Available online at www.sciencedirect.com

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

Survival to hospital discharge with biphasic fixed 360 joules versus 200 escalating to 360 joules defibrillation strategies in out-of-hospital cardiac arrest of presumed cardiac etiology

Jan-Aage Olsen[a,b], *Cathrine Brunborg*[c], *Mikkel Steinberg*[a,d], *David Persse*[e], *Fritz Sterz*[f], *Michael Lozano Jr.*[g], *Mark Westfall*[h,i], *Pierre M. van Grunsven*[j], *E. Brooke Lerner*[k], *Lars Wik*[a,*]

[a] *Norwegian National Advisory Unit on Prehospital Emergency Medicine, Oslo University Hospital, Oslo, Norway*
[b] *Department of Oncology, Oslo University Hospital, Oslo, Norway*
[c] *Department of Biostatistics and Epidemiology, Oslo University Hospital, Oslo, Norway*
[d] *Institute of Clinical Medicine, University of Oslo, Oslo, Norway*
[e] *Houston Fire Department and the Baylor College of Medicine, Houston, TX, United States*
[f] *Department of Emergency Medicine, Medical University of Vienna, Vienna, Austria*
[g] *Department of Internal Medicine, Morsani College of Medicine, University of South Florida, Tampa, FL, United States*
[h] *Gold Cross Ambulance Service, Appleton Neenah-Menasha and Grand Chute Fire Departments, WI, United States*
[i] *Theda Clark Regional Medical Center, Neenah, WI, United States*
[j] *Regional Ambulance Service Gelderland-Zuid, Nijmegen, The Netherlands*
[k] *Department of Emergency Medicine, Medical College of Wisconsin, Milwaukee, WI, United States*

Abstract

Introduction: Guidelines recommend constant or escalating energy levels for shocks after the initial defibrillation attempt. Studies comparing survival to hospital discharge with escalating vs fixed high energy level shocks are lacking. We compared survival to hospital discharge for 200 J escalating to 360 J vs fixed 360 J in patients with initial ventricular fibrillation/pulseless ventricular tachycardia in a post-hoc analysis of the Circulation Improving Resuscitation Care trial database.

Methods and Results: Pre-shock rhythm, rhythm 5 s after shock, shock energy levels, termination of ventricular fibrillation/pulseless ventricular tachycardia (TOF), and survival to hospital discharge were recorded. Association between defibrillation strategy and survival to hospital discharge was investigated with multivariable logistic regression. The escalating energy group included 260 patients and 883 shocks vs 478 patients and 1736 shocks in the fixed-high energy group. There was no difference in survival to hospital discharge between escalating (70/255 patients, 28%) and fixed energy group (132/478 patients, 28%) (unadjusted OR 1.00, 95% CI 0.72–1.42 and adjusted OR 0.81, 95% CI 0.54–1.22, p = 0.32). First shock TOF was 86% in the escalating group compared to 83% in the fixed-high group, p = 0.27.

* Corresponding author at: Norwegian National Advisory Unit on Prehospital Emergency Medicine, Oslo University Hospital, Postboks 4956 Nydalen, 0424 Oslo, Norway.
E-mail address: lars.wik@medisin.uio.nos (L. Wik).

https://doi.org/10.1016/j.resuscitation.2019.01.020
Received 30 November 2018; Received in revised form 2 January 2019; Accepted 18 January 2019
0300-9572/© 2019 Elsevier B.V. All rights reserved.

Conclusion: There was no difference in survival to hospital discharge or the frequency of TOF between escalating energy and fixed-high energy group. ClinicalTrials.gov Identifier: NCT00597207.

Keywords: Defibrillation, Out of hospital cardiac arrest, Cardiopulmonary resuscitation, Heart arrest, Survival, Ventricular fibrillation

Introduction

In patients requiring defibrillation the BIPHASIC trial[1] compared termination of ventricular fibrillation (VF) and restoration of organized rhythm for fixed lower-energy (150 J) vs escalating higher energy (200–300–360 J) using defibrillators with biphasic truncated exponential waveform (BTE) technology. They concluded that patients requiring multiple shocks could benefit from higher energy levels using the escalating energy strategy.

The 2015 European Resuscitation Council (ERC) guidelines state that "both strategies are acceptable; however, if the first shock is not successful and the defibrillator is capable of delivering shocks of higher energy, it is reasonable to increase the energy for subsequent shocks."[2] and "If a shockable rhythm recurs after successful defibrillation with ROSC, and the defibrillator is capable of delivering shocks of higher energy, it is reasonable to increase the energy for subsequent shocks."[2]

The 2015 American Heart Association (AHA) guidelines[4] state that "selection of fixed vs escalating energy for subsequent shocks be based on the specific manufacturer's instructions" (Class IIa, level of evidence (LOE)) C-limited data (LD) and "If using a manual defibrillator capable of escalating energies, higher energy for second and subsequent shocks may be considered (Class IIb, LOE C-LD)". These statements indicate that the optimal energy level (fixed low-, escalating-, or fixed high-energy) of the first and subsequent biphasic defibrillation attempts are not firmly established.

To add to the knowledge base, we have investigated how biphasic defibrillation technology with escalating energy levels compared with fixed high-energy levels (360 J) influenced rates of termination of VF/ventricular tachycardia (VT) (TOF) and survival to hospital discharge in a post-hoc cohort study based on the Circulation Improving Resuscitation Care trial (CIRC) database.

Methods

Study population

CIRC[5] was a multicenter, randomized, controlled trial of manual cardiopulmonary resuscitation (CPR) vs manual CPR integrated with a mechanical load-distributing band (LDB) device (AutoPulse® (ZOLL Medical, Chelmsford, MA) in emergency medical services (EMS) treated adult patients with cardiac arrest of presumed cardiac etiology. Patients treated by both basic and advanced life support units between March 5, 2009 and January 11, 2011 were eligible for analysis if they had initial VF/VT and received at least one appropriate shock with interpretable electronic defibrillator data from a LifePak defibrillator. All study sites used sternal-apical pads position. Three sites used an escalating energy strategy (first shock 200 J, second shock 200, 300 or 360 J, and third shock and subsequent shocks 360 J). One site which was the biggest site used a fixed high-energy strategy (360 J for all shocks, data from one site). This latter site had implemented a policy of fixed 360 J defibrillation reasoning that some individuals may benefit from more energy while no negative effect due to increased myocardial damage had been demonstrated in human studies.[1,6]

The CIRC-trial was approved for an exemption from informed consent for emergency research as described in laws and regulations in the US, Austria and the Netherlands.[7] AHA 2005 guidelines[8] were followed at the United States (US) sites and the 2005 ERC guidelines[9] at the European sites, with the exception that three minutes CPR cycles were used.[10]

Data collection and processing

Case report forms were reviewed regarding patient, pre-hospital, hospital and outcome data between escalating group and fixed high-energy group. Electrocardiogram (ECG) and transthoracic impedance (TTI) were recorded by the defibrillators LifePak (LP) 500, 12 and/or 15 (Physio-Control, Redmond, WA, USA) and uploaded to a central server. Physio-Control EDGE System™ Electrodes with QUIK-COMBO® Connector were used with all defibrillators. We excluded inappropriate shocks, shocks without analyzable pre-shock or post-shock rhythm from TOF analysis, and patients not meeting either escalating or a fixed energy group. Patients who received shocks from AED Pro and/or E-Series (ZOLL Medical, Chelmsford, MA, USA) were excluded due to those devices employing a different defibrillation waveform technology.

Electronic files were reviewed using CODE-STAT™ 9.0 (Physio-Control, Redmond, WA). Chest compressions and calculation of chest compression fraction (defined as the percentage of time when the patient received compressions during resuscitation) were annotated based on the TTI graph.[11] The value of TTI (Ω) immediately before each shock delivery was recorded. JAO and MS annotated all initial rhythms independently. Cases where their initial rhythm annotations differed were revisited, and consensus reached. All rhythms were classified as asystole, pulseless electrical activity (PEA, ≥10 organized complexes per minute), VF, VT, or restoration of spontaneous circulation (ROSC). ROSC was defined as having QRS-complexes without any TTI signal of chest compressions for more than one minute combined with information of a palpable pulse from the case report forms.

For each shock the following variables were recorded: pre-shock rhythm, rhythm five seconds post-shock, impedance value immediately before each shock (Ω), joules (J), and current in ampere (A) were recorded. Peak current was calculated based on recorded impedance values, J as documented per shock in software used to analyze shocks, and information on defibrillator energy delivery.[4]

Pre-shock rhythms were annotated in periods without detected compressions. JAO and LW annotated together the first 200 post-shock rhythms, which had to be evaluated during either manual or LDB compressions. Thereafter, we annotated rhythms independently. Post-shock rhythms were annotated during continuous chest compressions and for continuous LDB-CPR there is an automatic one-second compression pause after each 9th compression that was used for a second rhythm evaluation and verification of the rhythm analyzed during chest compressions. If this differed from the

annotation during compressions, JAO and LW tried to reach consensus. If consensus could not be reached, the rhythm was classified as unknown. During M-CPR with compressions during rhythm evaluation, the annotated rhythm was compared to the rhythm in the pause closest to the primary annotation. Inter-rater reliability of post-shock rhythms was determined by Kappa statistic. Cases for this evaluation were selected using the random number generator in SPSS.

Outcome

Primary outcome was survival to hospital discharge. Secondary outcomes were TOF (defined as termination of VF/VT 5 s after shock[6]), survival to emergency department (ED) with spontaneous circulation, and 24-h survival.

Statistical analysis

For statistical analyses SPSS version 22.0 (IBM SPSS Inc., Chicago, IL) and R[12] using the MGCV package[13] were used. Normally distributed data are presented as means with standard deviation (SD), and skewed data as medians with 25 and 75 percentiles. The Chi-square test for contingency tables with different degrees of freedom was used to detect associations between categorical variables and escalating vs fixed group. Between groups differences in continuous variables were tested with Student *t*-test for normally distributed data and Mann–Whitney *U* test for skewed data. Impedance change between subsequent shocks for each patient within the escalating group and the fixed group were calculated with a paired samples *t*-test. Post-shock rhythm inter-agreement reliability with 95% confidence interval was calculated using unweighted Kappa statistic. Logistic regression analysis was performed to study the association between the groups and survival to ED, 24 h, and hospital discharge. We adjusted for confounding effects of age, witnessed arrest, cardiac arrest location and response interval as those were identified to be covariates in a backward elimination procedure. To account for different study sites we included the study site as a random effect in a mixed model. Multivariable analyses were preceded by estimation of correlations between variables. The associations were quantified by OR with its 95% confidence interval (OR [(95% CI), p-value]). Two tailed p-values of less than 5% were considered significant.

Results

In CIRC 1657 (39%) of 4231 patients received shocks with analyzable defibrillator data. A total of 912 patients had initial VF/VT, and we were able to categorize 752 of them into an escalating or a fixed high-energy group. One site had no LP500/12/15 and were excluded from analysis (n = 14). In the escalating energy group 260 patients received 913 shocks and in the fixed high-energy group 478 patients received 1765 shocks (Fig. 1). Consensus on post-shock rhythm was not reached for 59 shocks (30 escalating group, 29 fixed high-energy group), and they were excluded from analysis. Thus 883 shocks were included in the escalating group, and 1736 shocks in the fixed high-energy group.

Patient characteristics and pre-hospital treatment data are described in Table 1. Compared to the fixed-high energy group the escalating group had higher mean age and rate of bystander CPR. Their mean response interval was also higher, but with shorter time to first shock after the defibrillator was turned on. Mean time from 911 call to first shock was not different between the two groups (Table 1). Escalating group patients received less drugs and fewer needed multiple shocks [174/260 (67%) vs 378/478 (79%) ($p < 0.001$)], thus median number of shocks was lower [2 (1–5) vs 3 (2–5), $p < 0.001$], compared to fixed high-energy patients. Chest compression fraction was not statistically different, but with lower compression rates, the mean number of compressions per minute was lower in the escalating than in the fixed high-energy group.

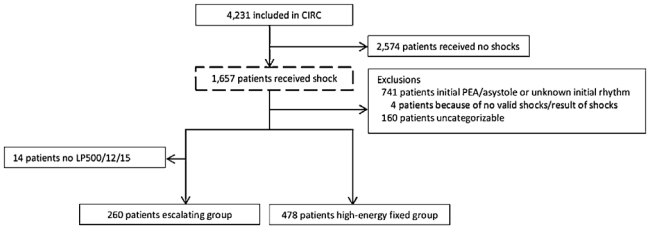

Fig. 1 – Flowchart of patients included in the analysis.

There was no difference between the groups in adjusted or unadjusted survival to hospital discharge, 24-h survival, adjusted survival to ED or TOF rate (Tables 2 and 3). Only unadjusted survival to ED was significantly higher for the fixed high-energy group (Table 2). The site which had implemented a fixed high-energy group did not have significant different survival to hospital discharge than the escalating energy sites for all patients included in CIRC (fixed high-energy 273/2672 (10.2%) vs escalating energy sites 144/1420 (10.1%), ($p = 0.94$).

Pre-shock pauses were longer in the escalating than the fixed high-energy group both for shocks 1, 2, 3 and rest of shocks (14, 13, 9.5, 7 s vs 4, 3, 3, 3 s, $p < 0.001$), respectively (Table 4). Post-shock pauses were not different (Table 4).

Mean TTI measured during charging was higher and calculated average current lower in the escalating group compared to the fixed high-energy group for the first and second shock ($p < 0.05$), not for third shock, but for the required shocks thereafter (Table 4). Impedance changed significantly from first to second shock [mean difference −3.0 (95% CI −4.8 to −1.1), $p = 0.002$ and −4.2 (95% CI −5.6 to −2.8), $p < 0.001$) for the escalating and the fixed group, respectively, with no further change between second and third shock.

For the whole dataset there was no difference in TTI or mean current for shocks that did vs those that did not terminate VF (mean TTI $84.8 \pm 28.2\ \Omega$ vs $84.6 \pm 28.3\ \Omega$ respectively (mean difference $0.3\ \Omega$ (95% CI −2.6 to 3.1), $p = 0.86$) and mean current 24.5 ± 9.6 A vs 24.5 ± 10.4 A, respectively (mean difference 0.0 A (−1.0 to 1.0), $p = 0.99$)). The same was true for first shock in each group studied separately as shown in Table 5.

Discussion

This is the first clinical study of escalating vs fixed high-energy level biphasic defibrillation strategies. There was no difference in survival to hospital discharge, 24-h survival, or rate of termination of VF/VT with shocks. The secondary outcome, survival to ED, was lower in the escalating compared with the fixed high-energy group only in the unadjusted analysis.

Table 1 – Prehospital and patient characteristics of treatment group.

	Escalating group (n = 260)	Fixed high-energy group (n = 478)	p-Value
Mean age	64 SD 15	62 SD 14	0.02
Male gender	203 (78%)	342 (72%)	0.05
Number of iA-CPR in each group	125 (48%)	215 (45%)	0.42
Public location	86 (33%)	126 (26%)	0.06
Witnessed arrests	186 (75%)	338 (72%)	0.33
Bystander CPR	167 (68%)	216 (46%)	<0.001
Median number of shocks per patient	2 (1, 5)	3 (2, 5)	<0.001
Mean time from 911 call to first shock (minutes)	17 SD 15	15 SD 6	0.25
Mean response interval (minutes)	8 SD 3	6 SD 2	<0.001
Mean time from defibrillator on to first shock[a] (minutes)	3 SD 3	4 SD 5	<0.001
Prehospital drug administration			
Amiodarone	134 (52%)	318 (67%)	<0.001
Lidocaine	2 (1%)	137 (29%)	<0.001
Atropine	111 (43%)	336 (70%)	<0.001
Adrenaline	210 (81%)	433 (91%)	<0.001
Vasopressin	1 (1%)	375 (79%)	<0.001
CPR fraction			
at 5 min	75.0 (67.0, 82.3)	76.0 (68.3, 82.8)	0.29
at 10 min	77.0 (69.6, 82.8)	77.2 (70.8, 82.2)	0.94
at 20 min	78.5 (72.8, 84.2)	77.8 (72.1, 83.1)	0.27
Median compressions in a minute (first 10 min)[b]	69.2 (60.8, 82.5)	73.3 (64.7, 90.6)	<0.001
Median compression rate (first 10 min)[b]	92.6 (80.0, 107.6)	102.4 (82.3, 118.2)	<0.001
Median ventilations in a minute (first 10 min)	7.7 (5.7, 11.0)	7.5 (5.7, 9.8)	0.35

Median is described with 25% and 75% percentile.
Mean described with standard deviation (SD).
[a] For time analyses negative time and time above 1 h excluded.
[b] A mixture of cases with LDB-device which delivers 80 compressions/min and manual CPR which should deliver 100/min.

Table 2 – Comparison of clinical outcome by treatment group.

Outcomes	Escalating group n = 260 (%)	Fixed high-energy group n = 478 (%)	Unadjusted odds ratio (95% CI)	Adjusted[c] odds ratio (95% CI)
Survival to hospital discharge	70/255 (28%)[a]	132/478 (28%)	1.00 (0.72–1.42), p = 0.96	0.81 (0.54–1.22), p = 0.32
Survival to 24 h	112/255 (44%)[a]	235/477 (49%)[b]	1.24 (0.91–1.68), p = 0.17	1.06 (0.74–1.52), p = 0.76
Survival to emergency Department	104/260 (40%)[d]	258/478 (54%)	1.76 (1.30–2.39), p < 0.001	1.55 (0.93–2.61), p = 0.10

[a] Missing outcome data for 5 patients.
[b] Missing outcome data for 1 patient.
[c] Adjusted for age, witnessed, location and response interval.
[d] Patients with no ROSC who were taken to ED achieved ROSC and consequently contribute to the number of survivals to 24 h.

Table 3 – Shock success by treatment group.

	Escalating group, n = 883 (%)	Fixed high-energy group, n = 1736 (%)	p-Value
Termination of VF/VT			
First shock	221/257 (86%)	392/473 (83%)	0.27
Second shock	143/173 (83%)	286/371 (77%)	0.15
Third shock	87/107 (81%)	240/303 (79%)	0.64
Rest of shocks	280/346 (81%)	498/589 (85%)	0.15
All shocks	731/883 (83%)	1416/1736 (82%)	0.44

A higher rate of ED admittance with ROSC is beneficial if it increases the number of patients discharged from hospital with good neurologic outcome. If not, it places an extra burden on the healthcare system without long-term benefit. In the current study, the higher rate of ED admittance in the fixed high-energy group was unfortunately not followed by a higher rate of survival to hospital discharge.

The fixed high-energy group more frequently received drugs, which in randomized studies has increased the rate of hospital admission with

Table 4 – Current, impedance, pre- and post-shock values by treatment group.

Shock number	Escalating group					Fixed high-energy group				
	Number of shocks	Current (A) (SD)	Impedance (Ω) (SD)	Median pre-shock pause (seconds) (IQR)	Median post-shock pause (seconds) (IQR)	Number of shocks	Current (A) (SD)	Impedance (Ω) (SD)	Median pre-shock pause (seconds) (IQR)	Median post-shock pause (seconds) (IQR)
First shock	257	18.5 (6.7)**	85.7 (26.4)≠	14 (3–19)**	5 (4–8)	473	27.4 (11.1)	79.2 (27.0)	4 (2–8)	5 (4–8)
Second shock	173	21.6 (9.5)**	89.3 (28.6)*	13 (1–19)**	4 (3–7)	371	25.6 (9.6)	83.4 (29.1)	3 (1–5)	4 (3–7)
Third shock	107	24.2 (12.0)	90.0 (30.7)	9.5 (1–20)**	4 (3–8)	303	25.5 (10.1)	83.6 (28.6)	3 (1–5)	4.5 (3–7)
Rest of shocks	346	23.6 (11.5)*	91.0 (30.3)**	7 (1–19)**	4 (3–7)	589	25.1 (9.2)	83.7 (26.5)	3 (0–5)	4 (3–7)

Mean described with standard deviation (SD).
* $p < 0.05$.
≠ $p < 0.01$.

** $p < 0.001$ between escalating group and fixed group.

Table 5 – Transthoracic impedance and current for first shocks with successful vs unsuccessful termination of VT/VF in the escalating and fixed high-energy groups.

Termination of VF/VT (TOF)	Escalating group				Fixed high-energy group			
	TOF+	TOF−	Mean difference	p Value	TOF+	TOF−	Mean difference	p Value
Mean impedance (Ω)	90.3 (36.2)	84.9 (24.5)	5.3 (−7.3 to 18.0)	0.4	79.0 (27.8)	80.5 (22.4)	1.6 (−5.0 to 8.1)	0.64
Mean current (A)	18.8 (8.5)	18.5 (6.4)	0.25 (−2.1 to 2.6)	0.84	27.7 (11.7)	25.7 (7.4)	−2.0 (−4.0 to 0.1)	0.05

TOF — termination of fibrillation.
Mean described with standard deviation (SD).

spontaneous circulation without increasing the rate of hospital discharge alive.[14–16] Meta-analysis of randomized studies analyzing both adrenaline and vasopressin found no different outcome for these drugs,[17] and a recent randomized controlled trial found no benefit of either lidocaine or amiodarone compared to placebo.[18]

More shocks were administered to the fixed high-energy group than the escalating group. This result could be coincidental, but we cannot rule out more drugs delivered to the fixed-high group could influenced the result. Both amiodarone and adrenaline have shown to increase survival to ED in patients with shock resistant VF.[14,19,20] A higher number of shocks may imply a lower rate of shock success (or higher rate of recurring VF) and a larger drug dose may be most likely due to more cycles of CPR (more shocks). Therefore, there may be hidden confounders, like comorbidities and socio-economic status that explains the difference. There is a difference in trends between survival to discharge vs survival to ED. We may speculate that higher energy causes more myocardial stunning. If some areas in the myocardium remain stunned for longer than others, this might promote re-entry circuits similar to those caused by scars. This may cause a higher percentage of recurrent VF (vs refractory) in the high energy cases.

Termination of VF/VT (TOF)

The present TOF values (77–86%), irrespective of group or number of shocks, are comparable with previous reported TOF of 79%–98% with 150–360 J biphasic truncated exponential defibrillators.[1,21–23] Stiell et al.[1] reported higher rate of TOF in patients requiring multiple shocks with escalating energy compared to fixed energy of 150 J, 83% vs 71% ($p = 0.027$), respectively. In the present study the fixed high-energy was 360 J, and the difference in results may be due to the difference in fixed energy levels.

TOF, transthoracic impedance (TTI) and calculated peak current

Chen et al found in retrospective analysis that current-based impedance compensated defibrillation resulted in equivalent TOF rate for patients with high and low TTI.[24] Biphasic defibrillators compensate for variations in TTI by adjusting the waveform to deliver the optimal amount of current.[25] TTI was higher in the escalating group, which cannot readily be explained. All sites used the same defibrillator pads. Kerber et al described that TTI was related to chest size, paddle size, and firmness of paddle application to the chest.[26] Earlier studies have indicated decreased TTI with subsequent shocks both for monophasic[26] and biphasic defibrillators, but the biphasic study by Deakin et al. was with elective cardioversion starting at 70 J for atrial fibrillation/flutter.[27] Chen et al. found decreased TTI from shock 1 to 2 and from 2 to 3, but not after the third.[24] In the present study TTI decreased in both groups from first to second shock, but not thereafter. Studying OHCA patients Walker et al concluded that TTI

change between consecutive shocks was minimal and inconsistent.[28] Average calculated transthoracic peak current were significantly higher in the fixed group for first, second, and rest of shocks, but this did not yield significantly higher TOF in the fixed group. First shock TTI and calculated mean current within the escalating and the fixed group that did not terminate VF were not significantly different from shocks that did terminate VF. This was also true when analyzing all shocks.

Some have advocated the development of current-based biphasic defibrillators.[29] The Physio-Control defibrillators used in this study measure impedance, before starting to charge, with a high-frequency carrier signal passed through the thorax to calculate correct charge voltage for the capacitor. For carrier frequency impedance (CFI) above 60 ohms, the voltage increases slightly linearly (at 200 ohms it is only up by 10–15%). Small variations in CFI will make very little difference in charge voltage. If the shock is at the 360 J setting, the defibrillator uses its maximum charge voltage for all transthoracic impedances.

Since in CIRC mechanical chest compression was not stopped for defibrillation we cannot rule out that this may have influenced our results. Olsen et al recently reported that TOF was lower with defibrillation during continuous LDB compressions for the first shock based on retrospective data from the CIRC trial.[30] During ongoing compressions, there is zero pre-shock pause and zero post-shock pause. One study published in 2010 found that chest compressions could case recurrence of VF after the first successful conversion by defibrillation.[31] This was questioned by a more recent study from 2014, which found no relationship between chest compression resumption and VF recurrence after analyzing all shocks.[32] Current CPR guidelines currently emphasizes early resumption of chest compressions.[2]

Pre- and post-shock pauses

Pre-shock pause was significantly longer in the escalating compared to the fixed high-energy group (median 13 s, IQR 1–19, vs median 3 s, IQR 0–7, $p < 0.001$, respectively). Shorter pre-shock chest compression pause duration has been reported to be associated with higher rate of TOF,[23] and survival to hospital discharge.[33,34] This was not the case in the present study where neither rate of TOF nor survival to hospital discharge were higher in the fixed high-energy group. Brouwer et al. also failed to show an association between pre-shock pause and TOF,[35] while a previous report from CIRC found such an association for LDB-CPR, but not for manual CPR.[30] It is difficult to explain this variability. It may be related to a threshold in the chest compression pause duration before it has a negative influence, or the association may be site related.

Limitations

The original CIRC study was not randomized for escalating vs fixed high-energy defibrillation, but for two chest compression strategies.[5] The present study is post-hoc analysis of data from one study site, which had implemented a fixed high-energy strategy vs three other sites in CIRC with escalating energy strategies.[5] Post-resuscitation care with a documented effect on survival was not standardized.[16,36,37] The high energy site's survival to hospital discharge did not show a significant difference from the escalating energy sites for patients all patients included in CIRC-trial. Baseline data in the two groups are skewed, but there was no significant difference in results after adjusting for confounding effects of age, witnessed arrest, cardiac arrest location and response interval as those were identified to be covariates in a backward elimination procedure. Other factors such as frequency of witnessed arrests, public location, time from 911 call to first shock, and CPR fraction were not different between the groups. It still cannot be ruled out that other between-sites differences such as administration of drugs not accounted for may have influenced outcome in this non-randomized comparison.[38–40]

Conclusion

There was no difference in survival to hospital discharge or the secondary outcomes rates of TOF and 24-h survival when adjusted for covariates between the fixed high-energy and the escalating energy groups. This post-hoc non-randomized analysis should be interpreted with caution.

Conflicts of interest

All authors' institutions received funding from ZOLL for their participation in the CIRC trial. LW represents NAKOS in the Medical Advisory Board of Physio-Control. The authors have no other relevant financial conflicts of interest to report.

Funding

ZOLL Medical funded the CIRC-trial. Olsen was partly funded by unrestricted grant from Norwegian Health Region South-East and partly by a research grant from ZOLL Medical to NAKOS in the period 2011–2015. Steinberg received a research scholarship from the Norwegian Research Council.

Acknowledgements

The authors would like to acknowledge all of the EMS providers and thanks to the coordinators and monitors at each of the participating sites for their careful and persistent work with the data collection. A special thanks to Petter A. Steen for valuable critique related to the manuscript, and Håvard W. Kongsgård with help on the mixed model analysis.

REFERENCES

1. Stiell IG, Walker RG, Nesbitt LP, et al. BIPHASIC trial: a randomized comparison of fixed lower versus escalating higher energy levels for defibrillation in out-of-hospital cardiac arrest. Circulation 2007;115:1511–7.
2. Soar J, Nolan JP, Böttiger BW, et al. European Resuscitation Council guidelines for resuscitation 2015: section 3. Adult advanced life support. Resuscitation 2015;95:100–47.
4. Link MS, Berkow LC, Kudenchuk PJ, et al. Part 7: adult advanced cardiovascular life support: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2015;132:S444–64.
5. Wik L, Olsen JA, Persse D, et al. Manual vs. integrated automatic load-distributing band CPR with equal survival after out of hospital cardiac arrest. The randomized CIRC trial. Resuscitation 2014;85:741–8.
6. Soar J, Callaway CW, Aibiki M, et al. Part 4: advanced life support: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Resuscitation 2015;95:e71–120.

7. Lerner EB, Persse D, Souders CM, et al. Design of the Circulation Improving Resuscitation Care (CIRC) trial: a new state of the art design for out-of-hospital cardiac arrest research. Resuscitation 2011;82:294–9.
8. ECC Committee, Subcommittees and Task Forces of the American Heart Association. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2005112: IV1-203.
9. Nolan JP, Deakin CD, Soar J, Bottiger BW, Smith G. European Resuscitation Council guidelines for resuscitation 2005. Section 4. Adult advanced life support. Resuscitation 2005;67:S39–86.
10. Lexow K, Sunde K. Why Norwegian 2005 guidelines differs slightly from the ERC guidelines. Resuscitation 2007;72:490–2.
11. Stecher FS, Olsen JA, Stickney RE, Wik L. Transthoracic impedance used to evaluate performance of cardiopulmonary resuscitation during out of hospital cardiac arrest. Resuscitation 2008;79:432–7.
12. R-Core-Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2013.
13. Wood SN. Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models. J R Stat Soc: Ser B (Stat Methodol) 2011;73:3–36.
14. Kudenchuk PJ, Cobb LA, Copass MK, et al. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. N Engl J Med 1999;341:871–8.
15. Jacobs IG, Finn JC, Jelinek GA, Oxer HF, Thompson PL. Effect of adrenaline on survival in out-of-hospital cardiac arrest: a randomised double-blind placebo-controlled trial. Resuscitation 2011;82:1138–43.
16. Olasveengen TM, Sunde K, Brunborg C, Thowsen J, Steen PA, Wik L. Intravenous drug administration during out-of-hospital cardiac arrest: a randomized trial. JAMA 2009;302:2222–9.
17. Lin S, Callaway CW, Shah PS, et al. Adrenaline for out-of-hospital cardiac arrest resuscitation: a systematic review and meta-analysis of randomized controlled trials. Resuscitation 2014;85:732–40.
18. Kudenchuk PJ, Brown SP, Daya M, et al. Amiodarone, lidocaine, or placebo in out-of-hospital cardiac arrest. N Engl J Med 2016;374:1711–22.
19. Dorian P, Cass D, Schwartz B, Cooper R, Gelaznikas R, Barr A. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. N Engl J Med 2002;346:884–90.
20. Herlitz J, Ekström L, Wennerblom B, Axelsson Å, Bång A, Holmberg S. Adrenaline in out-of-hospital ventricular fibrillation. Does it make any difference? Resuscitation 1995;29:195–201.
21. van Alem AP, Chapman FW, Lank P, Hart AA, Koster RW. A prospective, randomised and blinded comparison of first shock success of monophasic and biphasic waveforms in out-of-hospital cardiac arrest. Resuscitation 2003;58:17–24.
22. Morrison LJ, Henry RM, Ku V, Nolan JP, Morley P, Deakin CD. Single-shock defibrillation success in adult cardiac arrest: a systematic review. Resuscitation 201319: 00359-6.
23. Edelson DP, Abella BS, Kramer-Johansen J, et al. Effects of compression depth and pre-shock pauses predict defibrillation failure during cardiac arrest. Resuscitation 2006;71:137–45.
24. Chen B, Yin C, Ristagno G, et al. Retrospective evaluation of current-based impedance compensation defibrillation in out-of-hospital cardiac arrest. Resuscitation 2013;84:580–5.
25. Deakin CD, Nolan JP, Sunde K, Koster RW. European Resuscitation Council guidelines for resuscitation 2010 section 3. Electrical therapies: automated external defibrillators, defibrillation, cardioversion and pacing. Resuscitation 2010;81:1293–304.
26. Kerber RE, Grayzel J, Hoyt R, Marcus M, Kennedy J. Transthoracic resistance in human defibrillation. Influence of body weight, chest size, serial shocks, paddle size and paddle contact pressure. Circulation 1981;63:676–82.
27. Deakin CD, Ambler JJ, Shaw S. Changes in transthoracic impedance during sequential biphasic defibrillation. Resuscitation 2008;78:141–5.
28. Walker RG, Koster RW, Sun C, et al. Defibrillation probability and impedance change between shocks during resuscitation from out-of-hospital cardiac arrest. Resuscitation 2009;80:773–7.
29. Ristagno G, Yu T, Quan W, Freeman G, Li Y. Current is better than energy as predictor of success for biphasic defibrillatory shocks in a porcine model of ventricular fibrillation. Resuscitation 2013;84:678–83.
30. Olsen JA, Brunborg C, Steinberg M, et al. Pre-shock chest compression pause effects on termination of ventricular fibrillation/tachycardia and return of organized rhythm within mechanical and manual cardiopulmonary resuscitation. Resuscitation 2015;93:158–63.
31. Berdowski J, Tijssen JG, Koster RW. Chest compressions cause recurrence of ventricular fibrillation after the first successful conversion by defibrillation in out-of-hospital cardiac arrest. Circ Arrhythm Electrophysiol 2010;3:72–8.
32. Conover Z, Kern KB, Silver AE, Bobrow BJ, Spaite DW, Indik JH. Resumption of chest compressions following successful defibrillation and risk for recurrence of ventricular fibrillation in out-of-hospital cardiac arrest. Circ Arrhythm Electrophysiol 2014;7:633–9.
33. Cheskes S, Schmicker RH, Christenson J, et al. Perishock pause: an independent predictor of survival from out-of-hospital shockable cardiac arrest. Circulation 2011;124:58–66.
34. Cheskes S, Schmicker R, Powell J, et al. The impact of perishock pause on survival from out-ofhospital shockable cardiac arrest during the Resuscitation Outcomes Consortium (ROC) primed trial. Can J Emerg Med 2013;15:S2–3 Conference: 2013 CAEP/ACMU Vancouver, BC Canada. Conference Start: 20130601 Conference End: 20130605. Conference Publication: (var.pagings).
3. Brouwer TF, Walker RG, Chapman FW, Koster RW. association between chest compression interruptions and clinical outcomes of ventricular fibrillation out-of-hospital cardiac arrest. Circulation 2015;132:1030–7.
36. Sunde K, Pytte M, Jacobsen D, et al. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. Resuscitation 2007;73:29–39.
37. Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive Care Medicine guidelines for post-resuscitation care 2015: section 5 of the European Resuscitation Council guidelines for resuscitation 2015. Resuscitation 2015;95:202–22.
38. Idris AH, Guffey D, Aufderheide TP, et al. The relationship between chest compression rates and outcomes from cardiac arrest. Circulation 2012;125:3004–12.
39. Idris AH, Guffey D, Pepe PE, et al. Chest compression rates and survival following out-of-hospital cardiac arrest. Crit Care Med 2015;43:840–8.
40. Sasson C, Rogers MAM, Dahl J, Kellermann AL. Predictors of survival from out-of-hospital cardiac arrest a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes 2010;3:63–81.