**Physiologic effect of repeated adrenaline (epinephrine) doses during cardiopulmonary
resuscitation in the cath lab setting: a randomised porcine study**

Bjarne Madsen Hardig¹, Michael Götberg², Malin Rundgren³, Matthias Götberg², David Zughaft²,
Robert Kopotic⁴, Henrik Wagner².

¹Physio-Control/Jolife AB, Ideon Science Park, Lund, Sweden, ²Department of Cardiology, Lund
University, Lund, Sweden, ³Department of Anaesthesiology and Intensive Care, Lund University,
Lund, Sweden, ⁴CAS Medical Systems, Inc., Branford, CT 06405, USA

Corresponding author: Bjarne Madsen Hardig, RN, PhD, Physio-Control/Jolife AB, Ideon Science
Park, Lund, Sweden. Email: bjarne.madsen.hardig@physio-control.com

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16 **Abstract**

17 **Background**

18 This porcine study was designed to explore the effects of repetitive intravenous adrenaline doses on
19 physiologic parameters during CPR.

20 **Methods**

21 Thirty-six adult pigs were randomised to four injections of: adrenaline 0.02 mg/kg/dose, adrenaline
22 0.03 mg/kg/dose or saline control. The effect on systolic, diastolic and mean arterial blood pressure,
23 cerebral perfusion pressure (CePP), end tidal carbon dioxide (ETCO₂), arterial oxygen saturation
24 via pulse oximetry (SpO₂), cerebral tissue oximetry (SctO₂), were analysed immediately prior to
25 each injection and at peak arterial systolic pressure and arterial blood gases were analysed at
26 baseline and after 15 min.

27 **Result**

28 In the group given 0.02 mg/kg/dose, there were increases in all arterial blood pressures at all 4
29 pressure peaks but CePP only increased significantly after peak 1. A decrease in ETCO₂ following
30 peak 1 and 2 was observed. SctO₂ and SpO₂ were lowered following injection 2 and beyond. In the
31 group given a 0.03 mg/kg/dose, all ABP's increased at the first 4 pressure peaks but CePP only
32 following 3 pressure peaks. Lower ETCO₂, SctO₂ and SpO₂ was seen at peak 1 and beyond. In the
33 two adrenaline groups, pH and Base Excess were lower and lactate levels higher compared to
34 baseline as well as compared to the control.

35 **Conclusion**

36 Repetitive intravenous adrenaline doses increased ABP's and to some extent also CePP, but
37 significantly decreased organ and brain perfusion.

38 **The institutional protocol number:** Malmö/Lund Committee for Animal Experiment Ethics,
39 approval reference number: M 192-10.

40 **Key words**

41 Cardiac arrest, CPR, adrenaline

42

43 **Introduction**

44 Routine use of adrenaline during cardiopulmonary resuscitation (CPR) was first described in the
45 early 1960s and has ever since been recommended in guidelines during advanced life support.¹
46 Intravenous administration of 1mg of adrenaline every 3 – 5 minute during advanced life support is
47 recommended in current guidelines for resuscitation.^{2, 3} Advanced life support is most commonly
48 performed without monitoring capabilities, but in the coronary catheterization laboratory setting,
49 continuous monitoring of physiological parameters is possible during CPR.⁴ To strictly follow
50 guidelines regarding repetitive dosing of adrenaline in this situation might not be the optimal
51 treatment. In the coronary catheterization laboratory, we therefore administer adrenaline according
52 to the response of chest compressions on physiological parameters.⁴ Both experimental and clinical
53 studies have shown a higher frequency of return of spontaneous circulation when the coronary
54 perfusion pressure is over 15 mmHg before defibrillation.⁵⁻⁹ Clinical studies and randomised trials
55 have reported a similar increased frequency of return of spontaneous circulation in out-of-hospital
56 cardiac arrest after administration of adrenaline indicating a beneficial effect on the coronary
57 perfusion pressure.¹⁰⁻¹² However, the increased frequency of return of spontaneous circulation does
58 not translate into improved neurological outcome or long-term survival.¹²⁻¹⁴ We recently published
59 experimental data exploring the effects on the heart.¹⁵ This analysis did not show this beneficial
60 effect on return of spontaneous circulation and physiologic parameters important for the heart
61 perfusion if adrenaline was given repetitively.¹⁵ A similar result was demonstrated in a clinical
62 setting where a higher rate of adrenaline injections were an independent predictor of poor
63 neurological outcome and lower rate of return of spontaneous circulation.¹⁴ Earlier experimental
64 studies have shown that a single bolus dose of adrenaline impairs brain perfusion,^{16, 17} cerebral
65 oxygenation,¹⁸ reduce carotid blood flow and ET_{CO}₂.¹⁹ The association with poor neurological
66 outcome might be owing to the different pharmaceutical effects of adrenaline on the heart and the
67 brain.²⁰ The aim of this study was to explore the effects of repetitive doses of adrenaline according

68 to guidelines on arterial blood pressures (ABP), arterial blood gases (BG), end tidal carbon dioxide
69 (ETCO₂), arterial oxygen saturation via pulse oximetry (SpO₂) and cerebral tissue oximetry (SctO₂)
70 in a model that simulates cardiac arrest in the catheterization laboratory setting.²¹ The
71 cardiovascular effects of adrenaline in these experiments have previously been reported.¹⁵

72 **Methods**

73 **Ethical statement**

74 The study was approved by Malmö/Lund Committee for Animal Experiment Ethics, approval
75 reference number: M 192-10 and followed modern standards for reporting of animal research (eg
76 ARRIVE guidelines, PLoS Biology 2010, please see the supplementary material: Physiologic effect
77 of repeated EPI_BMH_et al_505959 arriveguidelines).

78 **Experimental animals and procedures**

79 Thirty-six, pathogen free, Swedish-bred, landrace pigs with a mean weight of 38 ± 4.1 kg were
80 studied. They were fasted overnight with free access to water. On the day of experiment, they were
81 pre-medicated with Ketamine 150mg/10kg (Ketaminol 100mg/ml, Intervet, Danderyd, Sweden) and
82 Xylazin 20 mg/10 kg (Rompun 20mg/ml, Bayer AG, Leverkusen, Germany), intramuscularly. The
83 procedure was carried out under general anaesthesia, induced by Sodium Pentothal 12.5 mg/kg/dose
84 (Pentothal 100mg/ml Abbott, Stockholm, Sweden) and included endotracheal intubation. To
85 maintain anaesthesia, an infusion of Fentanyl 1.25 µg/ml (Fentanyl Pharmed AB, Stockholm,
86 Sweden) in buffered glucose (25 mg/ml) was started at a rate of 2 ml/min. Meprobamat (Mebumal
87 DAK Copenhagen Denmark) and thiopental was titrated in small bolus doses, as needed thereafter.
88 During the preparation phase the animals were mechanically ventilated with a mixture of nitrous
89 oxide (70%), oxygen (30%) in volume-controlled mode, adjusted to normoventilation, i.e.,
90 maintaining ETCO₂ at 4.5 - 5.5 kPa (Siemens-Elema 900B, Solna, Sweden).

91 Animals were monitored with a three lead electrocardiogram, SpO₂ and ETCO₂ using an IntelliVue
92 MP90 monitoring system (Philips, Eindhoven, The Netherlands). Cerebral oximetry was measured
93 with the FORE-SIGHT monitoring system (CASMED, Branford, CT, USA) and the electrodes
94 were placed longitudinally on the forehead of the pig. Biochemical markers of pH, pCO₂, pO₂
95 (kPa), lactate and Base Excess (mmol/l) were collected through an arterial line and analysed using
96 an ABL 827 (Radiometer, Copenhagen, Denmark). A 6 French catheter was placed in the ascending
97 aorta through a femoral artery cutdown for ABP measurement. Central venous pressure was
98 measured (for calculation of CePP) from a right atrial catheter inserted in to the right atrium via the
99 right jugular vein. Blood pressures were monitored using LabChart 7 (AD Instruments Corp.,
100 Colorado Springs, CO). All blood pressure transducers were set at the height level of the right
101 atrium. Data were analysed immediately prior to and then when ABP reached the highest value
102 after each injection since these periods mirror minimal and maximal physiological response of the
103 administered drug. In the control group ABP and the other parameters were analysed immediately
104 prior to and then 90 seconds after each saline injection. Ten thousand units of unfractionated heparin
105 (LEO Pharma AB, Malmö Sweden) were administered intravenously at the start of instrumentation.
106 Catheter positions were confirmed by fluoroscopy (Shimadzu Corp., Kyoto, Japan).

107 **Study design and protocol**

108 Figure 1 is a representation of the experimental timeline for the study protocol. The pigs were
109 randomised using sealed envelopes; the person opening the envelope prepared the prescribed drug
110 while the remainder of the researchers were blinded to the drug administered during the experiment.
111 The animals either received repetitive injections of adrenaline 0.02 mg/kg/dose, per Pytte et al,²²
112 0.03 mg/kg/dose per Ristagno et al¹⁷ or saline (control). After initiation of the procedure,
113 ventricular fibrillation (VF, as confirmed by ECG) was induced using a 9 V direct current (Duracell
114 Battery, Procter & Gamble, Cincinnati OH, USA) between a skin electrode and an intracardiac
115 needle inserted into the epicardium (a stimulation time between 5 – 10 seconds). After one minute

116 of untreated VF, guideline compliant mechanical chest compressions (LUCAS™2, Physio-
117 Control/Jolife AB, Lund, Sweden) and manual ventilation at a rate of 8 – 10 inflations/minute with
118 100% of oxygen were started and continued for 15 minutes. During the first 4 minutes (baseline),
119 no drug or saline (control) was administered. At 5, 8, 11 and 14 minutes after induction of VF, an
120 injection of the allocated drug/saline was administered followed by a flush of 10 ml saline through a
121 peripheral cannula in an ear vein.

122 Due to large number of data collected in this analysis this material has been divided in two parts
123 where the effects on the heart has been presented earlier.¹⁵ The effects of adrenaline, regarding the
124 time to reach pressure peaks, and results on return of spontaneous circulation and the period beyond
125 this has been described previously¹⁵ and therefore omitted in this article. However no data has been
126 duplicated.

127 **Statistical analysis**

128 Following the experiments, all parameters were exported and analysed using LabChart 7 (AD
129 Instruments Corp., Colorado Springs, CO). Statistical comparisons were made in two manners; first,
130 all groups were compared at 10 minutes prior to VF induction and then during the 4 minute baseline
131 chest compressions epoch, using the unpaired Student T-test. All data regarding the effect of
132 adrenaline was summarised in table using mean and standard deviation, both for absolute values
133 and for the difference to the Injection 1 value, which constitutes the baseline value. (The "Baseline"
134 time point is not used in the statistical analyses). In descriptive plots, the difference to the Injection1
135 value is plotted by time point as mean value with error bars for the standard error of the mean
136 (standard deviation divided by the square root of the number of patients with data). Each variable
137 was analysed using a linear model including treatment group, time point, Injection 1 value and the
138 treatment group x time point and Injection 1 value x time point interactions, and the result was
139 presented as the adjusted mean difference between each of the adrenaline arms to the saline arm, for
140 each time point post Injection 1, with nominal 95% confidence intervals. All analyses were

141 performed for observed cases without imputation of missing data. No formal adjustment for
142 multiple comparisons was performed since the analyses are exploratory in nature and include no
143 formal hypothesis tests. The analyses were performed using R version 3.2.2 with a P-value <0.01
144 considered as significant. Sample size and power calculation that was done has been presented
145 previously.¹⁵

146 **Results**

147 In the period up to the 4 minute baseline chest compressions epoch and during the 4 minute period,
148 there were no significant differences between the three groups in any of the monitored physiologic
149 parameters. In the group given 0.02 mg/kg/dose, there were increases in all arterial blood pressures
150 (systolic, diastolic and mean) at all 4 pressure peaks but the CePP only increased significantly at
151 peak 1 (Table 1, Fig. 2 and Fig. 3). A decrease in ETCO₂ following peak 1 and 2 was observed.
152 SctO₂ and SpO₂ were lowered following injection 2 and beyond (Table 1, Fig. 2 and Fig. 3). In the
153 group given a 0.03 mg/kg/dose, all ABP's increased at the first 4 pressure peaks but CePP only
154 following 3 pressure peaks (Table 1, Fig. 2 and Fig. 3). Lower ETCO₂, SctO₂ and SpO₂ was seen at
155 peak 1 and beyond. (Table 1, Fig. 2 and Fig. 3). In the saline control group, systolic ABP was
156 significantly lower at pressure peak 1 and beyond; no other parameter changed significantly during
157 the. In the two adrenaline groups, pH and Base Excess were lower and lactate levels higher
158 compared to baseline as well as compared to the saline control (Table 2).

159 **Discussion**

160 This study shows that intravenous administration of repetitive doses of adrenaline increased all
161 ABP's and to some extent also CePP as expected, however with lower ETCO₂, SctO₂, SpO₂ and
162 significantly worse bio-chemistry, compared to the saline control group.

163 This study simulates a refractory cardiac arrest in the cath-lab as described previously,²¹ which is a
164 different setting compared to previous studies using adrenaline in the treatment of cardiac arrest that

show a good effect on both return of spontaneous circulation and cerebral perfusion.^{23, 24} However, compared to these publications, the present study differs in duration of VF and number of adrenaline doses given, which might impact the result. Still, earlier studies have shown that a single bolus of adrenaline impairs brain perfusion^{16, 17}, cerebral oxygenation¹⁸ and ETCO₂.¹⁹ These findings were all confirmed in the present study, although this is in conflict with other earlier studies.^{23, 24}

The effect of adrenaline will also be affected by the quality of circulation provided by CPR, i.e., the effectiveness of chest compressions.²² High quality CPR has been shown to improve cerebral oxygenation during resuscitation efforts²⁵ and poor cerebral oxygenation has been shown to relate to poor outcome.²⁶ The administration of repetitive doses of adrenaline reduces cerebral oxygenation as shown here and previously.¹⁷⁻¹⁹ Further, in the current study, repetitive doses of adrenaline also decrease ETCO₂, a surrogate marker for cardiac output.²⁷ High levels of ETCO₂ have been shown to correlate to a favourable outcome during resuscitation efforts.²⁷ In this study, adrenaline treatment according to the current guideline recommendation^{2, 3} resulted in several undesirable physiologic effects. Adrenaline seems to induce a more acidotic state, as shown in the present and previous studies, and acidosis might lead to a decreased pharmacological effect of the drug, which may be associated with a negative outcome.^{28, 29}

Also, the higher lactate levels noted in the present study in both of the adrenaline groups, has previously been shown to affect outcome negatively following cardiac arrest.³⁰⁻³¹ The increased lactate levels noted in the presenting study might be explained by vasoconstriction induced by adrenaline, but other mechanism as cellular metabolism; increasing lactate due to an effect on lactate release cannot be excluded.³² There was no difference in lactate level between the two groups treated with adrenaline after 15 min of chest compressions. This might be explained by the fact that both doses induce maximal vasoconstriction and thereby the same lactate levels, however this has not been analysed. Adrenalin administered repetitively, contrasted to the single dose

190 regimens used in experimental studies,^{23-24, 28-29} seems to exhibit a high rate of diminishing returns
191 of any potential beneficial effects. In the clinical setting, one study shows that the cumulative dose
192 of adrenaline decreases the possibility of achieving a good neurologic outcome¹⁴. After 6 injections
193 of adrenaline, almost no patients survived with a good neurological outcome. We did not evaluate
194 long term survival in the current study. However, an unfavourable CPC score was found by
195 Behringer et al after a median of 4 adrenaline doses¹⁴ and after the same number of adrenaline doses
196 in the present study, we observed no increase of arterial blood pressure and a concomitant reduction
197 of perfusion to vital organs. Earlier clinical publications have demonstrated that administration of
198 adrenaline according to guidelines has a positive effect on the possibility to attain return of
199 spontaneous circulation but without improved neurological/survival outcomes at discharge from
200 hospital.^{13, 33} This result has also been observed using higher cumulative doses of adrenaline.¹⁴ The
201 effect of adrenaline seems to differ depending on the cause of the cardiac arrest, as well as the
202 timing and dose of adrenaline.³³⁻³⁶ Further research is therefore needed to investigate how doses,
203 timing or mode of adrenaline administration can be optimized during resuscitation.

204 **Limitations**

205 This study design primarily reflects a very specific in-hospital cardiac arrest scenario, including a
206 prompt response to a cardiac arrest with chest compressions followed by prolonged CPR, and
207 consistent ventilatory support, as occurs in the catheterisation laboratory with a therapy resistant
208 VF, and therefore cannot be generalized to other situations.

209 While mechanical ventilation was adjusted for to achieve normoventilation during the preparation
210 phase, ETCO₂ and pCO₂ dropped precipitously in the adrenaline dosing groups in the experimental
211 phase. This condition was not corrected to achieve normoventilation so the reduction in SctO₂ could
212 also be from hypocarbic cerebral vasoconstriction, but ventilation was done as recommended in
213 current guideline for resuscitation (i.e., 10 times/min) to mimic the clinical setting and there were
214 no significant changes in.³

215 Since the animals were healthy and without coronary artery disease, it may be difficult to
216 extrapolate our findings into humans typically suffering a cardiac arrest.
217 Adrenaline was administered according to human guidelines, and the results should be interpreted
218 accordingly; different dose and time intervals might give different results.
219 This was an exploratory study and that did not seek to formally test a specific hypothesis. Statistical
220 tests were not adjusted for multiple comparisons which increases the chance that some of these
221 findings may be false positive. The findings of this study should thus be confirmed in further
222 studies.

223 **Conclusion**

224 Repetitive intravenous adrenaline doses increased ABP's and to some extent also CePP, but
225 significantly decreased organ and brain perfusion. These findings should however be confirmed in
226 further studies.

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233

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328

329 **Figure legends**

330 **Figure 1.**

331 Shows the experimental timeline.

332 **Figure 2.**

333 Change from Injection 1 value in arterial blood pressure. The red solid line indicates adrenaline

334 0.02 mg/kg/dose, the blue dotted line indicates adrenalin 0.03 mg/kg/dose and the black dotted line

335 indicates saline. Bars indicate standard error of the mean.

336 **Figure 3.**

337 Change from Injection 1 value in CePP, ETCO₂, SpO₂ and SctO₂. The red solid line indicates

338 adrenaline 0.02 mg/kg/dose, the blue dotted line indicates adrenaline 0.03 mg/kg/dose and the black

339 dotted line indicates saline. Bars indicate standard error of the mean.

340

341 **Table 1.**

342 Analysis of changes in physiological parameters from Injection 1. Mean difference from the Saline

343 group adjusted for Injection 1 value. ABP = Arterial blood pressure, CePP = Cerebral perfusion

344 pressure, ETCO₂ = End tidal carbon dioxide, SpO₂ = Arterial oxygen saturation via pulse oximetry

345 and SctO₂ = Cerebral tissue oximetry.

346

	Adrenaline			Adrenaline		
	0.02/kg/dose vs Saline			0.03/kg/dose vs Saline		
	Difference			Difference		
	to Saline	95 % C.I.	P-value	to Saline	95 % C.I.	P-value
ABP systole						
Pressure peak #1	47.8	(25.4-70.2)	<0.001	63.7	(41.9-85.6)	<0.001
Injection #2	17.5	(-4.5-39.5)	0.118	31.2	(8.8-53.5)	0.007
Pressure peak #2	59.5	(37.0-81.9)	<0.001	49.0	(26.2-71.9)	<0.001
Injection #3	15.8	(-6.6-38.2)	0.166	30.9	(8.6-53.3)	0.007
Pressure peak #3	51.5	(29.6-73.5)	<0.001	61.0	(39.1-82.8)	<0.001
Injection #4	15.0	(-7.5-37.5)	0.191	29.6	(7.8-51.5)	0.008
Pressure peak #4	48.7	(26.2-71.2)	<0.001	59.0	(37.2-80.9)	<0.001
ABP Diastole (mmHg)						
Pressure peak #1	26.6	(16.0-37.1)	<0.001	30.6	(20.7-40.6)	<0.001
Injection #2	2.9	(-7.5-13.4)	0.579	3.0	(-7.2-13.3)	0.558
Pressure peak #2	23.9	(13.2-34.6)	<0.001	17.1	(6.7-27.5)	0.001
Injection #3	-0.6	(-11.3-10.2)	0.914	-1.7	(-11.8-8.5)	0.745
Pressure peak #3	16.0	(5.6-26.4)	0.003	14.5	(4.5-24.4)	0.005
Injection #4	-1.0	(-11.8-9.7)	0.849	-3.6	(-13.5-6.4)	0.477
Pressure peak #4	14.6	(3.9-25.3)	0.008	9.0	(-1.0-18.9)	0.076
ABP Mean (mmHg)						
Pressure peak #1	31.3	(16.5-46.0)	<0.001	48.9	(34.6-63.2)	<0.001

Injection #2	4.2	(-10.2-18.6)	0.569	25.2	(10.6-39.9)	<0.001
Pressure peak #2	31.4	(16.6-46.1)	<0.001	36.6	(21.6-51.6)	<0.001
Injection #3	2.1	(-12.7-16.9)	0.777	22.8	(8.1-37.4)	0.002
Pressure peak #3	23.8	(9.4-38.2)	0.001	36.8	(22.5-51.1)	<0.001
Injection #4	1.2	(-13.6-16.0)	0.874	13	(-1.3-27.3)	0.075
Pressure peak #4	20.4	(5.6-35.1)	0.007	19.9	(5.6-34.2)	0.007
CePP (mmHg)						
Pressure peak #1	27.2	(8.6-45.9)	0.004	39.6	(21.0-58.3)	<0.001
Injection #2	1.9	(-16.8-20.5)	0.842	22.6	(3.9-41.2)	0.018
Pressure peak #2	21.1	(2.3-39.8)	0.028	29.5	(10.4-48.6)	0.003
Injection #3	0.1	(-19.1-19.3)	0.994	21.1	(1.9-40.3)	0.032
Pressure peak #3	12.9	(-6.0-31.9)	0.18	25.5	(6.2-44.7)	0.01
Injection #4	-1.8	(-21.5-17.8)	0.854	1.3	(-18.5-21.0)	0.900
Pressure peak #4	10.6	(-9.0-30.3)	0.287	11.3	(-8.4-31.0)	0.260
ETCO₂ (kPa)						
Pressure peak #1	-0.7	(-1.2--0.2)	0.005	0.0	(-0.5-0.5)	0.978
Injection #2	-0.6	(-1.1--0.1)	0.017	-0.7	(-1.1--0.2)	0.005
Pressure peak #2	-0.7	(-1.2--0.2)	0.005	-0.7	(-1.2--0.2)	0.004
Injection #3	-0.5	(-1.0-0.0)	0.046	-0.5	(-1.0-0.0)	0.043
Pressure peak #3	-0.4	(-0.9-0.1)	0.108	-0.5	(-1.0-0.0)	0.038
Injection #4	-0.5	(-1.0-0.1)	0.077	-0.5	(-1.0--0.1)	0.029
Pressure peak #4	-0.5	(-1.0-0.0)	0.049	-0.6	(-1.1--0.1)	0.016
SpO₂ (%)						
Pressure peak #1	-1.3	(-7.7-5.0)	0.682	0.0	(-6.0-6.1)	0.995
Injection #2	-10	(-16.3-3.6)	0.002	-7.7	(-14.0-1.4)	0.016
Pressure peak #2	-9.9	(-16.3-3.5)	0.002	-7.6	(-13.9-1.3)	0.018
Injection #3	-8.7	(-15.1-2.4)	0.007	-9.4	(-15.5-3.4)	0.002
Pressure peak #3	-6.0	(-12.3-0.4)	0.066	-6.2	(-12.3-0.1)	0.046
Injection #4	-8.1	(-14.6-1.5)	0.017	-7.5	(-13.8--1.2)	0.020
Pressure peak #4	-7.3	(-13.9-0.7)	0.030	-9.1	(-15.4--2.8)	0.005

SctO₂ (%)						
Pressure peak #1	-0.6	(-3.7-2.5)	0.699	0.2	(-2.9-3.3)	0.900
Injection #2	-3.1	(-6.2-0.0)	0.049	-5.5	(-8.7-2.3)	<0.001
Pressure peak #2	-3.6	(-6.7-0.5)	0.025	-4.9	(-8.1-1.8)	0.002
Injection #3	-4.1	(-7.2-1.0)	0.009	-6.7	(-9.8-3.6)	<0.001
Pressure peak #3	-4.6	(-7.7-1.5)	0.004	-6.1	(-9.2-3.0)	<0.001
Injection #4	-4.2	(-7.3-1.1)	0.008	-6.7	(-9.8-3.6)	<0.001
Pressure peak #4	-4.8	(-7.9-1.7)	0.003	-6.5	(-9.6-3.4)	<0.001

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Table 2.

Shows the arterial blood gas values (Mean $\pm$ SD) after 15 minutes of chest compressions and drug administration. Statistical comparisons were made for each group between the blood gas values at 15 minutes and those after the first 4 minutes of chest compressions without drug administration.

After 15 min of chest compressions and 4 Injection of adrenaline	Saline Control	Diff 4 min vs. 15 min	Saline control 4 min vs. 15 min p-value	ADR 0.02 mg/kg	Diff 4 min vs. 15 min	Adrenaline 0.02 4 min vs. 15 min p-value	ADR 0.03 mg/kg	Diff 4 min vs. 15 min	Adrenaline 0.03 4 min vs. 15 min p-value
pH	7.446 (0.112)	-0.081	0.061	7.328 (0.144)	-0.180	<0.001	7.323 (0.137)	-0.164	<0.001
pCO₂ (kPa)	4.2 (1.4)	-0.3	0.977	4.6 (1.6)	+0.50	0.665	5.2 (2.1)	+0.9	0.194
pO₂ (kPa)	36.2 (15.5)	+2.0	0.795	32.4 (13.4)	-3.4	0.544	24.8 (16.2)	-15.3	0.02
Lactate (mmol/L)	6.3 (1.6)	+2.1	0.001	8.7 (1.7)	+4.6	<0.001	7.8 (1.6)	+4.3	<0.001
Base Excess (mmol/L)	-2.9 (3.2)	-4.2	0.002	-8.3 (2.4)	-9.6	<0.001	-6.4 (3.4)	-7.2	<0.001

Figure 1

Figure 2

Figure 3