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## Experimental paper

# Shorter defibrillation interval promotes successful defibrillation and resuscitation outcomes



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### Abstract

**Aim:** Current cardiopulmonary resuscitation guidelines recommend performing defibrillation every 2 min during resuscitation. This study aimed to compare the rate of successful defibrillation using 1- and 2-min defibrillation intervals.

**Methods:** Twenty-six pigs were randomly assigned to 1- or 2-min interval groups. After inducing ventricular fibrillation (VF), we observed pigs for 2 min. Thereafter, basic life support was initiated with a 30:2 compression-to-ventilation ratio for 8 min. Defibrillation was performed with an energy of 2 J/kg at 10 min after VF and was repeated every 1 or 2 min according to randomization. Advanced cardiac life support, including continuous chest compression with ventilation every 6 s and intravenous injection of 1 mg epinephrine every 3 min, was performed until the return of spontaneous circulation (ROSC) or until 20 min after VF induction. Haemodynamic parameters and baseline arterial blood gas profiles were compared between groups. ROSC, 24-h survival, and the neurologic deficit score (NDS) were evaluated at 24 h.

**Results:** Haemodynamic parameters during resuscitation and baseline arterial blood gas profiles did not differ between groups. ROSC was more frequently observed in the 1-min interval group ( $p = 0.047$ ). Time to ROSC was not different between groups ( $p = 0.054$ ). The 24-h survival was higher ( $p = 0.047$ ) and NDS at 24 h was lower ( $92 \pm 175$ ) in the 1-min interval group than in the 2-min interval group ( $272 \pm 190$ ) ( $p = 0.028$ ).

**Conclusions:** Defibrillation success and resuscitation outcomes were superior when using a 1-min defibrillation interval in animal models of cardiac arrest.

**Keywords:** Cardiac arrest, Cardiopulmonary resuscitation, Electric defibrillation

## Introduction

Defibrillation is the most important intervention for resuscitating cardiac arrest patients with ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT). The VF waveform changes over time during cardiac arrest.<sup>1</sup> Coarse VF occurs earlier after the onset of cardiac arrest and is more likely to be converted by defibrillation, whereas fine VF occurs later and is less likely to be converted.<sup>2</sup> The probability of successful defibrillation is reduced by 7%–10% every minute; thus, it is important that defibrillation be performed as soon as possible.<sup>3</sup> Many trials and policies have aimed to minimize the time

from sudden collapse until medical personnel response, and public access defibrillation is one programme that has been applied in many developed countries.<sup>4</sup> Before the 2000 cardiopulmonary resuscitation (CPR) guidelines, three-stacked defibrillation was recommended for shockable rhythms<sup>5</sup>; however, this strategy has since been changed to a single shock at the highest energy every 2 min because the probability of successful defibrillation was the highest with the first shock and interruptions of chest compression could worsen the outcomes of cardiac arrest patients.<sup>6,7</sup> Defibrillation with a 2-min interval, as recommended by the current guidelines, is based on expert consensus and not on scientific evidence. The optimal interval to achieve effective defibrillation remains to be investigated.

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<https://doi.org/10.1016/j.resuscitation.2019.08.022>

Received 17 June 2019; Received in revised form 31 July 2019; Accepted 13 August 2019  
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Therefore, this study aimed to investigate the optimal interval for successful defibrillation by comparing the resuscitation outcomes between different defibrillation intervals in swine models of cardiac arrest.

## Materials and methods

### Study design

This laboratory study was designed to compare the probability of successful defibrillation using 1- and 2-min defibrillation intervals in swine models of cardiac arrest. This study was approved by the Institutional Animal Care and Use Committee of Yonsei University Wonju College of Medicine, Wonju, Republic of Korea (YWC-180612-1).

### Animal preparation

Twenty-six male Yorkshire pigs (weight 35–45 kg) were used in this study. The pigs were allowed full access to water and food until the day before the experiment and were then fasted from midnight. The pigs were initially sedated with an intramuscular ketamine (15 mg/kg) and xylazine (2 mg/kg), followed by inhaled 3% isoflurane. After sedation, the pigs were placed in the prone position, and endotracheal intubation was performed with a cuffed endotracheal tube. Animals were then placed in the supine position and ventilated with room air via a volume-controlled ventilator (MDS Matrix 3000, Matrix, Orchard Park, NY). The tidal volume was set at 10 mL/kg, with a ventilation rate of 18 breaths/min. Electrocardiography (ECG) with lead II and end-tidal CO<sub>2</sub> (ETCO<sub>2</sub>) were continuously monitored. Under aseptic conditions, the right femoral artery was cannulated using a 5.5-Fr introducer sheath via the Seldinger technique, and aortic blood pressure was continuously recorded using a 5-Fr micromanometer-tipped catheter that was introduced into the femoral artery. An introducer sheath was placed in the right external jugular vein, and right atrial pressure was recorded via a 5-Fr micromanometer-tipped catheter. The right internal carotid artery was exposed, and a vascular flowmeter (Transonic, NY) was used to monitor the carotid blood flow. An introducer sheath placed via the right internal jugular vein was used as an insertion route for a 5-Fr pacing catheter to induce VF and infuse saline and epinephrine. Left femoral artery cannulation was also performed for arterial blood sampling. Once the catheters were in place, a 100-unit/kg intravenous (IV) heparin bolus was administered to prevent thrombosis.

### Study protocol

The pigs were randomized into two groups according to the result indicated in a sealed, opaque envelope opened by an investigator before the induction of cardiac arrest. The randomization envelopes, which contained different defibrillation intervals (1- or 2-min), were randomized by shaking the box and drawing an envelope from the top of the resulting pile. Pre-defined energy was calculated based on 2 J/kg for the first shock and 4 J/kg for consecutive shocks. Because the minimum unit of energy selection with the defibrillator was 25 J, pre-defined defibrillation energy for the first shock was 75 J for pigs weighing 34–38 kg and 100 J for pigs weighing 39–41 kg, and consecutive shocks were doubled.

After baseline data were collected, a pacing catheter was positioned in the right ventricle. VF was induced by delivering an alternating

electrical current at 60 Hz to the endocardium, which was confirmed by the ECG waveform and a decrease in aortic pressure. Once VF was induced, the endotracheal tube was disconnected from the ventilator, and the pigs were observed for 2 min without any procedure or treatment. After 2 min of untreated VF, basic life support (BLS) was performed for 8 min to mimic a BLS situation in which a bystander recognises cardiac arrest and calls for help. The chest compression depth was set at 5 cm. Following 30 chest compressions given at a rate of 100 chest compressions/min, two consecutive ventilations were performed. Positive pressure ventilation at approximately 300 mL of tidal volume was delivered using a resuscitator bag (Silicone resuscitator 87005133, Laerdal Medical, Stavanger, Norway).

Defibrillation was performed after 8 min of BLS if the ECG rhythm was shockable, and consecutive defibrillation was performed every 1 or 2 min as indicated. During the next 10 min after BLS, chest compression was changed to a continuous mode, and ventilation with 15 L/min oxygen was delivered every 10 chest compressions, mimicking advanced cardiac life support (ACLS). One milligram of epinephrine with 20 mL of saline was delivered every 3 min until the return of spontaneous circulation (ROSC) or the end of the experiment.

If a pig did not achieve ROSC at 20 min after VF induction, the experiment was terminated, and the animal was considered dead. When a pig achieved ROSC, we observed it for 2 h under mechanical ventilation with inhalation anaesthesia. After 2 h, the animal was transferred to the breeding room, and we examined respiratory rate, oxygen saturation, rectal temperature, spontaneous movement, and feeding status every 2 h. Modified postcardiac arrest care, which included injection of intramuscular ketoprofen 1 mg/kg for pain control, intravenous infusion of normal saline 80 mL/hr to prevent dehydration, applying a face mask of 100% oxygen when oxygen saturation dropped under 90%, and controlling body temperature at approximately 36.0 °C with ice bag application and fanning, was performed for 24 h. If a pig could move spontaneously, feed well, and breathe comfortably within 24 h of observation after ROSC, we discontinued modified postcardiac arrest care and status checks such as respiratory rate, oxygen saturation, rectal temperature, spontaneous movement, and feeding, and the swine cerebral performance category was recorded as 1. The neurologic deficit score (NDS) was determined by another researcher who was blinded to our study 24 h after ROSC. The NDS includes type of behavior and level of consciousness, breathing pattern, cranial nerve function and motor and sensory function. A NDS of 0–40 is considered as absence of neurologic deficit, a NDS of 400 as brain death.<sup>8</sup> After the neurologic examination, the animals were euthanized by intravenously injecting potassium.

### Measurements

Data were digitised using a digital recording system (PowerLab, ADInstruments, Colorado Springs, CO). Aortic and right atrial pressures and carotid blood flow (CBF) were continuously recorded and analysed at baseline, at 2 min, and every 4 min until 20 min elapsed. Coronary perfusion pressure (CPP) during CPR was calculated as the difference between the aortic and right atrial pressures in the mid-diastolic phase using an electrical subtraction unit. Arterial blood gas analyses, including pH, PaCO<sub>2</sub>, PaO<sub>2</sub>, HCO<sub>3</sub><sup>-</sup>, oxygen saturation, and lactate, were performed using a blood gas analyser (i-STAT1, Abbott Laboratories, Abbott Park, IL) at baseline. Once a pig achieved ROSC, the measurement of haemodynamic parameters was discontinued owing to the possibility of a bias from spontaneous circulation.

Chest compression fraction (CCF) was defined as the proportion of time spent performing chest compressions during ACLS. ROSC was

defined as the maintenance of aortic perfusion pressure over 20 min. The 24-h survival rate and NDS at 24 h were evaluated for outcome variables.

### Sample size

The sample size was selected with reference to the preliminary study based on the results from eight pigs per group because ROSC followed by CPR with a 1-min defibrillation interval under recent CPR guidelines had never previously been evaluated. In the preliminary study, ROSC was observed in 6 out of 8 pigs (75%) in the 1-min interval group and in 1 out of 8 pigs (13%) in the 2-min interval group. The sample size was calculated as 11 pigs per group using tests for two proportions with a two-sided alpha value of 0.05 and a statistical power of 90%. Finally, 13 pigs from each group were chosen considering a 10% drop-out rate.

### Data analysis

Continuous variables were presented as mean  $\pm$  standard deviation (SD). Student's *t*-test or Mann-Whitney U test was used to compare the continuous variables between the 1- and 2-min interval groups as appropriate. The nominal variables were reported as counts and percentages and were compared using chi-squared or Fisher's exact test, as appropriate. A linear mixed-model analysis was used to compare haemodynamic parameters, including aortic systolic pressure, aortic diastolic pressure, right atrial systolic pressure, right atrial diastolic pressure, CBF, CPP, and ETCO<sub>2</sub>, between the two groups. The statistical results are presented as group-time interaction. A value of  $p < 0.05$  was considered significant. Analyses were performed using SPSS Statistics 23.0 for Windows (IBM Corp., Chicago, IL, USA).

## Results

### Baseline characteristics

Thirteen male pigs from each group were included in the analysis. There were no significant differences in baseline characteristics such as body weight, aortic systolic and diastolic pressures, right atrial systolic and diastolic pressure, CPP, CBF, ETCO<sub>2</sub>, and arterial blood gas profiles between the groups (Table 1).

### Haemodynamic parameters during CPR

There were no significant differences between the groups in the group-time interaction analyses of haemodynamic parameters such as aortic systolic and diastolic pressures, right atrial systolic and diastolic pressures, CPP, CBF, CP, and ETCO<sub>2</sub> during CPR (Table 2).

### Comparison of total defibrillation frequency and energy between the 1- and 2-min interval groups

Total defibrillation frequency was not different between groups ( $5.5 \pm 3.3$  times in the 1-min interval group and  $4.6 \pm 1.7$  times in the 2-min interval group,  $p = 0.675$ ). Cumulative defibrillation energy was not different between groups ( $918 \pm 704$  J in the 1-min interval group and  $734 \pm 310$  J in the 2-min interval group,  $p = 0.898$ ) (Fig. 1).

### Comparison of chest compression fraction during ACLS between the 1- and 2-min interval groups

CCF was higher in the 2-min interval group ( $0.972 \pm 0.007$ ) than in the 1-min interval group ( $0.941 \pm 0.019$ ) ( $p < 0.001$ ).

### Outcomes

ROSC was more frequently observed in the 1-min interval group than in the 2-min interval group ( $p = 0.047$ ). Time to ROSC was not different between groups ( $p = 0.054$ ). NDS at 24 h was lower in the 1-min interval group ( $92 \pm 175$ ) than in the 2-min interval group ( $272 \pm 190$ ) ( $p = 0.028$ ) (Fig. 2).

## Discussion

In our study, a higher rate of ROSC and better 24-h survival and neurologic outcomes were observed for defibrillation with a 1-min interval than for defibrillation with a 2-min interval. It is well known that early defibrillation is crucial for favourable outcomes in cardiac arrest patients with a shockable rhythm because the rate of successful defibrillation is reduced by 7%–10% per min.<sup>3</sup> Once VF is induced, myocardial adenosine triphosphate is gradually depleted during prolonged VF arrest and cannot be restored irrespective of the CPR quality.<sup>9</sup> Thus, this condition is detrimental to successful defibrillation.

**Table 1 – Baseline characteristics.**

Parameters	Defibrillation interval group		p-Value
	1-min (n = 13)	2-min (n = 13)	
Body weight (kg)	36.85 $\pm$ 1.95	36.92 $\pm$ 1.80	0.92
ETCO <sub>2</sub> (mmHg)	38.38 $\pm$ 4.61	36.54 $\pm$ 6.54	0.42
ABGA			
pH	7.46 $\pm$ 0.07	7.43 $\pm$ 0.07	0.40
PaCO <sub>2</sub>	39.331 $\pm$ 6.37	44.07 $\pm$ 7.19	0.09
PaO <sub>2</sub>	119.54 $\pm$ 40.45	110.00 $\pm$ 52.16	0.16
HCO <sub>3</sub> <sup>-</sup>	27.80 $\pm$ 3.16	29.53 $\pm$ 2.87	0.16
SaO <sub>2</sub>	98.38 $\pm$ 1.19	96.62 $\pm$ 3.55	0.16
Lactate	3.41 $\pm$ 1.38	2.99 $\pm$ 1.12	0.40

\*Variables are presented as mean  $\pm$  standard deviation.

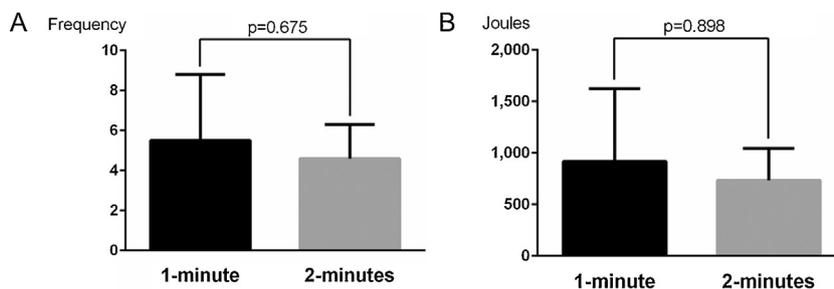
<sup>‡</sup>ETCO<sub>2</sub>: end tidal carbon dioxide, ABGA: arterial blood gas analysis.

**Table 2 – Comparison of hemodynamic parameters between 1-min and 2 min defibrillation interval groups.**

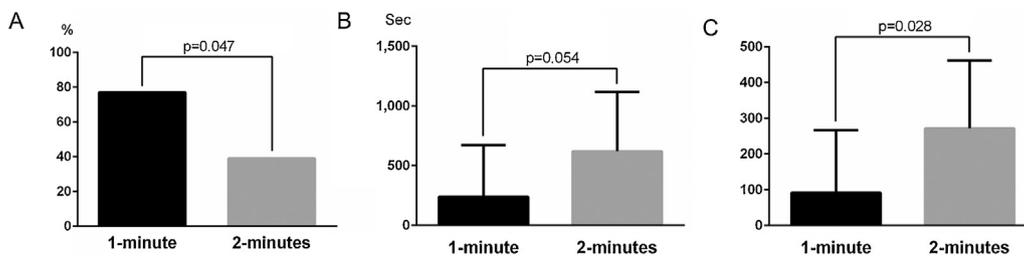
Parameters	Baseline	2 BLS start at 2 min	4	6	8	10	12 ACLS started at 10 min	14	16	18	20	p-Value
AoP systolic (mmHg)												0.486
1 min	114.88 (9.32)	117.32 (9.32)	103.94 (9.32)	91.72 (9.32)	83.84 (9.32)	78.56 (9.32)	67.92 (10.17)	88.22 (11.83)	88.22 (13.31)	71.86 (16.22)	70.34 (17.66)	
2 min	112.24 (9.32)	88.72 (9.32)	82.91 (9.32)	78.08 (9.32)	75.45 (9.32)	66.94 (9.32)	60.33 (9.68)	75.78 (10.36)	69.07 (11.04)	58.58 (11.41)	56.14 (11.62)	
AoP diastolic (mmHg)												0.569
1 min	83.96 (5.97)	40.87 (5.97)	31.88 (5.97)	24.45 (5.97)	22.13 (5.97)	21.91 (5.97)	20.92 (6.77)	40.11 (8.12)	42.76 (9.11)	30.05 (11.35)	29.01 (12.05)	
2 min	79.29 (5.97)	20.36 (5.97)	14.21 (5.97)	12.57 (5.97)	9.7 (5.97)	16.01 (5.97)	14.29 (6.31)	20.14 (6.88)	14.76 (7.36)	11.63 (7.52)	9.01 (7.58)	
RAP systolic (mmHg)												0.825
1 min	4.17 (16.42)	165.69 (16.42)	156.21 (16.42)	147.83 (16.42)	125.94 (16.42)	112.45 (16.42)	99.34 (17.54)	84.94 (19.87)	98.19 (22.17)	82.59 (26.56)	80.69 (29.18)	
2 min	5.35 (16.42)	143.23 (16.42)	131.33 (16.42)	137 (16.42)	117.79 (16.42)	109.1 (16.42)	100.65 (16.89)	99.1 (17.84)	92.5 (18.87)	89.32 (19.55)	90.8 (20)	
RAP diastolic (mmHg)												0.659
1 min	−1.63 (1.32)	0.98 (1.32)	0.84 (1.32)	0.15 (1.32)	0.65 (1.32)	1.63 (1.32)	2.02 (1.44)	3.42 (1.66)	2.86 (1.87)	4.3 (2.27)	3.64 (2.48)	
2 min	0.25 (1.32)	2.5 (1.32)	2.96 (1.32)	2.57 (1.32)	1.47 (1.32)	1.96 (1.32)	2.06 (1.37)	1.38 (1.46)	3.42 (1.56)	3.19 (1.61)	0.42 (1.64)	
CBF												0.994
1 min	356.77 (16.7)	159.19 (16.7)	110.66 (16.7)	98.02 (16.7)	82.22 (16.7)	70.76 (16.7)	54.68 (18.74)	32.06 (22.34)	27.43 (25.12)	47.22 (31.11)	36.38 (33.29)	
2 min	345.3 (16.7)	153.17 (16.7)	84.22 (16.7)	66.63 (16.7)	61.53 (16.7)	53.33 (16.7)	41.24 (17.56)	33.62 (19.07)	29.39 (20.39)	25.48 (20.92)	20.66 (21.14)	
CPP												0.856
1 min	114.65 (6.14)	56.9 (6.14)	45.16 (6.14)	40.69 (6.14)	33.36 (6.14)	32.07 (6.14)	27.38 (6.95)	44.64 (8.34)	45.84 (9.36)	32.55 (11.65)	31.36 (12.38)	
2 min	110.8 (6.14)	44.94 (6.14)	39.19 (6.14)	39.18 (6.14)	39.16 (6.14)	34.37 (6.14)	30.44 (6.49)	38.65 (7.07)	28.62 (7.56)	24.95 (7.73)	23.9 (7.8)	
ETCO <sub>2</sub> (mmHg)												0.267
1 min	38.38 (2.15)	30.62 (2.15)		31.54 (2.15)		31.62 (2.19)	31.84 (2.33)	27.61 (2.48)	30.65 (3.07)	24.63 (3.78)	13.73 (4.14)	
2 min	36.77 (2.15)	29.54 (2.15)		26 (2.15)		26.54 (2.15)	25.52 (2.26)	22.84 (2.38)	21.14 (2.5)	17.86 (2.64)	18.28 (3.15)	

\*Variables are presented as mean (standard error).

§BLS: basic life support, ACLS: advanced cardiac life support, AoP: aortic pressure, RAP: right atrial pressure, CPP: coronary perfusion pressure, CBF: carotid blood flow, ETCO<sub>2</sub>: end tidal carbon dioxide.



**Fig. 1 – Comparison of total defibrillation frequency (A) and energy (B) between the 1- and 2-min interval groups.**



**Fig. 2 – Comparison of resuscitation outcomes between the 1- and 2-min interval groups. (A) ROSC, (B) Time to ROSC, (C) NDS at 24 h.**

Recent guidelines recommend a 2-min defibrillation interval based on studies that demonstrated that chest compression interruption results in poor outcomes and that CPR quality begins to decline after 2 min of continuous chest compressions owing to rescuer fatigue.<sup>10</sup> However, this optimal interval of defibrillation was based on expert consensus, not scientific evidence.<sup>7</sup> A recent cohort study reported that a deferred second defibrillation was not associated with improved survival in in-hospital cardiac arrest<sup>11</sup>, a finding which may support a shorter defibrillation interval than that recommended in recent CPR guidelines, although patient monitoring systems and responding medical personnel are different with respect to out-of-hospital cardiac arrest. Our study design mimicked out-of-hospital cardiac arrest and showed that a shorter defibrillation interval resulted in more successful defibrillation and better neurologic outcomes. Our results may help define the optimal defibrillation interval to promote better outcomes.

Defibrillation frequency and cumulative energy were higher in the 1-min interval group than in the 2-min interval group, although neither were statistically significant. Several studies have reported that frequent or higher defibrillation energy can induce troponin elevation or myocardial dysfunction during and after resuscitation.<sup>12,13</sup> If myocardial injury or dysfunction is directly associated with resuscitation outcome, a shorter defibrillation interval strategy may be unfeasible because post-resuscitation myocardial dysfunction is one of the most significant causes of morbidity and mortality in postcardiac arrest syndrome.<sup>14,15</sup> However, one study demonstrated that myocardial dysfunction after multiple defibrillation was induced by a reduction in myocardial perfusion rather than the cumulative energy of defibrillation.<sup>16</sup> Furthermore, recent clinical studies have shown that the cumulative dose of defibrillation was not associated with resuscitation outcomes, a result similar to that shown in our study.<sup>17,18</sup> Therefore, it would be better to focus on early termination of VF/pulseless VT irrespective of the frequency or cumulative energy of defibrillation to promote better resuscitation outcomes.

Because CCF is directly related to resuscitation outcomes, recent CPR guidelines recommend that CCF be maintained effectively.<sup>19</sup> In our study, the 2-min interval group showed statistically higher CCF than the 1-min interval group in ACLS CPR. However, CCF in both groups was >90%, which was much higher than the 60% recommended in the CPR guidelines.<sup>20</sup> This result could imply that relatively prolonged chest compression interruption, although still within optimal limits, has little effect on CPR quality and that the defibrillation interval was more important for successful defibrillation. Therefore, it may be reasonable to interrupt chest compressions for a short time every minute to provide defibrillation if team CPR is well organised.

Current CPR guidelines recommend the injection of antiarrhythmics to terminate refractory VF or pulseless VT, which is unresponsive after two or more defibrillation attempts.<sup>21</sup> Therefore, under current guidelines, at least 6 min are needed to determine whether or not to administer antiarrhythmics, which is a relatively long time interval. In a previous antiarrhythmic administration study, there was reasonable doubt as to whether delayed administration of antiarrhythmics worsened outcomes.<sup>22</sup> A shorter defibrillation interval could make it possible to administer antiarrhythmics faster in refractory VF or pulseless VT, possibly resulting in better outcomes.

Our study had several limitations. First, this study was designed using a swine cardiac arrest model. Therefore, it would be difficult to apply results to humans, although the swine model was chosen because a 1-min defibrillation interval is not recommended in the current guidelines. Second, we did not use any antiarrhythmics, including amiodarone or lidocaine, to terminate refractory VF or pulseless VT. Our study was designed to verify the effect of the defibrillation interval on resuscitation outcomes, and these outcomes would have been different if we had used antiarrhythmics. Third, while we controlled fever conventionally, neurologic outcomes may have improved if we had performed strict targeted temperature management as with humans. Fourth, this study didn't include

histopathologic injury determination, which would show different cerebral injury patterns.

## Conclusions

Defibrillation success and resuscitation outcomes were superior when using a 1-min defibrillation interval compared with a 2-min interval in animal models of cardiac arrest.

## Conflicts of interest

None.

## Acknowledgements

This work was supported by a National Research Foundation of Korea (NRF) grant from the Korean government (MSIP) (NRF-2018R1D1A1B07050356).

## 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.2019.08.022>.

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