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Review

Defibrillation energy dose during pediatric cardiac arrest: Systematic review of human and animal model studies

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Abstract

Objective: To determine the initial defibrillation energy dose that is associated with sustained return of spontaneous circulation (ROSC) during paediatric cardiac arrest with ventricular fibrillation or pulseless ventricular tachycardia.

Methods: A systematic review was performed using four databases (PROSPERO: CRD42016036734). Human studies and animal model studies of pediatric cardiac arrest involving assessment of external defibrillation energy dosing were considered. The primary outcome was sustained ROSC. Survival and defibrillation-induced complications were also evaluated.

Results: The search strategy identified 14,471 citations of which 232 manuscripts were reviewed. Ten human and 10 animal model studies met the inclusion criteria. Human studies were prospective (n = 6) or retrospective (n = 4) cohort studies and included between 11 and 266 patients (median = 46 patients). Sustained ROSC rates ranged from 0 to 61% (n = 7). No studies reported a statistically significant association between the initial defibrillation energy dose and the rate of sustained ROSC (n = 7) or survival (n = 6). Meta-analysis was not considered appropriate due to clinical heterogeneity. Risk of bias was moderate. All animal studies were randomized controlled trials with 8 and 52 (median = 27) piglets. ROSC was frequently achieved (≥85%) with energy dose ranging from 2 to 7 J/kg (n = 7). The defibrillation threshold varied according to the body weight and appears to be higher in infant.

Conclusion: Defibrillation energy doses and thresholds varied according to the body weight and trended higher for infants. No definitive association between initial defibrillation doses and the sustained ROSC or survival could be demonstrated. Clinicians should follow local consensus-based guidelines.

Keywords: Cardiac arrest, Pediatric, Defibrillation, Ventricular fibrillation

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https://doi.org/10.1016/j.resuscitation.2019.04.028
Received 3 December 2018; Received in revised form 25 March 2019; Accepted 16 April 2019

Introduction

Cardiac arrest in the paediatric population is rare but associated with high mortality.[1–5] However, long-term outcomes are favorable for most survivors with up to 89% of paediatric patients having good neurological outcome following an arrest in intensive care units (ICU).[6,7] A shorter cardiopulmonary resuscitation duration and the presence of ventricular fibrillation (VF) or pulseless ventricular tachycardia (pVT) as the first documented rhythm are factors consistently associated with improved rates of return to spontaneous circulation (ROSC), survival and good functional outcomes.[7–9]

Paediatric cardiac arrest differs from adult cardiac arrest as the precipitating event is frequently shock or progressive respiratory failure rather than a primary arrhythmia.[10] Accordingly, the occurrence of shockable ventricular dysrhythmia such as VF or pVT is lower than during adult cardiac arrest and the frequency is age-dependant. VF is the first recorded rhythm in 5–24% of all paediatric cardiac arrests[9,11–17] but up to 65% may experience VF or pVT during the resuscitation.[13–17] In a large cohort study, 12% of cardiac arrests that occurred in the ICU had defibrillation performed.[7] Even though the optimal initial approach to resuscitation depends on the likelihood of having a shockable dysrhythmia, prompt defibrillation remains critical during pediatric cardiac arrest as VF or pVT carries a better prognosis but can quickly degenerate to asystole. However, the optimal initial defibrillation energy dose and the subsequent regimen of steady versus escalating energy dosing are controversial.

Paediatric guidelines are mostly extrapolated from indirect evidence such as data from adult cardiac arrest and animal studies.[18,19] The 2015 European Resuscitation Council (ERC) guidelines suggest a non-escalating dose of 4 J/kg while recognising that doses up to 9 J/kg have been used safely with negligible side effects.[20] The 2015 American Heart Association (AHA) guidelines[21] suggest an initial energy dose of 2 J/kg–4 J/kg and, in case of refractory VF, increased energy levels may be considered up to 10 J/kg (Class IIa or IIb recommendations). Resuscitation councils are therefore interpreting the available data differently or are, perhaps, weighting the results of relevant studies differently.[22]

The main objective of this systematic review was to determine the initial defibrillation energy dose for VF or pVT that is associated with sustained ROSC during paediatric cardiac arrest. Associations between initial defibrillation energy dose with any ROSC, survival, survival with favorable neurological outcomes, total energy use, myocardial function and defibrillation-induced complications were also assessed. Finally, the defibrillation energy dose administered after the initial electrical shock was analysed to determine the optimal regimen to compare escalating or fixed energy dose regimens using both human and pediatric animal studies.

Methods

Protocol and registration

The study protocol was registered beforehand in the International prospective register of systematic reviews (PROSPERO) database (Registration number: CRD42016036734). This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[23]

Information source

A literature search was developed with the help of a medical librarian and applied to the following databases: Medline (Pubmed), Embase, Cochrane Central Register of Controlled Trials, Database of Abstract of Reviews Effects (DARE) and Cochrane Database of Systematic Reviews (last update October 31st 2018). Mesh and Emtree terms were used for their respective databases. The database clinicaltrials.org was also review for completed or ongoing trials. No language, date of publication or type of study restriction were applied to any search strategy. The search strategy for Medline (Pubmed) is presented in Appendix 1 in Supplementary material. References of eligible articles and previous narrative reviews were scrutinized. Finally, abstracts from conferences and meetings of the following associations were reviewed from 2006 to 2017: American Academy of Emergency Medicine (AAEM), American Academy of Pediatrics (AAP), American College of Emergency Physicians (ACEP), Australasian College for Emergency Medicine (ACEM), American College of Sports Medicine (ACSM), American Heart Association (AHA), Canadian Association of Emergency Physicians (CAEP), European Pediatric Conference (EPC), European Society of Intensive Care Medicine (ESICM), French Society of Pediatrics (FSP), International Pediatric Association (ICP), International Symposium on Intensive Care and Emergency Medicine (ISICEM), Resuscitation, Society for Academic Emergency Medicine (SAEM), Society of Critical Care Medicine (SCCM), World Congress on Pediatric Intensive and Critical Care (PIIC), World Congress of Pediatric Cardiology & Cardiac Surgery (WCPCCS) and World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM).

Eligibility criteria

To be considered eligible for inclusion, cohort studies or randomised control trials were required to report on children aged between 30 days and 18 years old or on animal models used to simulate paediatric cardiac arrest and on the energy dosing during external defibrillation for termination of VF or pVT. Both out-of-hospital cardiac arrest (OHCA) and in-hospital events were considered. Case reports were excluded as well as studies reporting on traumatic cardiac arrest, neonatal patients ($<$30 days old patient), adult patients ($\geq$18 years old) or on internal defibrillation. Pediatric patients needed to represent $\geq$80% of the study population study unless paediatric patients' data could be extracted from the manuscript or obtained after having contacted the study's corresponding author. For non-human studies, all animal models explicitly used to simulate a pediatric cardiac arrest were considered for inclusion.

Study selection and data extraction

Two researchers (EM, EL) independently reviewed all the titles and abstracts of the retrieved citations. Full-text evaluation was then performed for all potentially eligible studies. Inclusion was determined independently by the two reviewers (EM, EL) and then compared. Disagreement were resolved by consensus. A third party was involved only when consensus could not be reached (SB). Potentially eligible studies in languages other than English or French were fully translated in English. When inclusion was finally determined, studies from human and animal model populations were reviewed independently.

Patient data, defibrillation energy dose and relevant outcome measures (sustained ROSC, ROSC of any duration, survival, survival

with good neurological outcome, total energy dose used, defibrillation-induced complication such myocardial damage and myocardial function) were retrieved independently by two reviewers (EM, EL) using a standardised form. Studies on human and animal models' populations were reviewed using different data collection forms and were evaluated separately. Authors of potentially included studies were contacted when clarifications were needed and if relevant data were not available in the manuscript.

Sustained ROSC was defined as ≥20 min of a perfusing rhythm after defibrillation. Diagnostic tools such as cardiac echography and cardiac magnetic resonance imaging were considered for the assessment of myocardial function.

Statistical analysis

Although performing a meta-analysis was initially considered in the protocol, the decision was made not to use any meta-analytic methods because of the clinical heterogeneity regarding the populations included, the resuscitation protocols performed, the defibrillator used, and type of waveforms applied. Furthermore, included studies inconsistently reported defibrillation energy doses as continuous or categorical variable using unstandardized and overlapping categories.

Risk of bias assessment and quality of the reporting

Risk of bias of human non-randomised studies were assessed using the ROBIN-I tool (formerly ACROBAT-NRSI) tool proposed by the Cochrane Collaboration group which is dedicated to intervention studies. Predetermined confounding factors for the risk of bias assessment were the presence of VF/pVT as the initial rhythm or as a subsequent rhythm,[9] the delay before initiation of CPR and defibrillation[24,25] and if the arrest was witnessed or not.[14] The randomised trials were assessed using Cochrane Collaboration's tool for assessing risk of bias in randomised trials.[26] The quality of the reporting for observational cohort studies was evaluated using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[27]

Results

Our search strategy yielded 14 471 citations after duplicate removal from which 232 manuscripts were retrieved and fully reviewed. One study (published in 1976) was retrieved by manual screening from the included studies list of references and one abstract was retrieved from conference proceedings. Finally, 10 human studies[28–37] and 10 paediatric animal models studies[38–47] were included in the systematic review (Fig. 1).

All included studies were in written English and published between 1976 and 2014 (<1980: 1 study; 1981–1990: 0 study; 1991–2000: 0 study; 2001–2010: 14 studies; >2010: 5 studies).

Human studies

There were 10 included human studies, six were prospective and four retrospective observational studies. Characteristics of included human studies are presented in Table 1. These studies included between 11 and 266 patients each (median = 46 patients) and reported on in-hospital cardiac arrest (n = 7), OHCA (n = 2) or both (n = 1). Defibrillations were performed using monophasic waveform only (n = 5),[28,30,32,35,48] biphasic waveform only (n = 2) [36,37] or monophasic or biphasic waveforms (n = 2).[31,33]

The initial rhythm was reported in 6 studies and was shockable in 8.6–22.5% of patients.[28,29,31–33,35] Biphasic waveform defibrillators were used in four studies. Four studies described how children's weight was obtained: they were retrieved either from hospital record (n = 2),[31,36] autopsy data (n = 1)[28] or used the 50th and 95th percentile of standard growth chart (n = 1).[34]

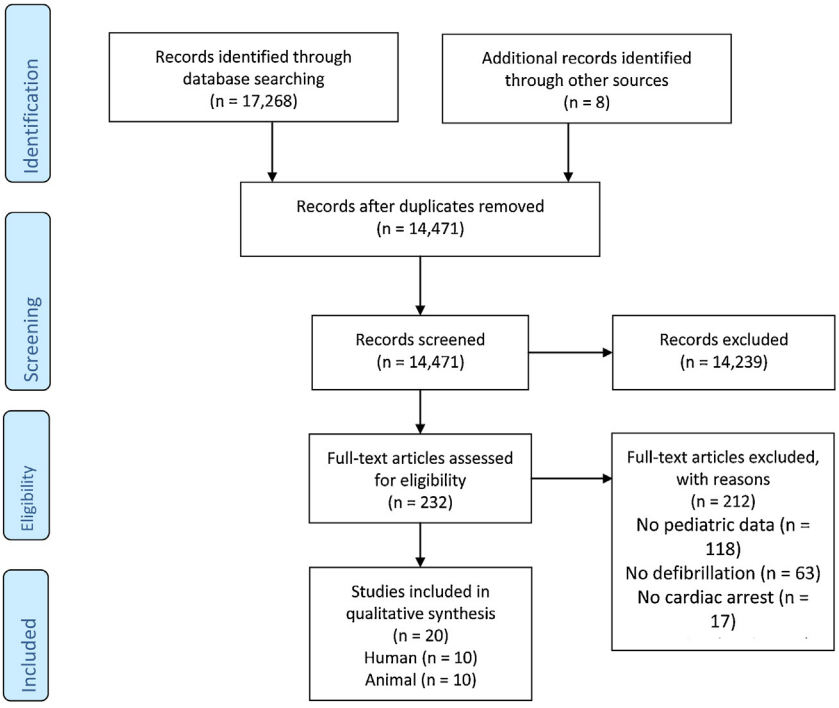

Fig. 1 – Flow diagram of included studies.

Table 1 – Characteristics of human studies included.

Study	Type of study	Patients included (n) Age	Defibrillations (n)	Cardiac arrest location	Inclusion criteria	Type of defibrillator and waveform
Berg et al. (2005)[28]	Retrospective	n = 13 Median age: 1 yo (range 1 m to 11 yo)	14	OHCA	<13 yo pulseless unresponsive child who received CPR and VF recorded	Monophasic damped sinusoidal (Lifepak12)
Castillo et al. (2011)[29]	Prospective	51	NR	In-hospital	CA with defibrillation required	NR
Gutgesell et al. (1976)[30]	Retrospective	n = 27 Age range 3 days to 15 yo	71	In-hospital	NR	Gurvich-Lown manual
Meaney et al. (2011)[31]	Prospective	n = 266 Mean age (SD) 6,8 (6,8) (range 0–18 yo)	First shock: 285 Total: 743	In-hospital	Age ≤18 yo CA with VF or Pvt Post-shock rhythm and weight reported	Biphasic 192 (67,4%) Monophasic 37 (13,0%) Unknown 56 (19,6%)
Rodríguez-Núñez et al. (2006)[32]	Prospective	n = 44 Mean age (SD) 6.5 (5,6) (range 1 m to 16 yo)	NR	In-hospital: 22 (50%) OHCA 22(50%)	>7 days to <18 yo CA and defibrillation attempted	Monophasic manual
Rodríguez-Núñez et al. (2014)[33]	Prospective	n = 37 Mean age (IQR) 48 (7–15) m	40 events	In-hospital	>1 month to <18 yo CA and defibrillation attempted	Biphasic 22 (55%) Monophasic 11 (27.5%) AED 2 (5%) Unknown 5 (12.5%)
Rossano et al. (2005)[34]	Retrospective	n = 57 Median age 14 (range 2 m to 17 yo)	185	OHCA	>1 month to <18 yo CA in which EMS attempted resuscitation with a shock	Monophasic mostly manual
Tibbals et al. (2006)[35]	Prospective	n = 111 CA (25 V F) Mean age (SD) 3.0 (5.1)	9	In-hospital	Age ≤21 years with external chest compression	Direct current monophasic waveform
Tibballs et al. (2011)[36]	Prospective	n = 48 Mean age (SD) 7,6 (7,3)	First shock: 61 Total: 117	In-hospital	NR	Biphasic manual
Woodruff et al. (2010)[37]	Retrospective	n = 18 Median age 2.5 yo	20	In-hospital	NR	Biphasic (ZOLL)

AED: automated external defibrillators; CA: cardiac arrest; EMS: emergency medical services; m: months; NR: not reported; OHCA: out-of-hospital cardiac arrest; SD: standard deviation; VF: ventricular fibrillation; yo: years old.

The main results of human studies are presented in Table 2. Substantial variations in initial defibrillation doses were reported ranging from fixed doses between 10–100 J and weight-based doses between 0.1 J/kg to 14.3 J/kg. Five studies presented and analysed energy defibrillation dosing using stratified dose groups rather than as a continuous variable. The differences in stratification made direct comparison of the studies difficult and involved overlaps between the categories presented within each study (2 vs 3–4 vs >4 J/kg,[29] <2 vs 2–4 vs >4 J/kg,[30] <1 vs 2–3 vs 4–5 vs >5 J/kg,[31] <2 vs ≥2 J/kg[32] and <2 vs 2–4 vs >4 J/kg[33]).

Sustained ROSC was reported in seven studies and ranged from 0 to 61% (n = 7, median = 45%). There was a statistically significant association between the initial defibrillation dose and the rate of sustained ROSC in only one study with a subgroup analysis reporting that the use of 3–5 J/kg for the initial shock was associated with a lower chance of sustained ROSC (OR: 0.40 (95%CI: 0.21−0.81) compared to higher and lower energy doses. Doses of 1–3 J/kg and 5–6 J/kg had a similar rate of sustained ROSC.[31] This finding was not replicated in other studies which showed no statistically significant difference between successful energy dosing.[28,29,32–34,37]

ROSC of any duration was achieved in 0–77% (n = 7, median = 62.5%) of VF or pVT cardiac arrest. No studies reported a statistically significant association between the defibrillation energy dose and the rate of ROSC. Two studies[29] reported a non-statistically significant trend towards improved ROSC rate using initial energy doses >4 J/kg relative to energy doses ≤4 J/kg(p = 0.11).[29,33] A second shock was more likely to be required if energy doses <2 J/kg was used.[32] One study reported that initial unsuccessful shock was associated with the use of lower energy.[36] The highest ROSC rate was obtained in a single centre study with 40% of cases having occurred in a cardiac operating room with defibrillation generally performed within 60 s and 96% had primary rather than subsequent VF.[36] Two studies highlighted that a smaller body weight seemed to be associated with a higher defibrillation threshold.[34,36]

Survival to hospital discharge was reported in six studies and ranged from 0% to 33%.[28,29,31,33,34] No association between survival to hospital discharge and the initial or the cumulative defibrillation energy dose were found. Survival at 12 months following the cardiac arrest was presented in two studies, varying between 6.8%[32] and 73%.[36] The number of shocks received was inversely associated with long term survival in one study.[36] Survival with good neurological outcome was 0%, 2.3% and 20%.[28,32,33] No association between defibrillation energy dosing and long-term survival or survival with good neurological outcome were reported. No human studies demonstrated an association between defibrillation-induced complications and energy dosing.[36]

The benefit of using a fixed or an escalating defibrillation energy dose following an unsuccessful first shock was not directly addressed by any study. Following an unsuccessful initial shock, a second dose of >2 J/kg were less likely to result in survival than a dose of 2 J/kg.[32] In

Table 2 – Associations between defibrillation energy dosing and outcome in human studies.

Study	Defibrillation energy doses	Delay before defibrillation	Outcomes	Results
Berg et al. (2005)[28]	Between 10 and 100 J	Median 11 min (IQR 9–15.5 min)	VF termination	7/14 (50%) in PEA (1/7) or asystole (6/7)
			Survival to hospital discharge	0/13 (0%)
Castillo et al. (2011)[29]	Between 2 and >4 J/kg	NR	ROSC	30/51 (58.8%) 2 J/kg: 54.4%, 3–4 J/kg: 47.4%, >4 J/kg: 87.5%, p > 0.05 ≤4 J/kg: 58% vs >4 J/kg: 87.5%, p = 0.11
			Sustained ROSC	23/51 (45.0%) 23/51 (45.0%)
			Survival to hospital discharge	15/51 (29.4%) 2 J/kg: 18.2%, 3–4 J/kg: 31.6%, >4 J/kg: 50.0%, p > 0.05 ≤ 4 J/kg: 26.7% vs >4 J/kg: 50%, p = 0.23 Better survival initial VF (52.4%) vs subsequent VF (13.3%), p = 0.004
Gutgesell et al. (1976)[30]	Around 2 J/kg as per local recommendations	NR	VF termination	63/71 (89%) <2 J/kg: 33/40 (82.5%), 2–4 J/kg: 21/23 (91.3%), >4 J/kg: 8/8 (100%) All VF terminated at shock <4 J/kg if second required
Meaney et al. (2011)[31]	Range 0.1–10.5 J/kg	Mean (SD) 1.5 (4.3) min, range 0–43 min	VF termination	152/285 (53%) <1 J/kg: 14/27 (51.9%), 1–3 J/kg: 100/182 (54.9%), 4–5 J/kg: 22/51 (43.1%), >5 J/kg: 12/19 (63.2%)
			ROSC	82/279 (29.4%) <1 J/kg: 9/27 (33.0%), 1–3 J/kg: 60/182 (33.0%), 4–5 J/kg: 8/51 (15.7%), >5 J/kg: 5/19 (26.3%)
			Sustained ROSC (>20 min)	171/279 (61.3%) <1 J/kg: 19/27 (70.4%), 1–3 J/kg: 119/182 (65.4%), 4–5 J/kg: 22/51 (43.1%), >5 J/kg: 11/19 (57.9%) if initial shock 3–5 J/kg, less likely to have sustained ROSC, p = 0.05 Initial dose: 4–5 J/kg vs 1–3 J/kg
			Survival to hospital discharge	61/266 (23%)
Rodríguez-Núñez et al. (2006)[32]	Range 1–12 J/kg Mean (SD) 2.4 (1.5) J/kg	<4 min: 29/37 vs >4 min: 8/27	ROSC	28/44 (63.6%) <2 J/kg: 35/48 (72.9%) vs ≥2 J/kg: 13/48 (27.1%), p > 0.05 >1 shock needed if shock <2 J/kg (42.9 vs 88.6%), p = 0.017
			Sustained ROSC	19/44 (43.1%) <2 J/kg vs ≥2 J/kg, p > 0.05
			Survival at 12 months	3/44 (6.8%) <2 J/kg vs ≥2 J/kg, p > 0.05
			Survival with good outcome	1/44 (2.3%) <2 J/kg vs ≥2 J/kg, p > 0.05
Rodríguez-Núñez et al. (2014)[33]	First shock: mean (SD) 3.7 (1.3) J/kg Second shock: mean (SD) 3.9 (0.8) J/kg	<1 min: 29/40 4 min: 8/40 4–10 min: 1/40 Unknown: 2/40	ROSC	25/40 (62.5%) <2 J/kg: (50.0%), 2–4 J/kg: (56.5%) >4 J/kg (100%), p = 0.11
			Sustained ROSC	20/40 (50.0%)
			Survival to hospital discharge	12/40 (30.0%) <2 J/kg: (25.0%), 2–4 J/kg: (43.5%) >4 J/kg (50%), p = 0.58
			Survival with good outcome	8/40 (20%)
Rossano et al. (2005)[34]	First shock: median (Range) 3.6 (0.67–14.3) J/kg	Overall mean response time 4 or 5 min	Admitted to hospital	24/57 (42%)
			Survival to hospital discharge	19/57 (33%) No association between cumulative dose groups and survival Cumulative doses: survivors (median 11 (IQR 4–34)) vs non-survivors (median 10 (IQR 4–23)), p < 0.05
Tibbals et al. (2006)[35]	First shock: mean (SD) 3.7 (2.1) J/kg	NR	ROSC	Following first shock: 6/9 (67%) ROSC (mean 4.0 (range 0.5–7.5)) vs (mean 3.4 (range 2–4.5)) J/kg, p = ns
Tibballs et al. (2011)[36]	First shock: mean (SD) 1.7 (0.8) J/kg	NR	ROSC	37/48 (77%) First shock doses: ROSC (mean 2.0 (SD 1.0)) vs No ROSC

(continued on next page)

Table 2 *(continued)*

Study	Defibrillation energy doses	Delay before defibrillation	Outcomes	Results
				(mean 1,5 (SD 0.7)), p = 0.05 No association between initial dose and ROSC
			Survival at 12 months	35/48 (73%) No association between initial dose and survival at 12 months Number of shock inversely associated with survival (p = 0.04)
Woodruff et al. (2010)[37]	First shock: mean 2.6 J/kg Second shock: mean 3.4 J/kg	NR	VR termination Sustained ROSC	Success first shock: 4/20 (20%) Success second shock: 2/10 (20%) 10/20 (50%)

*CPR: cardiopulmonary resuscitation; IQR: interquartile range; J: joule; min: minute; NR: not reported; kg: kilogram; ROSC: return of spontaneous circulation; PEA: pulseless electrical activity; SD: standard deviation; Sec: seconds; VF: ventricular fibrillation.

another study, a mean final shock of 2.6 ± 1.1 J/kg was more likely to result in ROSC than a higher dose (3.2 ± 1.2 J/kg) for non-responders although this was not statistically significant. However, this study is the same mentioned earlier including an important sub-group of patients that had VF in the cardiac operating room.[36] There was no association between the defibrillation waveform (monophasic or biphasic) and the outcomes assessed in the two largest studies included.[31,33]

The overall risk of bias was considered moderate for seven studies, serious for two and unable to determine for one study for which only the abstract is available. The risk of bias assessment using the ROBINS-I assessment tool for human studies is presented in Appendix 2 in Supplementary material. The quality of the reporting according to the STROBE criteria is available in Appendix 3 in Supplementary material. The assessment of bias and the funding source were the most frequently unreported data.

Animal studies

Ten studies having evaluated the defibrillation energy dosing using a paediatric cardiac arrest animal model were included. Each study included between 8 and 52 (median = 27) piglets weighing between 3 and 41 kg. VF was induced via direct current to the right ventricle in all studies (n = 10). Three of the animal studies were published by the same research group.[38–40] The delay between the VF initiation and the defibrillation was <30 s (n = 2),[41,46] 30 s(n = 3),[42,43,45] two minutes (n = 1)[47] or seven minutes (n = 3).[38–40] Characteristics of included animal model studies are presented in Table 3.

Association between defibrillation energy doses and outcomes are presented in Table 4. Sustained ROSC and ROSC of any duration were achieved frequently following the first shock with success rates up to 100%. The reported defibrillation threshold varied between the included studies according to the animal weight categories. One study reported an overall defibrillation threshold of 2.3 J/kg in young piglets using adult and paediatric electrodes with only transient and self-resolving hemodynamic changes.[42] Piglets weighing between 7.5 and 15 kg required fewer shock of 50 J before ROSC than those weighing 3.8 and 25 kg[44] while another study reported no difference in defibrillation success rates using a fixed energy dose in piglets weighing between 7.0 and 25 kg.[47] The association between defibrillation success and weight was reported to be statistically significant only when low energy levels (70 and 100 J) were used.[46] ROSC rates of 100% and 66% were achieved respectively for piglets weighing between 3 and 6 kg or between 7 and 12 kg using a biphasic fixed 30 J doses.[41] One study that compared a fixed regimen of 50 J in piglets weighing between 3.8 and 25 kg (between 2 and 11 J/kg) achieved 100% ROSC and reported no difference in post-resuscitation left ventricular function, myocardial damage during autopsy and neurological recovery.[44] One study reported that body weight was strongly associated with leading-edge current at energy levels below, but not above, 150 J.[46] Using biphasic waveform, rates of ROSC were improved with energy levels of 5 J/kg in 4 kg piglets and 3.3 J/kg in the 9 kg group.[41]

The association between survival and energy defibrillation doses were inconclusive. While a small study showed improved survival using attenuated pediatric electrodes rather than a weight-based approach, this finding was not replicated in a similar larger study.[39,40] The two studies presenting autopsy results reported no macroscopic myocardial damages following the resuscitation.[44,47]

The risk of bias for animal studies is presented in Appendix 4 in Supplementary material. The risk of bias associated with allocation concealment and blinding of outcome assessors were frequently not appraisable as these elements were not reported by five and seven studies, respectively.

Discussion

Our systematic review highlights the lack of data available to determine the optimal defibrillation energy dose to achieve sustained ROSC following VF or pVT during paediatric cardiac arrest. Evidence from human studies is limited to small cohort studies, mostly addressing in-hospital cardiac arrest, with high clinical heterogeneity and a lack long-term patient-centered outcome. The defibrillation threshold might vary according to the body weight and pediatric age group. Animal model studies consistently reported higher rates of successful defibrillation than human studies. This systematic review highlights the need for a randomized controlled trial.

This systematic review findings are in accordance with both the ERC and the AHA 2015 paediatric resuscitation guidelines which acknowledge that the ideal energy defibrillation for safe and effective defibrillation is unknown.[20,21] However, a few clinically relevant findings are worth emphasizing. Firstly, initial energy doses of ≤2 J/kg

Table 3 – Characteristics of animal model studies included.

Study	Type of study	Animal	Animal Weight	Method for arrhythmia's induction	Resuscitation protocol	Energy used	Delay before shock	Type of shock waveform (manufacturer)
Berg et al (2004)[38]	RCT	Domestic piglets (n = 48)	4 kg (n = 16); 14 kg (n = 16); 24 kg (n = 16)	100 Hz AC delivered to the RV	1–3 shocks then CPR for 90 s; epinephrine If required; end at ROSC or 27 min	Attenuated adult biphasic (50/75/86 J) vs monophasic weight based shocks (2 J/kg (followed by 4 J/kg if needed)	7 min	- Attenuated biphasic truncated exponential shocks (Lifepak 12) - Monophasic damped sinusoidal waveform (Lifepak 12)
Berg et al. (2005)[39]	RCT	Domestic piglets (n = 32)	13–26 kg (19 ± 1 kg)	100 Hz AC delivered to the RV	1–3 shocks then CPR for 90 s; epinephrine if required; end at ROSC or 27 min	Pediatric attenuated doses (50, 75, 86 J) vs adult doses (200, 300, 360 J)	7 min	Biphasic truncated exponential shocks (Lifepak 12) Paediatric shocks given through reduced energy electrodes
Berg et al. (2008)[40]	RCT	Domestic piglets (n = 52)	12–26 kg (19 ± 3.6 kg)	100 Hz AC delivered to the RV	1–3 shocks then CPR for 90 s; epinephrine If required; end at ROSC or 27 min	Pediatric attenuated doses (50, 75, 86 J) vs adult doses (200, 300, 360 J)	7 min	Biphasic truncated exponential shocks (Lifepak 12)
Clark et al. (2001)[41]	RCT	Domestic piglets (n = 27 + 8)	3–6 kg (n = 12 + 4), 7–12 kg (n = 15 + 4)	Rapid RV pacing (15 s)	NR	Fixed doses (7, 10, 20, 30, 50, 70, 100 J) monophasic vs biphasic	NR (brief)	Monophasic vs biphasic (NR)
Killingsworth et al. (2002)[42]	Controlled single case design	Domestic piglets (n = 10)	3.8–20.1 kg	60 Hz AC delivered to RV	Shock after 30 s, VF induction every 5 min	-Determination of defibrillation threshold Paediatric vs adult electrodes	30 s	Biphasic truncated exponential shocks (Lifepak 12)
Ristagno et al. (2012)[43]	RCT	Domestic piglets (n = 8)	12–15 kg	1–2 mA AC delivered to RV	NR	Fixed doses (10, 20, 30, 50, 70 J) using antero-posterior (AP) vs antero-lateral (AL) electrodes placement -10, 20, 30, 50 and 70 J for each electrode placement	30 s	Biphasic truncated exponential waveform (Welch-Allyn)
Tang et al. (2002)[44]	RCT	Domestic piglets (n = 29)	3.8 ± 0.3 kg (n = 8), 7.5 ± 1.0 kg (n = 5), 15 ± 1.0 kg (n = 8), 25 ± 1.2 kg (n = 8)	1–2 mA AC delivered to RV	Up to 3 shocks then mechanical CPR for 60 s until resuscitated	Fixed 50 J (similar to 11, 7, 3 or 2 J/kg depending on weight) manual vs AED	7 min	Manual defibrillation (20 piglets) vs biphasic adult AED with paediatric attenuating electrodes (9 piglets) (Philips Medical Systems)
Wang et al. (2007)[45]	RCT	Domestic piglets (n = 21)	4-8 kg (n = 10), 16-24 kg (n = 11),	AC delivered to RV	Shock using a randomly assigned dose then100 J if not successful, VF induction every 4 min	5 different energy doses for each waveform randomly assigned	30 s	Comparison of rectilinear biphasic waveform (RLB) vs biphasic truncated exponential (BTE) for five energy doses (Lifepak 12)
Zhang et al (2002)[46]	RCT	Domestic pigs (n = 22)	18–41 kg (mean = 26 kg)	60 Hz AC delivered to RV	Shock, if unsuccessful repeat then increased dose, epinephrine and pacing if PEA or asystole, VF induction when stable	Randomly assigned doses delivered (70, 100, 150, 200, 300, 360 J)	15 s	Truncated exponential biphasic waveform (NR)
Zhengyu et al. (2010)[47]	RCT	Domestic piglets (n = 30)	7 ± 1.4 kg (n = 10), 14 ± 2.8 kg (n = 10), 25 ± 5.0 kg (n = 10)	AC delivered to RV	1 shock then 2 min of CPR (as per 2005 AHA guidelines); Cycles repeated up to 5 times	Fixed 50 J then 70 J if required (manual biphasic vs AED)	2 min	Manual biphasic vs AED mode with paediatric attenuating electrodes (9200 Cardiac Science Corporation)

*AC: alternating current; AED: automated external defibrillation; AHA: American Heart Association; CPR: cardiopulmonary resuscitation; J: joule; mA: min: minute; kg: kilogram; RCT: randomised control trial; ROSC: return of spontaneous circulation; RV: right ventricule; Sec: seconds; VF: ventricular fibrillation.

Table 4 – Associations between defibrillation energy dosing and outcomes in animal model studies.

Study	Defibrillation energy doses	Outcomes	Results
Berg, et al. (2004)[38]	14 kg: (attenuated :3.5,5.3,6 J/kg vs weight based 2,4,4 J/kg) 24 kg: (attenuated 2,3,3.6 J/kg vs weight based 2,4,4 J/kg)	ROSC (sustained 1 min) Survival at 24 h with good neurological outcomes LVEF at 4 h post-resuscitation	14 kg: attenuated 8/8 (100%) vs weight based 6/8 (75%), $p < 0,01$ 24 kg: attenuated 7/8 (87.5%) vs weight based 3/8 (37.5%), $p < 0,01$ 14 kg: attenuated 7/8 (87.5%) vs weight based 5/8 (62.5%), $p < 0,01$ 24 kg: attenuated 6/8 (75%) vs weight based 0/8 (0%), $p < 0,01$ 14 kg: attenuated 30% vs weight based 32% baseline, $p > 0.05$ 24 kg: attenuated 32% vs weight based18% baseline, $p < 0.05$
Berg et al. (2005)[39]	Paediatric attenuated dose (50, 75, 86 J) vs. adult dose (200, 300, 360 J	ROSC after first shock ROSC Survival at 24 h with good neurological outcomes LVEF at 4 h post-resuscitation	Paediatric 4/16 (25%) vs adult 12/16 (75%), $p = 0.01$ Paediatric 15/16 (93.8%) vs adult 14/16 (87.5%) Paediatric 13/16 (81.3%) vs adult 4/16 (25%), $p = 0.004$ Paediatric 84% baseline function vs adults 62% of baseline, $p \leq 0.05$
Berg, et al. (2008)[40]	Paediatric attenuated dose (50, 75, 86 J) vs. adult attenuated dose (200, 300, 360 J	ROSC Survival at 24 h Survival at 24 h with good neurological outcomes LVEF post-ressucitation at 1 and 4 h	Paediatric 22/26 (84.6%) vs adult 23/26 (88.4%), $p > 0.05$ Paediatric 17/26 (65.4%) vs adult 14/26 (53.8%), $p > 0.05$ Paediatric 14/26 (53.8%) vs adult 9/26 (34.6%), $p > 0.05$ 1 h: paediatric 70% vs adult 51% of baseline function, $p < 0.05$ 4 h: paediatric 83% vs adult 65% of baseline function, $p < 0.05$
Clark et al. (2001)[41]	Predetermined fixed doses (7, 10, 20, 30, 50, 70, 100 J) monophasic vs biphasic	VF termination (excluding PEA-asystole)	Biphasic superior vs monophasic for 10, 20 and 30 J, $p < 0.05$ 3–6 kg: success rate >80% at 20 J (mean 5 J/kg) (n = 12) 7–12 kg: success rate >80% at 30 J (mean 3.3 J/kg) (n = 15) 3–6 kg: success rate (n = 4) 10 J monophasic 5% vs biphasic 31% 20 J monophasic 13% vs biphasic 83% 30 J monophasic 66% vs biphasic 100% 7–12 kg: success rate (n = 4) 10 J monophasic 0% vs biphasic 5% 20 J monophasic 0% vs biphasic 46% 30 J monophasic 13% vs biphasic 63%
Killingsworth,et al. (2002)[42]	Variables	ROSC Time to perfusing rhythm (s) Time to sinus rhythm (s)	2.3 J/kg is the defibrillation threshold for both paediatric and adult electrodes Paediatric 4.9 vs adult electrodes 5.2, $p > 0.05$ Paediatric 24.0 vs adult electrodes 29.3, $p > 0.05$
Ristagno, et al. (2011)[43]	Fixed doses (10, 20, 30, 50, 70 J) using antero-posterior (AP) vs antero-lateral (AL) electrodes placement	ROSC within 10 s following shock	Success rate (%) 10 J (0.7–0.8 J/kg): AP 0/9 (0%), vs AL 0/5 (0%), $p > 0.05$ 20 J (1.5–1.6 J/kg): AP 10/32 (31.1%) vs AL 0/21 (0%), $p = 0.003$ 30 J (2.1–2.3 J/kg): AP 21/32 (65.6%) vs AL 6/31 (0%), $p = 0.0003$ 50 J (5.1–5.4 J/kg): AP 30/32 (93.8%) vs AL 21/31 (67.7%), $p = 0.001$ 70 J: AP 23/23 (100%) vs AL 22/26 (84.6%), $p = 0.11$ Defibrillation threshold (50%): AP 27.7 ± 6.9 vs AL 49.3 ± 13.4, $p = 0.04$
Tang et al. (2002)[44]	Fixed 50 J manual vs AED 3.8 kg: 11 J/kg 7.5 kg: 7 J/kg 15 kg: 3 J/kg 25 kg: 2 J/kg	ROSC Survival at 72 h Cardiac index at 4 and 72 h Macroscopic myocardial damage at autopsy	28/28 (100%) 28/28 (100%) Similar to baseline for every piglet at 4 and 72 h, 0/28 (0%)
Wang et al. (2007)[45]	5 different energy doses for each waveform randomly assigned	Defibrillation threshold (50%) Defibrillation threshold (90%)	RLB 2.2 ± 1.1 vs BTE 2.5 ± 1.3 J/kg, $p = 0.02$ 4 kg (n = 6): RLB 2.2 ± 1.0 vs BTE 2.7 ± 1.4 J/kg 8 kg (n = 5): RLB 2.8 ± 1.7 vs BTE 3.3 ± 2.0 J/kg 16 kg (n = 5): RLB 2.0 ± 0.7 vs BTE 2.1 ± 0.7 J/kg 24 kg (n = 5): RLB 1.8 ± 0.5 vs BTE 2.1 ± 0.4 J/kg RLB 2.9 ± 1.6 vs BTE 3.4 ± 1.9 J/kg, $p = 0.02$ 4 kg (n = 6): RLB 3.2 ± 1.5 vs BTE 3.5 ± 2.3 J/kg 8 kg (n = 5): RLB 3.7 ± 2.6 vs BTE 4.3 ± 3.0 J/kg 16 kg (n = 5): RLB 2.6 ± 0.9 vs BTE 3.0 ± 1.2 J/kg 24 kg (n = 5): RLB 2.1 ± 0.6 vs BTE 2.6 ± 0.6 J/kg

Table 4 *(continued)*

Study	Defibrillation energy doses	Outcomes	Results
Zhang et al. (2002)[46]	Randomly assigned doses delivered (70, 100, 150, 200, 300, 360 J)	VF termination (5 s after shock)	70 J: 50%, 100 J: 66%, 150 J: 77%, 200J: 88%, 300J: 96%, 360 J: 92% Association between shock success and weight statistically significant at low energy level (70 and 100 J) but not at higher level
Zhengyu et al. (2010)[47]	Fixed 50 J then 70 J if required (Manual biphasic vs AED)	ROSC (5 min with mean aortic pressure ≥60 mmHg) Survival at 72 h and survival with good neurological outcome at 72 h Myocardial function Myocardial damage at autopsy	7.0 kg (7 J/kg): manual 5/5 (100%) vs AED 5/5 (100%) 14 kg (3 J/kg): manual 5/5 (100%) vs AED 5/5 (100%) 25 kg (2 J/kg): manual 4/5 (80%) vs AED 5/5 (100%) 7.0 kg (7 J/kg): manual 5/5 (100%) vs AED 5/5 (100%) 14 kg (3 J/kg): manual 2/5 (20%) vs AED 5/5 (100%) 25 kg (2 J/kg): manual 4/5 (80%) vs AED 5/5 (100%) Similar to baseline for every piglet at 72 h 0%

AL: antero-lateral; AP: antero-posterior; AED: automated external defibrillation; BTE: biphasic truncated exponential; J: joule; LEVF: left ventricular ejection fraction; kg: kilogram; PEA: pulseless electrical activity; ROSC: return of spontaneous circulation; RLB: rectilinear biphasic; Sec: seconds; VF: ventricular fibrillation.

seem associated with a lower likelihood of ROSC than higher dose and should therefore be avoided. Secondly, the use of a weight-based energy dosing can be impractical during pediatric cardiac arrest. Included human studies have shown that a wide range of initial defibrillation energy dose are delivered in real-time setting, often not in accordance with the published guidelines.[31] In the stressful event of a pediatric cardiac arrest, a predetermined fixed energy dosing aiming for 4 or 5 J/kg of the mean age group weight for different age group could represent a valuable option.[41,44,47] Thirdly, defibrillation threshold varies for different weight. A higher weight-based energy dose might be beneficial in infants to achieve ROSC.[45] Clinicians might aim for at least 4 J/kg in this group. Nevertheless, in the absence of conclusive studies demonstrating the superiority of a specific defibrillation energy level, clinicians should follow local guidelines.

The occurrence of a shockable rhythm ranged between 8.6 and 22.5% in the included human studies (n = 6).[28,29,31–33,35] During VF or pVT cardiac arrest, sustained ROSC was achieved in 0–77% of cardiac arrest events. The highest ROSC rate was achieved in cardiac theatre with defibrillation usually performed within 60 s[36] and early defibrillation (<4 min) was associated with increased survival.[32] Rapid defibrillation is therefore an important contributor to defibrillation success during pediatric cardiac arrest. Accordingly, in the adult population, OHCA defibrillation within the first 3 min can lead to survival higher than 60%.[24] Defibrillation thresholds increase with prolonged VF duration and therefore, prolonged duration of resuscitation was associated with lower chance of survival.[49] The occurrence of a shockable rhythm was reported to be similar during paediatric in-hospital cardiac arrest and OHCA.[50] However, some patients' characteristics such as the frequency and the nature of pre-existing conditions differ between those two scenarios.[50] Furthermore, in a large multicentre retrospective cohort, asystole as the initial rhythm was more frequent during OHCA.[50] This could potentially have an impact on the ideal initial energy defibrillation dose. Only three included studies[28,34,48] have assessed OHCA with one presenting without discrimination the results for in-hospital cardiac arrest and OHCA. Therefore, no specific interpretation for those two scenarios could be generated.

The initial defibrillation success rate might vary according to the patient's body weight and therefore, the pediatric patient age group. Animal model studies have reported different defibrillation threshold based on the animal weight[41,42,44] with higher energy doses per kg required to achieve ROSC in smaller animal models. The body weight was strongly associated with leading-edge current in one animal model study and a multiple logistic regression analysis showed that weight was the only predictor of defibrillation success for energy doses of less than 150 J.[46] The energy delivered by defibrillators is affected by thoracic impedance but there is no linear relationship between weight and thoracic impedance.[19] As a small fraction of the energy traverses the myocardium during defibrillation, small variations in energy doses might have a stronger influence in infants than their older counterparts. Accordingly, other physiologic factors that change with age, such as fat and water content, respiratory rate and the thorax shape, will influence the current delivered to the myocardium by increasing the impedance.[42,58]

The perceived risk of inducing myocardial histological damage and causing myocardial dysfunction following the use of high defibrillation energy dose is not supported by available literature. Macroscopic and microscopic myocardial damage have been reported following external[51–53] and endocardial defibrillation.[54] However, in anesthetised dogs, myocardial damage was sustained by 50% of the dogs at 30 J/kg while the energy required to convert 50% of the induced VF was 1.5 J/kg using a monophasic waveform.[55] This illustrates the wide margin of safety for defibrillation.[55] The monophasic dose associated with increased myocardial damage was as high as 159 J/kg in pigs.[56] Several case reports documented survival following the use of high biphasic energy doses (7–9 J/kg).[57–59] No included human studies reported defibrillation-induced complications. In animal model studies, less damage was observed on animal studies with brief VF[42] in comparison to longer VF duration[28,40] despite higher energy dosing up to 100 J/kg. Therefore, while the association between persistent post resuscitation myocardial dysfunction function and mortality in adult OHCA is well established,[60] factors such as the cardiac arrest duration might carry a stronger association with myocardial dysfunction than the defibrillation energy dose.

Given the many knowledge gaps not addressed by human studies, animal model studies were included in this review. However, the applicability of pediatric cardiac arrest animal model findings to human cardiac arrest is controversial. A recent systematic review reported

important variations in the cardiac arrest animal models, the protocols and the definition used that limits the opportunity to make comparison.[61] In this review, achievement of ROSC in animal studies was consistently higher than ROSC reported in human studies. Defibrillation performed in real-time resuscitation differs compared to laboratory settings and additional confounding factors are likely involved.[22] Animal studies were performed on animals with previously normally structured hearts with fewer pathophysiologic processes such as hypoxia or acidosis involved. Also, the in-hospital versus out-of-hospital settings have different characteristics that can likely affect the effectiveness of a weight-based electrical shock. Therefore, it is likely that the extrapolation of laboratory findings occurring in a highly controlled set-up to human real-time scenarios might be limited and the results generated by these studies must be carefully interpreted.[62]

Limitations

The quality of included studies was variable and human evidence was limited to observational studies. Given the critical nature of paediatric cardiac arrest and its low incidence, prospective randomised studies would be highly challenging to undertake. Therefore, it would have been inappropriate to limit the inclusion of human studies based on their design. Given the observational nature of included studies, confounding factors might not have been considered. Treatment factors (paddle position, electrode size, electrode type and defibrillation waveform) and patient factors (body weight, fat and water content, respiratory cycle, shape of the thorax) have all been reported to influence the defibrillation success rate. These factors were infrequently reported and not standardized in the observational human studies. Furthermore, the child weight was usually estimated although it might represent a scenario more compatible with real-time pediatric cardiac arrest.

Conclusion

Evidence for the optimal defibrillation energy dose to achieve sustained ROSC during pediatric cardiac arrest is of low quality and lacks precision. Evidence from human studies is limited to small cohort studies with high clinical heterogeneity mostly studying the in-hospital cardiac arrest population. The optimal defibrillation threshold varies according to the body weight but appear to be higher for infants. Initial defibrillation energy doses of $\leq$2 J/kg seem associated with a lower likelihood of ROSC than higher dose. The impact of the initial defibrillation energy dose on sustained post-resuscitation myocardial dysfunction relative to other factors such as the duration of resuscitation is imprecise. Translation of these results in terms of long-term patient-oriented outcome is still pending. In the absence of conclusive studies demonstrating the superiority of a specific defibrillation energy level, clinicians should follow consensus-based local guidelines.

Contributions

EM has had the original idea for this study. EM conceived the study's design and protocol with support, input and oversight from all other authors. EM and EL elaborated the original database search strategy. EM and EL performed the study selection and data extraction with oversight from SB, ME, NL, PAC and BM. Data synthesis and interpretation was oversight by BB and BM. EM wrote the manuscript first draft with initial comments by BB, PAC and JOP. All authors contributed to the manuscript revision and they all approved the final submitted version. EM is accountable for all aspects of this study.

Funding

This project was funded by the annual Bourse resuscitation award from the Fondation Jacques-de Champlain (2015 grant).

Conflicts of interest

The authors declare no conflict of interest.

Data sharing

No additional data are available.

Acknowledgement

We thank Adnan Bilgrami for his help with a prior version of this study.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.04.028.

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