Early adrenaline administration does not improve circulatory recovery during resuscitation from severe asphyxia in newborn piglets.

Linnér, Rikard; Werner, Olof; Perez de Sá, Valéria; Cunha Goncalves, Doris

Published in:
Resuscitation

DOI:
10.1016/j.resuscitation.2012.02.030

2012

Title: Early adrenaline administration does not improve circulatory recovery during resuscitation from severe asphyxia in newborn piglets

Authors:

*Rikard Linner[1], Olof Werner[2], Valeria Perez-de-Sa[2], and Doris Cunha-Goncalves[1]

Lund University,

[1]Department of Cardiothoracic Anaesthesia and Intensive Care,

[2]Department of Paediatric Anaesthesia and Intensive Care,

Skåne University Hospital, Lund, Sweden, SE-22185;

*Corresponding author:

Rikard Linner, MD

Department of Cardiothoracic Anaesthesia and Intensive Care

THAI Plan 8 Hisshall A,

Skåne University Hospital

Lund, Sweden, SE-221 85.

Tel: +46-46-17 73 76

Fax +46-46-17 60 71

Email: Rikard.Linner@googlemail.com

Word count of manuscript: 2805

Word count of abstract: 250

Abbreviations

Bpm – beats per minute

BW – body weight

CCCM – closed chest cardiac massage

CrS_{O_2} – cerebral regional oxygen saturation

HR – heart rate

MAP – mean arterial pressure

Pbt_{O_2} – brain tissue partial pressure of oxygen

RCCABF – right common carotid artery blood flow

ROSC – return of spontaneous circulation

P-adrenaline – plasma adrenaline

P-noradrenaline – plasma noradrenaline

SBH – severe bradycardia and hypotension

Abstract

Aim of the study: To investigate the effects of early intravenous adrenaline administration on circulatory recovery, cerebral reoxygenation, and plasma catecholamine concentrations, after severe asphyxia-induced bradycardia and hypotension.

Methods: One-day-old piglets were left in apnoea until heart rate and mean arterial pressure were less than 50 min^{-1} and 25 mmHg, respectively. They randomly received adrenaline, 10 µg kg^{-1} (n=16) or placebo (n=15) and were resuscitated with air ventilation and, when needed, closed-chest cardiac massage (CCCM). Eight not asphyxiated animals served as time controls.

Results: CCCM was required in 13 piglets given adrenaline and in 13 given placebo. Time to return of spontaneous circulation was: 72 (66–85) s *vs.* 77 (64–178) s [median (quartile range)] (p=0.35). Time until cerebral regional oxygen saturation (CrS_{O_2}) had increased to 30 % was 86 (79–152) s *vs.* 126 (88–309) s (p=0.30). The two groups did not differ significantly in CrS_{O_2}, heart rate, arterial pressure, right common carotid artery blood flow, or number of survivors: 13 and 11 animals. Plasma concentration of adrenaline, 2.5 min after resuming ventilation, was 498 (268–868) nmol l^{-1} *vs.* 114 (80–306) nmol l^{-1} (p=0.01). Corresponding noradrenaline concentrations were 1799 (1058–4182) nmol l^{-1} *vs.* 1385 (696–3118) nmol l^{-1} (ns). In the time controls, the concentrations were 0.4 (0.2–0.6) nmol l^{-1} of adrenaline and 1.8 (1.3–2.4) nmol l^{-1} of noradrenaline.

Conclusion: The high endogenous catecholamine levels, especially those of noradrenaline, may explain why early administered adrenaline did not significantly improve resuscitation outcome.

1. Introduction

Intravenous adrenaline has been widely used during resuscitation since the 1960s. No placebo-controlled study has evaluated its value in asphyxiated neonates, but one study, performed in older children, suggests that a high intravenous dose of adrenaline: 100 µg kg^{-1}, might worsen the outcome in relation to a 10 µg kg^{-1} dose.[1] The European Resuscitation Council and the American Heart Association recommend that, before adrenaline is administered, asphyxiated neonates with severe bradycardia should be treated with ventilation of the lungs and closed-chest cardiac massage (CCCM).[2, 3] The recommendations are based on the facts that many infants recover with these initial measures and that venous-access is seldom immediately available.[4] It is not known if early adrenaline administration would be beneficial in cases of severe asphyxia, if venous access could be quickly established.

In a randomised, observer-blinded study, we compared the effect of early administration of adrenaline, 10 µg kg^{-1}, to that of placebo in one-day-old piglets that had suffered severe asphyxia-induced bradycardia and hypotension. The primary hypothesis was that early administration of adrenaline would shorten the time to return of spontaneous circulation (ROSC). Secondary hypotheses were that recovery of brain blood flow and brain oxygenation would occur faster, and that myocardial injury would be less.

2. Methods

The Animal Ethics Research Committee of Lund University approved the study and thirty-nine domestic piglets (12–36 hours old) were cared for in accordance with the European Guidelines for Use of Experimental Animals.

2.1 Animal preparation and randomisation

The piglet was premedicated with intramuscular ketamine (3 mg) and midazolam (0.4 mg), weighed and placed in an incubator. Rectal temperature was kept at 38.5 – 40.0°C.

Anaesthesia was induced with propofol (4 mg kg^{-1}) and remifentanil (1 µg kg^{-1}), injected via an ear vein. After topical laryngeal anaesthesia with lidocaine, 10-20 mg, a cuffed tracheal tube was inserted and the lungs mechanically ventilated. The ventilator (Servo 300, Siemens, Sweden) was in pressure-regulated volume control mode with these settings: I/E ratio 1:1, inspired oxygen fraction 0.21, tidal volume 10 ml kg^{-1}, end-expiratory pressure +5 cm H_2O, and rate 40 min^{-1}. The rate was subsequently adjusted, aiming at a $PaCO_2$ of 5-6.5 kPa.

Anaesthesia was maintained with intravenous fentanyl, 30 µg kg^{-1} h^{-1}, and midazolam, 0.3 mg kg^{-1} h^{-1}. A solution with 50 g glucose, 70 mmol sodium, 45 mmol chloride, and 25 mmol acetate per litre was infused at 10 ml kg^{-1} h^{-1}. Both femoral arteries were cannulated for blood sampling and pressure monitoring (Powerlab monitor, ADInstruments, Hastings, UK). Three needle-electrodes were sutured subcutaneously to the chest, for electrocardiography. A self-adherent near-infrared spectroscopy probe (Pediatric SomaSensor probe, model SPFB-

USA, Somanetics Corporation, Troy, MI, USA) was placed over a shaved left scalp and connected to a Somanetics INVOS 5100C Cerebral/Somatic Oximeter monitor for measurement of regional cerebral saturation (CrS_{O_2}), which updates and stores the reading every 6 s.

A scalp incision exposed the left parietal bone, and a 3 mm diameter hole was drilled down to the dura mater, which was perforated with a bevel allowing a thermocouple probe and a flexible microcatheter probe to be advanced 1 cm into the brain. The latter (LICOX; GMS, Mielkendorf, Germany) contained a polarographic oxygen cell. Both probes were connected to a LICOX CMP monitor to obtain temperature-corrected brain tissue partial pressure of oxygen (Pbt_{O_2}). Measurements were updated every 20 s and the recordings stored using "LICOX for PC" Software (GMS, Mielkendorf, Germany).

The right external jugular vein was cannulated. The right common carotid artery, in which about two-thirds of the flow goes to the brain, was dissected free and an ultrasonic blood flow probe placed.[5] The right common carotid artery blood flow (RCCABF) signal was collected with a Transonic Blood Flowmeter T-206 (Transonic Systems Inc, Ithaca, NY, USA) and stored by a computer. The piglets were allowed to stabilize for at least 30 min, while we ensured that $PaCO_2$ reached target and remained unchanged during 10 min with fixed ventilator settings. Baseline measurements were then made, and a relaxant without anticholinergic effect: vecuronium, 2 mg kg^{-1}, injected i.v.

The animals were assigned to one of three groups. Two groups were exposed to asphyxia and were resuscitated with adrenaline (n=16) or placebo (n=15). The third group were time controls (n=8). A participant outside the lab carried out the randomisation and prepared coded syringes with adrenaline or placebo.

2.2. Induction of asphyxia

Asphyxia was induced in three steps. Firstly, the piglet was hypoventilated with air for 15 min at a ventilator rate of 5 min^{-1} and otherwise unchanged ventilator settings. The rate was then returned to the baseline value and the lungs ventilated with 8 % O_2 in N_2 for 5 minutes. Finally, ventilation was stopped by disconnecting the ventilator. A 60 ml deadspace was attached to the endotracheal tube to prevent entry of air into the lungs. The apnoea was maintained until severe bradycardia and hypotension (SBH) ensued, defined as a HR < 50 bpm with MAP < 25 mmHg. If SBH had not developed by 12 min of apnoea, resuscitation was nevertheless started, 1 min later and carried out as in the other animals.

2.3. Resuscitation

Air-ventilation with baseline ventilator settings was resumed 1 min after the diagnosis of SBH, or after 12 + 1 min of apnoea. Immediately after restarting ventilation, adrenaline, 10 µg kg^{-1}, or placebo, i.e. saline, was administered intravenously. ROSC was defined to have occurred when MAP exceeded 40 mmHg and HR exceeded 150 bpm. [6, 7] Thirty seconds after start of ventilation, it was decided whether ROSC was imminent as judged from the arterial pressure curve. If not, CCCM was given for 30 s. The arterial pressure and ECG were evaluated during the subsequent 30 s and if ROSC still had not occurred, a second 30 s session of CCCM was started. The cycle of 30 s observation followed by 30 s CCCM was repeated until ROSC. If this had not taken place within 3 min, a second dose of adrenaline, 10 µg kg^{-1}, or placebo, was given. After 5 min of unsuccessful resuscitation, a third dose of

adrenaline, 10 μg kg^{-1}, or placebo, was injected, followed by 5 ml kg^{-1} of i.v. sodium bicarbonate 0.6 mmol l^{-1}, given slowly. If there was no ROSC by 10 min, resuscitation attempts were stopped.

To re-expand possible atelectasis, end-expiratory pressure was held at 15 cm H_2O for 15 s. This was done 10, 30, 45, 105, 165 and 225 min after resuming ventilation.

The piglets were euthanized at 240 min.

2.4. Assessment of immediate circulatory recovery and recovery of cerebral oxygenation

The time from resumption of ventilation until ROSC was noted. The time until CrS_{O_2} reached 30 % and the time until Pbt_{O_2} had increased by 0.1 kPa from its nadir assessed speed of recovery of cerebral oxygenation. Measurements of Pbt_{O_2} and RCCABF were discontinued 60 min after resumption of ventilation.

2.5. Blood chemistry

Arterial samples taken 2.5 min after resumption of ventilation were analysed for plasma concentration of adrenaline and noradrenaline using high pressure liquid chromatography with fluorimetric detection.[8] Plasma samples obtained at 240 min were analysed for creatine kinase isoenzyme MB and for troponin I by quantitative chemiluminescence, using kits

provided by Beckman-Coulter Company, Sweden. The analyses were performed at the Skåne University Hospital Laboratory, using accredited methods (SWEDAC, Sweden).

Arterial samples at baseline, taken just before resuming ventilation (=end of asphyxia), and 2.5, 10, 30, 60, 120 and 240 min after resumption, were analysed for Hb, erythrocyte volume fraction (EVF), pH, base excess (BE), PCO_2, and PO_2 on an ABL 700 (Radiometer, Copenhagen, Denmark) with settings adjusted to porcine blood.

2.6. Estimation of circulating amounts of noradrenaline

The amount of noradrenaline in the whole plasma volume was estimated as:

(plasma concentration) x (1-EVF) x (blood volume)/weight

where (blood volume) /weight was set to 100 ml kg^{-1}.[9] The amount was expressed in µg per kg body weight. The molar mass of noradrenaline is 169.2 g mol^{-1}.

2.7. Procedure in non-asphyxiated time controls

Eight piglets were instrumented as the asphyxiated piglets and followed the same measurement protocol. From the baseline stage, and on, they were ventilated with unchanged ventilator settings.

2.8. Statistics

Differences between the three groups at baseline were assessed with one-way ANOVA on ranks. Mann-Whitney´s test compared the adrenaline and placebo groups at the end of the asphyxia stage. Survival analysis and a variant of two-way repeated measures ANOVA on ranks tested differences between the same two groups, in respect of measurements obtained after resumption of ventilation and injection of the study drug.[10] Differences in proportions were assessed by Fisher´s exact test. Microsoft Excel 2010 and statistical programs Sigmaplot 11 (Alfasoft AB, Gothenburg, Sweden) and SAS 9.3 (SAS Institute AB, Solna, Sweden) were employed. *P*-values <0.05 were considered significant.

3. Results

3.1. Baseline

Body weight was 1.6 (1.4–1.8) kg [all animals; median (quartile range)]. B-haemoglobin was 75 (64–83) g l^{-1}. Gender (female/male/not recorded) was 18/19/2. Ventilator rate was 49 (42-50). Arterial blood gases, HR, MAP, CrS_{O_2}, and Pbt_{O_2} are shown in Tables 1 and 2. The baseline measures did not differ between groups.

3.2. Response to asphyxia

All animals survived the hypoventilation phase. During the subsequent hypoxic normoventilation, one animal of the adrenaline group developed asystole and was resuscitated. The others went on to the final apnoea phase, which lasted 7 (6–9) min. Severe bradycardia and hypotension, as defined in Methods, ensued in all but one piglet from the adrenaline group, in whom HR and MAP at the end of the designated maximum apnoea period was 66 bpm and 21 mmHg, respectively.

During the last 30 s of apnoea, HR was 32 bpm (14 – 42 bpm). MAP was 17 mmHg (14 – 21 mmHg). CrS_{O_2} was at the minimum value displayed by the equipment (15 %), Pbt_{O_2} decreased to 0.0 (0.0–0.1) kPa, and RCCABF to 0.0 (0.0–1.0) ml min^{-1}. There was combined metabolic and respiratory acidosis, with a median arterial pH of 6.64 (Table 1). None of the above-mentioned measures differed significantly between the adrenaline and placebo groups.

3.3. Immediate outcome of resuscitation

Sixteen and fifteen pigs, respectively, received adrenaline and placebo. Thirteen in each group required CCCM after the initial 30 s of ventilation. Of these, one adrenaline and four placebo pigs required more than one round of CCCM (p=0.17) and the full resuscitation protocol failed in one and three pigs, respectively (p=0.33). Once effective heart activity was on its way of being re-established, HR increased fast in both groups: from below 100 to over 200

bpm within 15 s. MAP also increased abruptly (Fig 1). In all pigs, in which a HR of 150 bpm was reached, MAP already exceeded 40 mmHg. Thus, time to ROSC coincided with time to HR 150 bpm. Despite initially successful resuscitation, one piglet given adrenaline, and one given placebo developed ventricular fibrillation unresponsive to attempts at cardioversion and died 15 min after resumption of ventilation. One in the adrenaline group, died at 220 minutes in supraventricular tachycardia unresponsive to adenosine. There were no significant differences between groups in respect of time to ROSC, time until CrS_{O_2} reached 30 %, time until Pbt_{O_2} had increased by 0.1 kPa from nadir (Table 3), or proportion of survivors (Table 1).

3.4. Arterial blood gases and cerebral oxygenation during and after resuscitation

Arterial blood gases were similar after adrenaline and placebo (Table 1). RCCABF, CrS_{O_2} and Pbt_{O_2} increased rapidly during resuscitation (Figure 2), with no significant difference between the two treatments (Table 2).

3.5. Catecholamines 2.5 min after start of resuscitation

In asphyxiated piglets given placebo, median plasma adrenaline and noradrenaline concentrations were about 300 and 800 times greater, respectively, than among time controls (Table 4). Median P-adrenaline was four times greater after adrenaline than after placebo (p=0.001). P-noradrenaline was not significantly affected by the adrenaline injection.

3.6 Troponin I and creatine kinase isoenzyme MB (CK-MB) at 240 min

P-Troponin I and P-CK-MB were similar in the adrenaline and placebo groups (Table 4).

4. Discussion

4.1. Key findings

The main finding of the study was that early administration of adrenaline did not shorten time to ROSC (Table 3). The primary hypothesis was thus not confirmed. Furthermore, adrenaline did not increase common carotid arterial flow, and there was no statistically significant effect on the two measures of brain oxygenation (Fig. 2; Table 3), to support the secondary hypothesis.

The principal reason for giving adrenaline during resuscitation is to obtain peripheral vasoconstriction and redistribute blood flow to the brain and myocardium.[11, 12] That the early administration of adrenaline did not shorten time to ROSC might be due to the high levels of endogenous catecholamines (Table 4). We estimate the amount of noradrenaline in the whole plasma volume (see Methods) to have been 24 (13–55) μg kg^{-1} in piglets given adrenaline and 19 (9–40) μg kg^{-1} in those given placebo (*ns*). This exceeds the injected dose of adrenaline

(10 µg kg^{-1}). The estimate involved the assumption that measured P-noradrenaline was representative for the whole plasma volume. This may not have been strictly the case, but the figures do illustrate the huge amounts of noradrenaline released in response to asphyxia. Because noradrenaline is at least as potent an alfa-adrenoreceptor agonist as adrenaline, endogenous noradrenaline release probably played a greater role for vasoconstriction than did the exogenous adrenaline.[13] Acidosis has been reported to decrease the response to adrenaline, and this may have contributed to the inconspicuous adrenaline effect in the present study.[14]

There are few reports on levels of adrenaline and noradrenaline in newborns with asphyxia. In asphyxiated babies, mean concentration of total catecholamines was 218 nmol l^{-1} and in breech delivered infants it was 369 nmol l^{-1}.[15] Greenough *et al.* reported 19 nmol l^{-1} of P-adrenaline and 118 nmol l^{-1} of P-noradrenaline in a severely asphyxiated preterm neonate.[16] The short half-life of circulating catecholamines: 2–3 min[13] is probably a reason why we obtained much higher values (table 4). Therefore, timing of the blood sampling is important, as is illustrated by Schoffstal *et al.* They found a peak in P-adrenaline and P-noradrenaline 1 min after start of CPR in young swine with electrically induced ventricular fibrillation. [17] The mean concentrations were 508 nmol l^{-1} and 1655 nmol l^{-1} respectively. At 7 min, both had decreased considerably, and P-noradrenaline was only circa 250 nmol l^{-1}.[17] We took the samples 2.5 min after start of resuscitation, and found adrenaline and noradrenaline concentrations similar to theirs, at 1 min.

4.2. Limitations and strengths of the study

Piglets have been used in many resuscitation studies and the similarities between the human neonate and the piglet are well documented. But, little is known about possible interspecies differences in vascular sensitivity to catecholamines. The findings must therefore be interpreted cautiously. Also, the study was not powered for comparison of proportions. As an example, we found that 1/16 animals given adrenaline and 4/15 animals given placebo needed more than one round of CCCM, without these proportions being significantly different (p=0.17).

Our ambition was to simulate an asphyxia scenario, in which compromised gas exchange gradually worsens to total interruption of oxygen supply. The high levels of two indicators of myocardial injury (Table 4) and the profound mixed acidosis in the study groups (Table 1), are similar to what has been observed in severe asphyxia clinically, which supports the usefulness of the model and applicability to human newborns.[18, 19] In this study, 13/16 piglets in the adrenaline group and 11/15 given placebo survived until the end of the experiment with little more treatment than the initial resuscitation, normoventilation with air, and infusion of buffered glucose. This agrees with our experience from a previous study, but contrasts with Joynt *et al*. Those authors observed severe shock in 6/6 placebo treated piglets 2h after arrest.[6, 20] These contradictory findings might be explained by differences in methodology. In Joynt's study, piglets were subjected to extensive surgery, followed by a prolonged normocapnic hypoxic insult and were then ventilated with 100% oxygen for 1 h, all of which might have influenced the results.

This study was designed as randomised and observer-blinded. Haemodynamics after adrenaline was not notably different from that after placebo, so the risk of unblinding was small.

5. Conclusions

Early adrenaline administration did not shorten time to ROSC in piglets exposed to asphyxia-induced severe bradycardia and hypotension. Neither did recovery of common carotid arterial blood flow occur faster with adrenaline. The lack of distinct positive effects supports the current guidelines, that adrenaline should be given only when ventilation and cardiac massage have failed to restore adequate circulation in the asphyxiated neonate.[2, 3]

Conflict of interest statement

The authors declare that they have no conflicts of interest relevant to the manuscript submitted to *Resuscitation*.

Acknowledgements

This study was funded by grants from The Laerdal Foundation, Lund University Hospital and Lund University Medical Faculty. Peter Höglund, MD, PhD, Competence Centre for Clinical Research, Skåne University Hospital, Lund, Sweden, gave valuable statistical advice.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version

References

1. Perondi MB, Reis AG, Paiva EF, Nadkarni VM, Berg RA. A comparison of high-dose and standard-dose epinephrine in children with cardiac arrest. N Engl J Med. 2004;350:1722-30.

2. Kattwinkel J, Perlman JM, Aziz K, Colby C, Fairchild K, Gallagher J, et al. Part 15: neonatal resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2010;122:S909-19.

3. Richmond S, Wyllie J. European Resuscitation Council Guidelines for Resuscitation 2010 Section 7. Resuscitation of babies at birth. Resuscitation. 81:1389-99.

4. Palme-Kilander C. Methods of resuscitation in low-Apgar-score newborn infants--a national survey. Acta Paediatr. 1992;81:739-44.

5. Meadow W, Rudinsky B, Raju T, John E, Fornell L, Shankararao R. Correlation of flow probe determinations of common carotid artery blood flow and internal carotid artery blood flow with microsphere determinations of cerebral blood flow in piglets. Pediatr Res. 1999;45:324-30.

6. Linner R, Werner O, Perez-de-Sa V, Cunha-Goncalves D. Circulatory recovery is as fast with air ventilation as with 100% oxygen after asphyxia-induced cardiac arrest in piglets. Pediatr Res. 2009;66:391-4.

7. Perez-de-Sa V, Cunha-Goncalves D, Nordh A, Hansson S, Larsson A, Ley D, et al. High brain tissue oxygen tension during ventilation with 100% oxygen after fetal asphyxia in newborn sheep. Pediatr Res. 2009;65:57-61.

8. van der Hoorn FA, Boomsma F, Man in 't Veld AJ, Schalekamp MA. Determination of catecholamines in human plasma by high-performance liquid chromatography: comparison between a new method with fluorescence detection and an established method with electrochemical detection. J Chromatogr. 1989;487:17-28.

9. Linderkamp O, Berg D, Betke K, Koferl F, Kriegel H, Riegel KP. Blood volume and hematocrit in various organs in newborn piglets. Pediatr Res. 1980;14:1324-7.
10. Shah DA, Madden LV. Nonparametric analysis of ordinal data in designed factorial experiments. Phytopathology. 2004;94:33-43.
11. Penson PE, Ford WR, Broadley KJ. Vasopressors for cardiopulmonary resuscitation. Does pharmacological evidence support clinical practice? Pharmacol Ther. 2007;115:37-55.
12. Wyckoff MH, Perlman J, Niermeyer S. Medications during resuscitation -- what is the evidence? Semin Neonatol. 2001;6:251-9.
13. Goodman LS, Gilman A, Brunton LL, Lazo JS, Parker KL. Goodman & Gilman's the pharmacological basis of therapeutics. 11th ed. New York: McGraw-Hill; 2006.
14. Andersen MN, Border JR, Mouritzen CV. Acidosis, catecholamines and cardiovascular dynamics: when does acidosis require correction? Ann Surg. 1967;166:344-56.
15. Lagercrantz H, Bistoletti P. Catecholamine release in the newborn infant at birth. Pediatr Res. 1977;11:889-93.
16. Greenough A, Lagercrantz H, Pool J, Dahlin I. Plasma catecholamine levels in preterm infants. Effect of birth asphyxia and Apgar score. Acta Paediatr Scand. 1987;76:54-9.
17. Schoffstall JM, Spivey WH, Davidheiser S, Fuhs L, Kirkpatrick R, Jr. Endogenous and exogenous plasma catecholamine levels in cardiac arrest in swine. Resuscitation. 1990;19:241-51.
18. Barber CA, Wyckoff MH. Use and efficacy of endotracheal versus intravenous epinephrine during neonatal cardiopulmonary resuscitation in the delivery room. Pediatrics. 2006;118:1028-34.
19. Engle WD, Laptook AR, Perlman JM. Acute changes in arterial carbon dioxide tension and acid-base status and early neurologic characteristics in term infants following perinatal asphyxia. Resuscitation. 1999;42:11-7.

20. Joynt C, Bigam DL, Charrois G, Jewell LD, Korbutt G, Cheung PY. Milrinone, dobutamine or epinephrine use in asphyxiated newborn pigs resuscitated with 100% oxygen. Intensive Care Med.36:1058-66.

Figure Legends

Figure 1. Median values for heart rate and mean arterial pressure. Bold continuous line = Adrenaline. Bold dotted line = Placebo. Thin continuous line = Time controls. In addition, 1st and 3rd quartiles are shown for the time controls = thin interrupted lines. There was no significant difference between groups Adrenaline and Placebo.

Figure 2. Median values for regional cerebral oxygen saturation (A), brain tissue partial pressure of oxygen (B), and right common carotid artery blood flow per unit body weight (C). Bold line = Adrenaline. Interrupted bold line =Placebo. Thin line = Time controls. In addition, 1st and 3rd quartiles are shown for the time controls = thin interrupted lines There was no significant difference between groups Adrenaline and Placebo.

Table 1. Arterial blood-gas values

			Time from start of resuscitation			
Group	Baseline	End asphyxia	2.5 min	15 min	60 min	240 min
pH						
Adrenaline	7.41 (7.39 –	6.63 (6.58 –	6.86 (6.83 –	6.97 (6.94 –	7.27 (7.25 –	7.45 (7.34 –
Placebo	7.44 (7.39 –	6.64 (6.51 –	6.82 (6.74 –	7.01 (6.95 –	7.25 (7.23 –	7.42 (7.39 –
Time	7.43 (7.42 –	7.45 (7.42 –	7.44 (7.42 –	7.46 (7.42 –	7.47 (7.45 –	7.49 (7.48 –
Base excess (mmol l^{-1})						
Adrenaline	4 (2 – 5)	-23 (-25 to -19)	-20 (-21 to -19)	-18 (-19 to -16)	-8(-9 to -7)	5 (2 – 6)
Placebo	5 (3 – 8)	-22 (-26 to -19)	-20 (-24 to -18)	-16 (-21 to -14)	-7 (-11 to -4)	3 (0 – 6)
Time	4 (3 – 5)	5 (5 – 5)	5 (5 – 6)	5 (5 – 7)	6 (5 – 8)	7 (7 – 9)
PCO_2 (kPa)						
Adrenaline	5.8 (5.5 – 6.0)	19 (17 – 21)	8.3 (7.5 – 12)	7.1 (6.7 – 7.9)	5.3 (4.8 – 5.9)	5.6 (5.2 – 5.9)
Placebo	6.0 (5.5 – 6.3)	22 (20 – 23)	12 (10 – 13)	7.1 (6.3 – 7.4)	5.5 (5.1 – 6.1)	5.9 (5.8 – 6.2)
Time	5.9 (5.2 – 6.3)	5.9 (5.6 – 6.1)	5.8 (5.5 – 6.1)	5.6 (5.4 – 6.0)	5.6 (5.4 – 5.8)	5.4 (5.3 – 5.6)
PO_2 (kPa)						
Adrenaline	8.0 (7.6 – 8.6)	2 (1.2 – 2.7)	9.6 (7.5 – 10.8)	9.5 (8.8 – 10.2)	8.8 (7.8 – 9.3)	8.0 (7.6 – 8.8)
Placebo	8.3 (7.3 – 8.6)	1.6 (1.3 – 2.0)	7.4 (5.9 – 8.3)	10.0 (8.7 – 10.6)	9.2 (8.0 – 9.9)	8.5 (8.0 – 9.2)
Time	7.9 (7.4 – 8.7)	7.9 (7.6 – 8.8)	8.2 (7.6 – 8.7)	8.4 (7.8 – 9.3)	8.4 (7.5 – 9.2)	7.4 (7.2 – 8.6)
Survivors						
A/P/Time	16 / 15 / 8	16 / 15 / 8	16 / 15 / 8	14 / 11 / 8	14 / 11 / 8	13 / 11 / 8

Median (quartile range) for arterial pH, base excess and blood gases at baseline, just before resumption of ventilation (end asphyxia), and at various times after start of resuscitation. Number of survivors in groups Adrenaline (A), Placebo (P) and Time control (Time ctrl).

There was no significant difference between the three groups at baseline, nor between groups Adrenaline and Placebo from End asphyxia until end of experiment at 240 min.

Table 2. Haemodynamics, cerebral oxygenation, and right common carotid artery blood flow (see also Figures 1 and 2)

	Baseline	60 min	240 min
HR (min^{-1})			
Adrenaline	162 (136-173)	191 (181 – 214)	201 (185 – 245)
Placebo	160 (132 – 182)	209 (186 – 223)	170 (155 – 203)
Time control	153 (136 – 181)	173 (157 – 202)	171 (163 – 191)
MAP (mmHg)			
Adrenaline	64 (58 – 67)	49 (46 – 55)	55 (48 – 59)
Placebo	64 (59 – 77)	56 (46 – 65)	55 (46 – 60)
Time control	65 (58 – 73)	66 (62 – 68)	64 (56 – 67)
CrS_{O_2} (%)			
Adrenaline	42 (38 – 45)	42 (34 – 47)	49 (43 – 54)
Placebo	42 (39 – 46)	45 (40 – 47)	53 (47 – 57)
Time control	42 (40 – 48)	41 (38 – 47)	47 (44 – 50)
Pbt_{O_2} (kPa)			
Adrenaline	1.5 (1.1 – 2.0)	2.2 (0.9 – 2.7)	-
Placebo	1.4 (0.9 – 1.5)	1.4 (0.8 – 2.0)	-
Time control	1.7 (1.1 – 2.5)	1.9 (1.2 – 2.4)	-
RCCABF/BW ($mL\ min^{-1}\ kg^{-1}$)			
Adrenaline	12 (10 – 15)	9 (7 – 11)	-
Placebo	14 (10 – 17)	11 (9 – 11)	-
Time control	12 (9 – 18)	11 (9 – 16)	-
Survivors			

A / P / Time control	16 / 15 / 8	14 / 11 / 8	13 / 11 / 8

Median (quartile range) for haemodynamics (HR and MAP), cerebral oxygenation ($CrSO_2$ and $PbtO_2$) and right common carotid artery blood flow (RCCABF) in relation to body weight(BW) at baseline, 60 min after start of resuscitation, and at 240 min. Figures 1 and 2 show the same measures during the first 30 min after start of resuscitation.

Number of survivors in groups Adrenaline (A), Placebo (P) and Time control.

There was no significant difference between the three groups at baseline, nor between groups Adrenaline and Placebo at 60 or 240 min.

Table 3: Resuscitation outcomes

		Time (s) from start of resuscitation until:		
Group	N	ROSC	$CrSO_2$ > 30%	$PbtO_2$ > 0.1kPa
Adrenaline	16	72 (66 – 85)	86 (79 – 152)	181 (93 - 218)
Placebo	15	77 (64 – 178)	126 (88 – 309)	184 (140 - 339)
p		0.35	0.30	0.75

Median (quartile range) times from resumption of ventilation until return of spontaneous circulation (ROSC), regional cerebral oxygen saturation reached 30 %, and brain tissue PO_2 had increased by 0.1 kPa from its nadir.

N = no of subjects. *p* = *p*-value for difference between the two groups.

Table 4: Median (quartile range) plasma concentrations of adrenaline, noradrenaline, creatine kinase isoenzyme MB, and troponin I

	2.5 min after resumption of ventilation			240 min after resumption of ventilation		
Group	N	P-Adrenaline (nmol l^{-1})	P-Noradrenaline (nmol l^{-1})	N	P-CK-MB (µg l^{-1})	P-Troponin I (µg l^{-1})
Adrenaline	16	498 (268 – 868) *****	1799 (1058 – 4182)	13	7.9 (5.5 – 12)	5.2 (2.4 – 18.2)
Placebo	15	114 (80 – 306)	1385 (696 – 3118)	11	8.2 (6.2 – 16.2)	5.1 (1.6 – 24.1)
Time control	8	0.4 (0.2 – 0.6)	1.8 (1.3 – 2.4)	8	3.8 (2.8 – 7.2)	0.09 (0.06 – 0.12)

* Significant difference between groups Adrenaline and Placebo ($p < 0.05$).

N = no of subjects.

Figure 1. Early adrenaline administration does not improve circulatory recovery during resuscitation from severe asphyxia in newborn piglets

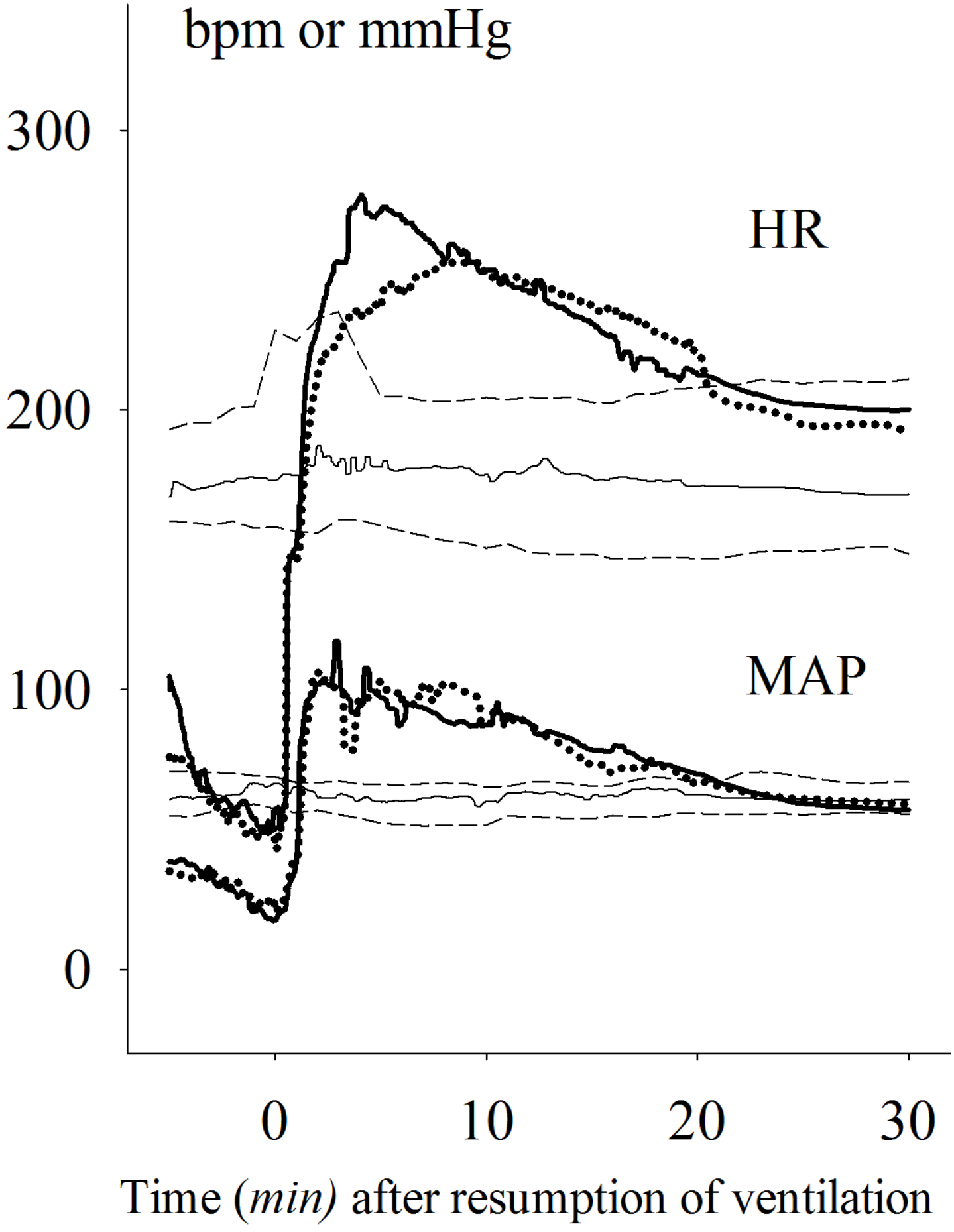

Figure 2. *Early adrenaline administration does not improve circulatory recovery during resuscitation from severe asphyxia in newborn piglets*