4 (7.0)	0.483
Chronic pulmonary disease	25 (9.8)	5 (8.8)	0.718
Diabetes mellitus	22 (8.6)	7 (12.3)	0.479
Liver disease	15 (5.9)	5 (8.8)	0.033
Renal disease	16 (6.3)	4 (7.0)	0.585
Cancer	98 (9.4)	5 (8.8)	0.475
Others	13 (5.1)	0 (0.0)	0.135
Not available	8 (3.1)	3 (5.3)	
Number of concurrent comorbidities			
0	138 (53.9)	34 (59.7)	0.090
1	44 (17.2)	5 (8.8)	
2	26 (10.2)	5 (8.8)	
3	25 (9.8)	2 (3.5)	
≥ 4	15 (5.9)	8 (14)	
Not available	8 (3.13)	3 (5.3)	
Active drug treatments			
Cardiac therapy	45 (17.6)	11 (19.3)	0.759
Antithrombotic drugs	67 (26.2)	14 (24.6)	0.802
Other antihypertensive drugs	7 (2.7)	1 (1.8)	1.000
β –blockers	47 (18.4)	9 (15.8)	0.647
Calcium channel blockers	48 (18.8)	10 (17.5)	0.832
Renin-angiotensin system antagonists	110 (43)	24 (42.1)	0.905
Lipid modifying agents	56 (21.9)	11 (19.3)	0.668
Selective β_2 -adrenoreceptor agonists	4 (1.6)	0 (0.0)	1.000
Number of concurrent drug treatments			
0	99 (38.7)	27 (47.3)	0.776
1	52 (20.3)	7 (12.3)	
2	40 (15.6)	9 (15.8)	
3	24 (9.4)	5 (8.8)	
4	28 (10.9)	6 (10.5)	
≥ 5	13 (5.1)	3 (5.3)	
Not available	0 (0.0)	0 (0)	
Outcome			
Defibrillation success	56 (21.9)	2 (3.5)	0.0008
Sustained ROSC	71 (27.7)	9 (15.8)	0.158
Survival to hospital discharge	31 (12.1)	2 (3.5)	0.150
Six-months survival	26 (10.2)	0 (0.0)	0.015
One-year survival	26 (10.2)	0 (0.0)	0.015

Data are reported as median [Q1-Q3] or number (%).

EMS, emergency medical system; ROSC, return of spontaneous circulation.

additional shocks for persistent VF) upon their arrival at the scene. This lack of information may explain the differences in rates of defibrillation success and sustained ROSC.

Fourth, the AMSA values were calculated only during pre-shock pauses and not in real time during CPR. Nevertheless, to evaluate

the effects of real-time AMSA value, we assessed the performance of a small cohort of patients with refractory VF from the AMSA trial, demonstrating an promising performance of true shock-refractory VF identification. Fifth, the specific time period of this retrospective study may influence the survival rates, as specific interventions in the post-

Table 4 – Univariable and multivariable logistic regression for prediction of true shock-refractory VF compared to refractory-recurrent VF.

	Unadjusted Univariable			Adjusted Multivariable		
	OR	95 % CI	p value	OR	95 % CI	p value
AMSA, mV-Hz	0.83	0.76–0.91	<0.001	0.81	0.73–0.88	<0.0001
Age, years	0.98	0.96–1.00	0.055	0.97	0.95–0.99	0.019
Number of concurrent comorbidities, ≥ 4	1.93	0.72–5.13	0.189	3.49	1.19–10.20	0.023

OR, odds ratio.

resuscitation phase might have differed. For instance, percutaneous coronary intervention may have been more frequent in recent times compared to the time frame of the study, which would impact survival. However, this would not affect the analysis of VF waveform with pre-hospital AMSA in these patients. Furthermore, recent updates of AED software may have modified duration of pre-shock pauses; however, the impact of their use on outcomes remains uncertain.²⁵ Sixth, the definition of defibrillation success utilized in this study aligns with our previous research¹² and does not encompass asystole and pulseless electrical activity, as included in the standard VF termination definition. While acknowledging that these rhythms may be considered a successful termination of VF, they solely reflect VF termination and not the quality of the resulting rhythm. Conversely, the criterion employed in this study to define defibrillation success provides a more effective identification of perfusing rhythms, which ultimately represent more clinically relevant defibrillation outcomes. Finally, we recognize that neurological outcome represents a more patient-centered outcome, however these data were not available for the entire cohort.

In the AMSA trial subcohort,¹⁴ the incidence of favorable neurological outcome at six months, defined as a Cerebral Performance Category of 1–2, was lower among patients with refractory VF compared to those with non-refractory VF (11 % vs. 50 %).

As a potential future clinical application, AMSA could be integrated into AEDs to alert on the probability of refractory VF with different thresholds and lower AMSA suggesting the presence of true shock-refractory VF, prompting earlier adoption of alternative defibrillation strategies (e.g., DSED, vector change) or E-CPR or early drug administration; while higher AMSA may indicate better myocardial viability and higher likelihood of successful defibrillation, potentially reducing unnecessary delays or advanced interventions.

Conclusions

This study reveals AMSA as a promising predictor for differentiating true shock-refractory VF from refractory-recurrent VF in OHCA. Lower AMSA values are observed in true shock-refractory VF and is associated with poorer outcomes. Early identification of true shock-refractory VF using AMSA could inform targeted treatment strategies, potentially improving outcomes. Further research is needed to validate these findings and explore their clinical application in optimizing resuscitation efforts.

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CRedit authorship contribution statement

Aurora Magliocca: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Carla Fornari:** Writing – review & editing, Software, Formal analysis, Data curation. **Francesca Fumagalli:** Investigation, Data curation. **Giulia Merigo:** Investigation, Data curation. **Mahbod Rahimi:** Investigation, Data curation. **Giuseppe Stirparo:** Investigation, Data curation. **Anna Coppo:** Resources, Investigation. **Maurizio Migliari:** Resources, Investigation. **Giacomo Grasselli:** Writing – review & editing, Supervision. **Sheldon Cheskes:** Writing – review & editing, Supervision. **Giuseppe Ristagno:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization.

Declaration of competing interest

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Appendix A. Supplementary material

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