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Clinical paper

The impact of alternate defibrillation strategies on shock-refractory and recurrent ventricular fibrillation: A secondary analysis of the DOSE VF cluster randomized controlled trial

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Abstract

Background: The DOSE VF randomized controlled trial (RCT) employed a pragmatic definition of refractory ventricular fibrillation (VF after three successive shocks). However, it remains unclear whether the underlying rhythm during the first three shocks was shock-refractory or recurrent VF.

Objective: To explore the relationship between alternate defibrillation strategies employed during the DOSE VF RCT and the type of VF, either shock-refractory VF or recurrent VF, on patient outcomes.

Methods: We performed a secondary analysis of the DOSE VF RCT. We categorized cases as shock-refractory or recurrent VF based on pre-randomization shocks (shocks 1–3). We then analyzed all subsequent (post-randomization) shocks to assess the impact of standard, vector change (VC) or double sequential external defibrillation (DSED) shocks on clinical outcomes employing logistic regression adjusted for Utstein variables, antiarrhythmics, and epinephrine.

Results: We included 345 patients; 60 (17%) shock-refractory VF, and 285 (83%) recurrent VF. Patients in recurrent VF had greater survival than shock-refractory VF (OR: 2.76 95% CI [1.04, 7.27]). DSED was superior to standard defibrillation for survival overall, and for patients with shock-refractory VF (28.6% vs 0%, p = 0.041) but not for those in recurrent VF. DSED was superior to standard defibrillation for return of spontaneous circulation (ROSC) and neurologic survival for shock-refractory and recurrent VF. VC defibrillation was not superior for survival or ROSC overall, for shock-refractory, or recurrent VF groups, but was superior for VF termination across all groups.

Conclusion: DSED appears to be the superior defibrillation strategy in the DOSE VF trial, irrespective of whether the preceding VF is shock-refractory or recurrent.

Keywords: Cardiopulmonary resuscitation, Cardiac arrest, Resuscitation, Defibrillation, Double sequential external defibrillation, Vector change defibrillation, Refractory VF, Recurrent VF

Introduction

Out-of-hospital cardiac arrest (OHCA) is a significant cause of morbidity and mortality worldwide, with an estimated incidence of 55 treated cases per 100,000 people annually.[1–6] Although, overall survival from OHCA remains low, patients who present to emergency medical services (EMS) with an initial rhythm of ventricular fibrillation (VF) have a higher likelihood of survival.[7] Early external defibrillation remains the primary critical factor for improving survival for patients in VF. There is a subset of patients, however, who remain in VF despite multiple standard defibrillation attempts, termed refractory VF (RVF). Prolonged RVF is associated with decreased overall survival and neurologically intact survival compared to patients who respond to initial defibrillation.[8] Although no standard definition of RVF exists, most studies define RVF as VF that is observed following three successive defibrillation attempts and standard advanced cardiac life support (ACLS) treatments.[9,10]

During the recently completed Double Sequential External Defibrillation for Refractory Ventricular Fibrillation (DOSE VF) RCT[11] this

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pragmatic definition was used to define RVF. The study found that the alternative defibrillation strategies of double sequential external defibrillation (DSED) and vector change defibrillation (VC) demonstrated a survival benefit when compared to standard defibrillation for patients in RVF. This pragmatic definition did not attempt to distinguish between recurrent VF (absence of VF for at-least 5 seconds, followed by spontaneous VF recurrence), from shock-refractory VF (continuous VF before and after the 1st three shocks). In the clinical setting it is challenging to differentiate these two scenarios since current guidelines advise immediate CPR after shock delivery. It is not known whether alternative defibrillation strategies improve outcomes in patients with shock-refractory VF, recurrent VF, or both. Patients with shock-refractory VF have poor outcomes, with a reported mortality of up to 97% when employing standard defibrillation.[10,12–15] In contrast, it has been postulated that patients with recurrent VF, who have briefly responded to standard defibrillation, may not require an alternate defibrillation strategy as standard defibrillation has been successful (albeit transiently) in terminating VF.[16] In these cases, it is thought that the cause of VF re-initiation may be related to the myocardial ischemic substrate (causing re-entry) and/or other mechanisms of spontaneous arrhythmia (triggered activity), as opposed to true "shock failure".[16,17] Given that a "pragmatic' definition of refractory VF is much easier to apply during a "real time" resuscitation than a "rhythm based" definition it is critical to understand whether alternative strategies are effective regardless of refractory VF definition. The main objective of this sub-study of the DOSE-VF trial was to determine the efficacy of alternate defibrillation strategies (DSED and VC) on clinical outcomes from both "shock-refractory" and "recurrent" VF when compared to standard defibrillation.

Methods

Study design

We performed a secondary analysis of prospectively collected data from patients enrolled in the recently published DOSE-VF RCT.[11] Briefly, the DOSE-VF RCT was a cluster-randomized controlled trial among six paramedic services within Ontario, Canada, to evaluate the strategies of DSED and VC defibrillation compared with standard defibrillation in adult patients with RVF during OHCA. Refractory ventricular fibrillation was defined pragmatically as an initial presenting rhythm of VF or pulseless ventricular tachycardia that was still present after three consecutive rhythm analyses and standard defibrillations each separated by 2-minute intervals of cardiopulmonary resuscitation (CPR). Patients were included in our current study if they were adults ($\geq$18 years of age), with non-traumatic OHCA and enrolled in the DOSE-VF study. Patients who were excluded in the DOSE VF RCT (patients with a traumatic cardiac arrest, patients with do-not-resuscitate medical directives and patients with cardiac arrest due to drowning, hypothermia, hanging, or suspected drug overdose) were similarly excluded from this analysis. Given our focus on dissecting the benefit of VC or DSED in shock-refractory and recurrent VF, we only assessed patients in the per-protocol population of the RCT (patients who received the allocated randomized treatment strategy).

Study definitions

For the purpose of this study, the definitions for our outcomes of VF termination, return of spontaneous circulation (ROSC), survival to hospital discharge, and neurologically intact survival remained consistent with the original study.[11]. Cases were defined as shock-refractory VF if the VF waveform remained continuous before and after the first three standard shocks (prior to randomization). Cases were defined as recurrent VF if an absence of VF waveform was demonstrated for a minimum of 5 seconds at any time during the first three standard shocks (prior to randomization).

Categorizing cases as RVF and recurrent VF

CPR quality data and defibrillation data were recorded from the ECG, compression acceleration signal and impedance channel measurements by the defibrillator (ZOLL AED Plus, X series defibrillators, ZOLL Medical, Chelmsford, Massachusetts, LP 15 Stryker Corporation, Seattle, Washington). For the purpose of this study each defibrillator file was analyzed independently by two reviewers, and a determination was made as to whether the case met the a priori definition of shock-refractory or recurrent VF. Each reviewer was blinded to the allocated defibrillation strategy. Any cases in which disagreement existed were decided by consensus of all reviewers. Save for the classification of cases as shock-refractory or recurrent, all variables abstracted for the current study were previously collected in the original trial.

Outcomes

The primary outcome for this study was survival to hospital discharge. The secondary outcomes were VF termination, ROSC, and neurologically intact survival defined as a modified Rankin Score (mRS) $\leq$ 2.

Data analysis

We report descriptive statistics for all included variables categorized by type of VF (shock-refractory or recurrent VF). Continuous variables are presented as means (standard deviation) or medians with interquartile range (IQR), where appropriate; categorical variables are presented using frequency distributions and percentages. For the primary analysis we performed both unadjusted and multivariable logistic regression analysis with survival to hospital discharge (yes/no) as our outcome of interest. Our exposure of interest was shock-refractory vs recurrent VF. We included the following other predetermined covariates in the model: age, sex, EMS response time interval, bystander CPR, anti-arrhythmic administered, and epinephrine administered. We were limited to only these variables due to constraints of limiting sample size in our outcome of interest. Results from the regression model are reported as odds ratio (OR) and 95% confidence intervals (CI).

We conducted similar analyses for each of our secondary outcomes listed above. For our secondary analysis we performed similar regression analysis as our primary analysis employing our secondary outcomes as our outcomes of interest. The exposure of interest in our secondary analyses was shock-refractory vs. recurrent VF.. For the subgroup of recurrent VF we performed multivariable regression analyses similar to our primary analyses, however, for the subgroup of shock-refractory VF we were limited in sample size and we considered it inappropriate to analyze as a regression model. For this subgroup we analyzed differences across defibrillation strategies using a Fisher exact test. A P value less than 0.05 was used to indicate a statistically significant difference between groups. Where the overall difference was found to be statistically significant between groups, we performed post hoc pairwise comparisons between groups using Bonferonni adjusted P values for multiple

comparisons. The study protocol was approved by the Sunnybrook Health Science Centre Research Ethics Board.

Results

A total of 405 patients were enrolled in the DOSE VF RCT, of whom 355 (88%) were included in the per protocol cohort. After exclusions 345 (97%) were included in our current analysis. Reasons for exclusion included: ICD shocks given (5), missing data on first three shocks (4), missing defibrillator file (1). Of the 345 patients included in the analysis, 60 patients (17%) were deemed to be in shock-refractory VF while 285 (83%) patients were deemed to be in recurrent VF (Table 1). Agreement after individual assessment was high amongst reviewers with agreement on 294/345 (85%) cases, and disagreements were mitigated by mutual consensus. There were no significant differences in the Utstein characteristics between shock-refractory and recurrent cases.

Table 2 depicts the per protocol defibrillation strategy in relation to the type of ventricular fibrillation (shock-refractory or recurrent) pre-randomization.

Event characteristics of those included in the study are reported in Table 3. As in the parent study, guideline compliant CPR[18,19] was provided regardless of whether the patient was in shock-refractory or recurrent VF. Higher cumulative doses of antiarrhythmics and epinephrine were more commonly given to those in shock-refractory VF. Time of arrival to antiarrhythmic and epinephrine administration, when given, were similar between shock-refractory and recurrent VF.

Unadjusted primary and secondary outcomes are displayed in Table 4. Overall, VC defibrillation was not found to be significantly better than standard defibrillation for any primary or secondary outcomes (other than VF termination) whereas all primary and secondary outcomes were significantly greater for those who received DSED compared to standard defibrillation. Amongst those in shock-refractory VF, no patients survived to hospital discharge who were in shock-refractory VF and only received standard defibrillation whereas survival to hospital discharge and neurologically intact survival (p = 0.01 for both outcomes) were significantly greater for DSED compared to standard defibrillation. Amongst those in recurrent VF, VF termination was significant for both DSED and VC compared to standard defibrillation (p = 0.01) while only DSED was significant for ROSC compared to standard defibrillation (p = 0.02). Survival to hospital discharge and neurologically intact survival were all greater in VC and DSED when compared to standard defibrillation but were not statistically significant.

In our adjusted primary analysis (Table 5), patients in recurrent VF had greater rates of survival than those in shock-refractory VF (OR 2.76, [95% CI 1.04, 7.27]). DSED was superior to standard defibrillation for survival to hospital discharge overall (27.2% vs. 14.0%; OR 2.18 [95% CI 1.05, 4.51]) as well as those in shock-refractory VF (28.6% vs 0%, P value 0.04). Survival to hospital discharge for DSED was not found to be superior to standard defibrillation for those in recurrent VF (27.0% vs 17.1%; OR 1.71 [95% CI 0.80, 3.68]). VC defibrillation was not found to be superior to standard defibrillation overall nor in either of the shock-refractory or recurrent VF subgroups. Our adjusted secondary analysis for the outcomes of VF termination, ROSC and neurologically intact survival are noted in Supplementary Tables 1 and 2. For the patient centered outcome of neurologically intact survival, DSED was found to be superior to standard defibrillation overall (OR 2.56 [95% CI 1.19, 5.52]) as well as in the shock-refractory VF cohort (P value = 0.04) but not in the recurrent VF cohort (OR 1.98 [95% CI 0.88, 4.44]). VC defibrillation was not found to be superior to standard defibrillation for the secondary outcome of neurologically intact survival overall (OR 1.54 [95% CI: 0.69, 3.48]) nor in shock-refractory (P value = 1.0) or recurrent (OR 1.33 [95% CI 057, 3.10]) cohorts.

Discussion

In our secondary analysis of the DOSE VF RCT employing a rhythm-based definition of shock-refractory and recurrent VF, we found that those who were categorized as being in recurrent VF had higher rates of survival to hospital discharge as well as occurring more frequently than those categorized as being in shock-refractory VF. A DSED alternative defibrillation strategy was found to be superior overall for survival to discharge, similar to the findings noted in the parent study. In patients with shock-refractory VF, DSED was found to be superior to standard defibrillation; no patient survived to hospital discharge employing a standard defibrillation strategy. DSED was associated with a non-statistically significant improved survival in the recurrent VF group, however, DSED did lead to a potentially clinically relevant absolute improvement of over 10% for the outcomes of survival to hospital discharge and neurologically intact survival (relative increase of 58% in survival, 74% in neuro intact survival) in the recurrent VF subgroup. In our adjusted analysis, vector change defibrillation was not found to be superior to standard defibrillation overall or in either of the shock-refractory or recurrent subgroups for survival, consistent with the per protocol findings of the parent study. Our findings suggest that DSED is a superior strategy to standard defibrillation regardless of the underlying pattern or trajectory of ventricular fibrillation but particularly so when patients present in shock-refractory VF. Our findings employing VC defibrillation are less clear

Table 1 – Characteristics of the study population.

Variable	Shock-Refractory VF N = 60	Recurrent VF N = 285
Age, mean (SD)	63.7 (16.0)	63.4 (14.5)
Male, n (%)	51 (85.0)	243 (85.3)
Bystander witnessed, n (%)	41 (68.3)	191 (67.0)
Bystander CPR, n (%)	32 (53.3)	169 (59.3)
Location (Public), n (%)	12 (20.0)	98 (34.4)
Median (IQR) response time (min)	7.4 (3.0)	7.5 (3.5)

VF = ventricular fibrillation IQR = interquartile range; CPR = cardiopulmonary resuscitation

Table 2 – Defibrillation randomization in relation to type of ventricular fibrillation.

Variable	Shock-Refractory VF	Recurrent VF
Standard shock randomization	24/60 (40.0%)	106/285 (37.2%)
Vector change randomization	22/60 (36.7%)	90/285 (31.6%)
DSED randomization	14/60 (23.3%)	89/285 (31.2%)

VF: ventricular fibrillation; DSED: double sequential external defibrillation

Table 3 – Event characteristics.

Variable	Shock-Refractory VF N = 60	Recurrent VF N = 285	*p*-Value[a]
Median (IQR) time from initial call to first shock (min)[b]	10.5 (4.2)	10.3 (3.9)	0.72
Prehospital intubation, n (%)	26 (43.3)	124 (43.5)	0.98
Pre-shock pause, mean sec (SD)[c]	5.8 (5.7)	6.2 (6.5)	0.67
Post-shock pause, mean sec (SD)[d]	4.6 (5.1)	4.7 (3.2)	0.89
Compression rate per min, mean (SD)[e]	110.5 (9.4)	111.2 (8.3)	0.58
Compression depth (cm), mean (SD)[f]	5.8 (0.7)	5.9 (1.0)	0.49
Chest compression fraction, mean (SD)[g]	82.1 (8.0)	81.1 (9.0)	0.45
Shocks to first ROSC, mean (SD)	6.0 (2.0)	5.6 (1.8)	0.45
Amiodarone or lidocaine administered (Y/N), n (%)	52 (86.7)	212 (74.4)	0.04
Amiodarone dose (mg), mean (SD)	414.1 (64.7)	390.6 (78.1)	0.04
Lidocaine dose (mg), mean (SD)	223.3 (75.3)	163.3 (65.2)	0.08
Median (IQR) time of arrival EMS vehicle to first anti-arrhythmic drug administration[h] (min)	11.0 (9.0)	11.0 (7.0)	0.64
Epinephrine administered (Y/N), n (%)	59 (98.3)	260 (91.2)	0.06
Epinephrine dose (mg), mean (SD)	4.7 (2.0)	4.0 (2.1)	0.02
Median (IQR) time of arrival EMS vehicle to epinephrine administration[i]	9.0 (7.0)	9.0 (6.5)	0.36
Median (IQR) time of arrival EMS vehicle to first ROSC[j]	18.4 (9.8)	15.0 (9.8)	0.43
Median (IQR) time of arrival EMS vehicle to depart scene[k]	28.3 (9.4)	26.0 (11.4)	0.13

IQR = interquartile range; DSED = double sequential external defibrillation; ROSC = return of spontaneous circulation; EMS = emergency medical services.

[a] Pearson chi-square test was used to test independent proportions. The 2-sample t-test and the Mann-Whitney U test were used for parametric and nonparametric continuous variables, respectively.

[b] Cases witnessed by emergency medical services (EMS) were excluded (2 in the refractory group and 23 in the recurrent group). Data on this variable were missing for 9 patients in the recurrent group.

[c] Values are the mean for the first three shocks. Data missing for 13 patients (all in the recurrent group).

[d] Values are the mean for the first three shocks. Data missing for 14 patients (all in the recurrent group).

[e] Data missing for 3 patients (1 in the refractory group, 2 in the recurrent group).

[f] Data missing for 1 patient in the recurrent group. Data were available only for Zoll defibrillators (249 patients).

[g] Data missing for 3 patients (1 in the refractory group, 2 in the recurrent group).

[h] Cases witnessed by EMS were excluded (2 in the refractory group, 17 in the recurrent group).

[i] Cases witnessed by EMS were excluded (2 in the refractory group, 20 in the recurrent group).

[j] Cases witnessed by EMS were excluded (1 in the refractory group, 10 in the recurrent group).

[k] Cases witnessed by EMS or with termination of resuscitation in the field were excluded (7 in the refractory group, 31 in the recurrent group).

but are compatible with the hypothesis that a VC strategy may be superior to standard defibrillation when two defibrillators are not available on scene to perform DSED.

Our study demonstrates a much higher rate of shock-refractory VF (17%) than previously described, despite employing a similar methodology to determine shock efficacy.[20–24] The reasons for this may simply relate to differences in the characteristics of the populations studied. The DOSE VF RCT required patients to present in VF or pulseless VT and remain in this rhythm after three successive standard shocks. The fact that the shocks were required to be successive (with 2 minutes of CPR between each shock, for up to 3 shocks) as opposed to total shocks may imply that our study cohort may have been more "shock-refractory" to defibrillation. As well, our cohort excluded prior bystander AED shocks as shocks counted prior to a VC or DSED shock (only fire or EMS shocks were included), as such our subset of shock-refractory VF patients may be more likely to suffer from a more prolonged downtime form of VF, which has previously been described as more resistant to standard defibrillation.[24,25] Differences between study populations such as BMI, the incidence of underlying structural heart disease and ischemic heart disease may all contribute to the incidence of shock-refractory VF in our patient population.

For those patients who were categorized to be in shock-refractory VF, it is noteworthy that the probability of eventually terminating VF was similar between standard, VC, and DSED shocks. While the proportion of patients with shock-refractory VF in whom VF is eventually terminated is similar between the three strategies, the clinical outcomes in patients treated with DSED were significantly better than outcomes in patients treated with additional standard or VC shocks. We hypothesize that there is less cardiac injury during the course of

Table 4 – Unadjusted outcomes according to randomization group and VF definition (Shock-refractory or recurrent) Overall VF.

Outcome	Standard N = 130	Vector change N = 112	DSED N = 103	Standard vs VC *p*-Value[a]	Standard vs DSED *p*-Value[a]
VF termination, n (%)	90/130 (69.2)	91/112 (81.3)	85/103 (82.5)	0.03	0.02
ROSC, n (%)	35/130 (26.9)	41/112 (36.6)	46/103 (44.7)	0.11	0.01
Survival to hospital discharge[b], n (%)	18/129 (14.0)	23/112 (20.5)	28/103 (27.2)	0.18	0.01
Neurologically intact survival MRS (≤2) [b,c], n (%)	15/129 (11.6)	17/111 (15.3)	26/102 (25.5)	0.40	0.01

[a] Pearson chi-square test
[b] If known to have survived to hospital admission. Data missing for one case in the standard group.
[b,c] Data missing for one survivor from each randomization group.

Shock- Refractory VF

Outcome	Shock-Refractory VF (standard) N = 24	Shock-Refractory VF (vector change) N = 22	Shock-Refractory VF (DSED) N = 14	Standard vs VC *p*-Value[a]	Standard vs DSED *p*-Value[a]
VF termination, n (%)	17/24 (70.8)	15/22 (68.2)	9/14 (64.3)	0.85	0.68
ROSC, n (%)	2/24 (8.3)	5/22 (22.7)	4/14 (28.6)	0.23	0.17
Survival to hospital discharge[b], n (%)	0/24 (0.0)	2/22 (9.1)	4/14 (28.6)	0.22	0.01
Neurologically intact survival MRS (≤2) [b,c], n (%)	0/24 (0.0)	1/21 (4.8)	4/14 (28.6)	0.47	0.01

[a] Pearson chi-square test except where cells had expected counts less than 5, where Fisher's exact test was used.
[b] If known to have survived to hospital admission.
[b,c] Data missing for one survivor from the vector change group.

Shock Recurrent VF

Outcome	Recurrent VF (standard) N = 106	Recurrent VF (vector change) N = 90	Recurrent VF (DSED) N = 89	Standard vs VC *p*-Value[a]	Standard vs DSED *p*-Value[a]
VF termination, n (%)	73/106 (68.9)	76/90 (84.4)	76/89 (85.4)	0.01	0.01
ROSC, n (%)	33/106 (31.1)	36/90 (40.0)	42/89 (47.2)	0.20	0.02
Survival to hospital discharge[b], n (%)	18/105 (17.1)	21/90 (23.3)	24/89 (27.0)	0.28	0.10
Neurologically intact survival MRS (≤2) [b,c], n (%)	15/104 (14.4)	16/90 (17.8)	22/88 (25.0)	0.53	0.06

[a] Pearson chi-square test
[b] If known to have survived to hospital admission. Data missing for one in the standard group
[b,c] Data missing for one survivor from the standard group and one from the DSED group.
VF= ventricular fibrillation; VC= vector change; DSED= double sequential external defibrillation; MRS= Modified Rankin Scale; ROSC= return of spontaneous circulation

resuscitation in patients treated with DSED, leading to a threefold higher probability of ROSC, and less metabolic, or CNS damage, leading to all of the patients with ROSC, after DSED treatment, surviving to hospital discharge. Similarly, amongst the patients with recurrent VF who have VF termination, 29% of patients treated with DSED survive to neurologically intact hospital discharge, compared to 18% of patients treated with standard shocks. These observations suggest that it is not merely the ability to eventually terminate VF that is responsible for the better clinical outcomes in the DSED treated patients. Those in whom VF was terminated in our study were more likely to have the resulting rhythm be an organized rhythm or ROSC when DSED is employed, compared to standard defibrillation (Table 4). Although not specifically analyzed, the total time spent in VF which has been shown to be a critical factor in resuscitation success, may have been shorter with DSED than standard defibrillation.[26] This hypothesis is a focus of ongoing research into the potential benefit of alternate defibrillation strategies.

The clinical relevance of our study findings challenge the long-held belief that "failure of defibrillation" during recurrent VF is most likely due to a failure of resuscitation as opposed to a failure of defibrillation.[16] Our findings suggest that regardless of whether one uses a "pragmatic" definition of refractory VF as in the parent study or a "shock based" definition of refractory VF as in the current study, alternative defibrillation strategies, in particular DSED are superior to standard defibrillation. This is critically important from a treatment perspective as a "pragmatic" definition of refractory VF is much easier for providers to apply in a "real time" resuscitation than a "rhythm based" definition

No patients in the cohort of shock-refractory VF survived with only standard defibrillation. Strategies that could predict which patients are more likely to be in shock-refractory VF than recurrent VF could allow for earlier application of alternate therapies such as DSED. Coult et al. described the use of a novel machine learning algorithm that has the potential to automatically identify patients

Table 5 – Primary Analysis Overall VF Cohort and Recurrent Ventricular Fibrillation Cohort Survival to Hospital Discharge Overall Cohort.

Variables	OR	95% CI	P Value
Age (years)	0.94	0.92, 0.96	<0.001
Male Sex	0.83	0.36, 1.96	0.670
Response Time (min)	0.89	0.80, 0.98	0.024
Epinephrine Given	0.24	0.08, 0.75	0.014
Antiarrhythmics Given	1.18	0.51, 2.72	0.700
DSED	2.18	1.05, 4.51	0.036
VC	1.84	0.88, 3.87	0.108
Recurrent	2.76	1.04, 7.27	0.041
DSED = Double Sequential External Defibrillation; VC = Vector change defibrillation; Recurrent = recurrent Ventricular Fibrillation			

Survival to Hospital Discharge Cohort			
Variables	OR	95% CI	P Value
Age (years)	0.94	0.92, 0.96	<0.001
Male Sex	1.16	0.45, 3.00	0.758
Response Time (min)	0.89	0.80, 0.99	0.03
Epinephrine Given	0.26	0.08, 0.81	0.021
Antiarrhythmics Given	1.08	0.46, 2.52	0.865
DSED	1.71	0.80, 3.68	0.167
VC	1.55	0.72, 3.37	0.266
DSED= Double Sequential External Defibrillation; VC= Vector change defibrillation			

likely to experience refractory ventricular fibrillation during resuscitation using the defibrillator ECG.[27] Based on our study findings, the application of such an algorithm could allow for earlier use of a DSED strategy (as early as the initial shock) if a shock-refractory defibrillator ECG was identified. Although not yet proven during clinical care, the use of amplitude spectrum area of ventricular fibrillation (AMSA) may have the potential to guide defibrillation when compared to traditional defibrillation strategies.[28]

Our study is not without limitations. Given that our focus was on mechanism of DSED efficacy, we employed data from the per protocol population of the study as opposed to the intention to treat population. This had the impact of lowering the number of patients overall as well as decreasing our power to be able to adjust for variables in the shock-refractory cohort. Due to sample size restrictions we were unable to adjust for in-hospital care such as provision of angiography or percutaneous coronary intervention, but neither was found to be preferentially provided to DSED or VC in the parent study. While we were successful in identifying cases as shock-refractory or recurrent VF, the calculation of time to refibrillation in each strategy was beyond the scope of this work and remains a focus for further research. Finally, variables such as BMI or changes in defibrillation impedance, which may impact shock success were not assessed in our research.

Conclusion

Among patients enrolled in the DOSE VF RCT, survival was improved for those who were found to be in recurrent VF as well as those who received DSED defibrillation. DSED appears to be the optimal alternate therapy after 3 shocks in the DOSE VF trial, irrespective of whether the preceding VF is shock-refractory or recurrent.

CRediT authorship contribution statement

Sheldon Cheskes: Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ian R. Drennan:** . **Linda Turner:** Writing – review & editing, Validation, Software, Resources, Methodology, Formal analysis, Data curation. **Sandeep V. Pandit:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Paul Dorian:** Writing – review & editing, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2024.110186.

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