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Clinical paper

The impact of double sequential shock timing on outcomes during refractory out-of-hospital cardiac arrest

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Abstract

Background: Animal studies suggest the efficacy of double sequential external defibrillation (DSED) may depend on the interval between the two shocks, or "DSED interval". No human studies have examined this concept.

Objectives: To determine the relationship between DSED interval and termination of ventricular fibrillation (VFT), return of spontaneous circulation (ROSC), survival to hospital discharge, and favourable neurological status (MRS $\leq$ 2) for patients in refractory VF.

Methods: We performed a retrospective review of adult ($\geq$18 years) out-of-hospital cardiac arrest between January 2015 and May 2022 with refractory VF who received $\geq$1 DSED shock. DSED interval was divided into four pre-defined categories. We examined the association between DSED interval and patient outcomes using general estimated equation logistic regression or Fisher's exact test.

Results: Among 106 included patients, 303 DSED shocks were delivered (median 2, IQR 1–3). DSED intervals of 75–125 ms (OR 0.39, 95% CI 0.16–0.98), 125–500 ms (OR 0.36, 95% CI 0.16–0.82), and >500 ms (OR 0.27, 95% CI 0.11–0.63) were associated with lower probability of VF termination compared to <75 ms interval. DSED interval of >75 ms was associated with lower probability of ROSC compared to <75 ms interval (OR 0.37, 95% CI 0.14–0.98). No association was noted between DSED interval and survival to hospital discharge or neurologic outcome.

Conclusions: Among patients in refractory VF a DSED interval of less than 75 ms was associated with improved rates of VF termination and ROSC. No association was noted between DSED interval and survival to hospital discharge or neurologic outcome.

Keywords: Cardiopulmonary resuscitation, Cardiac arrest, Resuscitation, Defibrillation, Double sequential external defibrillation, Prehospital care

Introduction

Out-of-hospital cardiac arrest (OHCA) is a significant cause of morbidity and mortality worldwide, with an estimated 55 to 110 cases per 100,000 people annually and survival of less than 10%.[1–3] Patients who present to emergency medical services (EMS) with an initial rhythm of ventricular fibrillation (VF) have the highest likelihood of neurologically intact survival.[4] However, a subset of patients remain in VF despite multiple defibrillation attempts, termed refractory VF (RVF). Although no standard definition of RVF exists, most studies define RVF as persistent VF following three successive defibrillations with or without standard Advanced Cardiac Life Support (ACLS) interventions.[5–9] Regardless of the definition of RVF, defibrillation remains the standard of care with the goal of terminating fibrillatory activity. Patients with RVF have poor survival and neurological outcome.[10,11]

Double sequential external defibrillation (DSED) has been proposed as an alternative treatment for patients in RVF. During DSED, two defibrillators are used (most commonly, one in anterior-lateral pad placement and a second in anterior-posterior pad placement, Fig. 1) to administer two defibrillatory shocks in rapid succession. DSED has been previously studied for patients in atrial fibrillation, VF, and RVF using monophasic[12–19] and biphasic[7–11,20,21] waveforms. Most recently, the DOuble SEquential External Defibrillation for Refractory VF (DOSE-VF) trial showed that survival to hospital

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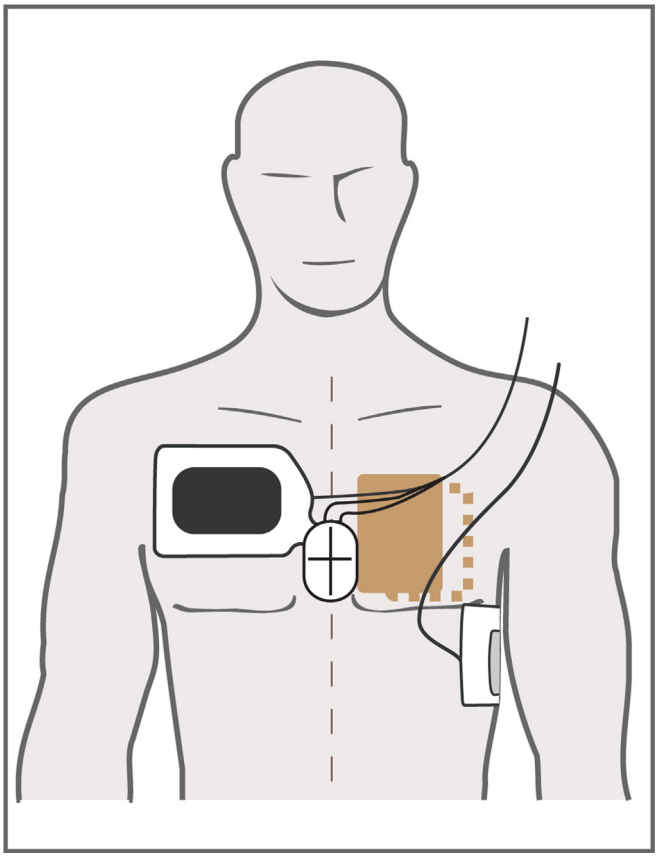

Fig.1 – Pad position for Double Sequential External Defibrillation.

discharge was higher among RVF OHCA patient who received DSED than among those who received standard defibrillation.[21]

Despite the improvements in outcomes noted in the DOSE VF trial, the mechanism by which patients may respond to DSED is not completely understood. When DSED is delivered, shocks may interact with each other resulting in a higher efficacy compared to standard single shock.[22,23] Animal research and experimental studies have explored the optimal DSED interval; however, no studies have assessed the question of optimal timing of DSED shocks in humans.[24] The objective of our study was to assess the relationship between DSED shock interval and the outcomes of VF termination, ROSC, survival to hospital discharge, and neurologically intact survival (MRS $\leq$ 2).

Methods

Setting and design

We performed a retrospective cohort study of prospectively collected data between January 1, 2015, and May 22, 2022, of adult ($\geq$18 years) OHCA patients who presented in RVF (presented in VF and remained in VF after three successive defibrillations) and received a minimum of one DSED shock. Six paramedic agencies in Ontario, Canada were involved in this study. The agencies (Peel Regional Paramedic Service, Halton Region Paramedic Service, Toronto Paramedic Service, County of Simcoe Paramedic Service, Middlesex London Paramedic Service and Ottawa Paramedic Service) provide emergency care and transport to a population of 4.8 million people in both urban and rural settings within a geographic area of 2841 km^2. Paramedics in these regions treat over 4000 OHCA per year. The care provided by paramedics has been previously described.[9]

Beginning in January 2015, paramedics were able to perform DSED for patients who did not respond to standard defibrillation (after physician authorization via on-line medical control). Between January 1, 2015, and March 6, 2018, the decision to request authorization for DSED was made at the discretion of the attending paramedics. After March 6, 2018, all paramedic agencies began enrolling patients into the DOSE-VF RCT.[21] In brief, the DOSE-VF RCT was a cluster crossover randomized trial. All adult ($\geq$18 years) patients presenting in RVF during OHCA with presumed cardiac etiology were randomly assigned to be treated by one of the three defibrillation strategies following three failed standard shocks: (1) continued resuscitation using standard defibrillation (pads placed in the anterior-lateral position); (2) continued resuscitation using DSED (pads placed in the anterior-lateral position and the anterior-posterior position, (Fig. 1); or (3) continued resuscitation using vector change defibrillation (defibrillation pads moved from anterior-lateral to anterior-posterior position). During the DOSE-VF RCT, paramedics enrolled all eligible patients based on a protocolized medical directive in the absence of any contraindications. During the DOSE-VF RCT period, only patients who were randomized to the DSED arm of the RCT and received at least one DSED using Zoll X series defibrillators (Zoll Medical, Chelmsford, Massachusetts) were included in our current study. Patients who were enrolled in the DOSE-VF RCT but did not have defibrillator files from both

defibrillators available or received DSED employing Stryker defibrillators were excluded from the current study.

During the time frame of this study, DSED was performed utilizing one of two methods (simultaneous or sequential method). In each case, a second set of defibrillation pads was applied to the patient in the anterior–posterior position in addition to the pre-existing anterior-lateral defibrillation pads, with a specific focus on minimizing interruptions in CPR. Prior to the start of the DOSE-VF trial, DSED shocks were provided using a "simultaneous method" (single paramedic pressing the shock buttons on both defibrillators at the same time). Starting in March 2018, as part of the DOSE-VF RCT, shocks were provided in a "sequential manner" (single paramedic pressing the shock button on the first defibrillator followed rapidly by the second defibrillator) to allay any agency concerns of potential defibrillator damage expressed by manufacturers and a previous case report of defibrillator damage employing the technique (although for a different indication than in our study).[25] The study protocol was approved by the Sunnybrook Health Science Centre Research Ethics Board.

Measurement and study definitions

Patients with RVF were defined as patients who presented in VF, had three consecutive standard defibrillation attempts separated by two minutes of CPR and remained in VF at the time of the fourth rhythm analysis. VF termination, was defined as the absence of refibrillation at the subsequent rhythm check following the defibrillation (DSED) and two minutes of CPR. For the purpose of our study, VF could be terminated into a perfusing rhythm (ROSC), pulseless electrical activity (PEA), or asystole. ROSC was defined as the restoration of organized cardiac activity noted on the defibrillator file with corresponding documentation of a pulse or blood pressure by the paramedics (lasting at least 30 seconds). We defined favourable neurological status as hospital discharge as a modified Rankin Scale (mRS) ≤ 2. For the outcomes of survival and favourable neurological status our analyses were confined to cases from the DOSE-VF trial since we did not have these outcomes for patients who received DSED prior to the trial.

The DSED shock interval was defined as the time between initiation of the first defibrillation and the initiation of the second defibrillation. To calculate the DSED shock interval, we identified the defibrillator used to deliver the second defibrillation by reviewing the impedance channel measurements and defibrillator recordings from both defibrillators. The recording from the second defibrillator had a characteristic large amplitude distorted signal prior to the defibrillation (caused by the first defibrillation). We marked the beginning of this distorted signal (dotted red line) as the time of the first defibrillation (Supplemental Fig. 1). The exact time of the second defibrillation was downloaded directly from the second defibrillator file. The timing of events on the defibrillator recordings are reported to the closest second; therefore, to increase the precision we analyzed the change in voltage (recorded by the defibrillator pads) from each defibrillator, which allowed us to assess the time of defibrillation to within seven milliseconds (msec). After determining the time of each defibrillation separately, we calculated the DSED shock interval by subtracting the time of the second shock from the first shock. When the DSED shock interval was less than 70 ms, the large amplitude distorted signal (characteristic of DSED) did not appear on the defibrillator impedance channel measurements. For these cases, we recorded the interval as 70 ms or less, since we were unable to calculate the exact interval (Supplemental Fig. 2). Supplemental Figs. 1 and 2 are only for illustration and were not used to calculate the shock intervals. A detailed explanation of the calculation of the DSED interval from the voltage table, in millisecond increments is included in Supplementary File 1. Cardiac rhythm interpretation was performed independently by two investigators. Disagreements were resolved through arbitration by a third investigator.

Data collection of patient demographics, prehospital treatments, and CPR quality has been previously described.[9] The total number of defibrillations delivered, total number of DSED shocks delivered, and the timing of DSED shocks during the resuscitation were abstracted from both the defibrillator files and the paramedic ePCR. All defibrillations were abstracted up to the point of first noted ROSC on the ePCR or transfer of care at the receiving emergency department.

Our primary objective was to examine the relationship between DSED shock interval and termination of VF. Our secondary objectives were to examine the relationship between DSED shock interval and ROSC, survival, and survival with good neurological status. To assess the relationship between DSED shock interval and our outcome measures, we divided the time interval between two defibrillations into four pre-defined intervals; <75 ms, 75–125 ms, 125–500 ms, and >500 ms. This was consistent with previous literature examining DSED shock interval employing animal models.[24] For the outcomes of VF termination and ROSC, we considered all DSED shocks in each patient; therefore, the reported rate of VF termination and VF termination to ROSC are based on total number of DSED attempts, as opposed to an individual case basis. For example, if a patient received three DSED shocks and the third shock resulted in VF termination, we calculated the interval for all three attempts and recorded the third DSED attempt interval as associated with VF termination but the first two intervals as failure. For the outcomes of survival and survival with favourable neurological status, we only included patients who had sustained ROSC and we assessed the association of the DSED interval that resulted in sustained ROSC and the outcomes of survival and favourable neurological outcome.

Statistical analyses

Descriptive statistics were summarized using medians with interquartile range (IQR), means with standard deviation (SD), or counts and percentages. For the outcome of VF termination, since each person was potentially represented multiple times, we used logistic regression based on general estimated equation model to adjust for clustering within individuals in addition to DSED interval. The test for association of DSED shock interval and outcome of ROSC, was performed using a similar method. However, we combined 75–125 ms, 125–500 ms, >500 ms intervals into one larger interval due to low number of events (ROSC) overall. For the outcomes of survival and survival with a favourable neurological status, we confined our analysis to patients who had a sustained ROSC and used the interval of the DSED shock that resulted in the sustained ROSC for the association analysis. Since for these two outcomes each patient could have only been represented once, we used Fisher's exact test to determine the association. We did not perform any adjusted analyses due to sample size restrictions. DSED shock intervals were combined for the outcomes of survival and neurologically intact survival similar to our approach with the outcome of ROSC. The outcome of the regression analysis was reported using odds ratios (OR) and corresponding 95% confidence intervals (CI).

All statistical analyses were two-sided, with a P value of <0.05 considered statistically significant and performed using IBM SPSS Statistics, version 25 (IBM, Armonk, NY, USA). The RECORD

statement (extension of STROBE statement for reporting of observational studies) is included as Supplemental File 2.

Results

During the study period 106 patients met the inclusion criteria. Of these patients 69 (65%) were enrolled in the DOSE-VF RCT and 37 (35%) received DSED prior to the RCT. Descriptive characteristics for included patients are reported in Table 1. Both epinephrine dose and number of standard shocks prior to first DSED were significantly greater in the pre-RCT time frame as would be expected by the protocolized care provided during the RCT. Chest compression fraction (CCF), chest compression rate, pre- and post-shock pauses, and chest compression depth were all compliant with current guideline recommendations regardless of method of DSED defibrillation used.[26] The majority of the included patients received epinephrine (92.5%) and amiodarone (82.1%).

Among the 106 patients, 303 DSED shocks were delivered (median 2 (IQR 1–3); maximum 11). The median (IQR) DSED shock interval overall was 549.0 (268.0, 879.0) ms. The value was shorter when DSED was delivered using the simultaneous method prior to the start of the RCT as compared to the sequential method used during the RCT (103.0 ms (73.7, 288.2) versus 646.0 ms (472.0, 983.0)). However, there was significant dispersion in shock intervals during both periods (Fig. 2).

The relationship between DSED shock interval and VF termination are reported in Table 2. DSED shock interval of 75–125 ms (OR 0.39, 95% CI 0.16–0.98), 125–500 ms (OR 0.36, 95% CI 0.16–0.82), and >500 ms (OR 0.27, 95% CI 0.11–0.63) were associated with lower probability of VF termination compared to <75 ms. The relationship between DSED shock interval and ROSC is reported in Table 3. DESD shock interval of >75 ms was associated with lower probability of ROSC compared to <75 ms (OR 0.37, 95% CI 0.14–0.98).

The relationship between DSED shock interval that resulted in sustained ROSC and survival and survival with neurological status are summarized in Table 4. Our analysis did not show any significant difference in survival or survival with good neurological status and DSED shock interval (Fisher's exact $p = 1.0$ for both outcomes).

Discussion

The findings of this first-ever human study exploring the relationship between DSED shock interval and clinical outcomes suggests shorter DSED time intervals (<75 ms) may be associated with improved rates of VF termination and ROSC. While there was no significant difference in survival or survival with good neurological status based on DSED interval, we acknowledge our analysis was impacted by a lack of data in the cohort with the shortest DSED intervals. Of note, despite late application of DSED in the pre-RCT cohort, shorter DSED intervals were associated with improved rates of VF termination and ROSC suggesting simultaneous DSED may in fact yield improved outcomes compared to sequential DSED despite the potential for a slightly increased rate of defibrillator damage noted in previous research (0.11% vs 0%).[27].

Despite applying a pragmatic definition of VF termination our study has striking similarities when compared with previously published animal experiments suggesting that shock success depends on DSED shock interval. Our finding that a DSED shock interval <75 ms is associated with higher efficacy in terminating VF and ROSC is slightly shorter than the 75–125 ms reported optimal interval in animal models.[24] In animal models, the 25–75 ms interval is

Table 1 – Patient, CPR, and Treatment Characteristics.

Patient Characteristics	Cohort n = 37	RCT n = 69	Total N = 106
Age (years), median (IQR)	62 (18)	64 (24)	63 (23)
Male, n (%)	30 (81.1)	59 (85.5)	89 (84.0)
Public Location, n (%)	7 (18.9)	25 (36.2)	32 (30.2)
Paramedic Witnessed, n (%)	2 (5.4)	7 (10.1)	9 (8.5)
Bystander Witnessed, n (%)[a]	27 (75.0)	49 (71.0)	76 (72.4)
Bystander CPR, n (%)	20 (54.1)	41 (59.4)	61 (57.5)
Chest Compression Rate (/min), median (IQR)[b]	113 (10)	113 (11)	113 (10)
Chest Compression Depth (cm), median (IQR)[b]	5.7 (1.1)	5.7 (1.0)	5.7 (1.0)
Chest Compression Fraction, median (IQR)[b]	84.9 (9.2)	81.9 (8.9)	82.9 (9.4)
Pre-shock Pause (sec), mean (SD)[c]	6.0 (4.8)	5.7 (6.1)	5.8 (5.8)
Post-shock Pause (sec), mean (SD)[d]	4.4 (1.8)	4.2 (2.1)	4.3 (2.0)
EMS Response Time (min), median (IQR)	7.0 (5.4)	7.3 (3.0)	7.2 (3.5)
Time to Patient Contact (min), median (IQR)[b]	9.0 (4.9)	8.9 (4.1)	9.0 (4.1)
Epinephrine given, n (%)	36 (97.3)	62 (89.9)	98 (92.5)
Total Dose of Epinephrine (mg), mean (SD)	5.1 (1.9)	4.1 (2.0)	4.5 (2.0)
Amiodarone given, n (%)	34 (91.9)	53 (76.8)	87 (82.1)
Total Dose of Amiodarone (mg), mean (SD)	423.5 (58.0)	390.6 (74.1)	403.5 (69.8)
Number of Shocks prior to first DSED, median (IQR)	7 (3.0)	3 (1.0)	4 (3.0)

IQR = interquartile range; CPR = cardiopulmonary resuscitation; EMS = emergency medical services; DSED = Double sequential external defibrillation

[a] Data missing for 1 patient in the cohort group.

[b] Data missing for 2 patients in the cohort group.

[c] Values are the mean for the first three shocks. Data missing for 12 patients (9 in the cohort group and 3 in the RCT group).

[d] Values are the mean for the first three shocks. Data missing for 7 patients (4 in the cohort group and 3 in the RCT group).

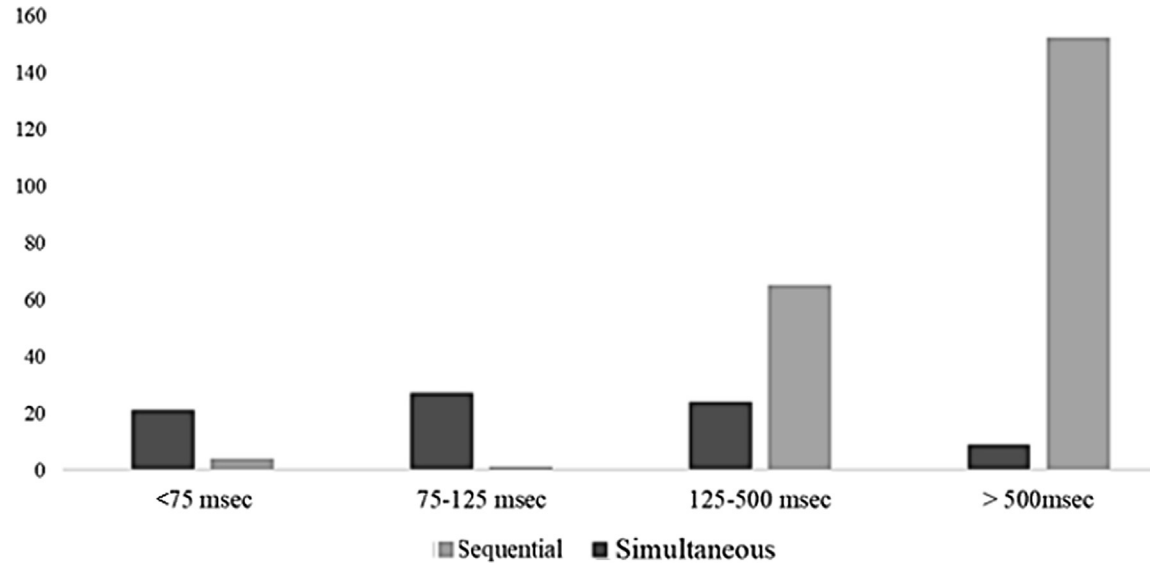

Fig. 2 – Distribution of DSED shock intervals according to the method of delivery. Based on previous literature, the time interval between two defibrillations was divided into four intervals; <75 ms, 75–125 ms, 125–500 ms, >500 ms. For the >500 ms interval, the 1st and 3rd quartiles were 626.25 ms and 1086.5 ms respectively with a maximum DSED interval of 2046 ms. DSED = double sequential external defibrillation; msec = milliseconds.

Table 2 – Relationship between DSED Interval and Outcome of VF Termination.

	Total Number of DSED n (%)	VF Termination n (%)	VF Termination OR (95% CI)
Total	303	81 (26.7)	
Time intervals			
< 75 ms	25 (8.2)	12 (48.0)	Ref
75–125 ms	29 (9.6)	7 (24.1)	0.39 (0.16–0.98)
125–500 ms	89 (29.4)	24 (27.0)	0.36 (0.16–0.82)
> 500 ms	160 (52.8)	38 (23.8)	0.27 (0.11–0.63)

DSED = double sequential external defibrillation; VF = ventricular fibrillation; ms = milliseconds.

Table 3 – Relationship between DSED Interval and ROSC.

	Total Number of DSED n (%)	VF Termination to ROSC n (%)	VF Termination to ROSC OR (95% CI)
Total	303	35 (11.6)	
Time intervals			
< 75 ms	25 (13.5)	6 (24.0)	Ref
> 75 ms	278 (86.5)	29 (10.4)	0.37 (0.14–0.98)

DSED = double sequential external defibrillation; VF = ventricular fibrillation; ROSC = return of spontaneous circulation, ms = milliseconds.

consistent with the reported post-shock relative refractory period in the early stages of VF, and DSED shocks within this interval were associated with lower efficacy.[28] In this study, we were not able to measure the exact time interval for DSED shocks in the <70 ms interval due to the limitation in calculating this interval with the available data. Unlike animal studies, in our study patients received DSED after failure of three or more standard defibrillation attempts. The difference in optimal DSED interval seen between animal studies and our study may be explained by longer duration of VF prior to defibrillation, and multiple failed shocks which can alter the mechanism of VF maintenance. Some studies have suggested that defibrillation might need to be adjusted based on these factors.[29–31]

The variation noted in DSED shock interval has previously been demonstrated by Hamilton et al.[32] and has been confirmed in our study in a clinical environment. We noted considerable variability in the DSED shock interval when the “simultaneous” vs “sequential” approach was employed with the median values mimicking those seen in the previous lab environment. Our slightly longer values for

Table 4 – Relationship between DSED Interval and Survival or Survival with Good Neurological Outcome among Those Who Had Sustained ROSC with a Known Neurological Outcome (N = 25).

	0–75 ms	> 75 ms	*p* value[a]
Survival to Hospital Discharge			1.00
Yes	1	18	
No	0	6	
Neurological Outcome at Discharge			1.00
MRS $\leq$ 2	1	17	
MRS > 2	0	7	

DSED = double sequential external defibrillation; ROSC = return of spontaneous circulation; MRS = Modified Ranking scale; ms = milliseconds.
[a] Fisher's exact p value.

similar shock techniques as demonstrated in the work by Hamilton et al. are not surprising given the application of DSED in a "real world" environment.

In our study, shorter DSED interval (<75 ms) was associated with higher rate of ROSC. In the recently published DOSE-VF RCT,[21] rates of ROSC were greater with DSED than standard defibrillation (46% vs 26%) despite the longer DSED shock intervals noted using the "sequential approach" in our current study. This finding suggests that DSED shock interval may be one of many factors responsible for DSED efficacy. Other factors may have an impact on DSED efficacy such as variations in transthoracic impedance between anterolateral shocks early in the resuscitation and the anterior-posterior vector of the subsequent DSED shocks. Given the findings of this study, it is possible that advances in technology that optimize the DSED shock interval may produce further improvements in clinical outcomes. Our study suggests that technological advancements should focus on achieving a DSED interval of less than 75 ms. Investments in technology directed towards enhancing the precision of the DSED interval are critical for exerting more precise control over this variable in the future.

This study has several limitations. This was a retrospective observational study and has all of the associated inherent limitations of this type of study design, including the inability to infer a cause-and-effect relationship. In this study, we reported on patient-important outcomes such as survival to hospital discharge and neurologically intact survival; however, our analysis is underpowered to accurately assess such outcomes and lacks survival outcome data for a significant portion of patients with DSED intervals less than 75 ms. Although defibrillator files were reviewed for cases in which DSED was employed we could not calculate the exact time interval for DSED shocks when the interval was <70 ms and we were not able to consider the DSED interval as a continuous variable. Additionally, we did not have a mechanism to calculated DSED interval in Stryker defibrillators although we have no reason to believe they would be different from the intervals calculated in our study. Our study did not assess the BMI of patients nor shock impedance, which as noted, may impact shock efficacy.

Conclusion

Among patients in refractory VF a DSED shock interval of less than 75 ms may be associated with improved rates of VF termination and ROSC. No significant association was noted between DSED shock interval and survival to hospital discharge or neurologically intact survival although our analysis was impacted by a lack of survival data on those with DSED interval <75 ms.

Author contributions

MR and SC conceived the study and designed the protocol. MR, SC, LT supervised the conduct of the study and data collection. MR, ID, LT and SC managed the data, including quality control. MR, ID, LT and SC provided statistical advice on study design and analyzed the data. ID and SC provided clinical advice on study interpretation. MR drafted the manuscript, and all authors contributed substantially to its revision. SC takes responsibility for the paper as a whole.

CRediT authorship contribution statement

Mahbod Rahimi: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ian R. Drennan:** . **Linda Turner:** Writing – review & editing, Methodology, Data curation. **Paul Dorian:** Writing – review & editing, Validation, Formal analysis, Conceptualization. **Sheldon Cheskes:** .

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Cheskes sits on the editorial board of the Journal Resuscitation.

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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.2023.110082.

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