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Experimental paper

First-time evaluation of ascending compared to rectangular transthoracic defibrillation waveforms in modelled out-of-hospital cardiac arrest

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ABSTRACT

Aim of the study: Prognosis in out-of-hospital cardiac arrest (OHCA) depends on cardiopulmonary resuscitation (CPR) duration. Therefore, the optimal biphasic defibrillation waveform shows high conversion rates besides low energy. Matthew Fishler theoretically predicted it to be truncated ascending exponential. We realised a prototypic defibrillator and compared ascending with conventional rectangular waveforms in modelled OHCA and CPR.
Methods: Approved by the authorities, 57 healthy swine (Landrace × Piétrain) were randomised to ASCDefib (*n* 26) or CONVDefib (*n* 26). Five swine served as sham control. We induced ventricular fibrillation (VF) electrically in anaesthetised swine randomised to ASCDefib or CONVDefib and discontinued mechanical ventilation. After 5 min of untreated cardiac arrest, we started CPR with mechanical chest compressions and ventilation. We performed transthoracic biphasic defibrillations after 2, 4, 6 and 8 min CPR targeting 4 J/kg in either group. Depending on the randomised group, the defibrillation protocol was either three ascending followed by one rectangular waveform (ASCDefib) or three rectangular followed by one ascending waveform (CONVDefib).
Results: Under our model-specific conditions, VF was initially terminated by 13/80 ascending waveforms and 13/79 rectangular waveforms and persistent return of spontaneous circulation was achieved in 8/26 (ASCDefib) vs. 10/26 (CONVDefib) animals. Mean current rather than waveform design was predictive for defibrillation success in a generalised linear model.
Conclusion: Contrary to theoretical assumptions, transthoracic biphasic defibrillation with ascending waveforms is not superior to rectangular waveforms in modelled OHCA. We advocate defibrillation dosage to be guided by current, that has proven its predictive value again.
Institutional protocol number: 84–02.04.2017.A176.

Introduction

Cardiac arrest (CA) with shockable heart rhythm is ideally terminated by the first defibrillation attempt. However, the optimal biphasic defibrillation waveform is yet unknown.[1] Therefore, Matthew Fishler undertook a theoretical study comparing defibrillation success and required energy of four feasible waveforms termed ascending exponential, ascending ramp, rectangular and descending waveform. Modelling the myocardium as a circuit comprising a resistor and a capacitor in parallel[2,3] and following the "charge banking/charge burping" hypotheses,[4] he predicted first phase ascending exponential waveforms to raise the myocardial voltage to the threshold level of successful defibrillation with the minimum amount of energy. Next were ascending ramp, rectangular and descending exponential waveforms. No particular waveform demonstrated relevant advantages for the second phase.[5] We will use Fishler's terminology to describe waveforms within the following manuscript.

We are not aware of ascending waveform usage within market approved implantable cardioverter defibrillators (ICD) or external ones: A recent survey of ours (personal communication with D. Steven)

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among ICD manufacturers Biotronik (Berlin, Germany), Boston Scientific (Marlborough, MA) and St. Jude Medical (Abbott Laboratories, Chicago, IL) revealed that currently, all are using conventional biphasic truncated exponential defibrillation waveforms with differing but in every case descending waveshapes. External defibrillators are available with either truncated descending exponential or roughly rectangular waveforms.[6]

Furthermore, the concept of ascending waveform defibrillation has not yet been tested in treating ventricular fibrillation (VF) or ventricular tachycardia after a relevant no-flow-time, where defibrillation efficacy and adverse defibrillation effects may be influenced by ischaemia-reperfusion injury and various therapeutic approaches.[7]

Our objective was whether ascending defibrillation waveforms show clinical superiority over rectangular waveforms at identical levels of discharged energy in out-of-hospital cardiac arrest (OHCA).

Our hypotheses were:

- Ascending defibrillation waveforms terminate VF with better efficacy than rectangular waveforms.
- Among all electrical measurements, the waveform itself is an independent predictor of defibrillation success.
- Myocardial function is less affected if return of spontaneous circulation (ROSC) is achieved by ascending defibrillation waveform.

Methods

Expanded methods are provided as an online supplement. We conducted a prospective, randomised, controlled trial on 57 swine, approved by the animal welfare authority (reference number 84–02.04.2017.A176) and in accordance with relevant laws and guidelines.[8,9] Our reporting follows the ARRIVE[10] and the Utstein-style guidelines.[11]

An investigator-blinded, computer-based complete randomization of 52 swine to the two intervention groups ASCDefib and CONVDefib was performed. Anaesthesia or surgery related effects were identified using another 5 sham-operated animals that received identical treatment but neither CA nor CPR.

Medical engineering

To perform this study, corpuls | GS Elektromedizinische Geräte G. Stemple realised a prototype defibrillator with the ability to deliver both biphasic waveforms without the need for replugging with the following specifications:

We aimed both waveforms to deliver the same amount of electrical energy with fixed target values for first phase mean current.[12] To investigate predictive variables of successful defibrillation in electrical properties, we induced variation in the target values for first phase mean current: In a subgroup of 36 swine we set general target values for first phase mean current to 22.5 A for ascending and 23.4 A for rectangular defibrillation waveforms. If the pre-shock measurement of transthoracic impedance exceeded 50 Ω these target values were reduced. In the remaining 16 swine we used fixed target values of 24.5 A for ascending and 26.4 A for rectangular defibrillation waveforms without adaption to higher impedance.

The two different waveforms were similarly designed as 10 ms impulses with 6 ms and 4 ms for first and second phase with about 85% of the total energy allocated to the first phase (Fig. 1). Prior to each defibrillation, voltage was adapted to interelectrode resistance to meet the set energy value. During each defibrillation, a microcontroller regulated voltage on the fly to readjust for impedance changes. We sampled current and voltage measured within the circuit at 4 kHz.

Pregelled self-adhesive defibrillation electrodes (corPatch easy, Leonhard Lang, Innsbruck, Austria, attached to the right of the upper sternum and to the left postero-lateral chest wall) were connected to the prototype defibrillator.

Animal preparation

We used healthy F1-hybrids Landrace × Piétrain of both sexes with bodyweight (bw) 39.0 [interquartile range 37.5; 41.5] kg. Following sedation, all swine were intubated and mechanically ventilated. Throughout the whole experimentation we maintained the stage of surgical anaesthesia using propofol, sufentanil and midazolam.

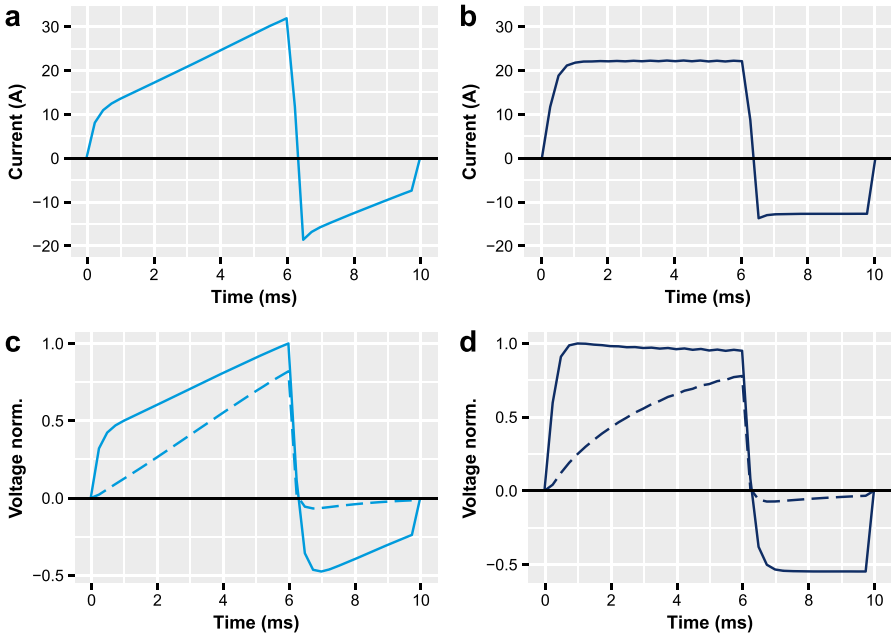

Fig. 1. Current (ampere) over time (milliseconds) for ascending [a] and rectangular [b] waveforms, as well as voltage (normalised to maximum voltage) over time and the modelled membrane response (dashed line) according to the simplified resistor capacitor model[3] for ascending [c] and rectangular [d] waveforms assuming a membrane time constant of 3.5 ms and ignoring voltage drops. Average of all respective defibrillator discharges.

Arterial blood pressure and cardiac output were measured via PiCCO thermodilution catheter in one femoral artery (Getinge, Rastatt, Germany). After surgical cut-down, we positioned a perivascular flow probe (Transonic Systems, New York, NY) around the left carotid artery in 36 animals.

Experimental protocol

After a 30 minute (min) hands-off period, we bedded all swine inside a V-shaped positioning aid to ensure optimal positioning during CPR. We monitored electrocardiogram, endtidal carbon dioxide partial pressure ($etCO_2$), peripheral oxygen saturation, arterial and central venous blood pressure via a corpuls3 defibrillator/monitor (corpuls, Kaufering, Germany) and carotid blood flow throughout the whole experimentation. Following baseline sampling, we applied alternating current (11 V, 0.5 A) to a pacing catheter to induce VF in the intervention groups. When CA was confirmed, we discontinued mechanical ventilation but maintained anaesthesia.

After 5 min of untreated CA, we resumed ventilation and started CPR with closed chest compressions (CC) applied to the lower sternal half. Seeking a high level of standardization, we used the mechanical CC device corpuls cpr set to continuous mode, depth 60 mm, 100 min^{-1}, duty-cycle 50%.

We designed the CPR protocol in accordance to current ACLS guidelines[1,13]: For rhythm checks, CC were only briefly (< 5 s) interrupted prior to defibrillation or if a marked increase in systolic arterial blood pressure of > 20 mmHg (2.67 kPa) or $etCO_2$ of > 5 mmHg (0.67 kPa) suggested ROSC. In order to control for vasopressor related modulation of ischaemia-reperfusion injury we assigned animals open-label to either adrenaline (epinephrine) 0.01 mg/kg bw or vasopressin 0.5 IU/kg bw administered after defibrillation no. 3.

If indicated, defibrillations (target value for each 4 J/kg bw) were performed after 2, 4, 6 and 8 min following the group-specific defibrillation protocol:

ASCDefib

- defibrillations no. 1–3 ascending waveforms
- defibrillation no. 4 rectangular waveform (crossover rescue procedure)

CONVDefib

- defibrillation no. 1–3 rectangular waveforms
- defibrillation no. 4 ascending waveform (crossover rescue procedure)

Animals not showing signs of ROSC within 2 min after defibrillation no. 4 were termed "non-survivors". Whenever ROSC was achieved, we stopped CPR and continued haemodynamic measurements for 60 min. If indicated, we performed synchronised cardioversion using the corpuls3 as a market-approved defibrillator.

Measurement protocol

Success rates

We distinguished between initially successful defibrillations and ROSC:

Initially successful defibrillation – conversion to an organised rhythm that generates arterial pressure pulsation for ≥ 5 s.

ROSC – conversion to an organised rhythm that generates a systolic blood pressure of at least 60 mmHg (8 kPa) for > 10 consecutive minutes.[11]

We defined the primary objective "first shock success" as ROSC after the first defibrillation. We noted the consecutive number of initially successful defibrillations and those leading to ROSC. Furthermore, we evaluated the frequency of re-fibrillation after initially successful defibrillation plus the frequency of arrhythmia with relevant hypotension.

Medical engineering

The data for current and voltage recorded by the prototype defibrillator were analysed for mean and peak values. The absolute energy of each defibrillation and the cumulated defibrillation energy for each animal was calculated and related to bodyweight. In addition, we calculated net charge and transthoracic impedance. All electrical properties were examined for their value in predicting initial defibrillation success.

Haemodynamic measurements

We performed transpulmonary thermodilution at baseline and 10 and 60 min after ROSC and computed cardiac index post hoc.[14]

Blood samples

We drew blood at baseline and prior to euthanization and analysed for troponin T in swine that survived 60 min after ROSC as well as in sham-operated animals.

Statistical analysis

We calculated the sample size ex ante based on previous experiences[15] for the primary objective first shock success for $\alpha < 0.05$ and $1 - \beta > 0.80$. Assuming a "number needed to treat" of 4 to be of clinical relevance, the required sample size was 26 for each group.

We used R[16] and ggplot2[17] for data analysis and visualization. Frequency distributions were analysed by Fisher's exact test. We fitted a Cox proportional hazards regression model of ROSC events and plotted Kaplan-Meier curves. Depending on normality testing, we compared numerical data by two-sided Welch t-tests or Mann-Whitney tests. A p-value < 0.05 was considered statistically significant and corrected by the Bonferroni method, if required. We present numerical data as median [25% quartile; 75% quartile] if not stated otherwise.

We screened electrical properties for their predictive value on initial defibrillation success by single binomial regression at first: energy, mean and peak current, mean and peak voltage, net charge and the waveshape itself. We included variables associated to initial defibrillation success with a p-value < 0.10 into a generalised linear model.

Results

Success rates

Under our model-specific conditions, first shock success was achieved by 5/26 ascending versus 7/26 rectangular defibrillation waveforms. At least one of the first three defibrillations was initially successful in 12/26 (ASCDefib) and in 11/26 (CONVDefib) swine. Finally, persistent ROSC was achieved in 8/26 (ASCDefib) and in 10/26 (CONVDefib) animals.

If ROSC had not been achieved by the first three defibrillations, the crossover rescue procedure was initially successful in 2/18 swine (ASCDefib, 1 after vasopressin, 1 after adrenaline) and in 1/16 swine (CONVDefib, after adrenaline); due to re-fibrillation in no case ROSC was achieved (Online supplement, Supplemental Table 1).

Cox proportional hazards regression model did not show significant differences for ROSC (hazard ratio (= chance for ROSC) 0.76, 95% confidence interval 0.30 to 1.92, n. s., Fig. 2).

Overall, we applied 159 waveforms of which 13/80 ascending and 13/79 rectangular defibrillation waveforms were initially successful. Re-fibrillation occurred following 4 ascending and 3 rectangular waveforms. We observed arrhythmia with relevant hypotension after 4 ascending waveforms: in 1 swine arrhythmia was self-limiting, in 3 others cardioversion was attempted but unsuccessful in 1 swine.

None of the above described frequency distributions were significant.

Medical engineering

Mean current, mean voltage and, consequently, transthoracic impedance did not differ significantly between intervention groups. Peak current was significantly different by design and voltage being the dependant variable showed similar differences. Due to different regulatory mechanisms in the microcontroller, the defibrillation energy of the two waveforms differed between groups and stayed below the target value for both intervention groups (Table 1). However, cumulated energy (sum of up to four defibrillations) between animals randomised to ASCDefib (11.6 [6.7; 13.0] J/kg bw) or CONVDefib (11.2 [4.8; 12.0] J/kg bw) showed no relevant differences.

Mean current, net charge and energy showed the most significant correlation to initial defibrillation success (p-value < 0.10) in single binomial regression and were included into a generalised linear model (Table 2). Predictions by this model were able to discriminate between initially successful defibrillations and non-terminating ones with an area under ROC curve of 0.7215 but relied almost completely on mean current (Table 3).

Haemodynamic measurements

CPR quality measured by $etCO_2$, arterial and central venous blood pressure, and carotid blood flow did not differ between intervention groups. We did not observe significant differences on heart rate, cardiac index[14] or mean arterial blood pressure between the intervention groups during baseline measurements and 10 and 60 min after ROSC (Table 4).

Blood samples

The increase of troponin T from baseline, broken down by the number of defibrillations leading to persistent ROSC, did not show significant differences between the intervention groups (online supplement, Supplemental Fig. 2). In ASCDefib, troponin T increase in animals with first shock success ranged from 0.009 to 0.027 µg/L ($n = 4$) and from 0.016 to 0.030 µg/L ($n = 3$) in animals with ROSC after the second defibrillation. In CONVDefib, values in animals with first shock success ranged from 0.009 to 0.058 µg/L ($n = 6$) and from 0.031 to 0.065 µg/L ($n = 2$) in animals with ROSC after the second defibrillation. One animal achieved ROSC after the third defibrillation in CONVDefib with a troponin T increase by 0.144 µg/L. Troponin T increase in sham-operated animals ranged from 0.000 to 0.011 µg/L ($n = 5$).

Discussion

Our findings seemingly contradict previous studies that showed lower defibrillation thresholds for ascending ramp compared to truncated descending exponential waveforms in terminating VF by ICD.[18,19] This may be explained by the more extensive ischaemia-reperfusion injury in our model due to longer no-flow-time. Our study was designed and powered to measure success rates, and further research is needed to understand the contribution of the altered electrical properties of the ischaemic myocardium.

Consistent to a previous study, current was more predictive than any other electrical property.[20] In contrast to their findings, mean current predicted defibrillation success with higher accuracy than peak current. Even if we added peak current to our generalised model, mean current for the whole biphasic waveform stayed the only reliable predictor. This is even more remarkable as our two waveform designs differed especially in peak current.

Considering the above, the observed differences in energy between the waveforms do not reduce the informative value of our study: Dosing defibrillation by energy has weaknesses because impedance varies. Impedance compensating mechanisms were proposed decades ago[12] but have physical limitations and show wide variation among the different external defibrillators unknown to most users.[21,22]

In ICD discharge, less myocardial tissue damage after ascending ramp exponential waveform defibrillation was demonstrated.[19,23] Our results do not contradict these studies as our experimentation had been designed to compare early defibrillation success and therefore the frequency of ROSC (and consequently of blood samples) was low on purpose.

Limitations

We modelled OHCA in swine under general anaesthesia, which may have influenced overall defibrillation outcome. Our study compares two specific waveforms with fixed target values for energy, mean current and durations. We did not determine defibrillation thresholds and therefore it remains unclear whether ascending waveforms would show the same efficacy at lower energy. For the same reasons our predictive model is not generalizable beyond reasonable levels of energy, current and voltage.

Conclusions

Under the specific circumstances of ischaemia and reperfusion in modelled OHCA and CPR, transthoracic biphasic defibrillation with ascending waveforms is not superior to rectangular waveforms. We strongly advocate physiology guided approaches in understanding the electrical properties of the ischemic myocardium. Until then, defibrillation dosage should be guided by current, that yet again has proven its predictive value.

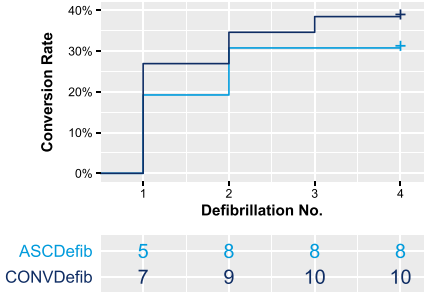

Fig. 2. Kaplan-Meier curves increasing when the respective defibrillation led to persistent return of spontaneous circulation. Please note that defibrillation no. 4 was performed as a crossover rescue procedure (rectangular waveform defibrillation in group ASCDefib and ascending waveform defibrillation in group CONVDefib). Cox proportional hazards regression model has not shown significant differences.

Table 1
Electrical properties of the two different defibrillation waveforms.
Current and Voltage measured within the circuit during defibrillation and the resulting energy, net charge and impedance (interelectrode resistance).

Electrical Property (unit)	Ascending ($n = 80$)	Rectangular ($n = 79$)	p-value (Mann-Whitney test)
Mean current (ampere)	17.7 [17.1; 19.8]	17.6 [16.8; 20.7]	n. s.
Peak current (ampere)	31.2 [30.1; 34.7]	21.7 [20.8; 25.4]	$p < 0.001$
Mean voltage (volt)	651 [617; 679]	657 [626; 679]	n. s.
Peak voltage (volt)	1133 [1065; 1194]	838 [806; 864]	$p < 0.001$
Energy (joule per kilogram bodyweight)	3.3 [3.0; 3.5]	3.0 [2.8; 3.4]	$p = 0.03$
Net charge (coulomb)	1.38 [1.31; 1.44]	1.35 [1.30; 1.48]	n. s.
Impedance (Ω, average during defibrillation)	37.0 [35.1; 38.9]	36.5 [34.5; 38.5]	n. s.

Table 2
Prediction of defibrillation success from electrical properties.
Single binomial regression results for mean and peak current (ampere), mean and peak voltage (volt), net charge (millicoulomb), energy (joule) and waveform ordered by *p*-value. Example interpretation: The single binomial regression model predicts an increasing chance for successful defibrillation if mean current increases by 1 A with an odds ratio of 1.56 (95% confidence interval 1.20–2.07).

Electrical property	Odds ratio	95 % confidence interval	*p*-value
Mean current	1.557 per 1 A	1.195–2.065	$p = 0.0014$
Net charge	1.004 per 1 mC	1.000–1.007	$p = 0.0270$
Energy	1.017 per 1 J	0.997–1.036	$p = 0.0903$
Peak current	1.062 per 1 A	0.980–1.155	$p = 0.1461$
Peak voltage	1.000 per 1 V	0.997–1.002	$p = 0.8483$
Waveform	0.985 for ascending	0.422–2.300	$p = 0.9720$
Mean voltage	1.000 per 1 V	0.993–1.007	$p = 0.9824$

Table 3
Generalised linear model to predict defibrillation success.
Mean current, net charge and energy were included into a generalised linear model. Predictions by this model relied almost completely on mean current with net charge and energy being insignificant confounders.

Electrical property	Odds ratio	95 % confidence interval	*p*-value
Mean current	2.171 per 1 A	1.281–3.758	$p = 0.004$
Net charge	0.998 per 1 mC	0.992–1.004	$p = 0.475$
Energy	0.983 per 1 J	0.950–1.014	$p = 0.289$

Table 4
Haemodynamic performance at baseline and after ROSC.
Heartrate, cardiac index and mean arterial pressure (MAP) did not show significant differences between the two intervention groups during the course of the experimentation, neither at baseline nor 10 or 60 min (min) after return of spontaneous circulation (ROSC).

Time of measurement	Group	Heart rate (min^{-1})	Cardiac index ($L / min \cdot m^{-2}$)	MAP (mmHg)
Baseline	ASCDefib (n = 26)	82 [75; 94]	7.3 [6.6; 7.9]	75 [70; 85]
	CONVDefib (n = 26)	79 [74; 86]	6.9 [6.0; 7.5]	74 [69; 82]
ROSC 10 min	ASCDefib (n = 7)	165 [147; 170]	9.0 [7.7; 10.4]	80 [69; 101]
	CONVDefib (n = 10)	162 [124; 185] [a]	8.4 [7.1; 9.5] [a]	86 [83; 94] [a]
ROSC 60 min	ASCDefib (n = 5)	121 [119; 124]	7.4 [6.4; 9.0]	68 [63; 68]
	CONVDefib (n = 9)	109 [95; 123] [a]	8.2 [6.3; 8.8] [a]	79 [66; 87] [a]

[a] Nonparametric testing; normal distribution was not confirmed.

Declaration of competing interest

T. Annecke reports research funding from Aerogen, B. Braun Foundation, CIO Koeln Bonn, CytoSorbents Europe, Medtronic and PULSION Medical Systems; outside the submitted work. Prof Steven reports research grants from Abbott, Boston and Medtronic, outside the submitted work; honoraria from Abbott and Boston Scientific, outside the submitted work. The remaining authors have disclosed that they do not have any conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resplu.2020.100006.

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